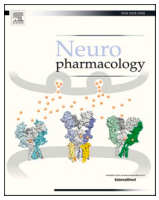
Neuropharmacology 195 (2021) 108626

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Invited review

Endocannabinoids, cannabinoids and the regulation of anxiety

Gavin N. Petrie, Andrei S. Nastase, Robert J. Aukema, Matthew N. Hill *

Hotchkiss Brain Institute and the Mathison Centre for Mental Health Education and Research, Departments of Cell Biology and Anatomy & Psychiatry, Cumming School of Medicine, University of Calgary, Calgary, AB, T2N 1N4, Canada

ARTICLE INFO

Keywords:
Anxiety
CB1R
FAAH
AEA
Cannabinoids
Stress

ABSTRACT

Cannabis has been used for hundreds of years, with its ability to dampen feelings of anxiety often reported as a primary reason for use. Only recently has the specific role cannabinoids play in anxiety been thoroughly investigated. Here we discuss the body of evidence describing how endocannabinoids and exogenous cannabinoids are capable of regulating the generation and termination of anxiety states. Disruption of the endogenous cannabinoid (eCB) system following genetic manipulation, pharmacological intervention or stress exposure reliably leads to the generation of an anxiety state. On the other hand, upregulation of eCB signaling is capable of alleviating anxiety-like behaviors in multiple paradigms. When considering exogenous cannabinoid administration, cannabinoid receptor 1 (CB1) agonists have a biphasic, dose-dependent effect on anxiety such that low doses are anxiolytic while high doses are anxiogenic, a phenomenon that is evident in both rodent models and humans. Translational studies investigating a loss of function mutation in the gene for fatty acid amide hydrolase, the enzyme responsible for metabolizing AEA, have also shown that AEA signaling regulates anxiety in humans. Taken together, evidence reviewed here has outlined a convincing argument for cannabinoids being powerful regulators of both the manifestation and amelioration of anxiety symptoms, and highlights the therapeutic potential of targeting the eCB system for the development of novel classes of anxiolytics.

1. Fear and anxiety

Fear and anxiety are adaptive biological processes that prepare an individual for potential harm through behavioural, physiological, autonomic, and hormonal responses. This is beneficial in the short-term; vigilance enhances rapid identification of any potential threat, and arousal facilitates a rapid response to a potential threat. However, prolonged, unnecessary, or exaggerated fear and anxiety responses contribute to substantial negative health outcomes. Anxiety disorders exhibit lifetime prevalence in 28.8% of Americans (Kessler et al., 2005); however, therapeutic treatments have demonstrated limited success in many individuals (Calhoon and Tye, 2015; Griebel and Holmes, 2013). Thus, understanding the neurobiology and key neuromodulators of these disorders is essential to develop novel therapeutics.

Despite largely overlapping circuitry of fear and anxiety (Tovote et al., 2015) they differ significantly in several key features. Fear is a rapid and transient response to a distinct, known, acute sensory stimulus; in contrast, anxiety is a prolonged, generalized response in anticipation of an ambiguous or unknown threat, often one which is less immediate (Davis et al., 2010). As such, fear typically induces an organized behavioural reaction while anxiety is often characterized by a state of heightened vigilance and generalized physiological arousal lacking organized behaviour (Lang et al., 2000). Further, clinical measures suggest only a moderate relationship between fear and anxiety; specifically, fear is characterized by harm avoidance behaviours only while the potential threat is present, while anxiety is characterized by sustained hypervigilance and arousal even as the threat dissipates (Sylvers et al., 2011). Thus, anxiety is characterized by a more general, sustained response than fear.

1.1. Measures of anxiety

Anxiety consists of both a subjective experience (e.g. "worry") and a physiological experience (e.g. increased heart rate; (Calhoon and Tye, 2015)). In humans, the subjective experience is the primary measure and is conducted through self-report scales. For example, the **State-trait anxiety inventory (STAI**; (Julian, 2011)) is a 40-item self-report questionnaire that captures both current feelings (state anxiety) and frequency of feelings (trait anxiety). More simply, the **Visual Analogue Scale for Anxiety (VAS-A)** is a singular measure of self-reported anxiety

* Corresponding author. 3330 Hospital Drive NW, Calgary, AB, T2N 1N4, Canada.
E-mail address: mnhill@ucalgary.ca (M.N. Hill).

https://doi.org/10.1016/j.neuropharm.2021.108626
Received 1 February 2021; Received in revised form 11 May 2021; Accepted 24 May 2021
Available online 8 June 2021
0028-3908/

"in this moment". It consists of a 10 cm line between the statements "not at all anxious" and "very anxious"; the subject indicates their perceived level of anxiety by placing a mark on the line, and anxiety is scored by measuring the distance from the "not at all anxious" end (Hornblow and Kidson, 1976). The **Hospital Anxiety and Depression Scale (HADS-A)** attempts to separate symptoms of anxiety and depression and is measured through a four-point scale across 14 self-report questions (Zigmond and Snaith, 1983). Finally, the **Hamilton Rating Scale for Anxiety (HAM-A)** was developed specifically for anxiety disorders, and encompasses multiple subjective and physiological components of anxiety through a self-report scale of emotional (e.g. worry, irritability), somatic (e.g. feelings of weakness), cardiovascular (e.g. chest pain), and gastrointestinal symptoms (e.g. vomiting) (Hamilton, 1959).

In rodents, the physiological experience of anxiety is directly measurable, including components such as increased thermogenesis (Kataoka et al., 2020; Liebsch et al., 1998; Xie et al., 2019), increased blood pressure and heart rate (Scopinho et al., 2013), and release of stress hormones such as corticosterone (Herman et al., 2003; Pellow et al., 1986). In contrast, the subjective experience of anxiety is arguably impossible to measure in rodents. Thus, researchers have attempted to measure this indirectly through observation of approach-avoidance behaviour (Lezak et al., 2017). Animals encountering a novel environment are confronted with an internal conflict to explore (i.e. approach) vs reduce their risk of predation or other harm (i.e. avoid; Montgomery, 1955)). Anxiety is perceived to be high when avoidance behaviour is particularly evident. As a result, several widely-used laboratory tests have been invented to measure anxiety-like behaviour by placing animals in environments that are open, brightly lit, and isolated from familiar conspecifics (Choleris et al., 2001; Lezak et al., 2017). In the **open field test (OFT)**, animals are placed alone into a large, open, brightly-lit arena with high walled edges, and anxiety is inferred by the combined measures of time spent motionless, number of fecal pellets, and time spent travelling along the outside edges of the arena ("thigmotaxis"; (Barnett, 1976; Grossen and Kelley, 1972). The **elevated plus maze (EPM)** is comprised of two open arms and two closed arms elevated from the ground, with increased avoidance of entering or spending time in the open arms operationalized as a read-out of anxiety-like behaviour (Pellow et al., 1985). Similarly, the **light-dark (LD)** test allows the animal to travel between two compartments, one that is large, more open, brightly lit, and therefore aversive, and the other which is smaller, closed, and dark; in this case, anxiety-like behaviour is inferred by both a reduction in transitions between compartments (Crawley, 1985) as well as increased time spent in the dark compartment (Chaouloff et al., 1997). In the **novelty-suppression of feeding test (NSFT)**, animals are food restricted and then subsequently placed in an open field with food secured in the center of the novel environment; anxiety is inferred by latency of the animal to cross into the center to approach the food (D. R. Britton and Britton, 1981). The **social interaction test (SIT)** is slightly more complex but is founded on the same approach-avoidance conflict. A pair of unfamiliar animals are placed into a novel environment and allowed to socially interact; anxiety is inferred by a decreased time spent interacting (File and Hyde, 1978). Finally, increased **grooming and overall changes in an animal's behavioural repertoire** have also been recognized as indicators of anxiety (Bindra and Spinner, 1958; Füzesi et al., 2016); however, the standardization and operationalization of these particular observations are much less well established than the previous tests outlined above.

Importantly, validated and established anxiolytic drugs in humans have been reliably found to reduce anxiety-like behaviour in all of these tests [**OFT**: (Choleris et al., 2001); **EPM**: (Pellow and File, 1986); **LD**: (Chaouloff et al., 1997); **NSFT**: (D. R. Britton and Britton, 1981; Shephard and Broadhurst, 1982); **SIT**: (File and Pellow, 1985); **grooming**: (Kalueff and Tuohimaa, 2005; Nin et al., 2012)]. Further, exposure to stressful or aversive stimuli has also been found to amplify anxiety-like behaviour in each of these tests [**OFT**: (Di et al., 2016; McCall et al., 2015; Xiao et al., 2020); **EPM**: (Luo et al., 2020; Pawlak et al., 2003); **LD**: (Kinsey et al., 2007); **NSFT**: (Gamaro et al., 2003; Roth et al., 2012); **SIT**: (Bagot et al., 2015); **grooming**: (Gispen and Isaacson, 1981; Mu et al., 2020)].

However, it must be noted that several factors influence whether anxiety-like behaviour is observed in a given test. Firstly, stressor modality may influence behaviour in certain tests but not others. For example, chronic social defeat stress routinely leads to increased anxiety-like behaviour measured in the social interaction test (Bagot et al., 2015) but is less frequently observed in the EPM (Hayashida et al., 2010). In contrast, anxiety-like behaviour in the EPM (Doremus-Fitzwater et al., 2009) or OFT (Di et al., 2016) is more commonly observed and measured following restraint stress. Secondly, time of testing may also influence animals' behavior; work from Huynh et al. (2011), suggests that anxiety-like behaviour following chronic restraint stress is more evident when tested in the dark phase than the light phase. Thirdly, there is also evidence of sex-differences in tests of anxiety-like behavior (Donner and Lowry, 2013). For instance, female rodents display higher basal locomotor and rearing activity in the OFT and EPM than males (Brotto et al., 2000; Domonkos et al, 2017; Fernandes et al, 1999; Van Swearingen et al, 2013), irrespective of estrous cycle (Scholl et al, 2019). Importantly, males and females also differ in expression of distinct stress-induced changes in behavioral repertoire such as grooming and tail-rattling (Borkar et al, 2020), as well as exhibiting overall differences in behavioral strategies during various tasks (Shansky et al., 2018). Thus, it is important to consider that both the magnitude of response and type of behaviour observed may differ between sexes in each test. Therefore, and importantly, normative behaviors validated in male rodents may not necessarily be generalizable to females (Shansky, 2018). Lastly, different strains of mice exhibit differing levels of basal and stress-induced anxiety-like behaviour, a phenotype that is reflected by differences in amygdala excitability (Mozhui et al., 2010). Thus, modality of the stressor, timing of the test, and sex and strain of the animal all strongly influence whether anxiety-like behaviour is observed in a given test.

1.2. Neurobiology of anxiety

Anxiety-like states can be precipitated by many factors. This includes genetic predisposition (Gottschalk and Domschke, 2017; Mozhui et al, 2010), previous history such as early-life stress (Bai et al., 2012; Klengel et al, 2013; Lähdepuro et al, 2019; Lee et al, 2007), exposure to physiological (Bernstein et al, 2019; Vecchiarelli et al, 2021) or psychological stressors (Bagot et al, 2015; Di et al, 2016; Thiemann et al, 2020), and withdrawal from chronic alcohol or drug exposure (Becker, 2008; Kliethermes et al., 2006; Schulteis et al, 1998).

Given the wide range of autonomic, hormonal, physiological, and behavioural effects of anxiety, it is unsurprising that the generation of anxiety involves coordinated activation of multiple brain regions. This is well-reviewed elsewhere (Dias et al., 2013; Grupe and Nitschke, 2013; Martin et al., 2009; Ressler, 2020; Tovote et al., 2015) and will only be briefly reviewed here.

The **basolateral amygdala (BLA)** is an especially influential structure in initiating anxiety-like responses. It receives sensory input from all modalities as well as higher-order cognitive information encoding memory and motivational drive (Sah et al., 2003). As such, it has a fundamental role of assigning valence ("attractiveness" or "aversiveness") to stimuli and driving a subsequent behavioural and physiological response through activation of downstream targets (Janak and Tye, 2015; LeDoux, 2007). Indeed, the BLA influences stress-induced release of glucocorticoids (Bhatnagar et al., 2004) as well as anxiety-like behaviour in rodents (Arendt et al., 2014; Di et al., 2016; Grissom et al., 2008; Jochman et al., 2005). Notably, activation of the amygdala is strongly correlated with anxiety in response to a loud, aversive stimulus in humans (Carlson et al., 2011), is highly responsive to images related to specific phobias (Dilger et al., 2003), and is hyperactive to social cues (particularly angry faces) in individuals with generalized

anxiety disorder (GAD) and social anxiety disorder (SAD; (Martin et al., 2009). Thus, activation of the amygdala is heavily implicated in the generation of anxiety.

The **medial prefrontal cortex (mPFC)** has an important regulatory role of behaviour. In general, the dorsal subregion (prelimbic cortex; PL) promotes anxiety-like states and the ventral subregion (infralimbic cortex; IL) inhibits anxiety-like states.

Indeed, pharmacological excitation of the **prelimbic cortex** promotes anxiety-like behaviour (Saitoh et al, 2014), and lesions reduce anxiety-like behaviour (Lacroix et al, 1998; Maaswinkel et al, 1996). Generation of anxiety-like states is likely initiated by inputs from other brain regions, as optogenetic stimulation of discrete inputs from the BLA or ventral hippocampus to the prelimbic cortex is anxiogenic (Burgos--Robles et al., 2017; A.C. Felix-Ortiz et al., 2016; Parfitt et al, 2017). In turn, the prelimbic cortex sends strong direct projections to several downstream brain capable of promoting anxiety-like behavior, such as the amygdala (Liu et al., 2020) and paraventricular thalamus (Kirouac, 2021).

In contrast, the **infralimbic cortex** promotes resilience to stress-induced anxiety by encoding perception of behavioural control (Christianson et al., 2009) and safety (Milad et al., 2007; Sangha et al., 2014). More specifically, stimulation of the infralimbic cortex reduces anxiety-like behaviour in the EPM (Shimizu et al, 2018). This regulation occurs through top-down control of limbic circuits involved in the generation of emotional states, such as the amygdala (Motzkin et al., 2015). In humans, adults with diagnosed anxiety disorders exhibit reduced vmPFC activation coincident with reporting greater fear to a threat cue (J. C. Britton et al., 2013). Additionally, patients treated for anxiety also exhibit resting-state functional uncoupling of the vmPFC and amygdala (Hamm et al., 2014; M. J. Kim et al., 2011). Collectively, this suggests that the infralimbic cortex plays a critical role in suppression of anxiety-like states through top-down regulation of brain regions such as the amygdala.

In rodents, the **ventral hippocampus (VH)** is required for anxiety-like behaviour in novel contexts (Bannerman et al., 2003; Kjelstrup et al., 2002) as well as generation of social anxiety (Deacon et al., 2002; Ada C. Felix-Ortiz and Tye, 2014; McHugh et al., 2004). Interestingly, anxiogenic environments enhance synchrony between the VH and the mPFC, perhaps acting in conjunction to signal behavioural inhibition (Adhikari et al., 2010).

The **central amygdala (CeA)** and **bed nucleus of the stria terminalis (BNST)** are critical relay structures between the VH, mPFC, and BLA, and hypothalamic and brainstem structures regulating neuroendocrine, autonomic, and behavioural output (Goode and Maren, 2017). The CeA and BNST have a substantial role in learned fear, but also contribute to the generation of unlearned behavioural (Y. Lee et al., 2008; Lungwitz et al., 2012; Mazzone et al., 2018) and autonomic responses to stressors (S.-Y. Kim et al., 2013). Importantly, the BNST is a critical inhibitory relay for the VH and mPFC to exert influence on the HPA axis (Radley et al., 2009; Radley and Sawchenko, 2011). However, both of these structures exhibit substantial heterogeneity of function and circuit dynamics are extremely complex; indeed, manipulation of discrete microcircuits within the same brain structure can produce opposite influences on anxiety-like behaviour (Fadok et al., 2018; S.-Y. Kim et al., 2013).

The **insular cortex (INS)** has recently been implicated as having an important role in anxiety, possibly to predict future aversive physical states (Gogolla, 2017; Paulus and Stein, 2006). Indeed, the INS is highly connected with many of the above structures involved in anxiety, especially the amygdala (Gogolla, 2017; Ju et al., 2020). INS activity is very high in rodents when in closed arms of the EPM (Gehrlach et al., 2019), and is predictive of self-reports of anxiety in humans anticipating (but not yet experiencing) an aversive stimulus (Carlson et al., 2011). Likewise, pharmacological inactivation of the rostral INS reduces anxiety-like behaviour (Méndez-Ruette et al., 2019). Collectively, this suggests that the INS may be involved in anticipatory anxiety, although work in this field is still growing.

The **paraventricular nucleus of the hypothalamus (PVN)** has been established as the primary site of integration of hypothalamic-pituitary-adrenal (HPA) axis activation and subsequent endocrine response to threatening stimuli (Martin et al., 2009). Indeed, exposure to a stimulus previously paired with a shock reliably induces glucocorticoid release in both rodents (Campeau et al., 1997) and humans, and higher cortisol response is associated with greater subjective anxiety (Grillon et al., 2006). There is also strong evidence in humans that alterations in cortisol release occur in anxiety disorders (Hilbert et al., 2014; Zorn et al., 2017). For example, individuals diagnosed with various anxiety disorders exhibit elevated waking salivary cortisol levels (Vreeburg et al., 2010), and individuals with general anxiety disorder reliably demonstrate elevated cortisol (Tafet and Nemeroff, 2020). In contrast to anxiety disorders, individuals with trauma-related disorders (i.e. post-traumatic stress disorder; PTSD) demonstrate low basal levels of cortisol (Meewisse et al., 2007). Therefore, although anxiety disorders are characterized by alterations in the HPA axis, the specific impact of PTSD on HPA axis function may be unique from other disorders. Apart from regulation of the HPA axis, the PVN – and in particular the CRH+ neurons – has recently been implicated in complex anxiety-like behavioural changes including social transmission of stress (Sterley et al., 2018), initiation of escape behaviour (Daviu et al., 2020), and stress-induced grooming behaviours (Füzesi et al., 2016; Kruk et al., 1998). Thus, the contribution of the PVN is more complex than simply initiation of the neuroendocrine response to stress and may be involved in the social transmission of stress as well as guiding appropriate coping behaviours to specific environmental contexts.

2. Endocannabinoid primer

As discussed above, there is a strong relationship between fear and anxiety, although these are distinct processes. Given that there are several excellent reviews which elegantly summarize the state of knowledge regarding the role of endocannabinoids (eCB) in emotional fear memory (Gunduz-Cinar, 2021; Lutz, 2007; Marsicano and Lafenêtre, 2009; Zer-Aviv et al., 2016; Morena and Campolongo, 2014; Sbarski and Akirav, 2020), this review will explicitly focus on the influence of eCB signaling on the regulation of anxiety.

The present and growing interest in the eCB system for the treatment of neuropsychiatric disorders finds its roots in the enduring attention cannabis has received for millennia over its psychoactive, euphoric, and remedial properties (Mechoulam and Parker, 2013). The main psychoactive component of cannabis, Δ9-tetrahydrocannabinol (THC), was isolated and structurally described in 1964 (Gaoni and Mechoulam, 1964). Cannabidiol (CBD), another active plant cannabinoid compound with non-intoxicating but biologically relevant effects, was structurally described in 1963 after having been isolated decades earlier (Mechoulam and Shvo, 1963). Synthetic cannabinoid (CP-55,940) binding in the rat brain provided evidence for a membrane-bound cannabinoid receptor (Devane et al., 1988). Cannabinoid receptor type 1 (CB1R; Matsuda et al., 1990; Devane et al., 1992) and type 2 (CB2R; Munro et al., 1993) were ultimately found to be the principal receptors mediating the actions of cannabinoids. Subsequent to the discovery of the receptors, it was identified that there are two primary endogenous ligands N-arachidonyl ethanolamine (Anandamide (AEA); Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG; Mechoulam et al., 1995; Sugiura et al., 1995). 2-AG is present in rat brain at a level that is approximately 1000x greater than AEA (Stella et al., 1997), however, the vast majority of this 2-AG has been identified as “bulk” membrane incorporated 2-AG which functions as a storage reservoir of arachidonic acid (Nomura et al., 2011). Microdialysis studies have revealed that within the extracellular space 2-AG concentrations are only 5-10× higher then AEA (Wiskerke et al., 2012), suggesting that a considerable proportion of detectable 2-AG in the brain is not synaptically available and that the concentration of the signaling pools of AEA and 2-AG are likely not that

different from one another. 2-AG is a CB1/2R full agonist, while AEA is a CB1/2R partial agonist (Pertwee et al., 2010). AEA (and 2-AG though less potently; Petrosino et al., 2016), also acts as an agonist of the postsynaptic transient receptor potential vanilloid 1 (TRPV1) channel (Zygmunt et al., 1999; Smart et al., 2000).

There are several routes of 2-AG biosynthesis, but the dominant synthetic pathway involves the hydrolysis of inositol phospholipids by phospholipase C into diacylglycerol which is then hydrolyzed into 2-AG by diacylglycerol lipase (DAGL; Sugiura et al., 1995; Bisogno et al., 2003; Murataeva et al., 2014). Anandamide can be biosynthesized through N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) dependent (Cadas et al., 1997) and independent processes (Tsuboi et al., 2018). Activation of CB1R and CB2R results in the inhibition of adenylyl cyclase activity, while CB1R induction also activates inward rectifying K+ channels and inhibits Ca2+ channels via functional coupling to Gi/o proteins (Howlett et al., 2002). Neurons produce eCBs "on-demand" when depolarized and with Ca2+ influx (Di Marzo et al., 1994; Stella et al., 1997; Freund et al., 2003), which then retrogradely activate presynaptic cannabinoid receptors to suppress neurotransmitter release (Ohno-Shosaku et al., 2001; Kreitzer and Regehr, 2001; Wilson and Nicoll, 2001). Canonically, presynaptic CB1R are activated by eCBs from depolarized postsynaptic neurons and mediate depolarization-induced suppression of inhibition (inhibition of presynaptic GABA release; DSI) or excitation (inhibition of presynaptic glutamate release; DSE) (Katona and Freund, 2012; but see Busquets-Garcia et al., 2018 for a more in-depth discussion of non-canonical actions of eCB signaling). After synthesis, release, and reuptake, AEA is degraded by the enzyme fatty acid amide hydrolase (FAAH; Cravatt et al., 2001) whereas 2-AG is inactivated by the enzyme monoacylglyceride lipase (MAGL; Dinh et al., 2002). FAAH and MAGL are largely localized in the postsynaptic somatodendritic and presynaptic axonal compartments of cells, respectively (Gulyas et al., 2004). The discovery of these hydrolyzing enzymes revealed the possibility of indirectly modulating the eCB system for therapeutic benefit. Indeed, an early insight into the potential of indirect eCB manipulation to modulate anxiety was through the development of the selective, irreversible FAAH inhibitor URB597 (Kathuria et al., 2003).

An abundant distribution of CB1R and its gene has been detected throughout the animal brain (Herkenham et al., 1990; Matsuda et al., 1993; Tsou et al., 1998), including microglia, though it is also detectable throughout peripheral tissues (Howlett et al., 2002); CB2R is primarily found in immune cells and tissue (Howlett et al., 2002) although there is also evidence for CB2R localization in discrete neuronal populations of the central nervous system (Van Sickle et al., 2005; Zhang et al., 2017). Human brain, though more structurally elaborate than rodent, features a similarly heterogeneous and widespread CB1R distribution (Glass et al., 1997; Laere et al, 2008; Normandin et al., 2015; Laurikainen et al., 2019). CB1R are found on glutamatergic, GABAergic, serotonergic, noradrenergic, and cholinergic neurons, dispersed among these cell types in a region-specific manner (Marsicano and Lutz, 1999; Hu and Mackie, 2015). It has also been shown that CB1R show relative differences in their levels of G-protein activation per receptor throughout the brain (Breivogel et al., 1997).

The natural, plant-derived cannabinoids (phytocannabinoids) exhibit pharmacodynamic and behavioural effects that are expressed through interaction with the endogenous cannabinoid system. The stage was set for understanding not only their properties and exploiting their therapeutic potential, but also that of the entire eCB modulatory complex and beyond, with the isolation of THC more than half a century ago. THC and CBD have profound and diverse interactions with the eCB system. THC is well established as a partial agonist at CB1R and CB2R. The intoxicating effects of THC are also well known to be mediated through activation of CB1R, and specifically, it appears that CB1R on glutamatergic neurons drives many of the psychoactive effects of THC (Monory et al., 2007). Though CBD shows little affinity as a ligand to the CB1/2R orthosteric site (Pertwee, 2008), it has been shown to act as an allosteric antagonist to CB1/2R agonists (Thomas et al., 2007). The role of CBD was later suggested to more specifically be that of a negative allosteric modulator (Laprairie et al., 2015), capable of diminishing the action of other ligands to the CB1R orthosteric receptor site. At CB2R, however, CBD is also capable of acting as a partial agonist on the orthosteric receptor site (Tham et al., 2019). CBD can indirectly enhance AEA signaling as well, although the mechanism for this effect has been suggested to be mediated by CBD inhibiting AEA uptake (Bisogno et al., 2001), inhibiting FAAH-mediated AEA hydrolysis (Leweke et al., 2012), displacing AEA from intracellular fatty acid binding proteins (Elmes et al., 2015) or stimulating NAPE-PLD mediated AEA biosynthesis (Leishman et al., 2018). CBD is further capable of binding to TRPV1, as well as allosterically potentiating agonism of the serotonin 1A (5-HT1A) receptor, another GPCR (Rock et al., 2012).

With respect to neural circuits regulating anxiety, the CB1R is expressed in many of the previously described brain regions involved in anxiety, including moderate or high expression in the VH, BNST, mPFC, BLA, CeA, and INS (Herkenham et al., 1991; Tsou et al., 1998; Puente et al., 2010; Massi et al., 2008). Notably, CB1R efficacy and distribution in key limbic regions enables substantial and specific influence on distinct neural circuits. For instance, despite relatively sparse CB1R expression in the hypothalamus, receptors exhibit very high efficacy in the activation of G-proteins in this brain region (Breivogal et al., 1997). These properties have even been uncovered within the same brain region. Contrary to the massive decrease in hippocampal CB1R protein levels and agonist binding observed following GABAergic CB1R–KO, glutamatergic CB1R–KO shows minimal impact on hippocampal CB1R content and binding capacity; surprisingly, however, neuron-type specific CB1R–KO reduced G protein activation in an opposite fashion, suggesting much greater CB1R signalling efficiency (or G protein coupling) in hippocampal glutamatergic versus GABAergic neurons (Steindel et al., 2013). Likewise, high CB1R expression on a small, distinct subpopulation of GABAergic interneurons in the BLA (Katona et al., 2001; McDonald and Mascagni, 2001) allows considerable CB1R influence on this specific population, and therefore can substantially influence BLA microcircuitry. Further, there is notable overlap between CB1R and neurons which express dopamine receptors in the forebrain (Hermann et al., 2002) and localization of CB1R on noradrenergic neurons in the frontal cortex (Oropeza et al., 2007). Conditional CB1R–KO on neurons co-localizing dopamine D1 receptors (D1Rs) has been shown to result in anxiety-like behaviours in the novelty-induced grooming test and during less aversive SIT conditions, but not in the EPM or LDT (Terzian et al., 2011). There is recent evidence also suggesting that dopaminergic neurons themselves may possess CB2R, which may play a role in classical anxiety measures, as conditional KO of the CB2R on dopamine neurons was anxiolytic in the EPM and LDT (Liu et al., 2017). Thus, the expression profile of CB1R at key circuits involved in the generation and maintenance of anxiety suggests it may have substantial influence on emotional regulation by acting as a crucial regulator of circuit dynamics (Vogel et al., 2016).

The ubiquitous yet highly heterogenous expression pattern of the eCB system reflect, parallel, and punctuate its complexity in relation to affecting behaviour. The eCB system is a profound regulator of synaptic transmission and neural circuits, and there is evidence that the eCB system exerts both tonic (ongoing, persistent regulation in the absence of overt neuronal excitation) and phasic signaling (excitation-triggered eCB mobilization that produces short lived and robust impacts on synaptic transmission). While there is evidence to suggest that, depending on brain circuit and cell type, both 2-AG and AEA can contribute to both tonic and phasic forms of eCB signaling, there is increasing evidence that the ligands may primarily subserve distinct roles. Specifically, several lines of evidence suggest that in many circumstances, AEA may act as the primary "tonic" signaling molecule that regulates synaptic dynamics during basal conditions, while 2-AG may primarily act as the "phasic" signaling counterpart that activates during sustained depolarization (i.e., in response to salient events) and is involved in synaptic plasticity

(Ahn et al., 2008; Gorzalka et al., 2008; Hill and Tasker, 2012; Katona and Freund, 2012). In this review, we will explore the function of the eCB system, and its manipulation, as it relates to the expression of anxiety-like behaviours in humans and animals. Of note, the sex of subjects in each experiment referred to can be seen in the Tables, but unless otherwise mentioned all studies referred to were performed exclusively in male subjects.

3. Tonic regulation of anxiety

The eCB system is traditionally seen as a phasic neuromodulatory system, reacting to stimuli to restore homeostasis. However, studies disrupting CB1R signaling in a low stress environment have revealed a role for tonic eCB regulation of anxiety. Mice with a global knockout of the CB1R reliably showed increased anxiety-like behaviors in multiple paradigms. For example, KO mice exhibit reduced open arm time and entries in the elevated plus maze (Haller et al., 2002, 2004a, 2004b; Ruehle et al., 2013); reduced time and entries into lit compartment of a light dark box (Martin et al., 2002; Bura et al., 2010; Maccarrone et al., 2002; Ruehle et al., 2013); and decreased probe burying in the shock probe test (Degroot and Nomikos, 2004). Interestingly, this is a sexually dimorphic effect as female mice with genetic disruption of the CB1R gene do not exhibit the anxiogenic phenotype seen in male mice (Bowers and Ressler, 2016).

Pharmacological blockade of tonic cannabinoid signaling using the CB1R antagonists/inverse agonists AM251, AM281 or Rimonabant also increases baseline anxiety. Indeed, acute, systemic administration of a CB1R antagonist has been shown to increase anxiety-like behavior in the elevated plus maze in both male and female mice (Bowers and Ressler, 2016; Patel and Hillard, 2006; Rodgers et al., 2005; Navarro et al., 1997) and the novelty induced hypophagia paradigm (Gamble-george et al., 2013). These anxiogenic effects appear to be CB1R dependent seeing as AM251 administration decreased % open arm time compared to vehicle in Male WT but not CB1R KO mice (Haller et al., 2004b). Conversely, some studies have reported SR141716 (Rimonabant)-induced reductions in baseline anxiety (Haller et al., 2002, 2004; Rodgers et al., 2003; Griebel et al., 2005). However, the anxiolytic effects of Rimonabant do not appear to be present in CB1R KO mice, suggesting an off-target mechanism (Haller et al., 2004b). While requiring more work to fully explore the relationship, there is some evidence that CB2R activity could have anxiolytic properties similar to that of CB1R. Acute peripheral application of the CB2 antagonist AM630 dose-dependently decreases time spent in the light compartment of a light-dark box (Garcia-Gutierrez et al., 2012), indicative of increased anxiety-like behaviors. In line with this, CB2KO mice exhibit more baseline anxiety-like behaviours in the light-dark box and EPM (Ortega-Alvaro et al., 2011). Interestingly, elevations in 2-AG signaling also appear to reduce anxiety via activation of CB2R, supporting these findings that activation of this receptor is also anxiolytic (Busquets-Garcia et al., 2011). Data from studies investigating the impact of disrupting CB1R signaling on anxiety-like behavior can be seen in Table 1.

Neuroanatomical circuits responsible for the role of tonic CB1R activation in anxiety are nuclei and cell specific. Administrations of AM251 directly into the basolateral nucleus of the amygdala decreased % open arm time and entries in baseline conditions (Dono and Currie, 2012). However, administrations of a CB1R antagonist directly into the central nucleus of the amygdala before an EPM test had no effect on baseline anxiety-like behaviors in both male and female Wistar rats (Zarrindast et al., 2008; Blasio et al., 2013). In the hippocampus, local AM251 administration into the CA1 increases % open arm time and open arm entries in the elevated plus maze, suggesting disruption of eCB signaling in the hippocampus may actually be anxiolytic (Roohbakhsh et al., 2007). In the BNST, local administration of AM251 increases while the CB2R antagonist JTE907 decreases % open arm time, indicating respective anxiolytic and anxiogenic roles of CB1Rs and CB2Rs in this region (Gomes-de-Souza et al., 2021). This contrast may be due to the cellular localization of where CB1 and CB2 receptors are found in the BNST, although more work is required in this area.

Investigation of cell specificity has provided evidence for CB1R specifically on glutamatergic neurons as being responsible for gating anxiety at a baseline level. Indeed, genetic deletion of glutamatergic CB1R in the amygdala, hippocampus and neocortex decreased investigation of a novel object in both low and high light conditions (Jacob et al., 2009). Moreover, brain-wide recovery of CB1R in glutamatergic neurons of a CB1R KO mouse normalized CB1R KO-induced increases in anxiety-like behavior as seen by reductions of time in the open arms and light compartment of respective EPM and LD paradigms (Ruehle et al., 2013). Reductions of anxiety like behaviors following Glutamatergic CB1R rescue coincided with an enhancement of DSE in the hippocampus and amygdala (Ruehle et al., 2013).

On the other hand, GABAergic CB1Rs appear to promote anxiety. Deletion of forebrain GABAergic CB1R decreased, while Glutamatergic CB1R deletion increased, anxiety-like behaviors in the Novelty suppressed feeding, novel object investigation and resident intruder paradigms (Lafenêtre et al., 2009; Häring et al., 2011). Collectively, CB1R residing on glutamatergic neurons exhibit anxiolytic properties while GABAergic CB1R exhibits anxiogenic properties. This distinction has also been found to explain the biphasic effects by cannabinoid agonists on anxiety (Rey et al., 2012), whereby the anxiolytic effects of low dose cannabinoid were lost in glutamatergic specific CB1 KO mice while the anxiogenic effects of high dose cannabinoid were lost in GABAergic specific CB1 KO mice. Action at either GABAergic or Glutamatergic terminals due to preferential binding or dose could determine whether a specific CB1R agonist dose will produce anxiogenic or anxiolytic effects. Taken together, these data suggest that tonic eCB signaling, particularly at glutamatergic synapses in the BLA, likely acts to constrain anxiety in non-threatening environments, and disruption of this signal results in the generation of a state of anxiety.

Disruption of CB1Rs is a gross approach to investigating the role of tonic eCB signaling in anxiety, however, and does not provide insight into which eCB molecule may be mediating these tonic actions. Recent technological advancements have allowed for genetic or pharmacological disruption of ligand specific signaling. Due to available tools, studies have focused on the disruption DAGL activity, the main biosynthetic enzyme for 2-AG. Both male and female DAGLalpha KO animals, which have profound reductions in baseline 2-AG levels, exhibit increased anxiety-like behavior in the L/D box, novelty induced hypophagia, OFT and EZM when compared to their WT counterparts (Shonesy et al., 2014; Jenniches et al., 2016). These effects were specific to a loss of 2-AG signaling given that administration of a MAGL inhibitor (JZL184) reversed the anxiety like behavior in KO animals (Shonesy et al., 2014). However, both studies reported decreased movement in DAGL KO animals, which should be considered when interpreting differences in anxiety-like behaviors. That being said, acute pharmacological disruption of DAGL activity using DO34 significantly reduced distance and time spent in the light compartment of a LD box while having no effects on overall locomotion (Bedse et al., 2017), suggesting that suppressing 2-AG signaling can enhance anxiety in the absence of alterations in motor function. The development of tools to deplete AEA in the brain have been lacking until the recent development of the NAPE-PLD inhibitor LEI401. To date, no studies on anxiety-like behavior have been performed following AEA depletion, but LEI401 has been found to both impair fear extinction and induce activation of the HPA axis (Mock et al., 2020) similar to CB1R antagonism, so it certainly seems reasonable to predict that depletion of AEA would also produce an increase in anxiety. In line with this theory, global deletion of the FAAH gene unveils a tonic AEA signal, reducing anxiety like behaviour in the open field test and increasing 5-HT in the frontal cortex (Cassano et al., 2010). Interestingly, the FAAH inhibitor URB597 is capable of increasing 5-HT neuron firing in the dorsal raphe nucleus and noradrenergic neuron activity in the locus coeruleus, suggesting an interaction between cannabinoid signaling and catecholaminergic activity in the regulation of baseline

Table 1
Influence of genetic or pharmacological disruption of CB1R signaling on anxiety in rodent models.

Paper	Animal (Sex/strain)	Treatment (dose)	Route of Administration/ Region of Genetic Expression	Test	Results
Griebel et al. (2005)	SD/Wistar (Male)	(1,3,10) SR	Oral	EPM	10 mg/kg ↑ open arm time
	Mice	0.3, 1, 3, 10 SR And KO	I.P. Global	Defense test battery	1 mg, 10 mg, CB1R −/− ↓ upright postures and bites
	Mice	10 mg/kg SR	Oral for 2 weeks	EPM Chronic Mild Stress (7weeks)	SR ↑ open arm time after chronic
Haller et al. (2002)	CD1 Mice (Male)	CB1R KO	KO	EPM	↓ open arm time and entries
	CD1 Mice (male)	1, 3 mg/kg SR	I.P.	EPM	↑ open arm time and entries
Rutkowska et al. (2006)	Balb/c mice (male)	1, 2, 4 mg/kg AM281	I.P.	OFT	No effect on center time ↓ rearing (1, 4 mg/kg) and crossings between outside and inside (1, 2, 4 mg/kg)
				L/D	No effect on time in light compartment ↓transitions from light to dark at 4 mg
Gamble-George et al, 2013	Juvenile male ICR mice	1, 3, 10 SR	I.P.	NIH	↑ latency to eat in novel environment (3, 10 mg/kg) No effect on latency in home cage ↓ eating palatable food in novel environment and homecage (1, 3, 10 mg/kg) ↑ grooming and scratching in both novel environment and homecage (3, 10 mg/kg)
Navarro et al. (1997)	Male Wistar Rats	SR 3 mg/kg	I.P.	EPM	↓ time and entries in open arms
Patel & Hillard (2006)	ICR male mice	AM and SR (1, 3, 10 mg/kg; same doses)	I.P.	EPM	SR: ↓ % open arm time (3, 10 mg/kg) ↓ Total open arm time (10 mg/kg) AM251: ↓ % open arm time (3, 10 mg/kg) ↓ Total open arm time time (3, 10 mg/kg) ↓ Open arm entries (10 mg/kg)
Martin et al. (2002)	Male CD1 mouse background	CB1R KO		L/D RIT CUS	↓ time in lit compartment ↑ aggressive behavior in resident intruder test
Rodgers et al. (2005)	Male swiss webster mice	AM251 1.5, 3 mg/kg	I.P.		↓ % open arm time in naive animals No effect on % open arm time in experienced animals
				EPM	↓ center time in experienced animals but not naive animals
				Experienced Vs. Non-experience (high stress vs. low stress)	↑ Closed arm time in experienced animals
Degroot & Nomikos (2004)	Male Mice	SR 1, 3, 10 mg/kg	I.P.	Shock probe burying test	↓ burying of the probe (KO, 3 and 10 mg/kg)
	C57 Black	KO	Global	Shock probe burying test	↓ burying of the probe
Haller et al. (2004b)	Male CD1 background	CB1R KO	Global	EPM	↓ % time in open arms
		SR 1, 3 mg/kg	I.P.	EPM	↑ % time in open arms in both WT and CB1R KO mice (3 mg/kg)
		AM251 1, 3 mg/kg	I.P.	EPM	↑ % time spent in open arms. No effect in CB1R KO animals
Haller et al. (2004a)	Male CD1 background	CB1R KO	Global	EPM	↓ % open arm time and total open arm entries in the high light condition
				(high light (200 lux and low light 0.5 lux)	No effect in the low light conditions
Maccarrone et al. (2002)	CD1 mouse background Young (1 month)	CB1R KO	Global	OFT L/D	No effect in OFT
	Old (4 months)				Young KO animals showed ↑ latency to exit dark box, when compared to young WT.
Bura et al. (2010)	Male C57 Black Mouse background 8–10 weeks	CB1R KO	Global	L/D	↓ time and entries into light compartment
Rodgers et al. (2003)		SR 0.1, 0.3, 1, 10 mg/kg	I.P.		Naïve:
				EPM	No effect of SR on open arm time or entries
	Male Swiss Webster mice			Naïve	Experienced testers:
	10–12 weeks			Experienced (2nd trial of EPM)	↑ % open arm time and number of entries (1 mg/kg)
Fride et al., 2005	C57 black 6 Males and females	CB1R KO	Global	Vocalizations and locomotion after Auditory or swim stress	↓ vocalization after auditory stress ↓ vocalization and movement after swim
Shonesy et al. (2014)	C57Bl/6J Male and female	DAGLalpha KO	Global	OFT	↓ rearing in males ↓ rearing and center time in females

(*continued on next page*)

Table 1 (*continued*)

Paper	Animal (Sex/strain)	Treatment (dose)	Route of Administration/ Region of Genetic Expression	Test	Results
				L/D	↓ movement and time in light compartment in males and females ↓ overall movement in females
				NIH	↓ food intake in males
Jenniches et al. (2016)	C57Bl/6J mice background Mixed sex	DAGL alpha KO	Global	OFT (30 min)	↓ center time in minute 10-20
				L/D	↓ rearings in both light and dark compartments ↑ # of transitions in LD
				O maze	↑ distance in open arms No effect on time
Jacob et al. (2009)	Adult male C57 background	CB1R KO Glutamatergic CB1R KO	Global Glutamate expressing cells	EPM	No effect in time or entries ↑ stretch posture in global CB1R
				L/D	No effect in Glutamate KO Global KO ↓ time and entries into light compartment
				OFT Low light (0 lux)	Global KO ↓ thigmotaxis in low and high light
				High light (700 lux) NOI	Glutamate KO ↑ thigmotaxis in high light
				Low light (30 lux) High light (500 lux)	Global KO ↓ investigation in high light only Glutamate KO ↓ investigation in high and low light
Terzian et al. (2011)	Male Mice	Conditional CB1R KO	CB1R KO on dopamine receptor D1-expressing neurons	NG, OFT, EPM, L/D, SIT	KO ↑ grooming time/episodes (NG) KO ↓ interaction time/number (at low aversiveness/light; SIT)
Liu et al. (2017)	Male Mice	Conditional CB2R KO	CB2R KO on dopamine neurons	EPM, L/D	KO ↑ open arm time (EPM) KO ↑ lit area time (L/D)
Ruehle et al. (2013)	Adult male mice C57Bl/6J background	Conditional CB1R KO	Global	EPM	KO ↓ open arm time Partial rescue of open arm time with Glu-CB1R recovery
		CB1R recovery	Recovery in telencephalon glutamatergic neurons	L/D	KO ↓ time in light compartment KO ↑ latency to enter light compartment Partial rescue of time and full rescue of latency when recovering GluCB1R
Zarrindast et al. (2008)	Adult Male wistar	AM251 (2.5,25,100 ng)	Intra-Central Amygdala	EPM	No effect on % open arm time or entries
Dono and Currie, 2012	Adult Male SD	AM251 (0.25, 2.5, 25 pmol)	Intra Basolateral Amygdala	EPM	↓ % open arm time and entries (2.5 and 25 pmol)
Blasio et al. (2013)	Female wistar rats	Rimonabant (0.5 μg)	Intra Central Amygdala	EPM	↓ % open arm time during palatable food withdrawal No effect on chow diet
Roohbakhsh et al. (2007)	Male Wistar	AM251 (1, 10, 50 ng)	Intra Dorsal CA1	EPM	↑ % open arm time (10, 50 ng) and open arm entries (10 ng) WIN ↓ % open arm time (2.5, 5 μg)
Roohbakhsh et al, 2007	Male Wistar	AM251 (1, 10, 50 ng) URB597 (0.01, 0.1, 1 μg)	Intra Ventral Hippocampus		No Effects of AM251 URB597 ↓ % open arm time and entries (0.1, 1 μg)
Jiang et al. (2005)		HU210 (25 or 100 μg/kg) AM281 (3 mg/kg)	Intra dentate gyrus	NSF	Chronic HU (10 days) one month before testing reduced latency to eat in a novel environment but not home cage
		Chronic administration			No effect of AM281

Table 1. Sprague Dawley (SD), Elevated Plus Maze (EPM), Open Field Test (OFT), Intraperitoneal (IP), Novelty Induced Hypophagia (NIH), Morris Water Maze (MWM), Light Dark Box (L/D), Forced Swim Test (FST), Knockout (KO), Chronic Unpredictable Stress (CUS), Resident Intruder Test (RIT), Novel Object Investigation (NOI), Novelty Supressed Feeding (NSF), Novelty-induced Grooming (NG), Social Interaction Test (SIT), Cannabinoid Receptor 1 (CB1), Diacyl glycerol lipase (DAGL), Knockout (KO), SR141716A (SR).

anxiety (Gobbi et al., 2006). These data would suggest that eCB signalling maintains a tonic regulation of anxiety at a baseline level and if this eCB tone is disrupted, it results in the generation of a state of anxiety in the absence of any overt threat. This work has helped with identifying how eCB signaling fluctuates in a high stress environment to naturally bring about anxiety like behaviors.

4. Dynamic and phasic eCB regulation of anxiety

Acute exposure to a variety of psychological stressors generally elicits a rapid reduction of AEA signaling in brain regions responsible for regulating anxiety. Indeed, mice that have undergone acute social defeat or restraint for 30 min showed an immediate drop in hippocampal and amygdalar AEA, respectively (Rademacher et al., 2008; Gray et al., 2015) Fig. 1. This drop in amygdala AEA is believed to be a result of stress induced CRH signaling at CRHR1 receptors, which then rapidly

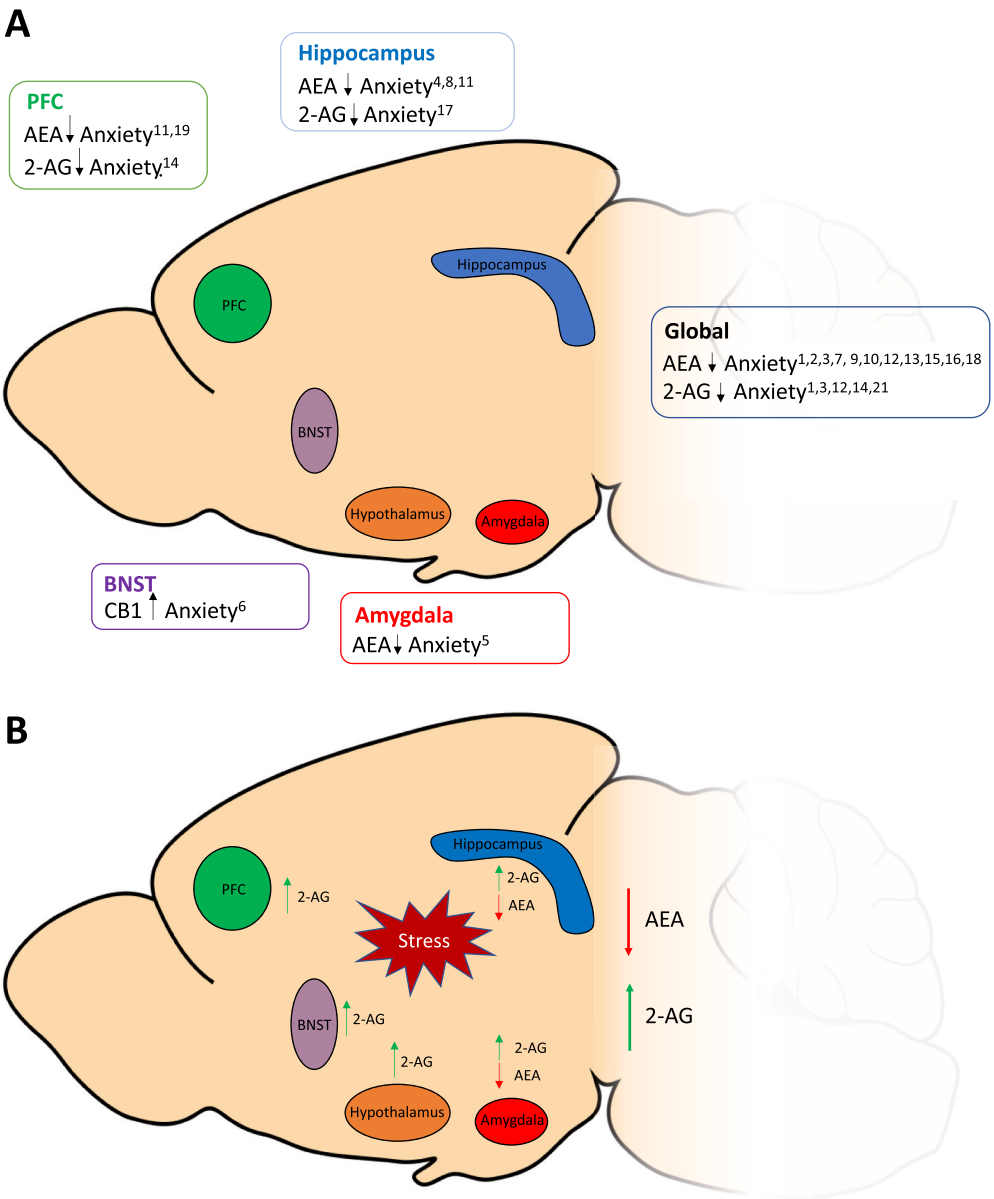


Fig. 1. ***A.*** Neuroanatomy of eCB regulation of anxiety. Statements describe evidence for the local and global function of each eCB via pharmacological manipulation in the context of anxiety. Upward and downward arrows denote a respective increase or decrease in anxiety-like behaviors. **B.** Stress induced alteration of eCB signaling that are known to contribute to anxiety. Arrows beside regions indicate local (beside brain regions) and global (most posterior area of brain) stress induced changes in eCB levels. Upward and downward arrows denote a respective increase or decrease in eCB levels following stress exposure. Prefrontal Cortex (PFC), Bed Nucleus of the Stria Terminalis (BNST), Dorsal Hippocampus (dHippo), Ventral Hippocampus (vHippo), Anandamide (AEA), 2-Arachadonyl Glycerol (2-AG), Endocannabinoid (eCB**1.** Bedse et al. (2018); **2.** Bluett et al. (2014); **3.** Busquets-Garcia et al. (2011); **4.** Campos et al., 2010; **5.** Gray et al. (2015) **6.** Gomes-do-souza et al., 2021; **7.** Griebel et al. (2018); **8.** Hakimizadeh et al. (2012); **9.** Haller et al. (2009); **10.** Kathuria et al. (2003); **11.** Lisboa et al. (2015); **12.** Lomazzo et al. (2015); **13.** Marco et al. (2015); **14.** Marcus et al. (2020); **15.** Moreira et al. (2008); **16.** Patel and Hillard (2006); **17.** Guggenhuber et al. (2016); **18.** Rossi et al. (2010); **19.** Rubino et al. (2008); **20.** Scherma et al. (2008); **21.** Sciolino, Zou & Hoffmann.

trigger an increase in FAAH activity (Gray et al., 2015). CRH induced disruptions of tonic AEA signaling are believed to contribute to the rapid development of anxiety resulting after stress exposure. Consistent with this, local BLA infusions of a FAAH inhibitor (URB597) ameliorates stress-like behaviors in the EPM following CRH administration (Gray et al., 2015) and FAAH inhibition can ameliorate both anxiety and elevations in glutamate release in the CeA in a rat line exhibiting elevated constitutive CRHR1 signaling (Natividad et al., 2017). A number of studies also report FAAH inhibition reducing anxiety-like behaviors following stress exposure (Bedse et al., 2018; Bluett et al., 2014; Haller et al., 2009; Duan et al., 2017; Griebel et al., 2018). For example, FAAH inhibitor PF-3845 increased light-compartment entries and time while decreasing latency after a foot shock stress (Bluett et al., 2014). Although systemic FAAH inhibitors show efficacy in alleviating baseline anxiety (Moreira et al., 2007; Scherma et al., 2008; Marco et al., 2015; Patel and Hillard, 2006; Busquets-Garcia et al., 2011) these effects are amplified under conditions of stress or threat, presumably due to their ability to reverse the elevations in FAAH activity. For instance, administration of URB597 increased open arm entries and time under conditions of high environmental aversiveness while having no effect in conditions of reduced aversiveness, an effect blocked by AM251 (Haller et al., 2009). Accordingly, elevation of FAAH activity and the resulting disruption of AEA tone within the BLA following stress contribute to the development of anxiety-like behaviors. These stress-induced increases in anxiety can be alleviated by counteracting the elevation of FAAH activity with FAAH inhibitors. Consistent with the model put forth in the previous section regarding tonic eCB regulation of anxiety being localized to the regulation of glutamatergic transmission in the BLA, inhibition of FAAH has been found to prevent stress-induced increases in glutamatergic synaptic transmission in the BLA (Yasmin et al., 2020).

In opposition to apparent reductions in AEA signaling, acute stress exposure enhances 2-AG signaling in the mPFC, hippocampus and hypothalamus and amygdala (Hill et al., 2011; Wang et al., 2012; Evanson et al., 2010; Bedse et al., 2017) Fig. 1. However, elevation of 2-AG levels tends to be delayed, emerging at least 30 min after stress. Indeed, mPFC 2-AG levels are elevated 30 min following a 30 min restraint (Hill et al., 2011), but remain unaltered immediately after a 15-min swim or 30-min social defeat stress (Dubreucq et al., 2012; Rademacher et al., 2008). The time course for phasic elevation of 2-AG signaling aligns with stress-induced CORT feedback on central circuits and may be in part

responsible for dampening anxiety like behaviors following stress (Bedse et al., 2017). Specifically, enhancing restraint-induced elevations of 2-AG in the amygdala via global MAGL inhibition reduced anxiety-like behaviors in a CB1R dependent manner (Bedse et al., 2017). Aligned with this, pharmacological blockade of CB1Rs dramatically enhances anxiety levels in the novelty induced hypophagia task (Gamble-george et al., 2013), while genetic CB1R KO potentiates stress induced anxiety in the EPM (Hill et al., 2011). Moreover, despite MAGL inhibition reportedly reducing baseline anxiety (Busquets-Garcia et al., 2011), it is more commonly known to alleviate anxiety in high stress conditions. Both acute and chronic JZL184 increased % open arm time and open arm entries in a bright and aversive EPM while acute administration had no effect in low light conditions (Sciolino et al., 2011). Moreover, acute JZL184 increased % time and distance in the light compartment of a L/D box only if mice had previously undergone a 30-min restraint while having no effect in unstressed animals (Bedse et al., 2018).

Despite extensive knowledge of 2-AG's role in blunting anxiety development following stress, only few recent studies have begun investigating the circuit level mechanisms of 2-AG in this context. A recent report provided evidence for 2-AG acting at CB1Rs on BLA-prelimbic prefrontal cortex (plPFC) circuits to mediate stress-induced anxiety (Marcus et al., 2020). Indeed, both specific deletion of CB1Rs on BLA-plPFC glutamatergic neurons or prelimbic DAGLalpha deletion increased this circuit's synaptic strength and anxiety like behaviors in the EZM following footshock stress. Based on evidence showing disruption of CB1R signaling (Roohbakhsh et al., 2007) and over-expression of MAGL in glutamatergic hippocampal neurons (Guggenhuber et al., 2016) led to increases in baseline anxiety, local upregulation of 2-AG levels may be regulating anxiety through hippocampal CB1R following stress. Evidently, blocking or augmenting the phasic 2-AG elevations in response to a stressor or aversive environment is capable of potentiating or ameliorating any resulting anxiety-like behaviors, respectively. This would suggest that delayed elevations in 2-AG signaling may play a role in a negative feedback mechanism responsible for curbing anxiety and terminating this behavioral state following the cessation of threat exposure.

Collectively, these data indicate that fluctuations in the eCB system are principle to the anxiety response following stress exposure. Notably, the rapid disruption of AEA and delayed enhancement of 2-AG signaling at the CB1R respectively initiate and buffer the development of anxiety in response to acute stress. With respect to neural circuits, the current state of research indicates that the BLA is a primary site for the anti-anxiety effects of AEA signaling, while discrete frontocortical circuits and the hippocampus seem to be important hubs for the actions of 2-AG on anxiety. Individual studies on the impacts of inhibition of FAAH or MAGL on anxiety-like behavior can be seen in Table 2.

5. ECBs and chronic stress

ECB signaling plays an important role in behavioral and brain morphological changes following chronic stress exposure. Indeed, chronic restraint stress increases dendritic length, branch points and spine numbers in BLA pyramidal and stellate neurons, sensitizing these stress-responsive circuits (Hill et al., 2013; Vyas et al., 2002; Rosenkranz et al., 2010). Interestingly, spine density changes on BLA dendrites after chronic immobilization positively correlate with both increased anxiety-like behaviors in the EPM (Govindarajan et al., 2006) and the increased frequency of glutamatergic synaptic events (Rosenkranz et al., 2010). These morphological and behavioral changes are thought to be mediated by increased FAAH activity in the amygdala, mPFC, and dorsal hippocampus also seen following chronic stress (Hill et al., 2013; Reich et al., 2009; Rademacher et al., 2008), as pharmacological inhibition or genetic deletion of FAAH activity mitigate anxiety-like behaviors and brain morphology changes brought about by chronic stress exposure (Rossi et al., 2010; Hill et al, 2013; Lomazzo et al., 2015; Duan et al., 2017). As tonic AEA signaling gates glutamatergic synaptic transmission in the BLA (Yasmin et al., 2020), it is likely that the loss of AEA signaling through sustained increases in FAAH activity following repeated stress (Hill et al., 2013; Gray et al., 2016) contribute to chronic stress-induced increases in glutamatergic transmission in the BLA (Rosenkranz et al., 2010), which in turn are believed to mediate stress-induced morphological changes in the BLA (Yasmin et al., 2018). Consistent with these findings, it has also recently been shown that sustained peripheral inflammation, a physiological stressor, can also promote anxiety through impairments in AEA signaling (Vecchiarelli et al., 2021).

While fluctuations in AEA signaling modulate stress sensitization, 2-AG appears to be more involved in stress adaptation processes. Daily restraint, from 5 to 10 days, elevates 2-AG levels in the amygdala, mPFC, forebrain and hypothalamus (Rademacher et al., 2008; Patel et al., 2004, 2005). This elevation in 2-AG, particularly within the BLA, has been linked to adaptive processes under chronic stress, including both habituation of the HPA axis and promoting resilience against the development of anxiety (Hill et al., 2010; Bluett et al., 2017). Specifically, blockade of CB1Rs in the BLA can reverse habituation of the HPA axis and dramatically amplify behavioral indices of anxiety following repeated stress exposure, while inhibition of 2-AG metabolism by MAGL promotes resilience to repeated stress (Hill et al., 2010; Bluett et al., 2017). Consistent with this, augmenting 2-AG signaling alleviates anxiety development after chronic stress exposure (Zhong et al., 2014). Alternatively, chronic exposure to alcohol appears to decrease circulating 2-AG, with an exacerbated reduction during a period of abstinence. However, alcohol abstinent animals exhibit trait anxiety-like behaviours in the EPM, which was mostly attenuated by MAGL inhibitors JZL184 and MJN110, further supporting the anxiolytic role of 2-AG (Serrano et al., 2018). Together these data suggest that the sustained loss of AEA signaling following chronic stress promotes sensitization of amygdala neurons and the generation of a persistent state of anxiety, while the elevations in 2-AG signaling act to promote adaptive responses to repeated stress and promote resilience against the development of anxiety, possibly via the regulation of excitatory inputs to the BLA (Bluett et al., 2017).

6. Exogenous cannabinoids and anxiety

Much of the therapeutic potential of the cannabis plant has been explored through the administration of isolated natural or synthetic exogenous cannabinoid compounds in animals. These methods have also permitted deeper insight into the overall function of the eCB system in the modulation of anxiety-like phenotype. THC demonstrates a biphasic, dose-dependent, and state-dependent effect on anxiety measures in animals. Specifically, acute administration at high doses is anxiogenic (Onaivi et al., 1990; Valjent et al., 2002; Patel and Hillard, 2006; Schramm-Sapyta et al., 2007; Rock et al., 2017; Todd and Arnold, 2016) while low doses are anxiolytic (Valjent et al., 2002; Berrendero and Maldonado, 2002; Rubino et al., 2007; Braida et al., 2007). Chronic administration of even low doses of THC can be anxiogenic in some models (Long et al., 2010; O'Brien et al., 2013). Acute, high dose THC administration promotes anxiogenic behaviours in both sexes, though to a greater extent in females than males (Manwell et al., 2019). These divergent effects may be the result of sex-differences in THC metabolism. For example, females produce more 11-hydroxy-THC (11-OH-THC) than males do following THC administration, including greater accumulation of 11-OH-THC in the brain (Ruiz et al., 2021; Browne and Weissman, 1981; Tseng and Craft, 2001; Wiley and Burston, 2014). 11-OH-THC is an efficacious agonist at CB1 receptors (Grotenhermen, 2003; Lemberger et al., 1972), perhaps more so then THC itself, and so the greater production of 11-OH-THC in females may account for some of the sex differences in sensitivity to THC.

Acute THC may differentially modulate rodent anxiety-like behaviours depending on animal strain, age during drug administration, and even behavioural test used (Kasten et al., 2017). Interestingly, administration of high THC doses shortly (1h) following stress exposure

Table 2
Influence of Genetic or Pharmacological Disruption of eCB Metabolism on Anxiety in Rodent Models.

Paper	Animal (Sex/ strain)	Drug (dose)	Route of Administration/ Region of Genetic Expression	Stress	Test	Results
Bedse et al. (2018)	Male ICR Mice		I.P.	Footshock Restraint	L/D	No effect in unstressed animals PF and JZL alone ↑ time and distance in light compartment after either stressor
				Novelty	NIH	JZL ↓ latency (15 mg/kg) and ↑ amount drank (10, 15 mg/kg) No effect of PF
	Male C57	FAAH inhibitor (PF-3845; 0.1, 1, 10 mg/kg)		Footshock	EZM	JZL↑ open arm entries and ↓ immobile time in open arm in stressed mice (10 mg/kg)
		MAGL inhibitor (JZL 184; 5, 8, 10, 40 mg/kg)			OFT	JZL195 ↓ distance moved in center while ↑ total distance (40 mg/kg) JZL195 ↓ fecal boli (10, 40 mg/kg) JZL184 ↓ fecal boli (5, 40 mg/kg)
	Male and Female ICR (female only used for FS) Male C57 for EZM	Dual FAAH/MAGL inhibitor (JZL 195; 5, 10, 40 mg/kg)		Restraint Footshock	MWM	No inhibitors affected MWM
Marcus et al. (2020)		JZL184	I.P.		EZM	JZL reversed stress induced anxiety in EZM
		DO34				DO34 exacerbated stress induced anxiety in EZM
Imperatore et al. (2015)	Adult male C57 background	MAGL KO	Global		Marble burying	↑ digging time ↓ latency to dig ↑ Immobility time
					L/D	↓ Time in light comparment ↓ latency to enter dark compartment
Kinsey et al. (2011)	Adult C57 male mice	PF-3845 (1, 3, 10 mg/kg) JZL184 (4, 16, 40 mg/kg)	I.P.		Marble Burying	PF (10 mg/kg) and JZL (16, 40 mg/kg) ↓ marbles buried
		THC (.03, .1, 1, 3, 10, 30 mg/kg)				THC ↓ burying (0.3, 10, 30 mg/kg)
Guggenhuber et al. (2016)	Adult male C57 background	MAGL OE	Hippocampal neurons		OFT EPM L/D	↓ time in center ↓ time in and entries to open arms No effect
Moreira et al. (2008)	Adult Male C57 Black background	FAAH KO	I.P.		EPM	KO ↑ open arm time and entries (CB1R dependent) URB ↑ % time and entries into open arms (CB1R dependent)
		URB597 1 mg/kg (3 mg/kg)			L/D	KO ↑ % time spent in lit compartment No effect of URB
Scherma et al. (2008)	Adult Male SD rats	URB597 (0.1, 0.3 mg/kg) AEA (1 mg/kg)	I.P.		Three consecutive days of L/D	URB ↑ time in light compartment (0.1, 0.3 mg/kg) AEA ↑ time in light compartment (0.3 mg/kg) AEA ↓ time in light compartment (3 mg/kg) AEA (0.3, 3 mg/kg) + URB (0.3 mg/kg) ↓ time in light compartment
Haller et al. (2009)	Adult male SD rats		I.P.	Low light	EPM	No effects of URB under continuous low light.
		AM251 (1 mg/kg)		High light		URB ↑ time in open arms in bright maze
		URB597 (0.1, 0.3 mg/kg)		Light changes throughout test		URB ↑ open arm entries and time in changing lighting conditions (0.3 mg/kg; CB1R dependent)
Morena et al. (2019)	Adult Male SD Rats	BLA specific FAAH overexpression	Intra Basolateral Amygdala		EPM	↓ Open arm entries ↑ latency to enter open arm
					L/D	↑ time and entries into light compartment ↓ latency to enter light compartment
					OFT	No effect of FAAH OE or URB
Bluett et al. (2014)	Male ICR mice 4–7 weeks	PF-3845 10 mg/kg	I.P.	Footshock	L/D	↑ entries into light compartment stress free ↑ time and entries into light compartment after stress ↓ latency to enter light compartment after stress

(*continued on next page*)

Table 2 (*continued*)

Paper	Animal (Sex/ strain)	Drug (dose)	Route of Administration/ Region of Genetic Expression	Stress	Test	Results
					NIH	↓ latency to eat after stress (CB1R dependent) No effect on total consumed
Marco et al. (2015)	Male CD1 mice Male Wistar Rats	ST4070 (FAAH inhibitor; 10, 30 mg/kg)	Oral		EPM L/D	↑ time in open arms (30 mg/kg) ↑ time in light compartment (30 mg/kg)
Lomazzo et al. (2015)	Male C57 (6 weeks)		I.P.	CUS (6 weeks)	EPM	JZL and combo ↓ time and entries in open arms in animals without stress
		URB597 (1 mg/kg/day) JZL184 (8 mg/kg/day)			FST L/D	No drug effects in stressed animals URB and JZL alone ↑ time in lit compartment after stress
		URB + JZL				URB, JZL and combo ↑ entries into lit compartment after stress
		Delivered chronically 1.5h before stress (starting 5 weeks after the start of CUS)			FST	JZL and combo ↑ immobility time and ↓ time to immobility in unstressed group No effects in stressed group
Kathuria et al. (2003)	Wistar rats (sex unknown)		I.P.		EZM	↑ time in open arms (URB597 0.1 mg/kg; URB597 1, 5, 10 mg/kg) (CB1R dependent)
		URB 597 (0.05, 0.1 mg/kg) URB 532 (.1, 1, 5, 10 mg/kg)			Isolation induced ultrasonic emissions test	↓ vocalizations (URB597 0.1 mg/kg; URB597 1, 5, 10 mg/kg) (CB1R dependent)
Patel & Hillard (2006)	Adult male ICR mice	CP55940 (0.001,0.01,0.03, 0.1,0.3 mg/kg)	I.P.		EPM	CP ↑ % open arm time (0.01, 0.03, 0.3 mg/kg) and total arm entries (0.3 mg/kg)
		WIN 55212 (0.3, 1, 3, 10 mg/kg)				WIN ↑ % open arm time, total open arm time and % open arm entries (1, 3 mg/kg)
		THC (0.25, 1, 2.5, 10 mg/kg)				THC ↓ % (1, 2.5, 10 mg/kg) and total (2.5, 10 mg/kg) open arm time as well as %open arm entries (2.5, 10 mg/kg)
		URB597 (0.03, 0.1,0.3 mg/kg)				URB ↑ % open arm time (0.1, 0.3 mg/kg), total open arm time (0.1 mg/kg) and %open arm entries (0.1 mg/kg)
		AM404 (0.3,1,3,10)				AM404 ↑ % (1, 3 mg/kg) and total (3 mg/kg) open arm time
Zhong et al. (2014)	Adult male C57Bl/6J Mice	JZL184 (8 mg/kg every 2 days for 4 weeks) Rimonabant (2 mg/kg)	I.P.	CUS (5 weeks)	NIH	Chronic JZL ↓ latency to feed in CUS group (CB1R dependent)
Sciolino et al. (2011)	Adult Male SD		I.P.		EPM	Acute JZL ↑ % open arm time and open arm entries under high environmental aversive conditions (CB1R dependent)
		JZL 184 (1, 4, 8 mg/kg)		High aversive (890/480 lux open/closed arms)		No effect under low aversive conditions
		Chronic (1/day for 6 days)		Low aversive (15/0 lux open/closed arms)		Chronic JZL ↑ open arm time and entries in high aversiveness
Busquets-Garcia et al. (2011)	Adult Male Swiss albino mice C57 mice	URB597 (1 mg/kg) JZL184 (8 mg/kg) Chronic = 6 days JWH133 (1,3,10; CB2 agonist) Rim (CB1R antagonist) SR144528, AM630 (CB2 antagonists) CB1 KO CB2 KO	I.P.		EZM	URB and JZL (acute and chronic) ↑ open area time (URB effects CB1R mediated; JZL effects CB2 mediated)
					EPM	URB and JZL (acute and chronic) ↑ open arm time (URB effects CB1R mediated; JZL effects CB2 mediated) JWH ↑ open arm time (all doses)
Duan et al. (2017)		PF3845 Acute (4, 8 mg/kg)	I.P.	Swim Stress Chronic CORT	EPM OFT	Chronic PF ↑ time in open arm (Astroglial CB1R mediated)
		Chronic: (4 mg/kg/day for 4 days)		(3 weeks)	Ephys in BLA pyramidal cells	Acute PF ↑ open arm time and entries (8 mg/kg)
	Male CD1 and C57 mice for behavior	URB597			NIH	Chronic PF ↓ latency to eat Acute PF ↓ latency to eat (8 mg/kg)
		AM281			OFT	

(*continued on next page*)

Table 2 (*continued*)

Paper	Animal (Sex/ strain)	Drug (dose)	Route of Administration/ Region of Genetic Expression	Stress	Test	Results
	Male SD rats for ephys					Chronic PF ↑ center time and entries (Astroglial CB1R mediated)
Hill et al, 2011	Adult male C57/Bl6	FAAH KO		CMS (21 days)	EPM	No effects of CUS in FAAH KO
Gray et al. (2015)	Male SD rats	URB597 10 ng CRH 1 μg	BLA	Restraint	EPM	CRH ↓ open arm time (sec and %) and CORT (blocked by intra-BLA URB)
Campos et al., 2010	Adult Male Wistar Rats		Ventral Hippocampus	Restraint	EPM	AM404 ↓ % open arm time and entries in non-stress conditions (50 pmol)
		AM404 (5, 50 pmol)				AM404 ↑ % open arm entries (5, 50 pmol) and time (5 pmol) following restraint
		AM251 (100 pmol)				All CB1 dependent
Lisboa et al. (2015)	Adult Male Wistar Rats	URB597 0.01 pmol AM404 50 pmol	Dorsal Hippocampus		EPM	AM404 and URB ↑ % time and entries into open arms (CB1R mediated)
		AM251 100 pmol	Prelimbic medial PFC			URB ↑ % OA entries (CB1R mediated)
Rubino et al. (2008)	Adult male SD		Prefrontal Cortex (PFC)		EPM	mAEA ↑ % OA time and entries and head dips (0.1 μg; CB1R mediated) mAEA ↓ % open arm time and entries (10 μg; TRPV1 mediated) mAEA ↑ stretch attend postures (10 μg; CB1R mediated)
		mAEA (0.1, 1, 10 μg)				Capsazapine ↓ % open arm time (5 μg) and entries (5, 10 μg)
		AM251 (1 μg)				URB ↑ % open arm time and entries, head dips and stretch attend postures (0.01 μg)
		Capsazepine (TRPV1 antagonist; 1,5,10 μg)				URB ↓ closed arm returns (0.01 μg)
		URB597 (0.01, 0.1, 1 μg)				FAAH OE ↓ % open arm time and entries
		FAAH OE				FAAH OE ↓ head dips and FAAH OE ↑ closed arm returns
Hakimizadeh et al. (2012)	Male Wistar Rats				EPM	URB ↑ % open arm time (0.1, 1 μg) URB ↑ % open arm entries (0.1 μg) (CB1R and TRPV1 mediated)
		URB597(0.01,0.1,1 μg) Capsaicin (0.003, 0.03, 0.3 μg)				Capsaicin ↓ open arm time (0.0003,0.03 μg) and entries (0.003 μg)
		AMG9810 (0.003, 0.03, 0.3 μg)				AMG ↑ % open arm time (0.03, 0.3 μg)
Griebel et al. (2018)	Long Evans and SD rats	SSR411298 (1, 3, 10 mg/kg)	I.P.	Social defeat stress	EPM	↑ % open arm time in stressed rats ↑ novel object investigation in stressed rats (all doses)
		FAAH inhibitor				↓ distress calls (3, 10 mg/kg)
Rossi et al. (2010)		URB597 (3 mg/kg)	I.P.	Social defeat stress	OFT	URB ↑ center time and entries following stress
		AM251 (6 mg/kg)			EPM	URB ↑ time in OA following stress (CB1R dependent)

Table 2. Fatty Acid Amide Hydrolase (FAAH), Anandamide (AEA), Monoacylglycerol (MAGL) Elevated Plus Maze (EPM), Open Field Test (OFT), Intraperitoneal (IP), Novelty Induced Hypophagia (NIH), Elevated Zero Maze (EZM), Morris Water Maze (MWM), Light Dark Box (L/D), Forced Swim Test (FST), Overexpression (OE), Knockout (KO).

promotes anxiolytic effects (alongside blunting of the HPA-response) in the short-term period of several hours, but no longer has an effect 24 h later (Mayer et al., 2014). Thus, the timing of administration following stress-exposure may strongly influence the impact of THC on anxiety-like behavior. Interestingly, the nature of the stressor can also differentially affect THC dose responses. One study explored this in terms of relatively low-dose, acute THC injection one day after extended stress (completion of a 10-day chronic unpredictable stress (CUS) paradigm) or stress-free conditions (Fokos and Panagis, 2010). Non-stressed animals exhibit anxiolytic responses in the EPM to both doses, whereas stressed animals show an anxiogenic response to the lower dose and an anxiolytic response to the higher dose (Fokos and Panagis, 2010).

The synthetic direct agonists of the eCB system exhibit similar dose-dependent properties to THC in their anxiety-modulating effects. The direct cannabinoid agonists CP-55940 and WIN-55212-2 are anxiolytic at low doses but begin to alter locomotion and anxiety-related behaviours at higher doses (Patel and Hillard, 2006). WIN-55212-2 exhibits its low-dose-dependent anxiolytic effects via CB1R (Haller et al., 2004b). These agonists also show state- or context-dependent effects, imitating THC (as described previously). Another cannabinoid agonist, HU-210, administered systemically at a low dose enhances anxiolytic behaviours in a novel environment, but is anxiogenic in familiar conditions in the defensive withdrawal test (De Fonseca et al., 1996). In the black tufted-eared marmoset, a nonhuman primate, WIN-55212-2 displays anxiolytic properties to a novel OFT environment (Cagni and Barros,

2013). Further, reduced anxiety- and depression-like behaviours were detected after a low dose of WIN-55212-2 following a footshock in a model of stressor-shock and situational reminders (Burstein et al., 2018). In a model of CUS, stressed animals experienced anxiogenic effects while non-stressed animals exhibited anxiolytic responses to an acute low dose of HU-210 (Hill and Gorzalka, 2004). These outcomes reflect the previously mentioned study using THC, where a low dose was anxiogenic in CUS animals while being anxiolytic in unstressed animals (Fokos and Panagis, 2010), indicating that the stress history of an animal can influence whether cannabinoids produce anxiolytic or anxiogenic effects.

The mechanism of exogenous cannabinoids is better understood when evaluated in the context of anxiety-related neurocircuitry. THC microinjection into the PFC and vHPC show dose-dependent anxiolytic behaviours in the EPM, while BLA microinjection is anxiogenic highlighting the region-specific effects of THC in the brain (Rubino et al., 2008). Acute systemic administration of THC ameliorates the cFOS-detected activation of PFC and AMY neurons in response to the EPM (Rubino et al., 2007). Conversely, high THC doses increase cFOS expression in the nucleus accumbens shell, CeA, BLA, laterodorsal BNST, cingular and piriform cortex, and the PVN (Valjent et al., 2002). Interestingly, Intra-mPFC (PL) CBD+THC ameliorated escape responses observed with THC alone in an elevated T-maze task (Szkudlarek et al., 2021). The anxiety-mediating properties of acute THC have been suggested to be under the regulation of CB1R (Berrendero and Maldonado, 2002; Rubino et al., 2007, 2008; Szkudlarek et al., 2019) and indirectly, activation of 5-HT receptors (Braida et al., 2007; Viñals et al., 2015). In mice, a study using low and high doses of CP-55,940 suggests that anxiolytic (low-dose) and anxiogenic (high-dose) biphasic responses to cannabinoids may be under the regulation of glutamatergic-CB1R and GABAergic-CB1R, respectively, independent of sex (Rey et al., 2012). The data from individual studies on the effects of CB1R agonists on anxiety-like behavior are summarized in Table 3.

CBD, as compared to THC, principally displays a bell-shaped, concentration-dependent anxiolytic response. CBD is anxiolytic at a range of doses from 2.5 to 20 mg/kg (Guimaraes et al., 1990, 1994; Moreira et al., 2006; Zieba et al., 2019), and has been shown to abolish anxiogenic-like behaviour caused by a prior stressor (Rock et al., 2017). Chronic CBD in male C57BL/6JArc mice is anxiolytic at a lower dose than is usually effective acutely (Long et al., 2010). Doses at the upper and lower limits of that range seem to be ineffective in some studies, however; for example, acute or chronic CBD administration is ineffective on anxiety-like behaviour in the LD task in rats (O'Brien et al., 2013), or acute CBD in OFT (Todd and Arnold, 2016) or EPM in mice (Long et al., 2010).

The anxiolytic effect of CBD may be primarily mediated through agonism of the 5-HT1A receptor, compared to THC which has relatively less affinity to this receptor (Russo et al., 2005) and, as mentioned above, primarily directs anxiety-like behaviours in a circuit-specific manner via CB1R. CBD administered directly into the dorsal periaqueductal gray (dPAG) has been shown to be anxiolytic in the EPM (Campos and Guimaraes, 2008) and elevated T-maze via action at the 5-HT1A receptor (De Paula Soares et al, 2010). Intra-BNST CBD administration showed dose-dependent anxiolytic effects with no locomotor or nociceptive effects, which were abolished with prior administration of a 5-HT1A receptor antagonist (Gomes et al., 2011). Intra-mPFC (PL) CBD produced anxiogenic behaviours in unstressed animals but anxiolytic behaviours in animals stressed 24 h earlier, in a 5-HT1A- and dose-dependent manner (Fogaça et al., 2014). Chronic CBD managed to eliminate anxiety resulting from neuropathic pain which was mediated by 5-HT1A but not TRPV1 receptors (Gregorio et al., 2019). Also, chronic CBD following predator exposure showed 5-HT1A receptor-dependent attenuated anxiety response in the EPM, while a single acute injection had no attenuating effect (Campos et al., 2012). Interestingly, though, chronic CBD administered following paradigms of daily stress is anxiolytic in EPM and novelty-supressed feeding tasks but seems to be mediated via cannabinoid receptors (Campos et al., 2013; Fogaça et al., 2018) and not 5-HT1A (Fogaça et al., 2018). Given that CBD can potentiate AEA signaling through various proposed mechanisms but does not seem to influence 2-AG signaling, and that chronic CBD treatment selectively down-regulates FAAH expression in stressed animals (Fogaça et al., 2018), it is likely that this cannabinoid receptor-dependent anxiolytic effect is a result of enhanced AEA tone (Campos et al., 2013). Thus, CBD has multiple routes of anxiolytic action depending on dose and context.

The vast majority of testing has so far been conducted following systemic THC injection. THC inhalation, a far more translationally representative route of THC administration, has been shown to produce increased blood THC levels with increasing drug concentrations in both male rats (Manwell et al., 2014) and mice (Wilson et al., 2002). This is similar to THC injection i.p. (Manwell et al., 2014) or i.v. (Wilson et al., 2002). This is true also between sexes, as plasma THC levels are comparable between sexes following THC inhalation and injection (i.p.) at different doses and time-measurements (Javadi-Paydar et al., 2018). Direct comparison between inhalation and other routes of administration is challenging due to the difficulty of quantifying absorbed THC doses during inhalation. However, it seems as though several fold increases in vaporized THC are required to elicit similar average blood THC levels to i.p. injection (Manwell et al., 2014). This pattern does not translate to 11-OH-THC, a psychoactive metabolite of THC, in that lower levels of the molecule are detected following inhalation compared to injection (Manwell et al., 2014), likely due to inhalation routes bypassing first pass hepatic metabolism, where the majority of 11-OH-THC is produced. Unlike i.p. (Torrens et al., 2020) or i.v. THC which results in greater brain to blood THC levels, inhaled THC produces comparable blood and brain THC levels in mice (Wilson et al., 2002). In rats, the pharmacokinetic profiles of THC, CBD, and THC+CBD in serum and brain seems to differ significantly between routes of administration (subcutaneous, inhalation, oral; Hložek et al., 2017); inhalation shows large and transient THC levels in serum but smaller yet still transient levels in brain, while oral administration shows higher magnitude and longer lasting THC increases in brain. One recent study established a linear relationship between cannabis compound mass applied to their vaporization mechanism and male mouse blood THC concentration (Farra et al., 2020); importantly, the authors found a diverse brain map of modulated BOLD signals (with the amygdala being predominantly negative) and detected an increase of anxiety-like behaviours in the OFT in response to an acute high dose of vaporized THC. With respect to anxiety measures, this is consistent with previous reports using acute systemic administration of THC. After an 8-week chronic regimen of near-daily vaporized THC, treatment animals show no change in anxiety-like behaviours in the OFT and EPM (Bruijnzeel et al., 2016); this result, on the other hand, varies from the anxiogenic effects seen following systemic THC administration.

7. Role of eCBs in human anxiety

Summarized data from all studies of endocannabinoid signaling or cannabinoid administration on anxiety in humans is found in Table 4. CB1Rs are expressed in high amounts within the human central nervous system. Radiolabeling studies reveal high CB1R density in the amygdala, hippocampus and cerebral cortex, brain regions intimately involved with anxiety regulation (Herkenham et al., 1990; Westlake et al., 1994). This role of eCB signaling in regulating human anxiety became evident during the clinical trials of the CB1R antagonist, rimonabant, for the treatment of obesity. In a meta-analysis of four randomized double-blind placebo-controlled studies, administering chronic rimonabant (20 mg/day) significantly increased baseline anxiety levels on the Hospital Anxiety and Depression Scale (Christensen et al., 2007). In fact, anxiety was one of the main reasons' participants in the rimonabant group discontinued the studies and was one of the primary psychiatric side effects that resulted in the FDA ultimately banning the release of it

Table 3
Influence of CB1R agonists on anxiety in rodent models.

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
Onaivi et al. (1990)	Male SD Rats Male ICR Mice	**THC** Acute: 0.3–10 mg/kg (rats) 1–20 mg/kg (mice) Chronic: 5 mg/kg (rats) 20 mg/kg (mice) **CBD** Acute: 0.01–100 mg/kg (mice) **THC+CBD** Combined Acute (mice): CBD 0.01 mg/kg + THC 10–20 mg/kg	**I.P.** Acute: 30 min before test Combined Acute: CBD: 10 min before THC; THC: 30 min before test Chronic: daily for 14 days; tested on treatment days 5, 10, 14, and during 2 days of withdrawal	EPM	**Acute (THC):** >1 mg/kg: ↓ open arm time & entries (rats and mice) **Acute (CBD):** 0.5-50 mg/kg: ↑ open arm time Combined: ↑ open arm time (for both doses vs THC alone) **Chronic (THC):** ↓ open arm time (all days but withdrawal) & total entries (all days including day 1 of withdrawal) (rats) ↓ open arm time & total entries (on day 10 and 14) (mice)
Valjent et al. (2002)	Male CD-1 Mice	**THC** Acute: 0.03–5 mg/kg	**I.P.** 30 min before test	LDT; OFT	(LDT) 0.3 mg/kg: ↑ % lighted area time and movement 5 mg/kg: ↓ % lighted area time and movement (OFT) 0.3 mg/kg: ↑ central area time & entries & total movement
Patel & Hillard (2006)	Male ICR Mice	**CP-55940** Acute: 0.001–0.3 mg/kg **WIN 55212–2** Acute: 0.3–10 mg/kg **THC** Acute: 0.25–10 mg/kg	**I.P.** 30 min before test	EPM	**CP-55940:** 0.01-0.03 mg/kg: ↑ % open arm time 0.3 mg/kg: ↑ open arm time & total entries; % open arm time & entries **WIN 55212–2:** 1-3 mg/kg: ↑ open arm time; % open arm time & entries 3 mg/kg: ↑ total entries 10 mg/kg: ↓ total entries **THC:** 1 mg/kg: ↓ % open arm time 2.5-10 mg/kg: ↓ open time; % open time & entries
Schramm-Sapyta et al. (2007)	Male CD Rats	**THC** Acute: 0.5–2.5 mg/kg (injected and tested during adolescence or adulthood)	**I.P.** 30 min before test	EPM; LDT	(EPM) 0.5 mg/kg: Adult < Adolescent (total entries & % open arm time) 2.5 mg/kg: Adult & Adolescent (↓ % open arm time) Adult < Adolescent (total entries) (LDT) Adults & Adolescents (↑ Dose = ↓ in time in lighted area) Adults (↑ Dose = ↑ emergence latency)
Rock et al. (2017)	Male SD Rats	**THC** Acute/Chronic: 0.1–10 mg/kg **CBD** Acute: 5 mg/kg **THC+CBD** Combined Acute: CBD 5 mg/kg + 1 mg/kg THC	**I.P.** Acute: 45 min before test Chronic: once daily for 21 days (including first acute day)	LDT; Foot-shock + LDT (24 h later)	(LDT) **Acute & Chronic THC** 1-10 mg/kg: ↓ lighted area time **Acute THC** 10 mg/kg: ↑ time to enter lighted area (Foot-Shock + LDT)

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
					Acute THC 1 mg/kg: ↓ lighted area time & ↑ time to enter lighted area (≈to vehicle treated animals) **Acute CBD** 5 mg/kg: ↑ lighted area time & time to enter lighted area **Combined Acute** No effect
Todd and Arnold (2016)	Male C57BL/6 Mice	**THC/CBD** Acute: 10 mg/kg	**I.P.** 30 min before test	OFT	**THC** ↓ distance moved & % center distance **CBD** no effect **Combined** ↓ distance moved no effect on % center distance
Berrendero and Maldonado (2002)	Male CB1R Mice	**THC** Acute: 0.3 mg/kg	**I.P.** 30 min before test	LDT	↑ lighted area time
Rubino et al. (2007)	Male SD Rats	**THC** Acute: 0.015–3 mg/kg	**I.P.** 30 min before test	EPM	0.075-1.5 mg/kg: ↑ open arm time and entries 3 mg/kg: ↓ spontaneous locomotor activity no effect on open arm time & entries
Braida et al. (2007)	Male SD Rats	**THC** Acute: 0.015–0.75 mg/kg	**I.P.** 30 min before test	EPM	0.075-0.75 mg/kg: ↑ % open arm times & entries
Manwell et al. (2019)	Male & Female CD (SD) IGS Rats	**THC** Acute: 0.5 mg/kg-5 mg/kg	**I.P.** 30 min before test	EMT (variant of the LDT); EPM; SIT	(EMT) 5 mg/kg: ↓ time spent in the open field & ↑ latency to emerge from the hide box (Males & Females) 2-5 mg/kg: ↓ open field entries (Males & Females) 2 mg/kg: ↓ movement speed (Females) 5 mg/kg: ↓ movement speed (Males & Females) (EPM) 2-5 mg/kg: ↓ open arm entries & time in open arms & time mobile (Males & Females) 2 mg/kg: ↓ movement speed (Females) 5 mg/kg: ↓ movement speed (Males & Females) (SIT) 2-5 mg/kg: ↓ conspecific sniffing (Females) 5 mg/kg: ↓ conspecific following (Females) 0.5 mg/kg: ↑ conspecific grooming (Females) 0.5-2 mg/kg: ↑ conspecific grooming (Males) 0.5 mg/kg: ↓ rearing time (Males & Females)
Mayer et al. (2014)	Male SD Rats	**THC** Acute: 1–10 mg/kg	**I.P.** 60 min after PSS exposure	PSS; EPM; ASR	(EPM & ASR (60 min after **THC**))

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
					5-10 mg/kg: ↑ open arm time 1-5 mg/kg: ↑ open arm entries ↓ "anxiety index" (EPM composite score, lower numbers = decreased anxiety-like behaviour) 1-10 mg/kg: ↓ startle amplitude (EPM & ASR (7 days after **THC**)) No **THC** effect within stress or no stress animal groups (EPM & ASR (1, 6, 24 h after 5 mg/kg **THC**)) At 6 h, stressed **THC** ↓ startle amplitude vs stressed vehicle By 24 h, no **THC** effect within stress or no stress animal groups
Fokos and Panagis (2010)	Male SD Rats	**THC** Acute: 0.5–1 mg/kg	**I.P.** 30 min before test	CUS (10 days); EPM (next day)	(Within Non-Stress Condition) 0.5-1 mg/kg: ↑ % open arm entries & time (Within Stress Condition) 0.5 mg/kg: ↓ % open arm entries 1 mg/kg: ↑ % open arm time 1 mg/kg ↑ % open arm entries & time (vs 0.5 mg/kg) (Between Stress and Non-Stress Condition) 0.5 mg/kg: Non-Stress > Stress % open arm entries & time
Manwell et al. (2014)	Male C57BL/6 Mice	**THC (10.3% THC; 0.05% CBD)** Acute: input mass = 450 mg; resulting blood concentration = 136.2 ± 5.04 ng/mL ("high")	**Vaporization/ Inhalation** Immediately before test (restrained)	OFT	↑ distance from inner zone ↓ inner zone time
Bruijnzeel et al. (2016)	Male Wistar Rats	**THC (5.7% THC, 0.02% CBD)** Chronic: cannabis cigarettes; resulting blood concentration = ~224 ng/mL (composite of two samples collected in weeks 2/4)	**Vaporization/ Inhalation** Immediately before test (unrestrained); 1 h/day, 5 days/week, 8 weeks	OFT, EPM	No effects
Haller et al. (2004b)	Male CD1 Mice (WT & CB1R–KO)	**WIN 55212–2** Acute: 1–3 mg/kg	**I.P.** 30 min before test	EPM	(WT) 1-3 mg/kg: ↑ % open arm time and entries (KO) No effects
De Fonseca et al. (1996)	Male Wistar Rats	**HU-210** Acute: 4–100 μg/kg	**I.P.** 5 min before test	DWT (in habituated and unhabituated context)	(Unhabituated) 4 μg/kg: ↓ emergence latency & average time in center ↑ movement & rearing (Habituated) 4-100 μg/kg: ↑ emergence latency & average time in center 100 μg/kg: ↓ movement & rearing
Cagni and Barros (2013)	Male Black Tufted-Ear Marmosets	**WIN 55212–2** Acute: 1 mg/kg	**I.P.** 30 min before test	OFT	↓ long calls, exploration & ↑ glances, scans (all reflecting an anxiolytic profile) ↑ center time
Burstein et al. (2018)	Male SD Rats	**WIN 55212–2** Acute: 0.5 mg/kg	**I.P.** 2 h after foot-shock	Footshock (& situational reminders); OFT (23 days after Footshock and WIN); ASR (31 days after Footshocks and WIN: separate experiment) CUS (3 weeks): then EPM	↓ freezing & "anxiety index" - periphery:total time (shocked WIN vs shocked controls) ↓ startle amplitude (shocked WIN vs shocked controls)

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
Hill and Gorzalka (2004)	Male Long-Evans Rats	**HU-210** Acute: 10–50 μg/kg	**I.P.** 30 min before test		10 mg/kg: ↑ open arm time & entries (non-stress) ↓ open arm time (stress) 50 μg/kg: ↓ open arm time (stress and non-stress)
Kasten et al. (2017)	Male C57B1/6J (B6) & DBA/2J (D2) Mice	**THC** Acute: 10 mg/kg (injected and tested acutely) Chronic: 6 × 10 mg/kg injections every 72 h, followed by 4-week abstinence (injected during adolescence or adulthood and tested after 4-week abstinence)	**I.P.** 30 min before test	EPM; OFT	Adolescent Acute: B6: (OFT) ↓ locomotion & % center time D2: (EPM) ↓ open arm time Adult Acute: B6: (EPM) ↓ open arm time (OFT) ↓ locomotion D2: (OFT) ↓ locomotion Adolescent Chronic: D2: (OFT) ↓ % center time Adult Chronic: B6: (OFT) ↑ % center time
Guimarães et al, 1990	Male Wistar Rats	**CBD** Acute: 2.5–20 mg/kg	**I.P.** 60 min before test	EPM	2.5-10 mg/kg: ↑ % open arm entries
Guimarães et al, 1994	Male Wistar Rats	**CBD** Acute: 5 mg/kg	**I.P.** 40 min before test	EPM	5 mg/kg: ↑ % open arm entries
Moreira et al. (2006)	Male Wistar Rats	**CBD** Acute: 2.5–10 mg/kg	**I.P.** 30 min before test	VCT	10 mg/kg: ↑ number of punished & total licks
Zieba et al. (2019)	Male C57BL/6J Mice (FMR1 gene KO & WT)	**CBD** Acute: 5–20 mg/kg	**I.P.** 30 min before test	EPM; OFT	20 mg/kg: ↑ open arm time & % open arm distance moved (all groups)
Long et al. (2010)	Male C57BL/6JArc Mice	**CBD** Acute: 1–50 mg/kg **THC/CBD** Chronic: x21 daily THC (0.3–10 mg/kg) or CBD (1–50 mg/kg)	**I.P.** Acute: 25 min before test	Acute: EPM Chronic: OFT (30–35 min after injection: days 1, 15, 21); LD (30 min after injection: day 17); EPM (45 min after injection: day 17); SIT (35 min after injection: day 18)	**THC (Chronic)** 10 mg/kg: (OFT) ↓ total distance travelled (all days) ↓ peripheral distance travelled (day 1, 21) ↓ % central distance (all days) ↓ exploratory activity (all days) ↓ central area time (days 15, 21) (LD) ↓ distance travelled & light compartment time & % distance (EPM) ↓ arm entries ↓ exploratory activity (all days) (SIT) ↓ social interaction 1-3 mg/kg: (OFT) ↓ total & peripheral distance travelled (day 21) 1 mg/kg: (OFT) ↓ exploratory activity (days 1, 15) 3 mg/kg: (EPM)

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
					↓ arm entries, (OFT) ↓ exploratory activity (all days) **CBD (Chronic)** 1 mg/kg: (LD) ↑ light compartment time & % distance 10 mg/kg: (LD) ↓ distance travelled 50 mg/kg: (OFT) ↑ central area time (day 15)
O'Brien et al. (2013)	Male SD Rats	**THC/CBD** Acute: 2.5 mg/kg Chronic: 14× daily 2.5 mg/kg	**I.P.** 30 min before test	LD (Chronic: day 0-drug free, 7, 14, 15-drug free)	**THC** ↓ lighted compartment time (all days except drug free days)
Rubino et al. (2008)	Male SD Rats	**THC** Acute: 2.5–25 ug	**I.C.** (Intra-PFC/vH/BLA) 30 min before test	EPM	**PFC** 10 μg ↑ % open arm time & entries ↓ closed arm returns 25 μg: ↑ closed arm returns **vHPC** 5 μg: ↑ % open arm time & entries ↓ closed arm returns **BLA** 1 μg: ↓ % open arm time & head dips
Rubino et al. (2007)	Male SD Rats	**THC** Acute: 0.75 mg/kg	**I.P.** 30 min before EPM, 35 min before cFOS	EPM (then cFOS)	**PFC; AMY** ↓ (cFOS vs vehicle)
Valjent et al. (2002)	Male CD-1 Mice	**THC** Acute: 5 mg/kg	**I.P.** 60 min before cFOS	cFOS	**nucleus accumbens shell, CeA, BLA, laterodorsal BNST, cingular and piriform cortex, PVN** ↑ cFos
Szkudlarek et al. (2021)	Male SD Rats	**THC/CBD/THC+CBD** Acute: 100 ng/500 nL	**I.C.** (Intra-mPFC; prelimbic) 5 min before test	ETM; OFT	(ETM) **THC** ↓ latency to escape **CBD/THC+CBD** ↑ latency to escape (compared to THC alone)
Szkudlarek et al. (2019)	Male SD Rats	**THC/CBD/THC+CBD** Acute: 10–500 μg/500 nL	**I.C.** (Intra-mPFC; prelimbic) 5 min before test	EPM; 3-CSAT	**THC_{100}** (EPM) ↓ open arm time & entries **THC_{100}+CBD_{500}** (EPM) ↑ open arm time & entries (compared to **THC_{100}**)
Campos and Guimarães, 2008	Male Wistar Rats	**CBD** Acute: 15–60 nmol	**I.C.** (Intra-dPAG) 10 min before test	EPM; VCT	30 nmol: (EPM) ↑ % open arm time & entries (VCT) ↑ punished licks
Viñals et al. (2015)	Male C57BL/6J Mice	**THC** Acute: 0.3–3 mg/kg	**I.P.** 0.3 mg/kg – 30 min before test 3 mg/kg – 5 h before test	EPM	0.3 mg/kg: ↑ % open arm time 3 mg/kg: ↓ % open arm time
Rey et al. (2012)	Male C57BL/6N Mice (Glu-CB1R-WT/KO; GABA-CB1R-WT/KO)	**CP-55940** Acute: 1–50 μg/kg	**I.P.** 30 min before test	EPM; HBT	(vs vehicle within same genotype unless noted) **GABA-CB1R-WT/KO** 1 μg/kg: ↑ % open arm entries ↑ % internal movement **GABA-CB1R-WT** 1 μg/kg: ↑ head dipping frequency 50 μg/kg: ↓ head dipping frequency ↑ stretch attend postures

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
					↓ % internal ambulation **GABA-CB1R–KO** 50 μg/kg: ↑ % open arm entries (vs vehicle and WT) ↑ % internal ambulation (vs vehicle and WT) ↑ head dipping frequency (vs WT only) ↓ stretch attend posture (vs WT only) **Glu-CB1R-WT** 1 μg/kg: ↑ % open arm entries ↑ internal ambulation 50 μg/kg: ↓ % internal ambulation **Glu-CB1R–KO** 1 μg/kg: ↓ % open arm entries (vs WT only) ↑ stretch attend posture (vs WT only) ↓ head dipping frequency (vs vehicle and WT) ↓ internal ambulation (vs vehicle and WT) **Glu-CB1R–KO** 50 μg/kg: ↓ % open arm entries ↓ head dipping frequency ↓ % internal ambulation
Arévalo et al. (2001)	Male Wistar Rats	**CP-55940** Acute: 0.075-0.125 mg/kg	**I.P.** 30 min before test	HBT; EPM	0.125–0.1 mg/kg: ↓ external/internal ambulation ↓ rearing frequency ↓ head dipping frequency/ time ↓ grooming frequency/time ↓ % open arm entries/time ↓ closed arm entries 0.075 mg/kg: ↓ head dipping frequency/ time ↓ % open arm entries/time
De Paula Soares et al, 2010	Male Wistar Rats	**CBD** Acute: 15–60 nmol	**I.C.** (Intra-dPAG) 10 min before test	ETM	60 nmol: ↓ inhibitory avoidance (2nd trial) 30-60 nmol: ↑ escape latency
Gomes et al. (2011)	Male Wistar Rats	**CBD** Acute: 15–60 nmol	**I.C.** (Intra-BNST) 10 min before test	EPM; VCT	60 nmol: (EPM) ↑ % open arm entries & time 30-60 nmol: (VCT) ↑ number of punished licks
Gregorio et al. (2019)	Male Wistar Rats (Sham & SNI)	**CBD** Chronic: 7× daily 5 mg/kg	**S.C.**	OFT; EPM; NSFT	**SNI+CBD** (OFT) ↑ center time & entries (EPM) ↑ open arm time (NSFT) ↓ latency to feed
Campos et al. (2012)	Male Wistar Rats	**CBD** Acute: 5 mg/kg Chronic: 7× daily 5 mg/kg	**I.P.** Acute: 1 h after predator stress, 7 days before test Chronic: day 1, 1 h after predator stress; day 7, 24 h before test	Predator Exposure Box; EPM	**Chronic CBD** ↑ % open entries & time (compared to vehicle) **Acute CBD** ↓ % open entries (compared to dummy stress)
Campos et al. (2013)	Male C57BL/6J Mice	**CBD** Chronic: 14× daily 30 mg/kg	**I.P.** 2 h after daily stressor (EPM) immediately after test (day 14; and day before test)	CUS; EPM; NSFT	**CUS+CBD** (EPM) ↑ % open area entries & time (NSFT) ↓ feeding latency

(*continued on next page*)

Table 3 (*continued*)

Paper	Animal (Sex/ strain)	Treatment (dose)	Route of admin (region)	Test	Results
			(NSFT) 24 h before test (test was day 15)		
Fogaça et al. (2014)	Male Wistar Rats	**CBD** Acute: 15–60 nmol	**I.C.** (Intra-mPFC; prelimbic) 10 min before test	Restraint Stress (2 h: 24 h before EPM); and/or EPM	(EPM) 30 nmol: ↓ % open arm entries & time (Restraint + EPM) 30 nmol: ↑ % open arm entries & time
Fogaça et al. (2018)	Male C57BL/6 Mice	**CBD** Chronic: 14× daily 30 mg/kg (each day of CUS)	**I.P.** 2 h after daily stressor (EPM) 2 h after test (day 14; and day before test) (NSFT) 22 h before test (test was day 15)	CUS (x14 days); EPM; NSFT	**CUS+CBD** (EPM) ↑ % open arm entries & time (NSFT) ↓ feeding latency

Table 3. Spared Nerve Injury (SNI), Elevated Plus Maze (EPM), Light-Dark Test (LDT), Open Field Test (OFT), Emergence Test (EMT), Social Interaction Test (SIT), Predator Scent Stress (PSS), Acoustic Startle Response (ASR), Chronic Unpredictable Stress (CUS), Defensive Withdrawal Test (DWT), 3-chambered social approach test (3-CSAT), Holeboard Test (HBT), Elevated T-Maze (ETM), Novelty-Supressed Feeding Test (NSFT), Intraperitoneal (I.P.), Intracranial (I.C.), Subcutaneous (S.C.), Δ9-tetrahydrocannabinol (THC), Cannabidiol (CBD), WIN 55212–2 (WIN), Prefrontal Cortex (PFC), medial PFC (mPFC), Ventral Hippocampus (VH), Basolateral Amygdala (BLA), dorsal Periaqueductal Gray (dPAG), Bed Nucleus of the Stria Terminals (BNST).

within the USA (Hill and Gorzalka, 2009).

The anxiogenic effects of rimonabant administration in humans suggest that eCB signaling is tonically gatekeeping the development of anxiety in humans, similar to what has been established in rodents. Consistent with this, individuals who have naturally elevated eCB signaling due to a common (~35% of populations with Caucasian ancestry possess one allele) functional single nucleotide polymorphism of the human FAAH gene (C385A; which increases proteolytic degradation of the FAAH protein, enhancing AEA signaling; Sipe et al., 2002) exhibit lower trait anxiety, reduced amygdala reactivity, enhanced habituation to aversive stimuli, less negative emotionality (including stress reactivity, aggression and alienation), enhanced prefrontal regulation of the amygdala, blunted physiological responses to stress and enhanced fear extinction memory (Gunduz-Cinar et al., 2013; Dincheva et al., 2015; Hariri et al., 2009; Mayo et al., 2020a; Gee et al., 2016). Similarly, circulating levels of AEA have been found to be inversely related to anxiety in healthy humans (Dlugos et al., 2012) and depressed populations (Hill et al., 2009). In corroboration with these data, administration of the FAAH inhibitor (PF-04457845) has been found to reduce anxiety associated with cannabis withdrawal (D'Souza et al., 2019), blunt physiological, sympathetic and affective responses to stress (Mayo et al., 2020b), blunt threat-induced amygdala reactivity (Paulus et al., 2020) and enhance the extinction of fear learning (Mayo et al., 2020b). Collectively, these data demonstrate that AEA signaling restricts anxiety in humans, similar to preclinical findings in rodents, while disruption of eCB signaling enhances anxiety.

8. Phytocannabinoids in human anxiety

Ever since the 1800s, the calming properties of cannabis have been taken advantage of in a therapeutic setting (Mikuriya et al., 1969). In fact, a review of epidemiological studies revealed that a majority of cannabis or cannabis extract users consume in order to reduce their anxiety, with women being more likely than men to report this purpose for use (Malone et al., 2009; Cuttler et al., 2016). Within the reviewed literature, up to 61% of medical cannabis users reported using cannabis in place of some or all other anti-anxiety pharmaceuticals (Malone et al., 2009). These epidemiological data suggest that cannabis could possess anxiolytic properties, but the experimental research shows a more complicated story. The effects of cannabis and its isolated chemical compounds on anxiety in humans depend on multiple variables, including dose, previous exposure and chemical makeup.

Animal research has thoroughly elucidated the dose dependent biphasic effect of THC on anxiety. This phenomenon is reflected in the human population. Indeed, smoking cannabis strains with 3.6% THC content are more likely to increase self-reported anxiety levels relative to those with 1.8% THC content (Ilan et al., 2005). Moreover, oral consumption of 7.5 mg of THC decreases subjective feelings of distress following a stressful event (Childs et al., 2017) and amygdalar activation while observing threatening faces (Phan et al., 2008). Meanwhile, oral THC administration reliably increases baseline levels of anxiety at doses 10 mg or higher. Four out of Five healthy male medical students reported waves of strong anxiety and near panic state peaking around 90 min post ingestion of 30 mg of THC (Karniol et al., 1974). Moreover, healthy adults consuming 10 mg THC reported increased subjective ratings of anxiety and elevated activation of the right amygdala in response to fearful faces. This effect appeared to be related to CB1R activation, with greater THC induced anxiety positively associated with higher CB1R availability (Bhattacharyya et al., 2017).

Interestingly, chronic cannabis users are reported as having lower central CB1R density, which return to normal after 4 weeks of abstinence (Hirvonen et al., 2012). Consistent with this functional loss of CB1R, when given THC (2.5 mg or 5 mg) intravenously, frequent cannabis users experience less feelings of anxiety and reduced increases in circulating cortisol than occasional users (D'Souza et al., 2008). Moreover, orally administered anxiogenic doses of THC produce less tense, jittery and uncontrollable feelings in weekly users when compared to occasional users (Peters et al., 1976). In the same vein, women experience more enhanced anxiogenic symptoms following acute cannabis consumption (Sholler et al., 2020). Sexual dimorphism in CB1R expression may explain this sensitivity as women have a higher density of CB1R availability than men (Normandin et al., 2015), although the increased production of 11-OH-THC by women, as described above, could also contribute to this increased sensitivity.

While somewhat equivocal, there is accumulating evidence that CBD may also possess anxiolytic effects in humans under some conditions. Indeed, oral administration of 600 mg CBD alone reduced both feelings of anxiety and amygdalar activity (Bhattacharyya et al., 2010). When combined, CBD has been reported to ameliorate the anxiety state brought about by high doses of THC. For instance, CBD is given in tandem with an anxiogenic dose of THC, participants report significantly less anxiety and panic while enhancing more pleasurable effects (Karniol et al., 1974). More specifically, oral THC (0.5 mg/kg) induced increases in baseline anxiety on the STAI scale were significantly reduced when administered alongside CBD (1 mg/kg; Zuardi et al., 1982). When smoking cannabis, healthy men and women show a trend towards decreased anxiety brought about by 3.8% THC strains if they also contain 1% CBD (Ilan et al., 2005). As such, there is the possibility that

Table 4
Human studies examining the influence of endocannabinoid signaling or cannabinoids on anxiety measures.

Paper	Participants	Groups/Drugs	Route of Administration/ Region of Genetic Expression	Stress Task	Anxiety measure	Results
Hariri et al. (2009)	82 healthy adult Caucasian volunteers Recruited from Adult Health and Behavior project (39 A carriers and 43 Control)	FAAH polymorphism FAAH C385A	Global	Exposed to angry and fearful expressions	STAI	↓ amygdalar reactivity to emotional faces ↓ relationship between amygdala reactivity and trait anxiety
Gunduz-Cinar et al. (2013)	Primarily white Middle aged 1037 participants (52% male)	FAAH C385A	Global	Exposed to angry and fearful expressions	Multidimensional Personality Questionnaire	↑ amygdalar habituation to stress ↓ trait stress reactivity
Conzelmann et al. (2012)	112 adults: 67c/c carriers and 45 A carriers	FAAH C385A	Global	Exposed to pleasant, neutral and unpleasant pictures	EMG STAI	↑ reactivity to unpleasant pictures ↓ inhibition to pleasant pictures No trait anxiety differences
Dincheva et al. (2015)	137 humans	FAAH C385A	Global		STAI	↓ levels of trait anxiety
Mayo et al., 2020	29 placebo 16 PF Healthy men and women over 18	DBPC PF-04457845 (4 mg/day) for 10 days	Oral	Fear Potentiated Startle The Affective Image Task The Maastricht Acute Stress Test	STAI POMS	↓ skin conductance ↓ subjective feeling of stress in response to stressor No effect on CORT ↓ corrugator activation in response to negative stimuli No effect on corrugator activation to neutral or positive stimuli
D'Souza et al. (2019)	58 Men (18–55) Cannabis dependent 30 joints in past 30 days or 180 joints in past 6 months Regular cannabis use for past 2 years	DBPC PF (4 mg/day) for 20–23 days	Oral	Cannabis withdrawal (5–8 days in hospital)	VAS	↓ scores on measures of depression, irritability and anxiety during withdrawal
Schmidt et al. (2020)	149 SAD patients 65% Males	DBPC JNJ-42165279 (25 mg)/day for 12 Weeks	Oral		LSAS HAD	Twice as many subjects showed improvement over 30% in symptom severity (LSAS)
Christensen et al. (2007)	Meta-analysis of total 3033 participants	Rimonabant (20 mg/day) Placebo	Oral		HAD	↑ anxiety compared to placebo
Martin-Santos et al. (2012)	30 right-handed healthy male English-speaking volunteers	THC (10 mg) CBD (600 mg)	Oral		VAMS STAI-S	THC ↑ feelings of anxiety CBD did not have an effect
Bhattacharyya et al. (2017)	14 healthy right-handed English-speaking males	THC (10 mg) Placebo	Oral	Viewed fearful and neutral faces	STAI-S	↑ anxiety ↑ activation of right amygdala in reaction to fearful faces
Bhattacharyya et al. (2010)	15 healthy right-handed English-speaking men 15 or less lifetime cannabis exposures	THC (10 mg) CBD (600 mg) Placebo	Oral	View Fearful faces	VAMS STAI-S	THC ↑ anxiety at 2 and 3h THC ↑ activation of amygdala in response to fearful faces. THC ↑ anxiety in response to fearful faces (associated with amygdalar activation) CBD ↓ amygdalar activation CBD ↓ feelings of anxiety (associated with amygdalar activation)
Fusar-Poli et al. (2009)	15 healthy right-handed men	THC (10 mg) CBD (600 mg) Placebo	Oral	Exposed to neutral, mildly fearful or intensely fearful faces	VAMS STAI-S Skin conductance (SCR)	THC ↑ baseline anxiety after 2h CBD did not affect anxiety THC ↑ # of SCR fluctuations in response to mild and intensely fearful faces CBD ↓ # of SCR fluctuations in response to intensely fearful faces
Karschner et al. (2011)	18–45 years old 15 people Have smoked at least once but less than daily	THC (5, 15 mg) THC (5 mg) +CBD (5 mg) THC (16.2 mg) + CBD (15 mg) Placebo	Oral		STAI-S	↑ state anxiety with all doses THC-induced anxiety onset faster without CBD
Ilan et al. (2005)	24 healthy men and women 21–45 year olds	Low: 1.8%THC High: 3.6%THC	Smoked (inhale)		VAS-A	High THC strain ↑ anxiety (main effect).

(*continued on next page*)

Table 4 (*continued*)

Paper	Participants	Groups/Drugs	Route of Administration/ Region of Genetic Expression	Stress Task	Anxiety measure	Results
	Reported using cannabis at least 10 times in lifetime	Low: 0.4%CBD High: 1%CBD Placebo 4 conditions with mixture of high and low THC/CBD				All low THC strains and High THC + High CBD strain did not affect anxiety All strains ↑ heart rate
Colizzi et al. (2018)	36 healthy right-handed, english-speaking males All but 3 were white Europeans Non users: Less than 5 uses Cannabis users: At least 15 times	DBPC THC (10 mg)	Oral		VAMS STAI	↑ anxiety in both users and non-users overall
Glass et al. (1980)	4 volunteers that had anxious levels similar to that of an anxiety outpatient based on self-reports	Nabilone (1, 2, 4, 5 mg) Placebo	Oral			Two of the four volunteers showed ↓ anxiety (1, 2 mg) ↑ heart rate (main effect) ↑ sedation as prominent self-report
Fabre & McLendon (1981)	5 caucasian males (average age 29) Suffer from psychoneurotic anxiety	Open Label without placebo Nabilone: Average of 2.8 mg a day Varied from 2 to 8 mg (28 days)	Oral		Hamilton Anxiety Rating Scale	↓ psychic and somatic anxiety
	20 patients (19 Caucasian, 1 black). Mean 29 YO Five of control patients dropped out because their anxiety wasn't being treated	DBPC 1 mg nabilone pills three times a day 28-day treatment 4-day washout	Oral		Hamilton Anxiety Rating Scale Self-rating symptom scale	↓ 50% of anxiety symptoms ↓ self-reported and physician rated anxiety symptoms
Zuardi et al. (1982)	6 men and 2 women (average age 27) Average weight 67 kg 5 had smoked cannabis previously	THC (0.5 mg/kg) CBD (1 mg/kg) Placebo	Oral		STAI	THC and THC+CBD ↑ anxiety Anxiety ↓ in THC+CBD vs. THC alone CBD did not effect anxiety
Childs et al. (2017)	42 healthy men and women with some history with cannabis use	7.5, 12.5 mg THC Placebo	Oral	Trier Social Stress Test (5 min speech followed by 5 min arithmetic)	VAS	THC ↓ feelings of distress following stress (7.5 mg) THC ↑ feelings of distress following stress (12.5 mg)
Phan et al. (2008)	15 male and female (50%) average age 20.8 Some experience with Cannabis	DBPC Marinol (THC; 7.5 mg)	Oral	Exposed to fearful and angry faces	fMRI	↓ right amygdala activation in response to threatening faces
Karniol et al. (1974)	40 male med students and doctors (21–34 years old) 50–91 kg 22 were previous cannabis users Groups were balanced for age and weight	THC (30 mg) CBD (15, 30, 60 mg; alone or each with THC) Placebo	Oral		(SDEQ)	THC ↑ BP, but CBD ↓ THC induced BP that (30, 60 mg) THC ↑ reported anxiety (4 of 5 participants) CBD ↓ anxiety
D'Souza et al. (2004)	22 healthy adults Variety of cannabis use	5 or 2.5 mg THC Placebo	Intravenous		VAS-A	↑ of anxiety at 10 min ↑ CORT levels (both doses)
D'Souza et al. (2008)	Current Frequent users (at least 10 exposures in last month; n = 30)and healthy controls (22)	DBPC 2.5 or 5 mg THC	Intravenous		VAS-A	↑ anxiety in both groups (2.5 and 5 mg) less anxiety after THC in users compared to non-users THC ↓ feelings of calm and relaxation in both groups equally ↓ CORT after THC in users compared to non-users
Bergamaschi et al. (2011)	24 generalized social anxiety disorder (SAD) participants and 12 healthy controls	DBPC CBD (600 mg)	Oral	Public speech	VAS-A	↓ anxiety and feelings of discomfort ↓ cognitive impairment during speech.
Crippa et al. (2011)	10 right handed men with SAD University students (average age 24.2)	DBPC CBD (400 mg)	Oral	Brain scan was considered stressor	VAMS	CBD ↓ feelings of anxiety Altered blood flow in the left parahippocampal gyrus, hippocampus and right posterior cingulate gyrus
Peters et al. (1976)	10 frequent (twice or more a week for 3–4 years)and 10 occasional cannabis users (no	THC (0.2, 0.4, 0.6 mg/kg) Placebo	Oral		(SDEQ)	↑ tense, jittery feelings and lack of control (anxiety) in both occasional and

(*continued on next page*)

Table 4 (*continued*)

Paper	Participants	Groups/Drugs	Route of Administration/ Region of Genetic Expression	Stress Task	Anxiety measure	Results
	more than twice a month for 3–4 years)(half males, half females in each group) 21-34 YO					frequent users Occasional users experienced more of these anxiety feelings

Double Blind Placebo Controlled (DBPC), Visual Analogue Scale for Anxiety (VAS-A), State Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HAD), Fatty Acid Amide Hydrolase (FAAH), Liebowitz Social Anxiety Scale (LSAS), Profile of Mood States Scale (POMS), Visual Analog Mood Scale (VAMS), Subjective Drug Effects Questionnaire (SDEQ), Δ9-tetrahydrocannabinol (THC), Cannabidiol (CBD).

CBD may act to counteract the anxiogenic effects of higher dose THC. Consistent with this, there are reports of CBD acting as an allosteric negative modulator at CB1R (Lapraire et al., 2015), however, several recent attempts to experimentally demonstrate CBD counteracting the effects of THC have failed (Arkell et al., 2019; reviewed in Freeman et al., 2019).

It is also worth noting that there is a proportion of people who experience more anxiogenic and panic responses to cannabis consumption, especially of strains with higher THC content, relative to others. This population may self-select out of cannabis use and therefore self-report studies focused on users, likely explaining why studies probing cannabis users reliably suggest anti-anxiety properties while studies selecting from broader population samples are more likely to identify subjects who exhibit anxiety responses. Notwithstanding, a large portion of clinical studies investigating cannabis and THC report anxiogenic effects when administered to healthy men and women.

9. Cannabinoids in anxiety disorders

A number of studies have noted people suffering with anxiety disorders, (Buckner et al, 2006, 2012, 2014; Van Dam et al., 2012). These epidemiological data would suggest that cannabinoids could have some therapeutic benefit for anxiety disorders.

Chronic administration of nabilone, a synthetic analog of THC, in an open label design was able to reduce scores on the Hamilton anxiety rating scale in patients suffering from "psychoneurotic" anxiety (Fabre and McLendon, 1981). To control for placebo effects in this study, researchers performed a double-blind placebo-controlled design where they reported significant reductions in self-reported and physician rated anxiety symptoms after 28 daily nabilone administrations and a four-day washout period (Fabre and McLendon, 1981). An earlier study investigating volunteers suffering with anxiety levels similar to that of an anxiety outpatient reported reduced anxiety in two of the four patients treated with low oral doses of nabilone (Glass et al., 1980).

More recently, researchers have been applying more targeted pharmacological therapies for the treatment of anxiety disorders. In a double-blind placebo-controlled study, daily administrations of the FAAH inhibitor JNJ-42165279 over 12 weeks improved SAD symptom severity in subjects, with the effects being amplified in those exhibiting the greatest degree of FAAH inhibition and elevation in AEA (Schmidt et al., 2020). This finding is particularly interesting in light of preliminary data indicating that central FAAH expression may be elevated in SAD (Ahmed et al., 2019), and is consistent with the preclinical work discussed previously regarding the role of AEA signaling in the regulation of anxiety and how impaired AEA signaling may enhance multiple behavioral facets of anxiety. This very exciting work, coupled to the experimental findings of reduced anxiety from stress exposure (Mayo et al., 2020b) or during cannabis withdrawal (D'Souza et al., 2019), and blunted threat-induced amygdala activation (Paulus et al., 2020), following FAAH inhibition in humans, provides encouraging signals that pharmacological targeting of the eCB system may be a viable therapeutic approach for the treatment of anxiety disorders.

10. Problematic cannabis use: cannabis use dependence and association with anxiety

Despite above evidence that therapeutics targeting the eCB system may be effective in relieving symptoms of anxiety, there is also considerable evidence that links excessive cannabis use with anxiety. Excess use may develop into cannabis dependence or cannabis use disorder (CUD), characterized by problematic use that includes escalation with a loss of control over use, repeated failures to reduce intake or quit, and continued use despite negative consequence (American Psychiatric Association, 2013). Indeed, 20–30% of cannabis users develop CUD; similarly, 13% of users develop dependence, a rate that substantially increases (to 33%) in individuals who began use early and frequently (Hasin et al., 2015; Leung et al., 2020). However, CUD is strongly influenced by various genetic and environmental factors, including comorbidity with other mental illness (particularly schizophrenia or anxiety) and incidence of traumatic childhood experiences (Ferland and Hurd, 2020). Complicating things further, frequency of high-potency (~15% THC), but not low-potency cannabis, is associated with a greater risk of developing negative outcomes such as CUD (Freeman and Winstock, 2015; Hines et al., 2020). Thus, multiple factors may contribute to whether frequent cannabis use develops into cannabis dependence or cannabis use disorder.

Cannabis use disorder is highly associated with anxiety disorders in humans (Kedzior and Laeber, 2014; Leadbeater et al., 2019). Indeed, social anxiety disorder is associated with over sixfold likelihood of later developing cannabis use disorder (Buckner et al., 2008). In fact, SAD symptoms were correlated with symptoms of problematic cannabis use in women but not in men (Buckner et al, 2006). However, given that one of the main reasons individuals self-report cannabis use is to relieve anxiety (Schofield et al., 2006; Turna et al., 2020), it is unclear if frequent cannabis use is causative of anxiety disorders or if individuals with anxiety disorders choose to use cannabis in order to relieve symptoms. This is important to consider, as initial use may be effective in relieving anxiety symptoms but over time may develop into problematic use if use is not controlled. Finally, multiple studies suggest that the association in adults between either cannabis use or CUD and anxiety is minimal (Twomey, 2017) or non-existent (Blanco et al., 2016; Gage et al., 2015) when controlling for other variables such as socioeconomic status, education, recent trauma, urban living, and family history of psychiatric illness. Thus, multiple factors also contribute to the association between cannabis use disorder and anxiety.

11. Conclusion

Anxiety is a wide-ranging, adaptive biological process involving coordinated activation of many brain regions. However, pathological anxiety (i.e. anxiety disorders) can occur in humans with inappropriate or excessive activation of these circuits. The eCB system is well-situated to modulate these circuits, with high expression in many key brain structures involved in the regulation of emotional behavior. Indeed, eCB signaling is intimately intertwined with the experience of anxiety as this system regulates both onset and offset of anxiety following exposure to a

stressor. However, different components of the system exhibit unique roles. AEA acts predominantly as the tonic gatekeeper of anxiety onset, only to be disrupted immediately following a stressful experience, promoting the development of anxiety. On the other hand, a delayed enhancement of 2-AG signaling acts to dampen anxiety following stress exposure. Similar fluctuations in eCB signaling appears in conditions of chronic stress, but with longer lasting influence. Functionally, stress-induced impairments in AEA signaling leads to sensitization of anxiety neural networks while enhanced 2-AG signaling strengthens adaptive processes.

Acute and chronic administration of exogenous cannabinoids reveals a more complex relationship between cannabinoids and anxiety that appears to be relatively conserved between rodents and humans. In particular, CB1R agonists reliably affect anxiety in a biphasic, dose-dependent manner such that low doses exhibit anxiolytic properties while high doses appear to be anxiogenic. Moreover, epidemiological studies sampling from cannabis users emphasize anxiety-reducing effects of cannabis use while experimental studies in a broader sample of humans and rodents depict predominantly anxiogenic properties of cannabis, outlining a range of reactions within a larger population to the consumption of the psychoactive compounds in cannabis. This phenomenon may be due to individual differences in baseline cannabinoid activity as well as cell-specific expression of CB1R; however, more research is needed to understand these bimodal effects and why different sub-populations have dramatically different experiences following cannabis use.

Notably, repeated cannabinoid use has been shown to exhibit risks in humans. In particular, chronic use is associated with anxiety disorders, especially when use begins in adolescence. However, multiple variables may contribute to these associations, and individuals experiencing anxiety may be more likely to use cannabis in order to self-medicate for anxiety symptoms. Thus, the relationship between anxiety and cannabis use in humans is complex. There is some evidence that CBD may counter the anxiogenic properties of high doses of THC in both rodent and human studies. Preclinical evidence suggests that CBD may exert anxiolytic effects via amplification of 5-HT1A receptor activity and/or augmentation of AEA signaling.

Anxiety can also be targeted through modulation of the degradative enzymes in the eCB system. Notably, the conserved role of cannabinoids in the regulation of anxiety becomes most apparent when considering the low anxiety phenotype exhibited in humans and rodents alike who have a genetic disruption of their FAAH gene, thus exhibiting enhanced eCB signaling (Dincheva et al., 2015). Thus, more targeted pharmacological therapies such as FAAH inhibitors represent exciting potential in cannabinoid-based therapies for psychiatric illness. Clinically, there is evidence, albeit sparse, that isolated phytocannabinoids and upregulation of eCB signaling via synthetic pharmacological tools may be able to improve symptoms of anxiety disorders, particularly SAD, although a similar case has been made for the role of eCB targeted therapies in PTSD (Hill et al., 2018). This provides potential that cannabinoid-based therapies may be effective across a broader range of anxiety disorders, although significantly more research needs to be conducted in both human and rodent studies in order to determine appropriate potency and timing of cannabinoid treatments as well as understand the individual contributions of sex differences, previous experience, and stressor modality.

Acknowledgement

This work was supported by operating funds from the Canadian Institutes of Health Research (CIHR - MOP426504) to MNH and salary support in the form of a Tier II Canada Research Chair from CIHR to MNH. Salary support also came from Branchout Neurological Foundation and CIHR to GNP and ASN respectively.

References

Adhikari, A., Topiwala, M.A., Gordon, J.A., 2010. Synchronized activity between the ventral hippocampus and the medial prefrontal cortex during anxiety. Neuron 65 (2), 257–269. https://doi.org/10.1016/j.neuron.2009.12.002.

Ahmed, M., Tyndale, R.F., Elsaid, S., Malik, S., Daskalakis, Z.J., Le Foll, B., Boileau, I., Kloiber, S., 2019. Investigating fatty acid amide hydrolase levels in social anxiety disorder: a PET study using [C11]CURB. Neuropsychopharmacology 44, 88.

Ahn, K., McKinney, M.K., Cravatt, B.F., 2008. Enzymatic pathways that regulate endocannabinoid signaling in the nervous system. Chem. Rev. 108 (5), 1687–1707.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (fifth edition). American psychiatric association. https://doi.org/10.1176/appi.books.9780890425596.

Arendt, D.H., Hassell, J., Li, H., Achua, J.K., Guarnieri, D.J., Dileone, R.J., Ronan, P.J., Summers, C.H., 2014. Anxiolytic function of the orexin 2/hypocretin A receptor in the basolateral amygdala. Psychoneuroendocrinology 40, 17–26. https://doi.org/10.1016/j.psyneuen.2013.10.010.

Arévalo, C., de Miguel, R., Hernández-Tristán, R., 2001. Cannabinoid effects on anxiety-related behaviours and hypothalamic neurotransmitters. Pharmacol. Biochem. Behav. 70 (1), 123–131.

Arkell, T.R., Lintzeris, N., Kevin, R.C., Ramaekers, J.G., Vandrey, R., Irwin, C., Haber, P. S., McGregor, I.S., 2019. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology (Berlin) 236, 2713–2724. https://doi.org/10.1007/s00213-019-05246-8.

Bagot, R.C., Parise, E.M., Peña, C.J., Zhang, H.-X., Maze, I., Chaudhury, D., Persaud, B., Cachope, R., Bolaños-Guzmán, C.A., Cheer, J.F., Deisseroth, K., Han, M.-H., Nestler, E.J., 2015. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. Nat. Commun. 6 (1), 7062. https://doi.org/10.1038/ncomms8062.

Bai, M., Zhu, X., Zhang, Y., Zhang, S., Zhang, L., Xue, L., Yi, J., Yao, S., Zhang, X., 2012. Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life. PLoS One 7 (10), e46921. https://doi.org/10.1371/journal.pone.0046921, 2012.

Bannerman, D.M., Grubb, M., Deacon, R.M.J., Yee, B.K., Feldon, J., Rawlins, J.N.P., 2003. Ventral hippocampal lesions affect anxiety but not spatial learning. Behav. Brain Res. 139 (1–2), 197–213. https://doi.org/10.1016/s0166-4328(02)00268-1.

Barnett, S.A., 1976. In: The Rat: A Study in Behavior. Australian National University Press.

Becker, H.C., 2008. Alcohol dependence, withdrawal, and relapse. Alcohol Res. Health 31 (4), 348–361. PMID: 23584009.

Bedse, G., Bluett, R.J., Patrick, T.A., Romness, N.K., Gaulden, A.D., Kingsley, P.J., Plath, N., Marnett, L.J., Patel, S., 2018. Therapeutic endocannabinoid augmentation for mood and anxiety disorders: comparative profiling of FAAH, MAGL and dual inhibitors. Transl. Psychiatry 8. https://doi.org/10.1038/s41398-018-0141-7.

Bedse, G., Hartley, N.D., Neale, E., Gaulden, A.D., Patrick, T.A., Kingsley, P.J., Uddin, M. J., Plath, N., Marnett, L.J., Patel, S., 2017. Functional redundancy between canonical endocannabinoid signaling systems in the modulation of anxiety. Biol. Psychiatr. 82, 488–499. https://doi.org/10.1016/j.biopsych.2017.03.002.

Bergamaschi, M.M., Queiroz, R.H.C., Chagas, M.H.N., De Oliveira, D.C.G., De Martinis, B. S., Kapczinski, F., Quevedo, J., Roesler, R., Schröder, N., Nardi, A.E., Martín-Santos, R., Hallak, J.E.C., Zuardi, A.W., Crippa, J.A.S., 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients. Neuropsychopharmacology 36, 1219–1226. https://doi.org/10.1038/npp.2011.6.

Bernstein, C.N., Hitchon, C.A., Walld, R., Bolton, J.M., Sareen, J., Walker, J.R., Graff, L. A., Patten, S.B., Singer, A., Lix, L.M., El-Gabalawy, R., Katz, A., Fisk, J.D., Marrie, R. A., 2019. Increased burden of psychiatric disorders in inflammatory bowel disease. Inflamm. Bowel Dis. 25 (2), 360–368. https://doi.org/10.1093/ibd/izy235.

Berrendero, F., Maldonado, R., 2002. Involvement of the opioid system in the anxiolytic-like effects induced by Δ9-tetrahydrocannabinol. Psychopharmacology (Berlin) 163, 111–117. https://doi.org/10.1007/s00213-002-1144-9.

Bhatnagar, S., Vining, C., Denski, K., 2004. Regulation of chronic stress-induced changes in hypothalamic-pituitary-adrenal activity by the basolateral amygdala. Ann. N. Y. Acad. Sci. 1032, 315–319. https://doi.org/10.1196/annals.1314.050.

Bhattacharyya, S., Egerton, A., Kim, E., Rosso, L., Riano Barros, D., Hammers, A., Brammer, M., Turkheimer, F.E., Howes, O.D., McGuire, P., 2017. Acute induction of anxiety in humans by delta-9-tetrahydrocannabinol related to amygdalar cannabinoid-1 (CB1) receptors. Sci. Rep. 7 https://doi.org/10.1038/s41598-017-14203-4.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C.M., Seal, M., Allen, P., Mehta, M.A., Stone, J.M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R.M., Zuardi, A.W., Crippa, J.A., Atakan, Z., McGuire, P.K., 2010. Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35, 764–774. https://doi.org/10.1038/npp.2009.184.

Bindra, D., Spinner, N., 1958. Response to different degrees of novelty: the incidence of various activities. JEAB (J. Exp. Anal. Behav.) 1 (4), 341–350. https://doi.org/10.1901/jeab.1958.1-341.

Bisogno, T., Howell, F., Williams, G., Minassi, A., Cascio, M.G., Ligresti, A., Matias, I., Schiano-Moriello, A., Paul, P., Williams, E.J., Gangadbaran, U., Hobbs, C., Marzo, V. Di, Doherty, P., 2003. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J. Cell Biol. 163, 463–468. https://doi.org/10.1083/jcb.200305129.

Blanco, C., Hasin, D.S., Wall, M.M., Flórez-Salamanca, L., Hoertel, N., Wang, S., Kerridge, B.T., Olfson, M., 2016. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. JAMA Psychiatr. 73 (4), 388–395. https://doi.org/10.1001/jamapsychiatry.2015.3229.

Blasio, A., Iemolo, A., Sabino, V., Petrosino, S., Steardo, L., Rice, K.C., Orlando, P., Iannotti, F.A., Di Marzo, V., Zorrilla, E.P., Cottone, P., 2013. Rimonabant precipitates anxiety in rats withdrawn from palatable food: role of the central Amygdala. Neuropsychopharmacology 38, 2498–2507. https://doi.org/10.1038/npp.2013.153.

Bluett, R.J., Báldi, R., Haymer, A., Gaulden, A.D., Hartley, N.D., Parrish, W.P., Baechle, J., Marcus, D.J., Mardam-Bey, R., Shonesy, B.C., Uddin, M.J., Marnett, L.J., Mackie, K., Colbran, R.J., Winder, D.G., Patel, S., 2017. Endocannabinoid signalling modulates susceptibility to traumatic stress exposure. Nat. Commun. 8, 1–18. https://doi.org/10.1038/ncomms14782.

Bluett, R.J., Gamble-George, J.C., Hermanson, D.J., Hartley, N.D., Marnett, L.J., Patel, S., 2014. Central anandamide deficiency predicts stress-induced anxiety: behavioral reversal through endocannabinoid augmentation. Transl. Psychiatry 4. https://doi.org/10.1038/tp.2014.53.

Borkar, C.D., Dorofeikova, M., Lea, Q.E., Vutukuri, R., Vo, C., Hereford, D., Resendez, A., Basavanhalli, S., Sifnugel, N., Fadok, J.P., 2020. Sex differences in behavioral responses during a conditioned flight paradigm. Behav. Brain Res. 389, 112623. https://doi.org/10.1016/j.bbr.2020.112623.R.

Bowers, Mallory, Ressler, Kerry, 2016. Sex-dependence of anxiety-like behavior in cannabinoid receptor 1 (Cnr1) knockout mice. Behavioural Brain Research 300, 65–69.

Braida, D., Limonta, V., Malabarba, L., Zani, A., Sala, M., 2007. 5-HT1A receptors are involved in the anxiolytic effect of Δ9-tetrahydrocannabinol and AM 404, the anandamide transport inhibitor, in Sprague-Dawley rats. Eur. J. Pharmacol. 555, 156–163. https://doi.org/10.1016/j.ejphar.2006.10.038.

Breivogel, C.S., Sim, L.J., Childers, S.R., 1997. Regional differences in cannabinoid receptor/G-protein coupling in rat brain. J. Pharmacol. Exp. Therapeut. 282.

Britton, D.R., Britton, K.T., 1981. A sensitive open field measure of anxiolytic drug activity. Pharmacol., Biochem. Behav. 15 (4), 577–582. https://doi.org/10.1016/0091-3057(81)90212-4.

Britton, J.C., Grillon, C., Lissek, S., Norcross, M.A., Szuhany, K.L., Chen, G., Ernst, M., Nelson, E.E., Leibenluft, E., Shechner, T., Pine, D.S., 2013. Response to learned threat: an FMRI study in adolescent and adult anxiety. Am. J. Psychiatr. 170 (10), 1195–1204. https://doi.org/10.1176/appi.ajp.2013.12050651.

Brotto, L.A., Barr, A.M., Gorzalka, B.B., 2000. Sex differences in forced-swim and open-field test behaviours after chronic administration of melatonin. Eur. J. Pharmacol. 402 (1–2), 87–93. https://doi.org/10.1016/s0014-2999(00)00491-x.

Browne, R.Q., Weissman, A., 1981. Discriminative stimulus properties of δ9-tetrahydrocannabinol: mechanistic studies. J. Clin. Pharmacol. 21 (S1), 227S–234S.

Bruijnzeel, A.W., Qi, X., Guzhva, L.V., Wall, S., Deng, J.V., Gold, M.S., et al., 2016. Behavioral characterization of the effects of cannabis smoke and anandamide in rats. PloS One 11 (4), e0153327.

Buckner, J.D., Schmidt, N.B., Lang, A.R., Small, J.W., Schlauch, R.C., Lewinsohn, P.M., 2008. Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. J. Psychiatr. Res. 42 (3), 230–239. https://doi.org/10.1016/j.jpsychires.2007.01.002.

Buckner, J.D., Crosby, R.D., Wonderlich, S.A., Schmidt, N.B., 2012. Social anxiety and cannabis use: an analysis from ecological momentary assessment. J. Anxiety Disord. 26, 297–304. https://doi.org/10.1016/j.janxdis.2011.12.006.

Buckner, J.D., Eggleston, A.M., Schmidt, N.B., 2006. Social anxiety and problematic alcohol consumption: the mediating role of drinking motives and situations. Behav. Ther. 37, 381–391. https://doi.org/10.1016/j.beth.2006.02.007.

Buckner, J.D., Zvolensky, M.J., Schmidt, N.B., Carroll, K.M., Schatschneider, C., Crapanzano, K., 2014. Integrated cognitive behavioral therapy for cannabis use and anxiety disorders: rationale and development. Addict. Behav. https://doi.org/10.1016/j.addbeh.2013.10.023.

Bura, S.A., Burokas, A., Martín-García, E., Maldonado, R., 2010. Effects of chronic nicotine on food intake and anxiety-like behaviour in CB1 knockout mice. Eur. Neuropsychopharmacol 20, 369–378. https://doi.org/10.1016/j.euroneuro.2010.02.003.

Burgos-Robles, A., Kimchi, E.Y., Izadmehr, E.M., Porzenheim, M.J., Ramos-Guasp, W.A., Nieh, E.H., Felix-Ortiz, A.C., Namburi, P., Leppla, C.A., Presbrey, K.N., Anandalingam, K.K., Pagan-Rivera, P.A., Anahtar, M., Beyeler, A., Tye, K.M., 2017. Amygdala inputs to prefrontal cortex guide behavior amid conflicting cues of reward and punishment. Nat. Neurosci. 20 (6), 824–835. https://doi.org/10.1038/nn.4553.

Burstein, O., Shoshan, N., Doron, R., Akirav, I., 2018. Cannabinoids prevent depressive-like symptoms and alterations in BDNF expression in a rat model of PTSD. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 84, 129–139. https://doi.org/10.1016/j.pnpbp.2018.01.026.

Busquets-Garcia, A., Bains, J., Marsicano, G., 2018. CB1 receptor signaling in the brain: extracting specificity from ubiquity. Neuropsychopharmacology. https://doi.org/10.1038/npp.2017.206.

Busquets-Garcia, A., Puighermanal, E., Pastor, A., De La Torre, R., Maldonado, R., Ozaita, A., 2011. Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. Biol. Psychiatr. 70, 479–486. https://doi.org/10.1016/j.biopsych.2011.04.022.

Cadas, H., Tomaso, E., Di Piomelli, D., 1997. Occurrence and biosynthesis of endogenous cannabinoid precursor, N- arachidonoyl phosphatidylethanolamine, in rat brain. J. Neurosci. 17 https://doi.org/10.1523/jneurosci.17-04-01226.1997.

Cagni, P., Barros, M., 2013. Cannabinoid type 1 receptor ligands WIN 55,212-2 and AM 251 alter anxiety-like behaviors of marmoset monkeys in an open-field test. Behav. Brain Res. 240, 91–94. https://doi.org/10.1016/j.bbr.2012.11.018.

Calhoon, G.G., Tye, K.M., 2015. Resolving the neural circuits of anxiety. Nat. Neurosci. 18 (10), 1394–1404. https://doi.org/10.1038/nn.4101.

Campeau, S., Falls, W.A., Cullinan, W.E., Helmreich, D.L., Davis, M., Watson, S.J., 1997. Elicitation and reduction of fear: behavioural and neuroendocrine indices and brain induction of the immediate-early gene c-fos. Neuroscience 78 (4), 1087–1104. https://doi.org/10.1016/s0306-4522(96)00632-x.

Campos, A.C., Ferreira, F.R., Guimarães, F.S., 2012. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. J. Psychiatr. Res. 46, 1501–1510. https://doi.org/10.1016/j.jpsychires.2012.08.012.

Campos, A.C., Guimarães, F.S., 2008. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology (Berlin) 199, 223–230. https://doi.org/10.1007/s00213-008-1168-x.

Campos, A.C., Ortega, Z., Palazuelos, J., Fogaça, M.V., Aguiar, D.C., Díaz-Alonso, J., Ortega-Gutiérrez, S., Vázquez-Villa, H., Moreira, F.A., Guzmán, M., Galve-Roperh, I., Guimarães, F.S., 2013. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. Int. J. Neuropsychopharmacol. 16 (6), 1407–1419. https://doi-org.ezproxy.lib.ucalgary.ca/10.1017/S1461145712001502.

Carlson, J.M., Greenberg, T., Rubin, D., Mujica-Parodi, L.R., 2011. Feeling anxious: anticipatory amygdalo-insular response predicts the feeling of anxious anticipation. Soc. Cognit. Affect Neurosci. 6 (1), 74–81. https://doi.org/10.1093/scan/nsq017.

Cassano, T., Gaetani, S., MacHeda, T., Laconca, L., Romano, A., Morgese, M.G., Cimmino, C.S., Chiarotti, F., Bambico, F.R., Gobbi, G., Cuomo, V., Piomelli, D., 2011. Evaluation of the emotional phenotype and serotonergic neurotransmission of fatty acid amide hydrolase-deficient mice. Psychopharmacology (Berlin) 214, 465–476. https://doi.org/10.1007/s00213-010-2051-0.

Chaouloff, F., Durand, M., Mormède, P., 1997. Anxiety- and activity-related effects of diazepam and chlordiazepoxide in the rat light/dark and dark/light tests. Behav. Brain Res. 85 (1), 27–35. https://doi.org/10.1016/s0166-4328(96)00160-x.

Childs, E., Lutz, J.A., de Wit, H., 2017. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 177, 136–144. https://doi.org/10.1016/j.drugalcdep.2017.03.030.

Choleris, E., Thomas, A.W., Kavaliers, M., Prato, F.S., 2001. A detailed ethological analysis of the mouse open field test: effects of diazepam, chlordiazepoxide and an extremely low frequency pulsed magnetic field. Neurosci. Biobehav. Rev. 25 (3), 235–260. https://doi.org/10.1016/s0149-7634(01)00011-2.

Christensen, R., Kristensen, P.K., Bartels, E.M., Bliddal, H., Astrup, A., 2007. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 370, 1706–1713. https://doi.org/10.1016/S0140-6736(07)61721-8.

Christianson, J.P., Thompson, B.M., Watkins, L.R., Maier, S.F., 2009. Medial prefrontal cortical activation modulates the impact of controllable and uncontrollable stressor exposure on a social exploration test of anxiety in the rat. Stress 12 (5), 445–450. https://doi.org/10.1080/10253890802510302.

Colizzi, M., McGuire, P., Giampietro, V., Williams, S., Brammer, M., Bhattacharyya, S., 2018. Previous cannabis exposure modulates the acute effects of delta-9-tetrahydrocannabinol on attentional salience and fear processing. Exp. Clin. Psychopharmacol 26, 582–598. https://doi.org/10.1037/pha0000221.

Conzelmann, A., Reif, A., Jacob, C., Weyers, P., Lesch, K.P., Lutz, B., Pauli, P., 2012. A polymorphism in the gene of the endocannabinoid-degrading enzyme FAAH (FAAH C385A) is associated with emotional-motivational reactivity. Psychopharmacology (Berlin) 224, 573–579. https://doi.org/10.1007/s00213-012-2785-y.

Cravatt, B.F., Demarest, K., Patricelli, M.P., Bracey, M.H., Giang, D.K., Martin, B.R., Lichtman, A.H., 2001. Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. Proc. Natl. Acad. Sci. U. S. A. 98 https://doi.org/10.1073/pnas.161191698.

Crawley, J.N., 1985. Exploratory behavior models of anxiety in mice. Neurosci. Biobehav. Rev. 9 (1), 37–44. https://doi.org/10.1016/0149-7634(85)90030-2.

Crippa, J.A.S., Nogueira Derenusson, G., Borduqui Ferrari, T., Wichert-Ana, L., Duran, F. L.S., Martin-Santos, R., Vinícius Simões, M., Bhattacharyya, S., Fusar-Poli, P., Atakan, Z., Santos Filho, A., Freitas-Ferrari, M.C., McGuire, P.K., Zuardi, A.W., Busatto, G.F., Hallak, J.E.C., 2011. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J. Psychopharmacol. 25, 121–130. https://doi.org/10.1177/0269881110379283.

D'Souza, D.C., Cortes-Briones, J., Creatura, G., Bluez, G., Thurnauer, H., Deaso, E., Bielen, K., Surti, T., Radhakrishnan, R., Gupta, A., Gupta, S., Cahill, J., Sherif, M.A., Makriyannis, A., Morgan, P.T., Ranganathan, M., Skosnik, P.D., 2019. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. Lancet Psychiatr. 6, 35–45. https://doi.org/10.1016/S2215-0366(18)30427-9.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. Te, Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29, 1558–1572. https://doi.org/10.1038/sj.npp.1300496.

D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Perry, E., Krystal, J., 2008. Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology 33, 2505–2516. https://doi.org/10.1038/sj.npp.1301643.

Cuttler, Carrie, Mischley, Laurie, Sexton, Michelle, 2016. Sex Differences in Cannabis Use and Effects: A Cross-Sectional Survey of Cannabis Users. Cannabis and Cannabinoid Research 1 (1).

Davis, M., Walker, D.L., Miles, L., Grillon, C., 2010. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 35 (1), 105–135. https://doi.org/10.1038/npp.2009.109.

Daviu, N., Füzesi, T., Rosenegger, D.G., Rasiah, N.P., Sterley, T.-L., Peringod, G., Bains, J. S., 2020. Paraventricular nucleus CRH neurons encode stress controllability and regulate defensive behavior selection. Nature Neuroscience 23 (3), 398–410. https://doi.org/10.1038/s41593-020-0591-0.

De Fonseca, F.R., Rubio, P., Menzaghi, F., Merlo-Pich, E., Rivier, J., Koob, G.F., Navarro, M., 1996. Corticotropin-releasing factor (CRF) antagonist [D-Phe12, Nle21,38,CαMeLeu37]CRF attenuates the acute actions of the highly potent cannabinoid receptor agonist HU-210 on defensive-withdrawal behavior in rats. J. Pharmacol. Exp. Ther. 276.

De Paula Soares, V., Campos, A.C., de Bortoli, V.C., Zangrossi, H., Guimarães, F.S., Zuardi, A.W., 2010. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. Behav. Brain Res. 213, 225–229. https://doi.org/10.1016/j.bbr.2010.05.004.

Deacon, R.M.J., Bannerman, D.M., Rawlins, J.N.P., 2002. Anxiolytic effects of cytotoxic hippocampal lesions in rats. Behavioral Neuroscience 116 (3), 494–497. https://doi.org/10.1037//0735-7044.116.3.494.

Degroot, A., Nomikos, G.G., 2004. Genetic deletion and pharmacological blockade of CB1 receptors modulates anxiety in the shock-probe burying test. Eur. J. Neurosci. 20, 1059–1064. https://doi.org/10.1111/j.1460-9568.2004.03556.x.

Devane, W.A., Dysarz, F.A., Johnson, M.R., Melvin, L.S., Howlett, A.C., 1988. Determination and characterization of a cannabinoid receptor in rat brain. Mol. Pharmacol. 34.

Devane, W.A., Hanuš, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 80, 258. https://doi.org/10.1126/science.1470919.

Di Marzo, Di, V., Fontana, A., Cadas, H., Schinelli, S., Cimino, G., Schwartz, J.C., Piomelli, D., 1994. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. Nature 372. https://doi.org/10.1038/372686a0.

Di, S., Itoga, C.A., Fisher, M.O., Solomonow, J., Roltsch, E.A., Gilpin, N.W., Tasker, J.G., 2016. Acute stress suppresses synaptic inhibition and increases anxiety via endocannabinoid release in the basolateral amygdala. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 36 (32), 8461–8470. https://doi.org/10.1523/JNEUROSCI.2279-15.2016.

Dias, B.G., Banerjee, S.B., Goodman, J.V., Ressler, K.J., 2013. Towards new approaches to disorders of fear and anxiety. Current Opinion in Neurobiology 23 (3), 346–352. https://doi.org/10.1016/j.conb.2013.01.013.

Dilger, S., Straube, T., Mentzel, H.-J., Fitzek, C., Reichenbach, J.R., Hecht, H., Krieschel, S., Gutberlet, I., Miltner, W.H.R., 2003. Brain activation to phobia-related pictures in spider phobic humans: an event-related functional magnetic resonance imaging study. Neuroscience Letters 348 (1), 29–32. https://doi.org/10.1016/s0304-3940(03)00647-5.

Dincheva, I., Drysdale, A.T., Hartley, C.A., Johnson, D.C., Jing, D., King, E.C., Ra, S., Gray, J.M., Yang, R., DeGruccio, A.M., Huang, C., Cravatt, B.F., Glatt, C.E., Hill, M. N., Casey, B.J., Lee, F.S., 2015. FAAH genetic variation enhances fronto-amygdala function in mouse and human. Nat. Commun. 6, 1–9. https://doi.org/10.1038/ncomms7395.

Dinh, T.P., Carpenter, D., Leslie, F.M., Freund, T.F., Katona, I., Sensi, S.L., Kathuria, S., Piomelli, D., 2002. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc. Natl. Acad. Sci. U. S. A. 99 https://doi.org/10.1073/pnas.152334899.

Dlugos, A., Childs, E., Stuhr, K.L., Hillard, C.J., De Wit, H., 2012. Acute stress increases circulating anandamide and other n-acylethanolamines in healthy humans. Neuropsychopharmacology 37, 2416–2427. https://doi.org/10.1038/npp.2012.100.

Dono, L.M., Currie, P.J., 2012. The cannabinoid receptor CB 1 inverse agonist AM251 potentiates the anxiogenic activity of urocortin i in the basolateral amygdala. In: Neuropharmacology. Pergamon, pp. 192–199. https://doi.org/10.1016/j.neuropharm.2011.06.019.

Doremus-Fitzwater, T.L., Varlinskaya, E.I., Spear, L.P., 2009. Social and non-social anxiety in adolescent and adult rats after repeated restraint. Physiology & Behavior 97 (3–4), 484–494. https://doi.org/10.1016/j.physbeh.2009.03.025.

Duan, T., Gu, N., Wang, Y., Wang, F., Zhu, J., Fang, Y., Shen, Y., Han, J., Zhang, X., 2017. Fatty acid amide hydrolase inhibitors produce rapid anti-anxiety responses through amygdala long-term depression in male rodents. J. Psychiatry Neurosci. 42, 230–241. https://doi.org/10.1503/jpn.160116.

Dubreucq, S., Matias, I., Cardinal, P., Häring, M., Lutz, B., Marsicano, G., Chaouloff, F., 2012. Genetic dissection of the role of cannabinoid type-1 receptors in the emotional consequences of repeated social stress in mice. Neuropsychopharmacology 37, 1885–1900. https://doi.org/10.1038/npp.2012.36.

Domonkos, E., Borbélyová, V., Csongová, M., Bosý, M., Kačmárová, M., Ostatníková, D., Hodosy, J., Celec, P., 2017. Sex differences and sex hormones in anxiety-like behavior of aging rats. Hormones and Behavior 93, 159–165. https://doi.org/10.1016/j.yhbeh.2017.05.019.0.

Donner, N.C., Lowry, C.A., 2013. Sex differences in anxiety and emotional behavior. Pflugers Arch 465 (5), 601–626. https://doi.org/10.1007/s00424-013-1271-7.

Elmes, M.W., Kaczocha, M., Berger, W.T., Leung, K., Ralph, B.P., Wang, L., Sweeney, J. M., Miyauchi, J.T., Tsirka, S.E., Ojima, I., Deutsch, D.G., 2015. Apr. 3. J Biol Chem 290 (14), 8711–8721.

Evanson, N.K., Tasker, J.G., Hill, M.N., Hillard, C.J., Herman, J.P., 2010. Fast feedback inhibition of the HPA Axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology 151, 4811–4819. https://doi.org/10.1210/en.2010-0285.

Fabre, L.F., McLendon, D., 1981. The efficacy and safety of nabilone (A synthetic cannabinoid) in the treatment of anxiety. J. Clin. Pharmacol. 21, 377S–382S. https://doi.org/10.1002/j.1552-4604.1981.tb02617.x.

Fadok, J.P., Markovic, M., Tovote, P., Lüthi, A., 2018. New perspectives on central amygdala function. Current Opinion in Neurobiology 49, 141–147. https://doi.org/10.1016/j.conb.2018.02.009.

Farra, Y.M., Eden, M.J., Coleman, J.R., Kulkarni, P., Ferris, C.F., Oakes, J.M., Bellini, C., 2020. Acute neuroradiological, behavioral, and physiological effects of nose-only exposure to vaporized cannabis in C57BL/6 mice. Inhalation toxicology 32 (5), 200–217.

Felix-Ortiz, A.C., Burgos-Robles, A., Bhagat, N.D., Leppla, C.A., Tye, K.M., 2016. Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. Neuroscience 321, 197–209. https://doi.org/10.1016/j.neuroscience.2015.07.041.

Felix-Ortiz, Ada C., Tye, K.M., 2014. Amygdala inputs to the ventral hippocampus bidirectionally modulate social behavior. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 34 (2), 586–595. https://doi.org/10.1523/JNEUROSCI.4257-13.2014.

Ferland, J.-M.N., Hurd, Y.L., 2020. Deconstructing the neurobiology of cannabis use disorder. Nature Neuroscience 23 (5), 600–610. https://doi.org/10.1038/s41593-020-0611-0.

Fernandes, C., Gonzalez, M.I., Wilson, C.A., File, S.E., 1999. Factor Analysis shows that female rat behaviour is characterized primarily by activity, male rats are driven by sex and anxiety. Pharmacology Biochemistry and Behavior 64 (4), 731–738. https://doi.org/10.1016/s0091-3057(99)00139-2.

File, S.E., Hyde, J.R., 1978. Can social interaction be used to measure anxiety? British Journal of Pharmacology 62 (1), 19–24. https://doi.org/10.1111/j.1476-5381.1978.tb07001.x.

File, S.E., Pellow, S., 1985. The effects of triazolobenzodiazepines in two animal tests of anxiety and in the holeboard. British Journal of Pharmacology 86 (3), 729–735. https://doi.org/10.1111/j.1476-5381.1985.tb08952.x.

Fogaça, M.V., Campos, A.C., Coelho, L.D., Duman, R.S., Guimarães, F.S., 2018. The anxiolytic effects of cannabidiol in chronically stressed mice are mediated by the endocannabinoid system: role of neurogenesis and dendritic remodeling. Neuropharmacology 135, 22–33. https://doi.org/10.1016/j.neuropharm.2018.03.001.

Fogaça, M.V., Reis, F.M.C.V., Campos, A.C., Guimarães, F.S., 2014. Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of 5HT1A receptors and previous stressful experience. Eur. Neuropsychopharmacol. 24, 410–419. https://doi.org/10.1016/j.euroneuro.2013.10.012.

Fokos, S., Panagis, G., 2010. Effects of δ9-tetrahydrocannabinol on reward and anxiety in rats exposed to chronic unpredictable stress. J. Psychopharmacol. 24, 767–777. https://doi.org/10.1177/0269881109104904.

Freeman, A.M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H.V., Saunders, R., Freeman, T.P., 2019. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2019.09.036.

Freeman, T.P., Winstock, A.R., 2015. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. Psychological Medicine 45 (15), 3181–3189. https://doi.org/10.1017/S0033291715001178.

Freund, T.F., Katona, I., Piomelli, D., 2003. Role of endogenous cannabinoids in synaptic signaling. Physiol. Rev. https://doi.org/10.1152/physrev.00004.2003.

Fusar-Poli, P., Crippa, J., Bhattacharyya, S., Borgwardt, S.J., Allen, P., Martin-Santos, R., Seal, M., Surguladze, S.A., O'Carrol, C., Atakan, Z., Zuardi, A.W., McGuire, P.K., 2009. Distinct effects of A9-Tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch. Gen. Psychiatry 66, 95–105. https://doi.org/10.1001/archgenpsychiatry.2008.519.

Füzesi, T., Daviu, N., Wamsteeker Cusulin, J.I., Bonin, R.P., Bains, J.S., 2016. Hypothalamic CRH neurons orchestrate complex behaviours after stress. Nature Communications 7 (1), 11937. https://doi.org/10.1038/ncomms11937.

Gage, S.H., Hickman, M., Heron, J., Munafò, M.R., Lewis, G., Macleod, J., Zammit, S., 2015. Associations of cannabis and cigarette use with depression and anxiety at age 18: findings from the avon longitudinal study of parents and children. PloS One 10 (4), e0122896. https://doi.org/10.1371/journal.pone.0122896.

Gamaro, G.D., Manoli, L.P., Torres, I.L.S., Silveira, R., Dalmaz, C., 2003. Effects of chronic variate stress on feeding behavior and on monoamine levels in different rat brain structures. Neurochemistry International 42 (2), 107–114. https://doi.org/10.1016/s0197-0186(02)00080-3.

Gamble-George, J.C., Conger, J.R., Hartley, N.D., Gupta, P., Sumislawski, J.J., Patel, S., 2013. Dissociable effects of CB1 receptor blockade on anxiety-like and consummatory behaviors in the novelty-induced hypophagia test in mice. Psychopharmacology (Berl) 228, 401–409. https://doi.org/10.1007/s00213-013-3042-8.

Gaoni, Y., Mechoulam, R., 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86 https://doi.org/10.1021/ja01062a046.

García-Gutiérrez, M.S., García-Bueno, B., Zoppi, S., Leza, J.C., Manzanares, J., 2012. Chronic blockade of cannabinoid CB2 receptors induces anxiolytic-like actions associated with alterations in GABAA receptors. Br. J. Pharmacol. 165, 951–964. https://doi.org/10.1111/j.1476-5381.2011.01625.x.

Gee, D.G., Fetcho, R.N., Jing, D., Li, A., Glatt, C.E., Drysdale, A.T., Cohen, A.O., Dellarco, D.V., Yang, R.R., Dale, A.M., Jernigan, T.L., Lee, F.S., Casey, B.J., 2016. Individual differences in frontolimbic circuitry and Anxiety emerge with adolescent

changes in endocannabinoid signaling across species. Proc. Natl. Acad. Sci. U. S. A. 113, 4500–4505. https://doi.org/10.1073/pnas.1600013113.
Gehrlach, D.A., Dolensek, N., Klein, A.S., Roy Chowdhury, R., Matthys, A., Junghänel, M., Gaitanos, T.N., Podgornik, A., Black, T.D., Reddy Vaka, N., Conzelmann, K.-K., Gogolla, N., 2019. Aversive state processing in the posterior insular cortex. Nature Neuroscience 22 (9), 1424–1437. https://doi.org/10.1038/s41593-019-0469-1.
Gispen, W.H., Isaacson, R.L., 1981. ACTH-induced excessive grooming in the rat. Pharmacology & Therapeutics 12 (1), 209–246. https://doi.org/10.1016/0163-7258(81)90081-4.
Glass, M., Dragunow, M., Faull, R.L.M., 1997. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77. https://doi.org/10.1016/S0306-4522(96)00428-9.
Glass, R.M., Uhlenhuth, E.H., Hartel, F.W., Schuster, C.R., Fischman, M.W., 1980. A single dose study of nabilone, a synthetic cannabinoid. Psychopharmacology (Berl) 71, 137–142. https://doi.org/10.1007/BF00434401.
Gobbi, G., Bambico, F.R., Mangieri, R., Bortolato, M., Campolongo, P., Solinas, M., Cassano, T., Morgese, M.G., Debonnel, G., Duranti, A., Tontini, A., Tarzia, G., Mor, M., Trezza, V., Goldberg, S.R., Cuomo, V., Piomelli, D., 2005. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc. Natl. Acad. Sci. U. S. A. 102, 18620–18625. https://doi.org/10.1073/pnas.0509591102.
Gogolla, N., 2017. The insular cortex. Current Biology: CB 27 (12), R580–R586. https://doi.org/10.1016/j.cub.2017.05.010.
Gomes, F.V., Resstel, L.B.M., Guimarães, F.S., 2011. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology (Berl) 213, 465–473. https://doi.org/10.1007/s00213-010-2036-z.
Gomes-de-Souza, L., Bianchi, P.C., Costa-Ferreira, W., Tomeo, R.A., Cruz, F.C., Crestani, C.C., 2021. CB1 and CB2 receptors in the bed nucleus of the stria terminalis differently modulate anxiety-like behaviors in rats. Prog. Neuro-Psychopharmacology Biol. Psychiatry 110, 110284. https://doi.org/10.1016/j.pnpbp.2021.110284.
Goode, T.D., Maren, S., 2017. Role of the bed nucleus of the stria terminalis in aversive learning and memory. Learning & Memory (Cold Spring Harbor, N.Y.) 24 (9), 480–491. https://doi.org/10.1101/lm.044206.116.
Gorzalka, B.B., Hill, M.N., Hillard, C.J., 2008. Regulation of endocannabinoid signaling by stress: implications for stress-related affective disorders. Neuroscience & Biobehavioral Reviews 32 (6), 1152–1160.
Gottschalk, M.G., Domschke, K., 2017. Genetics of generalized anxiety disorder and related traits. Dialogues Clin Neurosci. *Dialogues Clin Neurosci.* 19 (2), 159–168. https://doi.org/10.31887/DCNS.2017.19.2/kdomschke.
Govindarajan, A., Shankaranarayana Rao, B.S., Nair, D., Trinh, M., Mawjee, N., Tonegawa, S., Chattarji, S., 2006. Transgenic brain-derived neurotrophic factor expression causes both anxiogenic and antidepressant effects. Proc. Natl. Acad. Sci. U. S. A. 103, 13208–13213. https://doi.org/10.1073/pnas.0605180103.
Gray, M.J., Vecchiarelli, H.A., Morena, M., Lee, T.T.Y., Hermanson, D.J., Kim, A.B., McLaughlin, R.J., Hassan, K.I., Kuhne, C., Wotjak, C.T., Deussing, J.M., Patel, S., Hill, M.N., 2015. Corticotropin-releasing hormone drives anandamide hydrolysis in the amygdala to promote anxiety. J. Neurosci. 35, 3879–3892. https://doi.org/10.1523/JNEUROSCI.2737-14.2015.
Gregorio, D. De, McLaughlin, R.J., Posa, L., Ochoa-Sanchez, R., Enns, J., Lopez-Canul, M., Aboud, M., Maione, S., Comai, S., Gobbi, G., 2019. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain 160, 136–150. https://doi.org/10.1097/j.pain.0000000000001386.
Griebel, G., Holmes, A., 2013. 50 years of hurdles and hope in anxiolytic drug discovery. Nature Reviews. Drug Discovery 12 (9), 667–687. https://doi.org/10.1038/nrd4075.
Griebel, G., Stemmelin, J., Lopez-Grancha, M., Fauchey, V., Slowinski, F., Pichat, P., Dargazanli, G., Abouabdellah, A., Cohen, C., Bergis, O.E., 2018. The selective reversible FAAH inhibitor, SSR411298, restores the development of maladaptive behaviors to acute and chronic stress in rodents. Sci. Rep. 8, 1–25. https://doi.org/10.1038/s41598-018-20895-z.
Griebel, G., Stemmelin, J., Scatton, B., 2005. Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. Biol. Psychiatry 57, 261–267. https://doi.org/10.1016/j.biopsych.2004.10.032.
Grillon, C., Pine, D.S., Baas, J.M.P., Lawley, M., Ellis, V., Charney, D.S., 2006. Cortisol and DHEA-S are associated with startle potentiation during aversive conditioning in humans. Psychopharmacology 186 (3), 434–441. https://doi.org/10.1007/s00213-005-0124-2.
Grissom, N., Kerr, W., Bhatnagar, S., 2008. Struggling behavior during restraint is regulated by stress experience. Behavioural Brain Research 191 (2), 219–226. https://doi.org/10.1016/j.bbr.2008.03.030.
Grossen, N.E., Kelley, M.J., 1972. Species-specific behavior and acquisition of avoidance behavior in rats. Journal of Comparative and Physiological Psychology 81 (2), 307–310. https://doi.org/10.1037/h0033536.
Grotenhermen, F., 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical pharmacokinetics 42 (4), 327–360.
Grupe, D.W., Nitschke, J.B., 2013. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nature Reviews. Neuroscience 14 (7), 488–501. https://doi.org/10.1038/nrn3524.
Guggenhuber, S., Romo-Parra, H., Bindila, L., Leschik, J., Lomazzo, E., Remmers, F., Zimmermann, T., Lerner, R., Klugmann, M., Pape, H.C., Lutz, B., 2016. Impaired 2-AG signaling in hippocampal glutamatergic neurons: aggravation of anxiety-like behavior and unaltered seizure susceptibility. Int. J. Neuropsychopharmacol. 19, 1–13. https://doi.org/10.1093/ijnp/pyv091.
Guimarães, F.S., Aguiar, J.C.d., Mechoulam, R., Breuer, A., 1994. Anxiolytic effect of cannabidiol derivatives in the elevated plus-maze. Gen. Pharmacol. 25, 161–164. https://doi.org/10.1016/0306-3623(94)90027-2.
Guimarães, F.S., Chiaretti, T.M., Graeff, F.G., Zuardi, A.W., 1990. Antianxiety effect of cannabidiol in the elevated plus-maze. Psychopharmacology (Berl) 100, 558–559. https://doi.org/10.1007/BF02244012.
Gulyas, A.I., Cravatt, B.F., Bracey, M.H., Dinh, T.P., Piomelli, D., Boscia, F., Freund, T.F., 2004. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci 20 (2), 441–458. https://doi.org/10.1111/j.1460-9568.2004.03428.x.
Gunduz-Cinar, O., 2021. The endocannabinoid system in the amygdala and modulation of fear. Progress in Neuro-Psychopharmacology and Biological Psychiatry 105, 110116. https://doi.org/10.1016/j.pnpbp.2020.110116.
Gunduz-Cinar, O., MacPherson, K.P., Cinar, R., Gamble-George, J., Sugden, K., Williams, B., Godlewski, G., Ramikie, T.S., Gorka, A.X., Alapafuja, S.O., Nikas, S.P., Makriyannis, A., Poulton, R., Patel, S., Hariri, A.R., Caspi, A., Moffitt, T.E., Kunos, G., Holmes, A., 2013. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. Mol. Psychiatry 18, 813–823. https://doi.org/10.1038/mp.2012.72.
Hakimizadeh, E., Oryan, S., Moghaddam, A.H., Shamsizadeh, A., Roohbakhsh, A., 2012. Endocannabinoid system and TRPV1 receptors in the dorsal hippocampus of the rats modulate anxiety-like behaviors. Iran. J. Basic Med. Sci. 15, 795–802. https://doi.org/10.22038/ijbms.2012.4863.
Haller, J., Bakos, N., Szirmay, M., Ledent, C., Freund, T.F., 2002. The effects of genetic and pharmacological blockade of the CB1 cannabinoid receptor on anxiety. Eur. J. Neurosci. 16, 1395–1398. https://doi.org/10.1046/j.1460-9568.2002.02192.x.
Haller, J., Barna, I., Barsvari, B., Gyimesi Pelczer, K., Yasar, S., Panlilio, L.V., Goldberg, S., 2009. Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology (Berl) 204, 607–616. https://doi.org/10.1007/s00213-009-1494-7.
Haller, J., Varga, B., Ledent, C., Barna, I., Freund, T.F., 2004a. Context-dependent effects of CB1 cannabinoid gene disruption on anxiety-like and social behaviour in mice. Eur. J. Neurosci. 19, 1906–1912. https://doi.org/10.1111/j.1460-9568.2004.03293.x.
Haller, J., Varga, B., Ledent, C., Freund, T.F., 2004b. CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents. Behav. Pharmacol. 15, 299–304. https://doi.org/10.1097/01.fbp.0000135704.56422.40.
Hamilton, M., 1959. The assessment of anxiety states by rating. The British Journal of Medical Psychology 32 (1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.
Hamm, L.L., Jacobs, R.H., Johnson, M.W., Fitzgerald, D.A., Fitzgerald, K.D., Langenecker, S.A., Monk, C.S., Phan, K.L., 2014. Aberrant amygdala functional connectivity at rest in pediatric anxiety disorders. Biology of Mood & Anxiety Disorders 4 (1), 15. https://doi.org/10.1186/s13587-014-0015-4.
Häring, M., Kaiser, N., Monory, K., Lutz, B., 2011. Circuit specific functions of cannabinoid CB1 receptor in the balance of investigatory drive and exploration. PLoS One 6, e26617. https://doi.org/10.1371/journal.pone.0026617.
Hariri, A.R., Gorka, A., Hyde, L.W., Kimak, M., Halder, I., Ducci, F., Ferrell, R.E., Goldman, D., Manuck, S.B., 2009. Divergent effects of genetic variation in endocannabinoid signaling on human threat- and reward-related brain function. Biol. Psychiatry 66, 9–16. https://doi.org/10.1016/j.biopsych.2008.10.047.
Hasin, D.S., Saha, T.D., Kerridge, B.T., Goldstein, R.B., Chou, S.P., Zhang, H., Jung, J., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Grant, B.F., 2015. Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. JAMA Psychiatry 72 (12), 1235–1242. https://doi.org/10.1001/jamapsychiatry.2015.1858.
Hayashida, S., Oka, T., Mera, T., Tsuji, S., 2010. Repeated social defeat stress induces chronic hyperthermia in rats. Physiology & Behavior 101 (1), 124–131. https://doi.org/10.1016/j.physbeh.2010.04.027.
Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1991. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 11 (2), 563–583.
Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1990. Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci. 87 https://doi.org/10.1073/pnas.87.5.1932.
Herman, J.P., Figueiredo, H., Mueller, N.K., Ulrich-Lai, Y., Ostrander, M.M., Choi, D.C., Cullinan, W.E., 2003. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Frontiers in Neuroendocrinology 24 (3), 151–180. https://doi.org/10.1016/j.yfrne.2003.07.001.
Hermann, H., Marsicano, G., Lutz, B., 2002. Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain. Neuroscience 109 (3), 451–460.
Hilbert, K., Lueken, U., Beesdo-Baum, K., 2014. Neural structures, functioning and connectivity in Generalized Anxiety Disorder and interaction with neuroendocrine systems: a systematic review. Journal of Affective Disorders 158, 114–126. https://doi.org/10.1016/j.jad.2014.01.022.
Hill, M.N., Campolongo, P., Yehuda, R., Patel, S., 2018. Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. Neuropsychopharmacology. https://doi.org/10.1038/npp.2017.162.

Hill, M.N., Tasker, J.G., 2012. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience 204, 5–16.
Hill, M.N., Gorzalka, B., 2009. The endocannabinoid system and the treatment of mood and anxiety disorders. CNS Neurol. Disord. - Drug Targets 8, 451–458. https://doi.org/10.2174/187152709789824624.
Hill, M.N., Gorzalka, B.B., 2004. Enhancement of anxiety-like responsiveness to the cannabinoid CB 1 receptor agonist HU-210 following chronic stress. Eur. J. Pharmacol. 499, 291–295. https://doi.org/10.1016/j.ejphar.2004.06.069.
Hill, M.N., Kumar, S.A., Filipski, S.B., Iverson, M., Stuhr, K.L., Keith, J.M., Cravatt, B.F., Hillard, C.J., Chattarji, S., McEwen, B.S., 2013. Disruption of fatty acid amide hydrolase activity prevents the effects of chronic stress on anxiety and amygdalar microstructure. Mol. Psychiatry 18, 1125–1135. https://doi.org/10.1038/mp.2012.90.
Hill, M.N., McLaughlin, R.J., Bingham, B., Shrestha, L., Lee, T.T.Y., Gray, J.M., Hillard, C.J., Gorzalka, B.B., Viau, V., 2010. Endogenous cannabinoid signaling is essential for stress adaptation. Proc. Natl. Acad. Sci. U. S. A. 107, 9406–9411. https://doi.org/10.1073/pnas.0914661107.
Hill, M.N., McLaughlin, R.J., Pan, B., Fitzgerald, M.L., Roberts, C.J., Lee, T.T.Y., Karatsoreos, I.N., Mackie, K., Viau, V., Pickel, V.M., McEwen, B.S., Liu, Q. song, Gorzalka, B.B., Hillard, C.J., 2011. Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. J. Neurosci. 31, 10506–10515. https://doi.org/10.1523/JNEUROSCI.0496-11.2011.
Hill, M.N., Miller, G.E., Carrier, E.J., Gorzalka, B.B., Hillard, C.J., 2009. Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology 34, 1257–1262. https://doi.org/10.1016/j.psyneuen.2009.03.013.
Hines, L.A., Freeman, T.P., Gage, S.H., Zammit, S., Hickman, M., Cannon, M., Munafo, M., MacLeod, J., Heron, J., 2020. Association of high-potency cannabis use with mental health and substance use in adolescence. JAMA Psychiatry 77 (10), 1044–1051. https://doi.org/10.1001/jamapsychiatry.2020.1035.
Hirvonen, J., Goodwin, R.S., Li, C.T., Terry, G.E., Zoghbi, S.S., Morse, C., Pike, V.W., Volkow, N.D., Huestis, M.A., Innis, R.B., 2012. Reversible and regionally selective downregulation of brain cannabinoid CB 1 receptors in chronic daily cannabis smokers. Mol. Psychiatry 17, 642–649. https://doi.org/10.1038/mp.2011.82.
Hložek, T., Uttl, L., Kadeřábek, L., Balíková, M., Lhotková, E., Horsley, R.R., et al., 2017. Pharmacokinetic and behavioural profile of THC, CBD, and THC+ CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion in vivo of CBD to THC. European Neuropsychopharmacology 27 (12), 1223–1237.
Hornblow, A.R., Kidson, M.A., 1976. The visual analogue scale for anxiety: a validation study. The Australian and New Zealand Journal of Psychiatry 10 (4), 339–341. https://doi.org/10.3109/00048677609159523.
Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G., 2002. International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. https://doi.org/10.1124/pr.54.2.161.
Hu, S.S.-J., Mackie, K., 2015. Distribution of the endocannabinoid system in the central nervous system. Handb. Exp. Pharmacol. https://doi.org/10.1007/978-3-319-20825-1_3.
Huynh, T.N., Krigbaum, A.M., Hanna, J.J., Conrad, C.D., 2011. Sex differences and phase of light cycle modify chronic stress effects on anxiety and depressive-like behavior. Behavioural Brain Research 222 (1), 212–222. https://doi.org/10.1016/j.bbr.2011.03.038.
Ilan, A.B., Gevins, A., Coleman, M., ElSohly, M.A., De Wit, H., 2005. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. Behav. Pharmacol. 16, 487–496. https://doi.org/10.1097/00008877-200509000-00023.
Imperatore, R., Morello, G., Luongo, L., Taschler, U., Romano, R., De Gregorio, D., Belardo, C., Maione, S., Di Marzo, V., Cristino, L., 2015. Genetic deletion of monoacylglycerol lipase leads to impaired cannabinoid receptor CB $_1$ R signaling and anxiety-like behavior. J. Neurochem. 135, 799–813. https://doi.org/10.1111/jnc.13267.
Jacob, W., Yassouridis, A., Marsicano, G., Monory, K., Lutz, B., Wotjak, C.T., 2009. Endocannabinoids render exploratory behaviour largely independent of the test aversiveness: role of glutamatergic transmission. Genes, Brain Behav 8, 685–698. https://doi.org/10.1111/j.1601-183X.2009.00512.x.
Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517 (7534), 284–292. https://doi.org/10.1038/nature14188.
Javadi-Paydar, M., Nguyen, J.D., Kerr, T.M., Grant, Y., Vandewater, S.A., Cole, M., Taffe, M.A., 2018. Effects of Δ9-THC and cannabidiol vapor inhalation in male and female rats. Psychopharmacology 235 (9), 2541–2557.
Jenniches, I., Ternes, S., Albayram, O., Otte, D.M., Bach, K., Bindila, L., Michel, K., Lutz, B., Bilkei-Gorzo, A., Zimmer, A., 2016. Anxiety, stress, and fear response in mice with reduced endocannabinoid levels. Biol. Psychiatry 79, 858–868. https://doi.org/10.1016/j.biopsych.2015.03.033.
Jiang, W., Zhang, Y., Xiao, L., Van Cleemput, J., Ji, S.P., Bai, G., Zhang, X., 2005. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J. Clin. Invest. 115, 3104–3116. https://doi.org/10.1172/JCI25509.
Jochman, K.A., Newman, S.M., Kalin, N.H., Bakshi, V.P., 2005. Corticotropin-releasing factor-1 receptors in the basolateral amygdala mediate stress-induced anorexia. Behavioral Neuroscience 119 (6), 1448–1458. https://doi.org/10.1037/0735-7044.119.6.1448.
Ju, A., Fernandez-Arroyo, B., Wu, Y., Jacky, D., Beyeler, A., 2020. Expression of serotonin 1A and 2A receptors in molecular- and projection-defined neurons of the mouse insular cortex. Molecular Brain 13 (1), 99. https://doi.org/10.1186/s13041-020-00605-5.
Julian, L.J., 2011. Measures of anxiety: state-trait anxiety inventory (STAI), beck anxiety inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). Arthritis Care & Research 63 (Suppl. 11), S467–S472. https://doi.org/10.1002/acr.20561.
Kalueff, A.V., Tuohimaa, P., 2005. Mouse grooming microstructure is a reliable anxiety marker bidirectionally sensitive to GABAergic drugs. European Journal of Pharmacology 508 (1–3), 147–153. https://doi.org/10.1016/j.ejphar.2004.11.054.
Karniol, I.G., Shirakawa, I., Kasinski, N., Pfeferman, A., Carlini, E.A., 1974. Cannabidiol interferes with the effects of Δ9-tetrahydrocannabinol in man. Eur. J. Pharmacol. 28, 172–177. https://doi.org/10.1016/0014-2999(74)90129-0.
Karschner, E.L., Darwin, W.D., McMahon, R.P., Liu, F., Wright, S., Goodwin, R.S., Huestis, M.A., 2011. Subjective and physiological effects after controlled sativex and oral THC administration. Clin. Pharmacol. Ther. 89, 400–407. https://doi.org/10.1038/clpt.2010.318.
Kasten, C.R., Zhang, Y., Boehm II, S.L., 2017. Acute and long-term effects of Δ9-tetrahydrocannabinol on object recognition and anxiety-like activity are age-and strain-dependent in mice. Pharmacology Biochemistry and Behavior 163, 9–19.
Kataoka, N., Shima, Y., Nakajima, K., Nakamura, K., 2020. A central master driver of psychosocial stress responses in the rat. Science (New York, N.Y.) 367 (6482), 1105–1112. https://doi.org/10.1126/science.aaz4639.
Kathuria, S., Gaetani, S., Fegley, D., Valiño, F., Duranti, A., Tontini, A., Mor, M., Tarzia, G., Rana, G. La, Calignano, A., Giustino, A., Tattoli, M., Palmery, M., Cuomo, V., Piomelli, D., 2003. Modulation of anxiety through blockade of anandamide hydrolysis. Nat. Med. 9, 76–81. https://doi.org/10.1038/nm803.
Katona, I., Freund, T.F., 2012. Multiple functions of endocannabinoid signaling in the brain. Annu. Rev. Neurosci. https://doi.org/10.1146/annurev-neuro-062111-150420.
Katona, I., Rancz, E.A., Acsady, L., Ledent, C., Mackie, K., Hajos, N., Freund, T.F., 2001. Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 21 (23), 9506–9518.
Kedzior, K.K., Laeber, L.T., 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—a meta-analysis of 31 studies. BMC Psychiatry 14, 136. https://doi.org/10.1186/1471-244X-14-136.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry 62 (6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593.
Kim, M.J., Gee, D.G., Loucks, R.A., Davis, F.C., Whalen, P.J., 2011. Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cerebral Cortex (New York, N.Y. 21 (7), 1667–1673. https://doi.org/10.1093/cercor/bhq237, 1991.
Kim, S.-Y., Adhikari, A., Lee, S.Y., Marshel, J.H., Kim, C.K., Mallory, C.S., Lo, M., Pak, S., Mattis, J., Lim, B.K., Malenka, R.C., Warden, M.R., Neve, R., Tye, K.M., Deisseroth, K., 2013. Diverging neural pathways assemble a behavioural state from separable features in anxiety. Nature 496 (7444), 219–223. https://doi.org/10.1038/nature12018.
Kinsey, S.G., Bailey, M.T., Sheridan, J.F., Padgett, D.A., Avitsur, R., 2007. Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. Brain, Behavior, and Immunity 21 (4), 458–466. https://doi.org/10.1016/j.bbi.2006.11.001.
Kinsey, S.G., O'Neal, S.T., Long, J.Z., Cravatt, B.F., Lichtman, A.H., 2011. Inhibition of endocannabinoid catabolic enzymes elicits anxiolytic-like effects in the marble burying assay. Pharmacol. Biochem. Behav. 98, 21–27. https://doi.org/10.1016/j.pbb.2010.12.002.
Kirouac, G.J., 2021. The paraventricular nucleus of the thalamus as an integrating and relay node in the brain anxiety network. Front. Behav. Neurosci. 15, 627633. https://doi.org/10.3389/fnbeh.2021.627633, 2021.
Kjelstrup, K.G., Tuvnes, F.A., Steffenach, H.-A., Murison, R., Moser, E.I., Moser, M.-B., 2002. Reduced fear expression after lesions of the ventral hippocampus. Proceedings of the National Academy of Sciences of the United States of America 99 (16), 10825–10830. https://doi.org/10.1073/pnas.152112399.
Kliethermes, C.L., Cronise, K., Crabbe, J.C., 2006. Anxiety-like behavior in mice in two apparatuses during withdrawal from chronic ethanol vapor inhalation. Alcoholism: Clinical and Experimental Research 28 (7), 1012–1019. https://doi.org/10.1097/01.alc.0000131976.40428.8f.
Klengel, T., Mehta, D., Anacker, C., et al., 2013. Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. Nat Neurosci 16, 33–41. https://doi.org/10.1038/nn.3275.
Kreitzer, A.C., Regehr, W.G., 2001. Retrograde Inhibition of Presynaptic Calcium Influx by Endogenous Cannabinoids at Excitatory Synapses onto Purkinje Cells Studies of DSE in the cerebellum can provide insight into several fundamental issues regarding retrograde synaptic inhibition. A number of retrograde messengers have been identified at various synapses, including glu-tamate, GABA, and neuropeptides (Glitsch et al. Neuron.
Kruk, M.R., Westphal, K.G., Van Erp, A.M., van Asperen, J., Cave, B.J., Slater, E., de Koning, J., Haller, J., 1998. The hypothalamus: cross-roads of endocrine and behavioural regulation in grooming and aggression. Neuroscience and Biobehavioral Reviews 23 (2), 163–177. https://doi.org/10.1016/s0149-7634(98)00018-9.
Lacroix, L., Broerson, L.M., Weiner, I., Feldon, J., 1998. The effects of excitotoxic lesion of the medial prefrontal cortex on latent inhibition, prepulse inhibition, food

hoarding, elevated plus maze, active avoidance and locomotor activity in the rat. Neuroscience 84 (2), 431–442. https://doi.org/10.1016/S0306-4522(97)00521-6.
Laere, K. Van, Goffin, K., Casteels, C., Dupont, P., Mortelmans, L., de Hoon, J., Bormans, G., 2008. Gender-dependent increases with healthy aging of the human cerebral cannabinoid-type 1 receptor binding using [18F]MK-9470 PET. Neuroimage 39, 1533–1541. https://doi.org/10.1016/j.neuroimage.2007.10.053.
Lafenêtre, P., Chaouloff, F., Marsicano, G., 2009. Bidirectional regulation of novelty-induced behavioral inhibition by the endocannabinoid system. Neuropharmacology 57, 715–721. https://doi.org/10.1016/j.neuropharm.2009.07.014.
Lähdepuro, A., Savolainen, K., Lahti-Pulkkinen, M., et al., 2019. The impact of early life stress on anxiety symptoms in late adulthood. Sci Rep 9, 4395. https://doi.org/10.1038/s41598-019-40698-0.
Lang, P.J., Davis, M., Ohman, A., 2000. Fear and anxiety: animal models and human cognitive psychophysiology. Journal of Affective Disorders 61 (3), 137–159. https://doi.org/10.1016/s0165-0327(00)00343-8.
Laprairie, R.B., Bagher, A.M., Kelly, M.E.M., Denovan-Wright, E.M., 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br. J. Pharmacol. 172, 4790–4805. https://doi.org/10.1111/bph.13250.
Laurikainen, H., Tuominen, L., Tikka, M., Merisaari, H., Armio, R.L., Sormunen, E., et al., 2019. Sex difference in brain CB1 receptor availability in man. Neuroimage 184, 834–842.
Leadbeater, B.J., Ames, M.E., Linden-Carmichael, A.N., 2019. Age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults. Addiction (Abingdon, England) 114 (2), 278–293. https://doi.org/10.1111/add.14459.
LeDoux, J., 2007. The amygdala. Current Biology 17 (20), R868–R874. https://doi.org/10.1016/j.cub.2007.08.005.
Lee, J.H., Kim, H.J., Kim, J.G., Ryu, V., Kim, B.T., Kang, D.W., Jahng, J.W., 2007. Depressive behaviors and decreased expression of serotonin reuptake transporter in rats that experienced neonatal maternal separation. Neuroscience Research 58 (1), 32–39. https://doi.org/10.1016/j.neures.2007.01.008.
Lee, Y., Fitz, S., Johnson, P.L., Shekhar, A., 2008. Repeated stimulation of CRF receptors in the BNST of rats selectively induces social but not panic-like anxiety. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 33 (11), 2586–2594. https://doi.org/10.1038/sj.npp.1301674.
Leishman, E., Manchanda, M., Thelen, R., Miller, S., Mackie, K., Bradshaw, H.B., 2018. Nov. 30. Cannabis Cannabinoid Res 3 (1), 228–241.
Lemberger, L., Crabtree, R.E., Rowe, H.M., 1972. 11-hydroxy- 9 -tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marihuana in man. Science (New York, N.Y.) 177 (4043), 62–64. https://doi.org/10.1126/science.177.4043.62.
Leung, J., Chan, G.C.K., Hides, L., Hall, W.D., 2020. What is the prevalence and risk of cannabis use disorders among people who use cannabis? A systematic review and meta-analysis. Addictive Behaviors 109, 106479. https://doi.org/10.1016/j.addbeh.2020.106479.
Leweke, F.M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C.W., Hoyer, C., Klosterkötter, J., Hellmich, M., Koethe, D., 2012 Mar 20. Transl Psychiatry 2 (3), e94.
Lezak, K.R., Missig, G., Carlezon, W.A., 2017. Behavioral methods to study anxiety in rodents. Dialogues in Clinical Neuroscience 19 (2), 181–191.
Liebsch, G., Linthorst, A.C., Neumann, I.D., Reul, J.M., Holsboer, F., Landgraf, R., 1998. Behavioral, physiological, and neuroendocrine stress responses and differential sensitivity to diazepam in two Wistar rat lines selectively bred for high- and low-anxiety-related behavior. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 19 (5), 381–396. https://doi.org/10.1016/S0893-133X(98)00042-6.
Lisboa, S.F., Borges, A.A., Nejo, P., Fassini, A., Guimarães, F.S., Resstel, L.B., 2015. Cannabinoid CB1 receptors in the dorsal hippocampus and prelimbic medial prefrontal cortex modulate anxiety-like behavior in rats: additional evidence. Prog. Neuro-Psychopharmacology Biol. Psychiatry 59, 76–83. https://doi.org/10.1016/j.pnpbp.2015.01.005.
Liu, Q.R., Canseco-Alba, A., Zhang, H.Y., Tagliaferro, P., Chung, M., Dennis, E., et al., 2017. Cannabinoid type 2 receptors in dopamine neurons inhibits psychomotor behaviors, alters anxiety, depression and alcohol preference. Scientific reports 7 (1), 1–17.
Liu, W.-Z., Zhang, W.-H., Zheng, Z.-H., Zou, J.-X., Liu, X.-X., Huang, S.-H., You, W.-J., He, Y., Zhang, J.-Y., Wang, X.-D., Pan, B.-X., 2020. Identification of a prefrontal cortex-to-amygdala pathway for chronic stress-induced anxiety. Nature Communications 11 (1), 2221. https://doi.org/10.1038/s41467-020-15920-7.
Lomazzo, E., Bindila, L., Remmers, F., Lerner, R., Schwitter, C., Hoheisel, U., Lutz, B., 2015. Therapeutic potential of inhibitors of endocannabinoid degradation for the treatment of stress-related hyperalgesia in an animal model of chronic pain. Neuropsychopharmacology 40, 488–501. https://doi.org/10.1038/npp.2014.198.
Long, L.E., Chesworth, R., Huang, X.-F., McGregor, I.S., Arnold, J.C., Karl, T., 2010. A behavioural comparison of acute and chronic Δ9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice. Int. J. Neuropsychopharmacol. 13, 861–876. https://doi.org/10.1017/S1461145709990605.
Lungwitz, E.A., Molosh, A., Johnson, P.L., Harvey, B.P., Dirks, R.C., Dietrich, A., Minick, P., Shekhar, A., Truitt, W.A., 2012. Orexin-A induces anxiety-like behavior through interactions with glutamatergic receptors in the bed nucleus of the stria terminalis of rats. Physiology & Behavior 107 (5), 726–732. https://doi.org/10.1016/j.physbeh.2012.05.019.
Luo, Z.-Y., Huang, L., Lin, S., Yin, Y.-N., Jie, W., Hu, N.-Y., Hu, Y.-Y., Guan, Y.-F., Liu, J.-H., You, Q.-L., Chen, Y.-H., Luo, Z.-C., Zhang, S.-R., Li, X.-W., Yang, J.-M., Tao, Y.-M., Mei, L., Gao, T.-M., 2020. Erbin in amygdala parvalbumin-positive neurons modulates anxiety-like behaviors. Biological Psychiatry 87 (10), 926–936. https://doi.org/10.1016/j.biopsych.2019.10.021.
Lutz, B., 2007. The endocannabinoid system and extinction learning. Molecular Neurobiology 36 (1), 92–101. https://doi.org/10.1007/s12035-007-8004-x.
Maaswinkel, H., Gispen, W.H., Spruijt, B.M., 1996. Effects of an electrolytic lesion of the prelimbic area on anxiety-related and cognitive tasks in the rat. Behavioural Brain Research 79, 51–59.
Maccarrone, M., Valverde, O., Barbaccia, M.L., Castañé, A., Maldonado, R., Ledent, C., Parmentier, M., Finazzi-Agrò, A., 2002. Age-related changes of anandamide metabolism in CB $_1$ cannabinoid receptor knockout mice: correlation with behaviour. Eur. J. Neurosci. 15, 1178–1186. https://doi.org/10.1046/j.1460-9568.2002.01957.x.
Malone, D.T., Jongejan, D., Taylor, D.A., 2009. Cannabidiol reverses the reduction in social interaction produced by low dose Δ9-tetrahydrocannabinol in rats. Pharmacol. Biochem. Behav. 93, 91–96. https://doi.org/10.1016/j.pbb.2009.04.010.
Manwell, L.A., Charchoglyan, A., Brewer, D., Matthews, B.A., Heipel, H., Mallet, P.E., 2014. A vapourized Δ9-tetrahydrocannabinol (Δ9-THC) delivery system part I: development and validation of a pulmonary cannabinoid route of exposure for experimental pharmacology studies in rodents. Journal of pharmacological and toxicological methods 70 (1), 120–127.
Manwell, L.A., Miladinovic, T., Raaphorst, E., Rana, S., Malecki, S., Mallet, P.E., 2019. Chronic nicotine exposure attenuates the effects of Δ9-tetrahydrocannabinol on anxiety-related behavior and social interaction in adult male and female rats. Brain Behav 9. https://doi.org/10.1002/brb3.1375.
Marco, E.M., Rapino, C., Caprioli, A., Borsini, F., Laviola, G., Maccarrone, M., 2015. Potential therapeutic value of a novel FAAH inhibitor for the treatment of anxiety. PLoS One 10, e0137034. https://doi.org/10.1371/journal.pone.0137034.
Marcus, D.J., Bedse, G., Gaulden, A.D., Ryan, J.D., Kondev, V., Winters, N.D., Rosas-Vidal, L.E., Altemus, M., Mackie, K., Lee, F.S., Delpire, E., Patel, S., 2020. Endocannabinoid signaling collapse mediates stress-induced amygdalo-cortical strengthening. Neuron 105, 1062–1076. https://doi.org/10.1016/j.neuron.2019.12.024 e6.
Marsicano, G., Lafenêtre, P., 2009. Roles of the endocannabinoid system in learning and memory. Current Topics in Behavioral Neurosciences 1, 201–230. https://doi.org/10.1007/978-3-540-88955-7_8.
Marsicano, G., Lutz, B., 1999. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur. J. Neurosci. 11, 4213–4225. https://doi.org/10.1046/j.1460-9568.1999.00847.x.
Martin-Santos, R.A., Crippa, J., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., Allen, P., Seal, M., Langohr, K., Farre, M., Zuardi, A., K McGuire, P., 2012. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr. Pharm. Des. 18, 4966–4979. https://doi.org/10.2174/138161212802884780.
Martin, E.I., Ressler, K.J., Binder, E., Nemeroff, C.B., 2009. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. The Psychiatric Clinics of North America 32 (3), 549–575. https://doi.org/10.1016/j.psc.2009.05.004.
Martin, M., Ledent, C., Parmentier, M., Maldonado, R., Valverde, O., 2002. Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology (Berl) 159, 379–387. https://doi.org/10.1007/s00213-001-0946-5.
Massi, L., Elezgarai, I., Puente, N., Reguero, L., Grandes, P., Manzoni, O.J., Georges, F., 2008. Cannabinoid receptors in the bed nucleus of the stria terminalis control cortical excitation of midbrain dopamine cells in vivo. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 28 (42), 10496–10508. https://doi.org/10.1523/JNEUROSCI.2291-08.2008.
Matsuda, L.A., Bonner, T.I., Lolait, S.J., 1993. Localization of cannabinoid receptor mRNA in rat brain. J. Comp. Neurol. 327 https://doi.org/10.1002/cne.903270406.
Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.C., Bonner, T.I., 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346. https://doi.org/10.1038/346561a0.
Mayer, T.A., Matar, M.A., Kaplan, Z., Zohar, J., Cohen, H., 2014. Blunting of the HPA-axis underlies the lack of preventive efficacy of early post-stressor single-dose Delta-9-tetrahydrocannabinol (THC). Pharmacol. Biochem. Behav. 122, 307–318. https://doi.org/10.1016/j.pbb.2014.04.014.
Mayo, L.M., Asratian, A., Lindé, J., Holm, L., Nätt, D., Augier, G., Stensson, N., Vecchiarelli, H.A., Balsevich, G., Aukema, R.J., Ghafouri, B., Spagnolo, P.A., Lee, F. S., Hill, M.N., Heilig, M., 2020a. Protective effects of elevated anandamide on stress and fear-related behaviors: translational evidence from humans and mice. Mol. Psychiatry 25, 993–1005. https://doi.org/10.1038/s41380-018-0215-1.
Mayo, L.M., Asratian, A., Lindé, J., Morena, M., Haataja, R., Hammar, V., Augier, G., Hill, M.N., Heilig, M., 2020b. Elevated anandamide, enhanced recall of fear extinction, and attenuated stress responses following inhibition of fatty acid amide hydrolase: a randomized, controlled experimental medicine trial. Biol. Psychiatry 87, 538–547. https://doi.org/10.1016/j.biopsych.2019.07.034.
Mazzone, C.M., Pati, D., Michaelides, M., DiBerto, J., Fox, J.H., Tipton, G., Anderson, C., Duffy, K., McKlveen, J.M., Hardaway, J.A., Magness, S.T., Falls, W.A., Hammack, S. E., McElligott, Z.A., Hurd, Y.L., Kash, T.L., 2018. Acute engagement of Gq-mediated signaling in the bed nucleus of the stria terminalis induces anxiety-like behavior. Molecular Psychiatry 23 (1), 143–153. https://doi.org/10.1038/mp.2016.218.
McCall, J.G., Al-Hasani, R., Siuda, E.R., Hong, D.Y., Norris, A.J., Ford, C.P., Bruchas, M. R., 2015. CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. Neuron 87 (3), 605–620. https://doi.org/10.1016/j.neuron.2015.07.002.
McDonald, A.J., Mascagni, F., 2001. Localization of the CB1 type cannabinoid receptor in the rat basolateral amygdala: high concentrations in a subpopulation of

cholecystokinin-containing interneurons. Neuroscience 107 (4), 641–652. https://doi.org/10.1016/s0306-4522(01)00380-3.
McHugh, S.B., Deacon, R.M.J., Rawlins, J.N.P., Bannerman, D.M., 2004. Amygdala and ventral hippocampus contribute differentially to mechanisms of fear and anxiety. Behavioral Neuroscience 118 (1), 63–78. https://doi.org/10.1037/0735-7044.118.1.63.
Mechoulam, R., Parker, L.A., 2013. The endocannabinoid system and the brain. Annu. Rev. Psychol. https://doi.org/10.1146/annurev-psych-113011-143739.
Mechoulam, R., Shvo, Y., 1963. Hashish-I. The structure of cannabidiol. Tetrahedron 19. https://doi.org/10.1016/0040-4020(63)85022-X.
Mechoulam, R., El Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N.E., Schatz, A.R., Gopher, A., Almog, S., Martin, B.R., Compton, D.R., Pertwee, R.G., Griffin, G., Bayewitch, M., Barg, J., Vogel, Z., 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol.
Meewisse, M.-L., Reitsma, J.B., de Vries, G.-J., Gersons, B.P.R., Olff, M., 2007. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. The British Journal of Psychiatry: The Journal of Mental Science 191, 387–392. https://doi.org/10.1192/bjp.bp.106.024877.
Méndez-Ruette, M., Linsambarth, S., Moraga-Amaro, R., Quintana-Donoso, D., Méndez, L., Tamburini, G., Cornejo, F., Torres, R.F., Stehberg, J., 2019. The role of the rodent insula in anxiety. Frontiers in Physiology 10, 330. https://doi.org/10.3389/fphys.2019.00330.
Mikuriya, T.H., 1969. Marijuana in medicine: past, present and future. Calif. Med.
Milad, M.R., Wright, C.I., Orr, S.P., Pitman, R.K., Quirk, G.J., Rauch, S.L., 2007. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biological Psychiatry 62 (5), 446–454. https://doi.org/10.1016/j.biopsych.2006.10.011.
Mock, E.D., Mustafa, M., Gunduz-Cinar, O., Cinar, R., Petrie, G.N., Kantae, V., Di, X., Ogasawara, D., Varga, Z.V., Paloczi, J., Miliano, C., Donvito, G., van Esbroeck, A.C. M., van der Gracht, A.M.F., Kotsogianni, I., Park, J.K., Martella, A., van der Wel, T., Soethoudt, M., Jiang, M., Wendel, T.J., Janssen, A.P.A., Bakker, A.T., Donovan, C.M., Castillo, L.I., Florea, B.I., Wat, J., van den Hurk, H., Wittwer, M., Grether, U., Holmes, A., van Boeckel, C.A.A., Hankemeier, T., Cravatt, B.F., Buczynski, M.W., Hill, M.N., Pacher, P., Lichtman, A.H., van der Stelt, M., 2020. Discovery of a NAPE-PLD inhibitor that modulates emotional behavior in mice. Nat. Chem. Biol. 16, 667–675. https://doi.org/10.1038/s41589-020-0528-7.
Monory, K., Blaudzun, H., Massa, F., Kaiser, N., Lemberger, T., Schütz, G., et al., 2007. Genetic dissection of behavioural and autonomic effects of Δ 9-tetrahydrocannabinol in mice. PLoS Biol 5 (10), e269.
Montgomery, K.C., 1955. The relation between fear induced by novel stimulation and exploratory behavior. Journal of Comparative and Physiological Psychology 48 (4), 254–260. https://doi.org/10.1037/h0043788.
Moreira, F.A., Aguiar, D.C., Guimarães, F.S., 2006. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. Prog. Neuro-Psychopharmacology Biol. Psychiatry 30, 1466–1471. https://doi.org/10.1016/j.pnpbp.2006.06.004.
Moreira, F.A., Aguiar, D.C., Guimarães, F.S., 2007. Anxiolytic-like effect of cannabinoids injected into the rat dorsolateral periaqueductal gray. Neuropharmacology 52, 958–965. https://doi.org/10.1016/j.neuropharm.2006.10.013.
Moreira, F.A., Kaiser, N., Monory, K., Lutz, B., 2008. Reduced anxiety-like behaviour induced by genetic and pharmacological inhibition of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) is mediated by CB1 receptors. Neuropharmacology 54, 141–150. https://doi.org/10.1016/j.neuropharm.2007.07.005.
Morena, M., Campolongo, P., 2014. The endocannabinoid system: an emotional buffer in the modulation of memory function. Neurobiology of Learning and Memory 112, 30–43. https://doi.org/10.1016/j.nlm.2013.12.010.
Morena, M., Aukema, R.J., Leitl, K.D., Rashid, A.J., Vecchiarelli, H.A., Josselyn, S.A., Hill, M.N., 2019. Upregulation of anandamide hydrolysis in the basolateral complex of amygdala reduces fear memory expression and indices of stress and anxiety. J. Neurosci. 39, 1275–1292. https://doi.org/10.1523/JNEUROSCI.2251-18.2018.
Motzkin, J.C., Philippi, C.L., Wolf, R.C., Baskaya, M.K., Koenigs, M., 2015. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. Biological Psychiatry 77 (3), 276–284. https://doi.org/10.1016/j.biopsych.2014.02.014.
Mozhui, K., Karlsson, R.-M., Kash, T.L., Ihne, J., Norcross, M., Patel, S., Farrell, M.R., Hill, E.E., Graybeal, C., Martin, K.P., Camp, M., Fitzgerald, P.J., Ciobanu, D.C., Sprengel, R., Mishina, M., Wellman, C.L., Winder, D.G., Williams, R.W., Holmes, A., 2010. Strain differences in stress responsivity are associated with divergent amygdala gene expression and glutamate-mediated neuronal excitability. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 30 (15), 5357–5367. https://doi.org/10.1523/JNEUROSCI.5017-09.2010.
Mu, M.-D., Geng, H.-Y., Rong, K.-L., Peng, R.-C., Wang, S.-T., Geng, L.-T., Qian, Z.-M., Yung, W.-H., Ke, Y., 2020. A limbic circuitry involved in emotional stress-induced grooming. Nature Communications 11 (1), 2261. https://doi.org/10.1038/s41467-020-16203-x.
Munro, S., Thomas, K.L., Abu-Shaar, M., 1993. Molecular characterization of a peripheral receptor for cannabinoids. Nature 365. https://doi.org/10.1038/365061a0.
Murataeva, N., Straiker, A., MacKie, K., 2014. Parsing the players: 2-arachidonoylglycerol synthesis and degradation in the CNS. Br. J. Pharmacol. https://doi.org/10.1111/bph.12411.
Natividad, L.A., Buczynski, M.W., Herman, M.A., Kirson, D., Oleata, C.S., Irimia, C., Polis, I., Ciccocioppo, R., Roberto, M., Parsons, L.H., 2017. Constitutive increases in amygdalar corticotropin-releasing factor and fatty acid amide hydrolase drive an anxious phenotype. Biol. Psychiatry 82, 500–510. https://doi.org/10.1016/j.biopsych.2017.01.005.
Navarro, M., Hernández, E., Muñoz, R.M., Del Arco, I., Villanúa, M.A., Carrera, M.R.A., Rodríguez De Fonseca, F., 1997. Acute administration of the CB1 cannabinoid receptor antagonist SR 141716A induces anxiety-like responses in the rat. Neuroreport 8, 491–496. https://doi.org/10.1097/00001756-199701200-00023.
Nin, M.S., Couto-Pereira, N.S., Souza, M.F., Azeredo, L.A., Ferri, M.K., Dalprá, W.L., Gomez, R., Barros, H.M.T., 2012. Anxiolytic effect of clonazepam in female rats: grooming microstructure and elevated plus maze tests. European Journal of Pharmacology 684 (1–3), 95–101. https://doi.org/10.1016/j.ejphar.2012.03.038.
Nomura, D.K., Morrison, B.E., Blankman, J.L., Long, J.Z., Kinsey, S.G., Marcondes, M.C. G., Ward, A.M., Hahn, Y.K., Lichtman, A.H., Conti, B., Cravatt, B.F., 2011. Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science 80, 334. https://doi.org/10.1126/science.1209200.
Normandin, M.D., Zheng, M.Q., Lin, K.S., Mason, N.S., Lin, S.F., Ropchan, J., Labaree, D., Henry, S., Williams, W.A., Carson, R.E., Neumeister, A., Huang, Y., 2015. Imaging the cannabinoid CB1 receptor in humans with [11C] OMAR: assessment of kinetic analysis methods, test-retest reproducibility, and gender differences. J. Cereb. Blood Flow Metab. 35, 1313–1322. https://doi.org/10.1038/jcbfm.2015.46.
O'Brien, L.D., Wills, K.L., Segsworth, B., Dashney, B., Rock, E.M., Limebeer, C.L., Parker, L.A., 2013. Effect of chronic exposure to rimonabant and phytocannabinoids on anxiety-like behavior and saccharin palatability. Pharmacol. Biochem. Behav. 103, 597–602. https://doi.org/10.1016/j.pbb.2012.10.008.
Ohno-Shosaku, T., Maejima, T., Kano, M., 2001. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. Pio. Neuron.
Onaivi, E.S., Green, M.R., Martin, B.R., 1990. Pharmacological characterization of cannabinoids in the elevated plus maze. J. Pharmacol. Exp. Ther. 253.
Oropeza, V.C., Mackie, K., Van Bockstaele, E.J., 2007. Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex. Brain research 1127, 36–44.
Ortega-Alvaro, A., Aracil-Fernández, A., García-Gutiérrez, M.S., Navarrete, F., Manzanares, J., 2011. Deletion of CB2 cannabinoid receptor induces schizophrenia-related behaviors in mice. Neuropsychopharmacology 36, 1489–1504. https://doi.org/10.1038/npp.2011.34.
Parfitt, G.M., Nguyen, R., Bang, J.Y., Aqrabawi, A.J., Tran, M.M., Seo, D.K., Richards, B. A., Kim, J.C., 2017. Bidirectional control of anxiety-related behaviors in mice: role of inputs arising from the ventral Hippocampus to the lateral septum and medial prefrontal cortex. Neuropsychopharmacology 42, 1715–1728. https://doi.org/10.1038/npp.2017.56.
Patel, S., Hillard, C.J., 2006. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. J. Pharmacol. Exp. Ther. 318, 304–311. https://doi.org/10.1124/jpet.106.101287.
Patel, S., Roelke, C.T., Rademacher, D.J., Cullinan, W.E., Hillard, C.J., 2004. Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic-pituitary-adrenal Axis. Endocrinology 145, 5431–5438. https://doi.org/10.1210/en.2004-0638.
Patel, S., Roelke, C.T., Rademacher, D.J., Hillard, C.J., 2005. Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signalling. Eur. J. Neurosci. 21, 1057–1069. https://doi.org/10.1111/j.1460-9568.2005.03916.x.
Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biol Psychiatry 60 (4), 383–387. https://doi.org/10.1016/j.biopsych.2006.03.042.
Paulus, M.P., Stein, M.B., Simmons, A.N., Risbrough, V.B., Halter, R., Chaplan, S.R., 2020. The effects of FAAH inhibition on the neural basis of anxiety-related processing in healthy male subjects: a randomized clinical trial. Neuropsychopharmacology 1–9. https://doi.org/10.1038/s41386-020-00936-w.
Pawlak, R., Magarinos, A.M., Melchor, J., McEwen, B., Strickland, S., 2003. Tissue plasminogen activator in the amygdala is critical for stress-induced anxiety-like behavior. Nature Neuroscience 6 (2), 168–174. https://doi.org/10.1038/nn998.
Pellow, S., File, S.E., 1986. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. Pharmacology, Biochemistry, and Behavior 24 (3), 525–529. https://doi.org/10.1016/0091-3057(86)90552-6.
Pellow, S., Chopin, P., File, S.E., Briley, M., 1985. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. Journal of Neuroscience Methods 14 (3), 149–167. https://doi.org/10.1016/0165-0270(85)90031-7.
Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. British journal of pharmacology 153 (2), 199–215.
Pertwee, R.G., Howlett, A.C., Abood, M.E., Alexander, S.P.H., Marzo, V. Di, Elphick, M. R., Greasley, P.J., Hansen, H.S., Kunos, G., Mackie, K., Mechoulam, R., Ross, R.A., 2010. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol. Rev. https://doi.org/10.1124/pr.110.003004.
Peters, B.A., Lewis, E.G., Dustman, R.E., Straight, R.C., Beck, E.C., 1976. Sensory, perceptual, motor and cognitive functioning and subjective reports following oral administration of Δ9-Tetrahydrocannabinol. Psychopharmacology (Berl) 47, 141–148. https://doi.org/10.1007/BF00735812.
Petrosino, S., Schiano Moriello, A., Cerrato, S., Fusco, M., Puigdemont, A., De Petrocellis, L., Di Marzo, V., 2016. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. British journal of pharmacology 173 (7), 1154–1162.
Phan, K.L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., De Wit, H., 2008. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. J. Neurosci. 28, 2313–2319. https://doi.org/10.1523/JNEUROSCI.5603-07.2008.

Puente, N., Elezgarai, I., Lafourcade, M., Reguero, L., Marsicano, G., Georges, F., Manzoni, O.J., Grandes, P., 2010. Localization and function of the cannabinoid CB1 receptor in the anterolateral bed nucleus of the stria terminalis. PloS One 5 (1), e8869. https://doi.org/10.1371/journal.pone.0008869.

Rademacher, D.J., Meier, S.E., Shi, L., Vanessa Ho, W.S., Jarrahian, A., Hillard, C.J., 2008. Effects of acute and repeated restraint stress on endocannabinoid content in the amygdala, ventral striatum, and medial prefrontal cortex in mice. Neuropharmacology 54, 108–116. https://doi.org/10.1016/j.neuropharm.2007.06.012.

Radley, J.J., Sawchenko, P.E., 2011. A common substrate for prefrontal and hippocampal inhibition of the neuroendocrine stress response. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 31 (26), 9683–9695. https://doi.org/10.1523/JNEUROSCI.6040-10.2011.

Radley, J.J., Gosselink, K.L., Sawchenko, P.E., 2009. A discrete GABAergic relay mediates medial prefrontal cortical inhibition of the neuroendocrine stress response. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience 29 (22), 7330–7340. https://doi.org/10.1523/JNEUROSCI.5924-08.2009.

Reich, C.G., Taylor, M.E., McCarthy, M.M., 2009. Differential effects of chronic unpredictable stress on hippocampal CB1 receptors in male and female rats. Behav. Brain Res. 203, 264–269. https://doi.org/10.1016/j.bbr.2009.05.013.

Ressler, K.J., 2020. Translating across circuits and genetics toward progress in fear- and anxiety-related disorders. The American Journal of Psychiatry 177 (3), 214–222. https://doi.org/10.1176/appi.ajp.2020.20010055.

Rey, A.A., Purrio, M., Viveros, M.-P., Lutz, B., 2012. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA B receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology 37, 2624–2634. https://doi.org/10.1038/npp.2012.123.

Rock, E.M., Bolognini, D., Limebeer, C.L., Cascio, M.G., Anavi-Goffer, S., Fletcher, P.J., Mechoulam, R., Pertwee, R.G., Parker, L.A., 2012. Cannabidiol, a nonpsychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT 1A somatodendritic autoreceptors in the dorsal raphe nucleus. Br. J. Pharmacol. 165, 2620–2634. https://doi.org/10.1111/j.1476-5381.2011.01621.x.

Rock, E.M., Limebeer, C.L., Petrie, G.N., Williams, L.A., Mechoulam, R., Parker, L.A., 2017. Effect of prior foot shock stress and Δ9-tetrahydrocannabinol, cannabidiolic acid, and cannabidiol on anxiety-like responding in the light-dark emergence test in rats. Psychopharmacology (Berl) 234. https://doi.org/10.1007/s00213-017-4626-5.

Rodgers, R.J., Evans, P.M., Murphy, A., 2005. Anxiogenic profile of AM-251, a selective cannabinoid CB1 receptor antagonist, in plus-maze-naïve and plus-maze-experienced mice. Behav. Pharmacol. 16, 405–413. https://doi.org/10.1097/00008877-200509000-00013.

Rodgers, R.J., Haller, J., Halasz, J., Mikics, E., 2003. 'One-trial sensitization' to the anxiolytic-like effects of cannabinoid receptor antagonist SR141716A in the mouse elevated plus-maze. Eur. J. Neurosci. 17, 1279–1286. https://doi.org/10.1046/j.1460-9568.2003.02548.x.

Roohbakhsh, A., Moghaddam, A.H., Massoudi, R., Zarrindast, M.-R., 2007. Role of dorsal hippocampal cannabinoid receptors and nitric oxide in anxiety like behaviors in rats using the elevated plus-maze test. Clin. Exp. Pharmacol. Physiol. 34, 223–229. https://doi.org/10.1111/j.1440-1681.2007.04576.x.

Rosenkranz, J.A., Venheim, E.R., Padival, M., 2010. Chronic stress causes amygdala hyperexcitability in rodents. Biol. Psychiatry 67, 1128–1136. https://doi.org/10.1016/j.biopsych.2010.02.008.

Rossi, S., De Chiara, V., Musella, A., Sacchetti, L., Cantarella, C., Castelli, M., Cavasinni, F., Motta, C., Studer, V., Bernardi, G., Cravatt, B.F., Maccarrone, M., Usiello, A., Centonze, D., 2010. Preservation of striatal cannabinoid CB1 receptor function correlates with the antianxiety effects of fatty acid amide hydrolase inhibition. Mol. Pharmacol. 78, 260–268. https://doi.org/10.1124/mol.110.064196.

Roth, M.K., Bingham, B., Shah, A., Joshi, A., Frazer, A., Strong, R., Morilak, D.A., 2012. Effects of chronic plus acute prolonged stress on measures of coping style, anxiety, and evoked HPA-axis reactivity. Neuropharmacology 63 (6), 1118–1126. https://doi.org/10.1016/j.neuropharm.2012.07.034.

Rubino, T., Guidali, C., Vigano, D., Realini, N., Valenti, M., Massi, P., Parolaro, D., 2008. CB1 receptor stimulation in specific brain areas differently modulate anxiety-related behaviour. Neuropharmacology 54, 151–160. https://doi.org/10.1016/j.neuropharm.2007.06.024.

Rubino, T., Sala, M., Viganò, D., Braida, D., Castiglioni, C., Limonta, V., Guidali, C., Realini, N., Parolaro, D., 2007. Cellular mechanisms underlying the anxiolytic effect of low doses of peripheral Δ9-tetrahydrocannabinol in rats. Neuropsychopharmacology 32, 2036–2045. https://doi.org/10.1038/sj.npp.1301330.

Ruehle, S., Remmers, F., Romo-Parra, H., Massa, F., Wickert, M., Wörtge, S., Häring, M., Kaiser, N., Marsicano, G., Pape, H.C., Lutz, B., 2013. Cannabinoid CB1 receptor in dorsal telencephalic glutamatergic neurons: distinctive sufficiency for hippocampus-dependent and amygdala-dependent synaptic and behavioral functions. J. Neurosci. 33, 10264–10277. https://doi.org/10.1523/JNEUROSCI.4171-12.2013.

Ruiz, C.M., Torrens, A., Castillo, E., Perrone, C.R., Cevallos, J., Inshishian, V.C., et al., 2021. Pharmacokinetic, behavioral, and brain activity effects of Δ 9-tetrahydrocannabinol in adolescent male and female rats. Neuropsychopharmacology 46 (5), 959–969.

Russo, E.B., Burnett, A., Hall, B., Parker, K.K., 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem. Res. 30, 1037–1043. https://doi.org/10.1007/s11064-005-6978-1.

Rutkowska, M., Jamontt, J., Gliniak, H., 2006. Effects of Cannabinoids on the Anxiety-like Response in Mice "Innovative Technologies of Production of Biopreparations Based on New Generations of Eggs (OVOCURA)"-Effects of Cannabinoids on the Anxiety-like Response in Mice.

Sah, P., Faber, E.S.L., Lopez De Armentia, M., Power, J., 2003. The amygdaloid complex: anatomy and physiology. Physiological Reviews 83 (3), 803–834. https://doi.org/10.1152/physrev.00002.2003.

Saitoh, A., Ohashi, M., Suzuki, S., Tsukagoshi, M., Sugiyama, A., Yamada, M., Oka, J., Inagaki, M., Yamada, M., 2014. Activation of the prelimbic medial prefrontal cortex induces anxiety-like behaviors via N-Methyl-D-aspartate receptor-mediated glutamatergic neurotransmission in mice. J Neurosci Res. Aug 92 (8), 1044–1053. https://doi.org/10.1002/jnr.23391.

Sangha, S., Robinson, P.D., Greba, Q., Davies, D.A., Howland, J.G., 2014. Alterations in reward, fear and safety cue discrimination after inactivation of the rat prelimbic and infralimbic cortices. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 39 (10), 2405–2413. https://doi.org/10.1038/npp.2014.89.

Sbarski, B., Akirav, I., 2020. Cannabinoids as therapeutics for PTSD. Pharmacology & Therapeutics 211, 107551. https://doi.org/10.1016/j.pharmthera.2020.107551.

Scherma, M., Medalie, J., Fratta, W., Vadivel, S.K., Makriyannis, A., Piomelli, D., Mikics, E., Haller, J., Yasar, S., Tanda, G., Goldberg, S.R., 2008. The endogenous cannabinoid anandamide has effects on motivation and anxiety that are revealed by fatty acid amide hydrolase (FAAH) inhibition. Neuropharmacology 54, 129–140. https://doi.org/10.1016/j.neuropharm.2007.08.011.

Schmidt, M.E., Liebowitz, M.R., Stein, M.B., Grunfeld, J., Van Hove, I., Simmons, W.K., Van Der Ark, P., Palmer, J.A., Saad, Z.S., Pemberton, D.J., Van Nueten, L., Drevets, W.C., 2020. The effects of inhibition of fatty acid amide hydrolase (FAAH) by JNJ-42165279 in social anxiety disorder: a double-blind, randomized, placebo-controlled proof-of-concept study. Neuropsychopharmacology. https://doi.org/10.1038/s41386-020-00888-1.

Schofield, D., Tennant, C., Nash, L., Degenhardt, L., Cornish, A., Hobbs, C., Brennan, G., 2006. Reasons for cannabis use in psychosis. The Australian and New Zealand Journal of Psychiatry 40 (6–7), 570–574. https://doi.org/10.1080/j.1440-1614.2006.01840.x.

Scholl, J.L., Afzal, A., Fox, L.C., Watt, M.J., Forster, G.L., 2019. Sex differences in anxiety-like behaviors in rats. Physiology & Behavior 211, 112670. https://doi.org/10.1016/j.physbeh.2019.112670.

Schramm-Sapyta, N.L., Cha, Y.M., Chaudhry, S., Wilson, W.A., Swartzwelder, H.S., Kuhn, C.M., 2007. Differential anxiogenic, aversive, and locomotor effects of THC in adolescent and adult rats. Psychopharmacology (Berl) 191, 867–877. https://doi.org/10.1007/s00213-006-0676-9.

Schulteis, G., Yackey, M., Risbrough, V., Koob, G.F., 1998. Anxiogenic-like effects of spontaneous and naloxone-precipitated opiate withdrawal in the elevated plus-maze. Pharmacology Biochemistry and Behavior 60 (3), 727–731. https://doi.org/10.1016/S0091-3057(98)00034-3.

Sciolino, N.R., Zhou, W., Hohmann, A.G., 2011. Enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-arachidonoylglycerol hydrolyzing enzyme monoacylglycerol lipase, produces anxiolytic effects under conditions of high environmental aversiveness in rats. Pharmacol. Res. 64, 226–234. https://doi.org/10.1016/j.phrs.2011.04.010.

Scopinho, A.A., Lisboa, S.F.S., Guimarães, F.S., Corrêa, F.M.A., Resstel, L.B.M., Joca, S.R.L., 2013. Dorsal and ventral hippocampus modulate autonomic responses but not behavioral consequences associated to acute restraint stress in rats. PloS One 8 (10), e77750. https://doi.org/10.1371/journal.pone.0077750.

Serrano, A., Pavon, F.J., Buczynski, M.W., Schlosburg, J., Natividad, L.A., Polis, I.Y., Stouffer, D.G., Zorrilla, E.P., Roberto, M., Cravatt, B.F., Martin-Fardon, R., Rodriguez De Fonseca, F., Parsons, L.H., 2018. Deficient endocannabinoid signaling in the central amygdala contributes to alcohol dependence-related anxiety-like behavior and excessive alcohol intake. Neuropsychopharmacology 43, 1840–1850. https://doi.org/10.1038/s41386-018-0055-3.

Shansky, R.M., 2018. Sex differences in behavioral strategies: avoiding interpretational pitfalls. Current Opinion in Neurobiology 49, 95–98. https://doi.org/10.1016/j.conb.2018.01.007.

Shephard, R.A., Broadhurst, P.L., 1982. Hyponeophagia and arousal in rats: effects of diazepam, 5-methoxy-N,N-dimethyltryptamine, d-amphetamine and food deprivation. Psychopharmacology 78 (4), 368–372. https://doi.org/10.1007/BF00433744.

Shimizu, T., Minami, C., Mitani, A., 2018. Effect of electrical stimulation of the infralimbic and prelimbic cortices on anxiolytic-like behavior of rats during the elevated plus-maze test, with particular reference to multiunit recording of the behavior-associated neural activity. Behav Brain Res 353, 168–175. https://doi.org/10.1016/j.bbr.2018.07.005.

Sholler, D.J., Strickland, J.C., Spindle, T.R., Weerts, E.M., Vandrey, R., 2020. Sex differences in the acute effects of oral and vaporized cannabis among healthy adults. Addict. Biol., e12968 https://doi.org/10.1111/adb.12968.

Shonesy, B.C., Bluett, R.J., Ramikie, T.S., Báldi, R., Hermanson, D.J., Kingsley, P.J., Marnett, L.J., Winder, D.G., Colbran, R.J., Patel, S., 2014. Genetic disruption of 2-arachidonoylglycerol synthesis reveals a key role for endocannabinoid signaling in anxiety modulation. Cell Rep 9, 1644–1653. https://doi.org/10.1016/j.celrep.2014.11.001.

Sipe, J.C., Chiang, K., Gerber, A.L., Beutler, E., Cravatt, B.F., 2002. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc. Natl. Acad. Sci. U. S. A. 99, 8394–8399. https://doi.org/10.1073/pnas.082235799.

Smart, D., Gunthorpe, M.J., Jerman, J.C., Nasir, S., Gray, J., Muir, A.I., Chambers, J.K., Randall, A.D., Davis, J.B., 2000. The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1). Br. J. Pharmacol.

Steindel, F., Lerner, R., Häring, M., Ruehle, S., Marsicano, G., Lutz, B., Monory, K., 2013. Neuron-type specific cannabinoid-mediated G protein signalling in mouse hippocampus. J. Neurochem. 124, 795–807. https://doi.org/10.1111/jnc.12137.

Stella, N., Schweitzer, P., Plomelli, D., 1997. A second endogenous' cannabinoid that modulates long-term potentiation. Nature 388. https://doi.org/10.1038/42015.

Sterley, T.-L., Baimoukhametova, D., Füzesi, T., Zurek, A.A., Daviu, N., Rasiah, N.P., Rosenegger, D., Bains, J.S., 2018. Social transmission and buffering of synaptic changes after stress. Nature Neuroscience 21 (3), 393–403. https://doi.org/10.1038/s41593-017-0044-6.

Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., Yamashita, A., Waku, K., 1995. 2-arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem. Biophys. Res. Commun. 215 https://doi.org/10.1006/bbrc.1995.2437.

Sylvers, P., Lilienfeld, S.O., LaPrairie, J.L., 2011. Differences between trait fear and trait anxiety: implications for psychopathology. Clinical Psychology Review 31 (1), 122–137. https://doi.org/10.1016/j.cpr.2010.08.004.

Szkudlarek, H.J., Desai, S.J., Renard, J., Pereira, B., Norris, C., Jobson, C.E.L., Rajakumar, N., Allman, B.L., Laviolette, S.R., 2019. Δ-9-Tetrahydrocannabinol and Cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacology 44, 817–825. https://doi.org/10.1038/s41386-018-0282-7.

Szkudlarek, H.J., Rodríguez-Ruiz, M., Hudson, R., Felice, M. De, Jung, T., Rushlow, W.J., Laviolette, S.R., 2021. THC and CBD produce divergent effects on perception and panic behaviours via distinct cortical molecular pathways. Prog. Neuro-Psychopharmacology Biol. Psychiatry 104. https://doi.org/10.1016/j.pnpbp.2020.110029.

Tafet, G.E., Nemeroff, C.B., 2020. Pharmacological treatment of anxiety disorders: the role of the HPA Axis. Frontiers in Psychiatry 11, 443. https://doi.org/10.3389/fpsyt.2020.00443.

Terzian, A.L., Drago, F., Wotjak, C.T., Micale, V., 2011. The dopamine and cannabinoid interaction in the modulation of emotions and cognition: assessing the role of cannabinoid CB1 receptor in neurons expressing dopamine D1 receptors. Frontiers in Behavioral Neuroscience 5, 49.

Tham, M., Yilmaz, O., Alaverdashvili, M., Kelly, M.E.M., Denovan-Wright, E.M., Laprairie, R.B., 2019. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. Br. J. Pharmacol. 176 https://doi.org/10.1111/bph.14440.

Thiemann, P., Brimicombe, J., Benson, J., Quince, T., 2020. When investigating depression and anxiety in undergraduate medical students timing of assessment is an important factor - a multicentre cross-sectional study. BMC Medical Eduation 20, 125. https://doi.org/10.1186/s12909-020-02029-0.

Thomas, A., Baillie, G.L., Phillips, A.M., Razdan, R.K., Ross, R.A., Pertwee, R.G., 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB 1 and CB 2 receptor agonists in vitro. Br. J. Pharmacol. 150, 613–623. https://doi.org/10.1038/sj.bjp.0707133.

Todd, S.M., Arnold, J.C., 2016. Neural correlates of interactions between cannabidiol and Δ9-tetrahydrocannabinol in mice: implications for medical cannabis. Br. J. Pharmacol. 173, 53–65. https://doi.org/10.1111/bph.13333.

Torrens, A., Vozella, V., Huff, H., McNeil, B., Ahmed, F., Ghidini, A., et al., 2020. Comparative pharmacokinetics of Δ9-tetrahydrocannabinol in adolescent and adult male mice. Journal of Pharmacology and Experimental Therapeutics 374 (1), 151–160.

Tovote, P., Fadok, J.P., Lüthi, A., 2015. Neuronal circuits for fear and anxiety. Nature Reviews. Neuroscience 16 (6), 317–331. https://doi.org/10.1038/nrn3945.

Tseng, A.H., Craft, R.M., 2001. Sex differences in antinociceptive and motoric effects of cannabinoids. European journal of pharmacology 430 (1), 41–47.

Tsou, K., Brown, S., Sañudo-Peña, M.C., Mackie, K., Walker, J.M., 1998. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83 (2), 393–411. https://doi.org/10.1016/s0306-4522(97)00436-3.

Tsuboi, K., Uyama, T., Okamoto, Y., Ueda, N., 2018. Endocannabinoids and related N-acylethanolamines: biological activities and metabolism makoto murakami. Inflamm. Regen. https://doi.org/10.1186/s41232-018-0086-5.

Turna, J., Balodis, I., Munn, C., Van Ameringen, M., Busse, J., MacKillop, J., 2020. Overlapping patterns of recreational and medical cannabis use in a large community sample of cannabis users. Comprehensive Psychiatry 102, 152188. https://doi.org/10.1016/j.comppsych.2020.152188.

Twomey, C.D., 2017. Association of cannabis use with the development of elevated anxiety symptoms in the general population: a meta-analysis. Journal of Epidemiology and Community Health 71 (8), 811–816. https://doi.org/10.1136/jech-2016-208145.

Valjent, E., Mitchell, J.M., Besson, M.-J., Caboche, J., Maldonado, R., 2002. Behavioural and biochemical evidence for interactions between D9-tetrahydrocannabinol. Br. J. Pharmacol.

Van Dam, N.T., Bedi, G., Earleywine, M., 2012. Characteristics of clinically anxious versus non-anxious regular, heavy marijuana users. Addict. Behav. 37, 1217–1223. https://doi.org/10.1016/j.addbeh.2012.05.021.

Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie, K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Marzo, V. Di, Pittman, Q.J., Patel, K.D., Sharkey, K.A., 2005. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 80, 310. https://doi.org/10.1126/science.1115740.

Van Swearingen, A.E.D., Walker, Q.D., Kuhn, C.M., 2013. Sex differences in novelty- and psychostimulant-induced behaviors of C57BL/6 mice. Psychopharmacology (Berl) 225 (3), 707–718. https://doi.org/10.1007/s00213-012-2860-4.

Vecchiarelli, H.A., Morena, M., Keenan, C.M., Chiang, V., Tan, K., Qiao, M., et al., 2021. Comorbid anxiety-like behavior in a rat model of colitis is mediated by an upregulation of corticolimbic fatty acid amid hydrolase. Neuropsychopharmacology 1–12.

Viñals, X., Moreno, E., Lanfumey, L., Cordomí, A., Pastor, A., Torre, R.D. La, Gasperini, P., Navarro, G., Howell, L.A., Pardo, L., Lluís, C., Canela, E.I., McCormick, P.J., Maldonado, R., Robledo, P., 2015. Cognitive impairment induced by delta9- tetrahydrocannabinol occurs through heteromers between cannabinoid CB1 and serotonin 5-HT2A receptors. PLoS Biol 13. https://doi.org/10.1371/journal.pbio.1002194.

Vogel, E., Krabbe, S., Gründemann, J., Wamsteeker Cusulin, J.I., Lüthi, A., 2016. Projection-specific dynamic regulation of inhibition in amygdala micro-circuits. Neuron 91 (3), 644–651. https://doi.org/10.1016/j.neuron.2016.06.036.

Vreeburg, S.A., Zitman, F.G., van Pelt, J., Derijk, R.H., Verhagen, J.C.M., van Dyck, R., Hoogendijk, W.J.G., Smit, J.H., Penninx, B.W.J.H., 2010. Salivary cortisol levels in persons with and without different anxiety disorders. Psychosomatic Medicine 72 (4), 340–347. https://doi.org/10.1097/PSY.0b013e3181d2f0c8.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J. Neurosci. 22, 6810–6818. https://doi.org/10.1523/jneurosci.22-15-06810.2002.

Wang, P.-F., Jiang, L.-S., Bu, J., Huang, X.-J., Song, W., Du, Y.-P., He, B., 2012. Cannabinoid-2 receptor activation protects against infarct and ischemia–reperfusion heart Injury. J. Cardiovasc. Pharmacol. 59, 301–307. https://doi.org/10.1097/FJC.0b013e3182418997.

Westlake, T.M., Howlett, A.C., Bonner, T.I., Matsuda, L.A., Herkenham, M., 1994. Cannabinoid receptor binding and messenger RNA expression in human brain: an in vitro receptor autoradiography and in situ hybridization histochemistry study of normal aged and Alzheimer's brains. Neuroscience 63, 637–652. https://doi.org/10.1016/0306-4522(94)90511-8.

Wiley, J.L., Burston, J.J., 2014. Sex differences in Δ9-tetrahydrocannabinol metabolism and in vivo pharmacology following acute and repeated dosing in adolescent rats. Neuroscience letters 576, 51–55.

Wilson, R.I., Nicoll, R.A., 2001. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 410. https://doi.org/10.1038/35069076.

Wilson, D.M., Peart, J., Martin, B.R., Bridgen, D.T., Byron, P.R., Lichtman, A.H., 2002. Physiochemical and pharmacological characterization of a Δ9-THC aerosol generated by a metered dose inhaler. Drug and alcohol dependence 67 (3), 259–267.

Wiskerke, J., Irimia, C., Cravatt, B.F., Vries, T.J. De, Schoffelmeer, A.N.M., Pattij, T., Parsons, L.H., 2012. Characterization of the effects of reuptake and hydrolysis inhibition on interstitial endocannabinoid levels in the brain: an in vivo microdialysis study. In: ACS Chemical Neuroscience. American Chemical Society, pp. 407–417. https://doi.org/10.1021/cn300036b.

Xiao, Q., Xu, X., Tu, J., 2020. Chronic optogenetic manipulation of basolateral amygdala astrocytes rescues stress-induced anxiety. Biochemical and Biophysical Research Communications 533 (4), 657–664. https://doi.org/10.1016/j.bbrc.2020.09.106.

Xie, X., Yang, H., An, J.J., Houtz, J., Tan, J.-W., Xu, H., Liao, G.-Y., Xu, Z.-X., Xu, B., 2019. Activation of anxiogenic circuits instigates resistance to diet-induced obesity via increased energy expenditure. Cell Metabolism 29 (4), 917–931. https://doi.org/10.1016/j.cmet.2018.12.018 e4.

Yasmin, F., Colangeli, R., Morena, M., Filipski, S., van der Stelt, M., Pittman, Q.J., Hillard, C.J., Campbell Teskey, G., McEwen, B.S., Hill, M.N., Chattarji, S., 2020. Stress-induced modulation of endocannabinoid signaling leads to delayed strengthening of synaptic connectivity in the amygdala. Proc. Natl. Acad. Sci. U. S. A. 117, 650–655. https://doi.org/10.1073/pnas.1910322116.

Zarrindast, M.R., Sarahroodi, S., Arzi, A., Khodayar, M.J., Taheri-Shalmani, S., Rezayof, A., 2008. Cannabinoid CB1 receptors of the rat central amygdala mediate anxiety-like behavior: interaction with the opioid system. Behav. Pharmacol. 19, 716–723. https://doi.org/10.1097/FBP.0b013e3283123c83.

Zer-Aviv, T.M., Akirav, I., 2016. Sex differences in hippocampal response to endocannabinoids after exposure to severe stress. Hippocampus 26, 947–957. https://doi.org/10.1002/hipo.22577.

Zhang, H.Y., Gao, M., Shen, H., Bi, G.H., Yang, H.J., Liu, Q.R., Wu, J., Gardner, E.L., Bonci, A., Xi, Z.X., 2017. Expression of functional cannabinoid CB2 receptor in VTA dopamine neurons in rats. Addict. Biol. 22, 752–765. https://doi.org/10.1111/adb.12367.

Zhong, P., Wang, W., Pan, B., Liu, X., Zhang, Z., Long, J.Z., Zhang, H.T., Cravatt, B.F., Liu, Q.S., 2014. Monoacylglycerol lipase inhibition blocks chronic stress-induced depressive-like behaviors via activation of mTOR signaling. Neuropsychopharmacology 39, 1763–1776. https://doi.org/10.1038/npp.2014.24.

Zieba, J., Sinclair, D., Sebree, T., Bonn-Miller, M., Gutterman, D., Siegel, S., Karl, T., 2019. Cannabidiol (CBD) reduces anxiety-related behavior in mice via an FMRP-independent mechanism. Pharmacol. Biochem. Behav. 181, 93–100. https://doi.org/10.1016/j.pbb.2019.05.002.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 67 (6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

Zorn, J.V., Schür, R.R., Boks, M.P., Kahn, R.S., Joëls, M., Vinkers, C.H., 2017. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis.

Psychoneuroendocrinology 77, 25–36. https://doi.org/10.1016/j.psyneuen.2016.11.036.
Zuardi, A.W., Shirakawa, I., Finkelfarb, E., Karniol, I.G., 1982. Action of cannabidiol on the anxiety and other effects produced by δ9-THC in normal subjects. Psychopharmacology (Berl) 76, 245–250. https://doi.org/10.1007/BF00432554.
Zygmunt, P.M., Petersson, J., Andersson, D.A., Chuang, H.H., Sørgård, M., Marzo, V., Di Julius, D., Högestätt, E.D., 1999. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400. https://doi.org/10.1038/22761.