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Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives

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Abstract

Rich evidence has shown that cannabis products exert a broad gamut of effects on emotional regulation. The main psychoactive ingredient of hemp, Δ^9-tetrahydrocannabinol (THC), and its synthetic cannabinoid analogs have been reported to either attenuate or exacerbate anxiety and fear-related behaviors in humans and experimental animals. The heterogeneity of cannabis-induced psychological outcomes reflects a complex network of molecular interactions between the key neurobiological substrates of anxiety and fear and the endogenous cannabinoid system, mainly consisting of the arachidonic acid derivatives anandamide and 2-arachidonoylglycerol (2-AG) and two receptors, respectively termed CB_1 and CB_2. The high degree of interindividual variability in the responses to cannabis is contributed by a wide spectrum of factors, including genetic and environmental determinants, as well as differences in the relative concentrations of THC and other alkaloids (such as cannabidiol) within the plant itself. The present article reviews the currently available knowledge on the herbal, synthetic and endogenous cannabinoids with respect to the modulation of anxiety responses, and highlights the challenges that should be overcome to harness the therapeutic potential of some of these compounds, all the while limiting the side effects associated with cannabis consumption.

Keywords

cannabis; anxiety; CB receptors; endocannabinoids; Δ^9-tetrahydrocannabinol; cannabidiol

INTRODUCTION

Anxiety is generally defined as an emotional state characterized by maladaptive and excessive emotional responsiveness to potentially dangerous circumstances. The pathological expression of anxiety leads to enduring emotional perturbations with a consistent apprehension towards the possibility of future, vaguely defined negative events [1]. According to the current classification of anxiety disorders in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2], the main diagnostic entities in this category are:

- *generalized anxiety disorder* (GAD), featuring general irritability, anxiety attacks, chronic apprehension/anxious expectation and secondary phobic avoidance.

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- *panic disorder*, characterized by brief (2-10 min) spells of overwhelming anxiety or fear, accompanied by somatic and cognitive symptoms;
- *social anxiety disorder* (or social phobia), defined as extreme agitation in social contexts and avoidance of social situations;
- *obsessive-compulsive disorder* (OCD), characterized by recurrent and intrusive anxiogenic thoughts (obsessions), and stereotyped behaviors (compulsions) aimed at the reduction of the distress caused by the obsessions.
- *post-traumatic stress disorder* (PTSD), in which a prior intense trauma results in a long-lasting anxious response, with re-experiencing/flashback phenomena, avoidance and emotional numbing.

In keeping with their different clinical features and phenomenological presentations, these disorders are underpinned by divergent neurobiological alterations and respond to partially different pharmacotherapeutic strategies (outlined in Table 1). A fundamental contribution in our understanding of the neural bases of anxiety disorders and in the development of novel therapies has been afforded by animal models and testing paradigms for anxiety-like behaviors (summarized in Table 2).

Over the last decades, converging epidemiological, clinical and preclinical data have pointed to a key implication of cannabis and its endogenous system in the regulation of anxiety. In the following sections, we will present a brief synopsis on cannabinoids and the available classes of related agents, with a specific focus on their anxiolytic potential, and the scientific challenges that should be overcome to fully establish the applicability of such drugs in the therapy of anxiety disorders.

HERBAL AND SYNTHETIC CANNABINOIDS

Herbal cannabinoids

The three species included in the *Cannabis* genus (or sub-species, depending on the taxonomic classification; see [3], for a detailed discussion on the issue), *sativa, indica* and *ruderalis*, feature at least 85 unique terpenophenolic compounds, collectively named *phytocannabinoids* [4]. The main classes of phytocannabinoids are outlined in Figure 1. Quantitative analyses of cannabis constituents are usually performed by chromatographic techniques (generally Gas Chromatography, but also Thin-Layer Chromatography, or High-Performance Liquid Chromatography), often coupled with Mass Spectrometry. A detailed description of the instrumental methods used for classification and source tracing of Cannabis products (including DNA identification for forensic and intelligence purposes) is beyond the scope of this review, but can be found in [5-7].

The chemical fingerprinting of hemp products has revealed that the two most abundant phytocannabinoids are Δ^9-tetrahydrocannabinol (THC, also named dronabinol) and cannabidiol (CBD):

The main psychoactive constituent of Cannabis, THC is a highly lipophilic alkaloid produced mainly in the leaves, flowers and glandular trichomes of the plant. Most of the pharmacological effects elicited by hemp products, including emotional and cognitive changes, analgesia, hypothermia and appetite stimulation, are considered to be reflective of the action of THC as a partial agonist of cannabinoid CB_1 and CB_2 receptors (see below). Additionally, THC has been shown to act as an acetylcholinesterase inhibitor [8-10].

In contrast with THC, CBD is not psychotropic, but has nevertheless been shown to play a role in the modulation of behavioral effects of cannabis [11]. In fact, the THC: CBD ratio is

the main criterion to define different cannabis chemotypes [12] and has been posited to contribute to the variability in neurobehavioral outcomes of marijuana or hashish consumption [13,14]. Interestingly, most cannabis strains encountered in the illegal markets generally have elevated amounts of THC [15].

The different characteristics of THC and CBD are underpinned by their distinct mechanisms of action. Whereas THC has nanomolar affinity for both CB_1 (Ki = 25.1 nmol/L) and CB_2 (Ki = 35.2 nmol/L) receptors, CBD exhibits much lower affinity for either target [16-20]; however, the latter phytocannabinoid was recently found to act as a highly potent antagonist/inverse agonist of both CB receptors [21], possibly due to a non-competitive mechanism of receptor blockade [22]. Additionally, CBD has been shown to exert some of its actions through other receptors, including the vanilloid receptor VR_1 and the serotonin receptor 5-HT_{1A} (for a general overview of the topic, see [11]).

The other main phytocannabinoids, including cannabigerol (CBG), cannabichromene (CBC) and cannabinol (CBN) (Fig. 1) [4,23], have been shown to exert antibiotic and antiinflammatory properties, but have not been strongly associated with the behavioral effects of Cannabis; nevertheless, the recent discovery that CBG is a highly potent agonist for α_2 adrenoceptor and a blocker of serotonin 5-HT_{1A} receptor [24] underscores the potential importance of these and other alkaloids in the psychoactive profile of cannabis.

Synthetic cannabinoids

In addition to phytocannabinoids, several classes of synthetic CB receptor agonists have been developed; among these families, the best characterized are the synthetic analogs of THC - such as the bicyclic compounds CP 47,497, CP 55,244, CP 55,940 and the benxopyrans HU-210 and nabilone (Fig. 2) - and the aminoalkylindole derivatives - including WIN 55,212-2, JWH-015, JWH-018, JWH-073, JWH-081 and JWH-398 (for a general review, see [23]). Of these agents, only nabilone has been approved for clinical use as an antiemetic treatment and an adjunct analgesic for neuropathic pain [25]. Other more potent synthetic cannabinoids, such as CP 47,497, HU-210 and most JWH compounds, have regrettably gained great popularity in the market of recreational substances during the last decade, under the generic brand names of “Spice” or “K2”. Unlike THC, which is a partial agonist of CB_1 receptors, these agents are full, high-potency CB_1 receptor activators [26,27], thereby eliciting greater psychotropic effects than THC (as CB_1 receptors are the key mediators of the psychotropic actions of cannabis). This characteristic, together with their legal status (recently revoked across most Western countries, including USA as of March 2011) and lack of available testing procedures for the detection of urinary metabolites, has unfortunately contributed to the great diffusion of “Spice” blends in Central and Western Europe, as well as Australasia.

ENDOCANNABINOIDS AND THEIR RECEPTORS

Following the identification of THC in the 1960s [28], extensive research was devoted to the identification of its biological targets and endogenous counterparts. Both objectives were met around 30 years later, with the characterization of the two major cannabinoid receptors, CB_1 [29] and CB_2 [30] as well as the discovery of two most prominent endocannabinoids N-arachidonoylethanolamine (commonly named anandamide from the Sanskrit *ānanda*, bliss) [31] and 2-arachidonoylglycerol (2-AG) [32,33] (Fig. 3).

CB receptors

Although CB_1 and CB_2 receptors only share 44% sequence identity (68% in the transmembrane domains), they are both coupled to $G_{i/o}$ proteins [34] and activated by both anandamide and 2-AG. In line with their metabotropic nature, CB receptors mediate their

intracellular response through a number of changes affecting signaling cascades, such as inhibition of adenylyl cyclase, activation of G-protein-activated inwardly rectifying potassium channels (GIRKs) and phosphorylation of extracellular signal-related kinases (ERKs) [35,36]. The distribution pattern of CB_1 and CB_2 receptors is strikingly divergent, indicating diverse physiological functions: CB_1 is the most abundant metabotropic receptor in the brain, and is primarily distributed in the synaptic terminals of neurons across all the major structures that regulate emotional responsiveness, perception and memory, including prefrontal cortex, amygdala, septo-hippocampal system, striatum, thalamus, brainstem nuclei etc. [37-41]. CB_1 receptors are typically located on presynaptic terminals [42,43], but they have also been identified in postsynaptic locations [44,45]. Presynaptic CB_1 receptors are posited to serve critical functions for the regulation of synaptic plasticity and neurotransmitter release; in particular, they mediate the depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE), consisting in the reduction of γ-amino-butyric acid (GABA) or glutamate release, respectively, from presynaptic boutons following stimulation of the postsynaptic terminals [46-49]. In general, CB_1 activation has been shown to inhibit the neurotransmission of other mediators, including glycine, acetylcholine, norepinephrine and serotonin [50], but the underpinnings of these phenomena have not been completely elucidated. Additionally, CB_1 receptors have been implicated in short- and long-term synaptic depression, in relation to phasic or tonic endocannabinoid release (for a review on these topics, see [51]).

The function of CB_1 receptors may vary depending on the specific interactions that they entertain with other molecular targets. For example, CB_1 receptors have been found to associate with other G-protein complex receptors, such as dopamine D2, orexin Ox1, μ opioid and adenosine A_{2a}, to form heteromeric complexes (reviewed in [52,53])

The key role of CB_1 receptors as mediators of neurochemical homeostasis in the brain is maintained through a complex regulation of their expression. For example, these receptors are subjected to a rapid internalization (via clathrin-coated pits) following their binding with full agonists; on the other hand, the receptors are also recycled, with a process that requires endosomal acidification and dephosphorilation [54].

While CB_2 receptors are abundantly expressed in most peripheral organs (and particularly in immune cells, where they regulate cytokine secretion and modulate cell trafficking) [55], their distribution in the brain appears to be sparse and particularly confined to microglial cells; nevertheless, recent evidence has revealed the presence of CB_2 receptors in several areas of the brain [56-58]. Interestingly, a number of studies suggest that neuronal CB_2 receptors may be mainly located in postsynaptic terminals [58,59]; nevertheless, the functional role of these targets in the brain remains largely elusive and awaits further characterization.

The existence of cannabinoid receptors other than CB_1 and CB_2 has been postulated based on ample experimental evidence [60-62]. Interestingly, a number of investigations have pointed to GPR55 as a novel putative cannabinoid receptor [63,64]; nevertheless, evidence on the specificity of this receptor for endocannabinoid is still inconclusive [65].

Endocannabinoids

Both anandamide and 2-AG are derivatives of arachidonic acid, an unsaturated C20 fatty acid with 4 double bonds, which also serves as the precursor for synthesis of other eicosanoids, including prostaglandins and leukotriens. Anandamide is found in picomolar concentrations and acts as a high-affinity partial agonist for both CB_1 and CB_2 receptors. It is synthesized on demand by enzymatic hydrolysis of the membrane phospholipid N-arachidonoyl phosphatidylethanolamine (NAPE), a process catalyzed by several

phospholipases [66-68]. Following release and activation of CB receptors, anandamide is rapidly removed from the synaptic cleft by a carrier-mediated system [69-72] and subsequently hydrolyzed by the membrane enzyme fatty acid amide hydrolase (FAAH) [73-75]. FAAH serves the catabolism of other substrates, including oleoylethanolamine (OEA) and palmitoylethanolamine (PEA). Both these compounds do not activate CB1 receptors [76], although they may reduce or slow down anandamide degradation by competing with it for FAAH activity.

In comparison with anandamide, 2-AG is much more abundant (occurring in nanomolar concentrations across most tissues) and acts as a full agonist of both CB receptors. It is produced from 1,2diacylglycerol (DAG) by diacylglycerol lipase (DAGL) [77] and degraded mainly by the cytosolic serine hydrolase monoacylglycerol lipase (MAGL) [78], although other enzymes are known to contribute to this process [79].

The divergent neurochemical profiles of anandamide and 2-AG underscore their different physiological roles. Although our current understanding of the different functions entertained by each endocannabinoid is still rudimentary, the development of FAAH and MAGL inhibitors [80,81] has been instrumental to elucidate the implication of each mediator in synaptic and neurochemical regulation. While 2-AG is known as the retrograde mediator of DSI [82,83] and DSE [84-87], a number of studies suggest that anandamide may serve as an activity-dependent regulator of monoaminergic transmission [88-90]. Recent evidence points to a potential biological antagonism between anandamide and 2-AG [91,92]; on the other hand, emerging evidence points to a similar role of anandamide and 2-AG in the regulation of anxiety (albeit in relation to different receptors) and pain [93]. The development of JZL195, a potent FAAH/MAGL inhibitor, has in turn revealed that the behavioral effects of CB_1 receptor agonists can be only recapitulated by the combination of both endocannabinoid-mediated functions [94].

Other lipids have been indicated as putative endocannabinoids, including 2-arachidonoylglycerylether (noladin ether) [95] and O-arachidonoylethanolamine (virodhamine) [96] (Fig. 3). Additionally, recent evidence has identified that CB receptors may be modulated by peptidic ligands, such as hemopressin and its derivatives [97,98].

EFFECTS OF CANNABIS AND CANNABINOID AGENTS ON ANXIETY

Cannabis, THC and CB_1 receptor agonists

The employment of cannabis for its medicinal, relaxing and mood-enhancing properties has been documented across most ancient civilizations. Originally introduced in Chinese pharmacopoeia during the third millennium BCE [99,100], cannabis became a popular remedy throughout Asia and Europe in the following centuries [99,101]. The inclusion of cannabis in the medical treatises by Dioscorides and Galen secured the herb a stable reputation in the Roman Empire and the Arabic world [101]. Until the early 20^{th} century, the plant remained a valuable therapy for a large number of diseases [102]; however, growing concerns about the psychoactive and narcotic effects of cannabis led to a progressive restriction and ultimate ban of its usage in the United States and several European countries [100,103]. Despite its illicit status, cannabis remains one of the most popular recreational drugs, particular among adolescents and young adults, in view of its mood-enhancing and euphoriant characteristics [104-106].

Most psychological and behavioral effects of marijuana and other hemp products are induced by THC through activation of CB_1 brain receptors. In fact, although THC and most synthetic cannabinoids are known to activate both CB_1 and CB_2 receptors, their actions on

anxiety-like behaviors and emotional regulation are efficiently countered by selective CB_1 receptor antagonists, such as rimonabant (see next section) [107].

The studies on the psychological effects of cannabis and THC have unfolded a highly complex and often contradictory scenario, fostering a long-standing debate on the potential harms and benefits of its products. An important aspect of this discussion (particularly in consideration of its legal aspects and the potential therapeutic applications of hemp derivatives), revolves around the distinction between use and misuse of cannabis. In particular, whereas the abuse and dependence liability of cannabis is generally well-recognized [108,109], the definition of these phenomena has been heavily criticized as reflective of political agendas rather than scientific bases. For instance, the diagnosis of substance abuse, according to the criteria listed by the DSM–IV TR, is based on the manifestation of at least one of four symptoms: interference with major professional or personal obligations; intoxication in hazardous settings; substance-related legal problems; continued use in the face of persistent social or interpersonal problems [110]. The applicability of some of these standards to marijuana and other cannabis derivatives, however, has been questioned [99], also in view of their lower potential to induce physical harm in comparison with other legal substances, such as alcohol and tobacco [111].

While the controversies surrounding cannabis are far from subdued (and are often permeated and masked by conflicting ideological credos), standardized studies on cannabinoids have highlighted that the psychological and behavioral outcomes of this substance are highly variable and range from relaxation, euthymia and heightened sociability to panic, paranoid ideation and psychosis [112-116]. A corollary of this observation is that the high comorbidity rate between cannabis use disorders and psychiatric conditions [100-105] may indicate that cannabis consumption is either a concurring cause or a “self-therapeutic” strategy for anxiety and mood disorders [117-123]. The latter interpretation is supported by the observation that anxiety-spectrum disturbances and traumas in early developmental stages are a strong predictor for later cannabis use disorders [124-127]; furthermore, several lines of evidence suggest that the anxiolytic effects of THC may partially account for the high prevalence of cannabis use in patients affected by PTSD [128-131] and OCD [132]. Accordingly, recent clinical studies have shown that THC elicits therapeutic effects in OCD [133] and trichotillomania, an impulse-control disorder characterized by compulsive hair-pulling [134]. Nevertheless, prospective analyses show that cannabis use and dependence increase the risk for development of panic disorder [135], suggesting that the effect of cannabis may vary with respect to the nosological entities within the spectrum of anxiety disorders. Of note, chronic consumption of cannabis has been hypothesized to exacerbate depressive or anxious manifestations, and reduce the therapeutic efficacy of anxiolytic agents [122,136-138]; an interesting theoretical implication of this finding is that long-term exposure to cannabinoid agents may lead to profound alterations of synaptic plasticity and neurochemical homeostasis and alter the pathophysiological trajectory of anxiety and mood disorders. Thus, while cannabis may be initially used as a self-therapy for certain anxiety disorders, the prolonged exposure to this substance in vulnerable individuals may in turn alter or aggravate the clinical course of these conditions and render the patients refractory to standard treatments.

The ability of cannabis to either exacerbate or attenuate emotional reactivity is highly influenced by numerous factors, including its chemotype, as well as the influence of genetic, developmental and contextual variables. Unfortunately, little is still known about the susceptibility factors that govern the behavioral outcomes of cannabis in patients affected by anxiety-spectrum disorders. Indeed, several components have been shown to play a role in this link, including genetic background, age, gender, environmental stress and concurrent

use of other drugs; a detailed analysis of these determinants is outside the scope of the present work, but the interested reader should refer to [139].

Aside from the influence of vulnerability factors, the available evidence indicates that cannabis, THC and other CB_1 receptor agonists exercise a bidirectional influence on anxiety responses as a function of the dosage. The majority of users report that consumption of modest amounts of cannabis and CB_1 receptor agonists results in euphoria, relaxation, heightened perception, sociability and creativity, moderate to high doses have been reported to elicit phobia, agitation, panic, dysphoria, psychotic manifestations and cognitive impairments [112-116,124,140-143]. In line with these premises, early studies showed a robust anxiolytic efficacy of low-dose nabilone in comparison with placebo [144,145]. Additionally, the few available reports on the clinical outcomes of recreational cannabinoids show that a moderate consumption of “Spice” blends is generally associated with euphoria and disinhibition [146], but the abuse of these substances is conducive to high levels of anxiety, panic, paranoid ideation and mood disturbances [147-151].

The biphasic effects of cannabinoids on anxiety-related responses have been extensively documented in rodents. In agreement with human evidence, preclinical studies have elucidated that the acute administration of low doses of CB_1 receptor agonists elicits anxiolytic-like in approach/avoidance tasks [152-156]; conversely, high concentrations of the same compounds are generally associated with the opposite outcomes [157-162] (for complete reviews of the topic, see [163,164])

The bidirectional action of CB_1 receptors on anxiety responses may be related to the modulatory role of these targets on GABA and glutamate release across amygdala and other forebrain areas [41,165,166]. As these two major neurotransmitters affect anxiety in an opposite fashion, different doses of cannabinoids and synthetic CB_1 receptor agonists may indeed produce highly divergent effects, in relation to their ability to affect the homeostasis and the balance of GABA and glutamate (for a review on these issues, see [163]). Furthermore, CB_1 receptors have been shown to play critical roles in the regulation of most neurochemical substrates of anxiety, including the neurotransmitters serotonin, norepinephrine and acetylcholine, as well as stress hormones, colecystokynin and opioid peptides [50,163].

In line with this concept, the infusion in the periaqueductal grey of arachidonyl-2-chloroethylamide (ACEA), an anandamide synthetic analog with high CB_1 receptor selectivity, elicited anxiolytic-like effects in rats in an elevated plus maze, with a bell-shaped dose-response curve [167], the highest doses being associated to no significant behavioral change. Novel categories of compounds have been patented for potential efficacy as selective CB_1 receptor modulators, including sulfonyl-benzamides [168] and tetrasubstituted imidazole derivatives [169]. To the best of our knowledge, however, no findings on the action of these compounds in anxiety regulation have been reported to date.

CB_1 receptor antagonists/inverse agonists

The cannabinoid CB_1 receptor antagonists/inverse agonist rimonabant was introduced into clinical practice by Sanofi-Aventis in 2006 as a treatment for obesity [170] and smoking cessation [171]. The majority of preclinical studies found that these compounds are anxiogenic at high doses [158,159,172,173] and ineffective at low doses [174,175]. The anxiogenic properties of CB_1 antagonists, were unequivocally confirmed by clinical data on the psychiatric side effects of rimonabant. The significant increase in anxiety, depression and suicidality in patients under treatment with rimonabant [176-179], in particular, led to the withdrawal of the drug from the European market in October, 2008. As a consequence, several pharmaceutical companies announced the interruption of their clinical research on

CB_1 receptor antagonists, including taranabant (from Merck) and otenabant (from Pfizer), both in Phase 3 of development. Some of the anxiogenic properties of rimonabant and analogs have been speculated to be due to their activity as inverse agonists; as a result, the therapeutic use of newly-developed neutral CB_1 antagonists has been proposed, with the hypothesis that these compounds would not elicit the untoward psychological effects observed with rimonabant and its analogs [180,181]; this idea is supported by recent findings, showing that unlike CB_1 receptor inverse agonists, the neutral antagonists of this targets fail to facilitate the acquisition or consolidation of fear [182].

CB_2 receptor ligands

Few studies have actually evaluated the role of CB_2 receptor in anxiety and stress response. While this receptor was posited to be mainly expressed mainly in immune cells and peripheral areas, its identification in the brain under pathological conditions, such as Alzheimer's disease, multiple sclerosis and amyotrophic lateral sclerosis spinal cord [183-185], led to a number of studies aimed at the assessment of its potential role in brain function and behavioral regulation. Some of these investigations indicated that the suppression of CB_2 receptor in the brain, through intracerebroventricular injection of antisense nucleotide sequences, elicited anxiolytic effects in rodents [186]. In contrast, Garcia-Gutierrez and Manzanares [187] recently described that the overexpression of CB_2 receptors reduced anxiogenic-related behaviors in the light-dark box and elevated plus maze. These premises point to the possibility that CB_2 receptor ligands may also play a role in the modulation of anxiety disorders. This hypothesis, however, awaits further examination with proper pharmacological tools.

CBD

Several studies suggest that THC and CBD may exert opposite actions on brain function and psychopathology [188], possibly in relation to the action of CBD as a potent CB_1 receptor antagonist/inverse agonist [21] (see above). Several lines of preclinical work have shown that CBD reduces the effects of THC on several behavioral functions [189-191]. In line with these data, CBD has been found to reduce the anxiety and improve the sensation of well being induced by an acute, high THC dose in healthy volunteers [192].

In contrast with these data, a number of studies have shown that CBD pretreatment potentiated the behavioral effects induced by THC [193-195]. These actions may signify the ability of CBD to inhibit cytochrome P450-mediated drug metabolism [196,197], which may increase THC blood and brain concentrations [193,195].

Notably, the behavioral outcomes of CBD do not appear to be only due to potential pharmacodynamic/pharmacokynetic competition with THC; indeed, recent studies have shown that CBD exerts inherent anxiolytic effects, both in rodent models [157,198-201] and, more recently, in patients affected by social phobia [202,203]. The anxiolytic action of CBD may be linked to 5-HT_{1A} receptor, but not through benzodiazepine receptors [204]. Of note, the anxiolytic action of CBD also appears to be bidirectional, as only low to moderate doses, but not high doses, have been associated with exert anxiolytic effects [200,205].

The anxiolytic action of CBD do not appear to be mediated by benzodiazepine receptors [204], but rather by 5-HT_{1A} serotonin receptors in the bed nucleus of the stria terminalis [206], a critical component of the amygdaloid complex involved in the regulation of stress response.

Accordingly, CBD has been shown to reduce amygdalar responses to fearful stimuli [207]; this mechanism may be essential for the anxiolytic effects of this compound in social phobia [203]. Furthermore, CBD has been shown to elicit antipanic effects through the activation of

5-HT_{1A} receptors in the dorsal periaqueductal gray, a critical area for the modulation of emotional reactivity to stress [208,209].

Endocannabinoid transport blockers

The systemic administration of the endocannabinoid transport blocker AM404 (Fig. 4) was shown to elicit anxiolytic-like behaviors in the elevated plus maze and defensive withdrawal in adult rats, as well as an attenuation of ultrasonic vocalizations in rat pups [175]. The same compound was shown to attenuate marble burying (a paradigm for compulsivity testing) in mice, suggesting that this compound may have some potential efficacy for OCD [206]. Interestingly, the anxiolytic effects of AM404 were shown to be contributed by both CB_1 and 5-HT_{1A} receptors [152,210], in a fashion similar to the potent CB_1 receptor agonist CP 55,940 [160]. Additionally, AM404 has been suggested to act as a FAAH inhibitor [211], although evidence in this respect is controversial [72]. Indeed, despite the identification of potential candidate endocannabinoid binding sites [212], no final evidence is currently available on the existence and/or molecular identity of the endocannabinoid transporter.

Although the possibility of targeting the endocannabinoid carrier for the development of anxiolytic compounds is appealing and has been targeted by a patent proposing these compounds as a pharmacological support for psychotherapy [213], the elusive molecular identity of the transporter itself has greatly limited the studies. Furthermore, preliminary data indicate that AM404 elicits reward in animals and is self-administered by squirrel monkeys [175,214], raising the possibility that endocannabinoid transport blockers may be addictive.

FAAH inhibitors

The prototypical FAAH inhibitor URB597 (Fig. 4) has been shown to reduce anxiety-like behaviors in rats, in a rimonabant-sensitive fashion [155,163,215-217]. In addition to its anxiolytic-like properties, URB597 was found to exert also antidepressant-like effects in several animal models with high face and predictive validity, such as the forced swim, tail suspension and chronic mild stress paradigms [89,210,216,218]. The anxiolytic action of FAAH inhibitors has been suggested to depend on the enhancement of anandamide in the dorsolateral periaqueductal gray [219]; interestingly, however, only low doses of URB597 in the prefrontal cortex were found to elicit anxiolytic-like effects, through CB_1 receptor activation. However, higher doses ceased to elicit anxiolysis, in view of their interaction with TPRV1 vanilloid receptors [220]. Furthermore, the anxiolytic and antidepressant actions of FAAH inhibitors were observed only under conditions of high environmental aversiveness, but not under normal conditions [163,218,221]. Importantly, the psychotropic effects of FAAH inhibitors are partially distinct from those associated with cannabinoids, in that they appear to fail to reproduce the hedonic and interoceptive states produced by CB receptor agonists [89] and to induce self-administration in squirrel monkeys [222]. Taken together, these data suggest that FAAH inhibitors may be promising tools in the therapy of anxiety and mood disorders with a safer profile than cannabinoid direct agonists. This idea has been recently endorsed by several authors in recent articles and patents, featuring novel categories of highly selective and potent FAAH inhibitors [223-225] [226]. However, it should be noted that recent data have recently shown that URB597 induce a number of side effects in rats, including social withdrawal, working memory deficits [227] and impairments in auditory discrimination and reversal of olfactory discrimination [228].

MAGL inhibitors

The role of 2-AG in emotional regulation has been difficult to ascertain until the recent development of highly selective monoacylglycerol lipase (MAGL) inhibitors [35,223]. Several lines of evidence have suggested that 2-AG plays a pivotal role in the

pathophysiology of anxiety and defensive behaviors. The prototypical MAGL inhibitor, JZL184 (Fig. 4), has been shown to enhance the levels of 2-AG, but not anandamide; this effect is due to its extremely high selectivity for MAGL over FAAH and other brain serine hydrolases. Recent evidence has shown that this compound exerts anxiolytic-like effects in the elevated plus maze and in marble buyring, at doses that do not affect locomotor activity [93,229,230]. Similarly to the effects described for FAAH inhibitors (see above), the anxiolytic effects of this compound were observed in highly aversive (or anxiogenic) contextual settings [229]. The neurobiological role of 2-AG in anxiety is still poorly understood, although several studies have shown that environmental stressors alter its biosynthesis and degradation in key brain structures controlling emotional regulation, including periaqueductal grey, amygdala and hippocampus [231,232]. Interestingly, recent evidence has shown that the anxiolytic properties of JZL184 appear to be mediated by CB_2, rather than CB_1 receptors [93], pointing to a potential implication of this receptor in the role of 2-AG in anxiety regulation.

CURRENT AND FUTURE DEVELOPMENTS

In light of the limitations of our current pharmacological armamentarium for anxiety disorders, the ability of cannabinoids to modulate emotional responses is extremely attractive for the development of novel anxiolytic agents [217]. At the same time, great concern arises from the protean role of cannabinoids on the regulation of these responses, as well as their misuse liability and other side effects. The identification of operational strategies for the employment of cannabinoids in the therapy of anxiety disorders is therefore a fundamental goal in psychiatry research.

As outlined above, clinical evidence strongly suggests that acute administration of low doses of CB_1 receptor agonists results in anxiolytic effects, while excessive activation of these targets elicits opposite outcomes, following a reverse U-shaped dose-response pattern. Hence, a primary strategy to harness the anxiolytic properties of cannabinoids could consist in the employment of partial, low-affinity CB_1 agonists, which may ensure a relatively high therapeutic index and the stabilization of the activation of this target within a range associated with mood enhancement and/or anxiolysis. This idea is indirectly supported by the mirroring observation that anecdotal reports on highly potent, high-affinity synthetic cannabinoids (such as those contained in “Spice” blends) trigger greater psychoactive effects than the partial CB agonist THC [26]. This concept indicates a potential evolution in the search for direct CB agonists, in sharp contrast with the previous trend aimed at the identification of high-affinity CB receptor activators.

An alternative strategy to achieve a similar therapeutic goal may lie in the combination of CB_1 receptor agonists with low dosages of antagonists (preferably neutral, in order to avoid potential side effects linked to CB_1 inverse agonism); this intriguing approach, which has been indicated in a recent patent [233], is based on the likely mechanism of action of Sativex®, a cannabinoid mouth spray containing THC and CBD (in a ratio of 1.08:1) and marketed for the treatment of neuropathic pain, spasticity and overactive bladder, in consideration of the action of CBD as a CB_1 receptor antagonist. However, recent preliminary clinical studies have shown that this formulation did not significantly reduce anxiety (in fact, it was reported to induce a mild, yet not significant increase of this symptom) [234,235], and that CBD did not appear to elicit a significant opposition to the effect of dronabinol [235], plausibly indicating that a higher concentration of this ingredient (or lower relative amount of THC) may be necessary to elicit anxiolytic effects.

A third, highly promising avenue for the development of cannabinoid-based anxiolytic therapies may be afforded by FAAH inhibitors. Unlike endocannabinoid transport blockers

and direct CB receptor agonists, these compounds exhibit a number of highly desirable properties for anxiolytic agents: first, they appear to maintain their anxiolytic and antidepressant effect not only under conditions of acute administration, but also following long-term treatment [93,210]; second, they appear to elicit their effects only in conditions of highly aversive environmental circumstances (i.e., similar to those that would in fact require an anxiolytic treatment); third, they have no apparent addiction liability [89,222]. The neurobiological bases of this phenomenon are not completely understood, and may be related to the involvement of other FAAH substrates, such as OEA or PEA; however, recent investigations suggest that the lack of 2-AG enhancement ensuing FAAH inactivation may contribute to the lack of reinforcing properties of URB597 [236], potentially suggesting a different role of anandamide and 2-AG in the modulation of reward; this idea is actually consistent with the recent finding that 2-AG is induces self-administration in monkeys [237].

A key problem concerning the potential application of cannabinoid-related agents and cannabinoids is the relatively little information about their long-term effects following chronic administration. Indeed, the subjective effects of cannabis have been shown to be typically different in chronic users as compared to occasional marijuana smokers [238,239]. Prolonged consumption of cannabis has been shown to induce affective sequelae, including alexithymia and avolition [113,240-242]. Interestingly, tolerance has been shown to the effects of THC [243,244], while no information is available on endocannabinoid-related agents. Long-term administration of cannabinoids has been shown to result in a number of neuroplastic adaptive processes, including CB receptor down-regulation [245,246]. Some of these phenomena may indeed be critical in shaping the different emotional responsiveness to cannabis throughout life and reflect a potential pathophysiological loop which may compound the severity of pre-existing anxiety and affective disorders.

Finally, another important step for the employment of cannabinoid-based anxiolytic therapies will be the analysis of the vulnerability factors implicated in the differential responses and long-term sequelae induced by cannabis consumption. For example, numerous meta-analyses and longitudinal studies have established that cannabis consumption in adolescence is conducive to an increased risk for psychotic disorders [247-250]. This association is particularly significant in the presence of other genetic factors, such as the Val^{108}Met allelic variant of the gene encoding Catechol-O-methyltransferase (COMT) [251,252], one of the main enzymes for the degradation of the neurotransmitter dopamine. Interestingly, it has been shown that the synergistic effect of COMT haplotype and cannabis in adolescence is more robust in conjunction with predisposing environmental variables, such as the exposure to urbanicity and psychosocial stress [253]. Another gene that may modulate the behavioral responsiveness to cannabinoids is *Nrg1*, which encodes for the synaptic protein neuregulin 1. Indeed, the heterozygous deletion of this gene ablates the development of tolerance to the anxiogenic effects of CB receptor agonists [254,255]. These findings suggest that the employment of a pharmacogenetic approach may be a critical screening instrument to identify which patients may be treated with cannabis for medical purposes without risks of neuropsychiatric side effects. Notably, the role of genes in the mental sequelae of cannabis may also be contributed by epigenetic factors, in consideration of the recent finding that THC induces expression of histone deacetylase 3 [256].

While studies on the biological determinants of different responses to cannabis are still at their preliminary stages, advances in this area may be essential to allow a personalized approach for the employment of cannabinoid-based therapies in anxiety and mood disorders.

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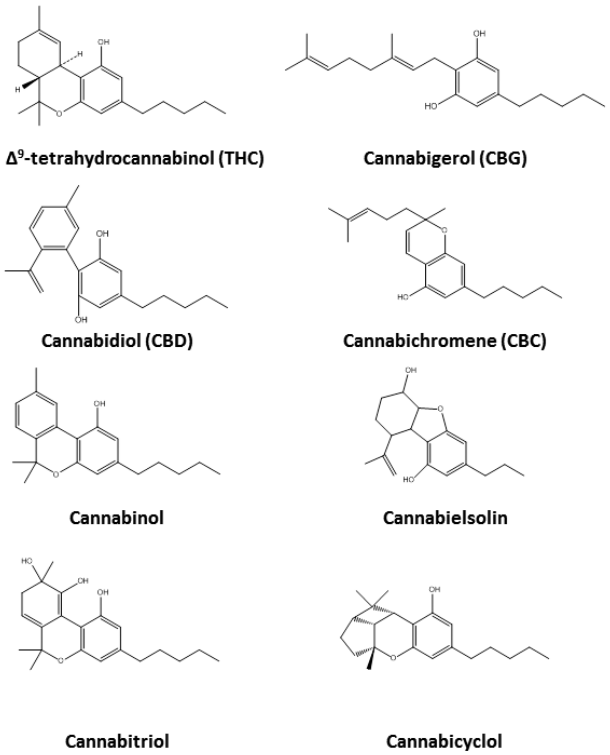

Fig. 1.
Chemical structures of the major phytocannabinoids. For more details, see text.

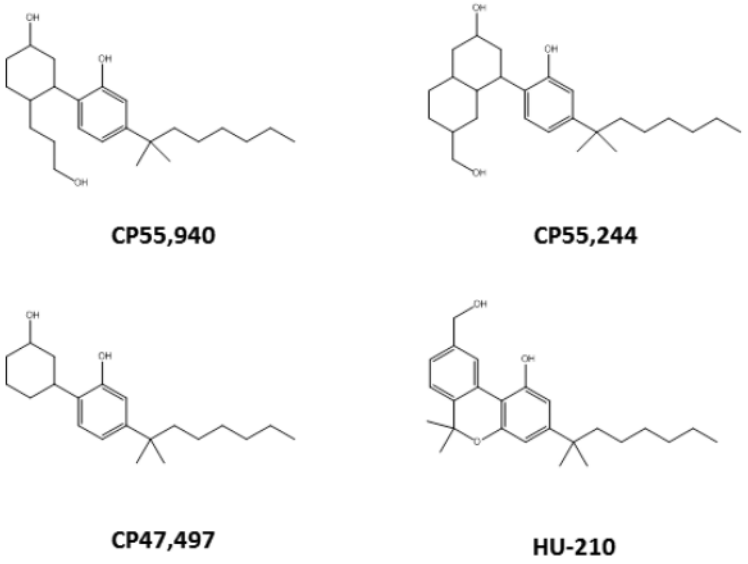

Fig. 2.
Chemical structures of the synthetic THC analogs CP55,940, CP55,244, CP 47,497 and HU-210. For more details, see text.

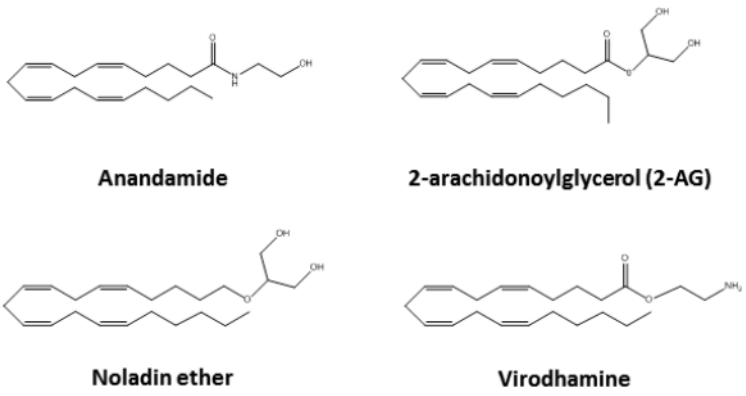

Fig. 3.
Chemical structures of the major endocannabinoids. For more details, see text.

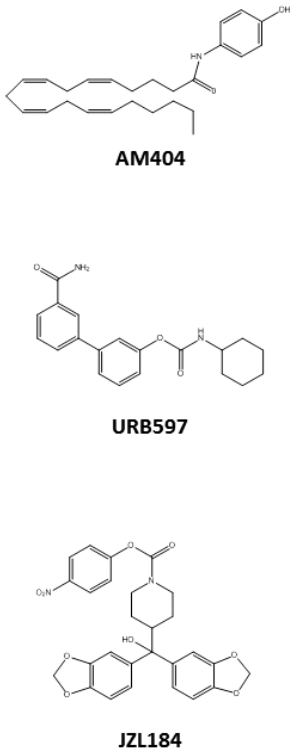

Fig. 4.
Chemical structures of endocannabinoid degradation inactivators. For more details, see text.

Table 1

Current pharmacological strategies for the treatment of anxiety disorders

1	Generalized anxiety disorder
	a. Benzodiazepines
	b. Buspirone
	c. Selective serotonin reuptake inhibitors
2	Panic attack
	a. High-potency benzodiazepines
	b. Tricyclic antidepressants
	c. Selective serotonin reuptake inhibitors
	d. Monoamine oxidase inhibitors
3	Post-traumatic stress disorder
	a. Selective serotonin reuptake inhibitors
	b. Low-dose antipsychotic agents
4	Obsessive-compulsive disorder
	a. Tricyclic antidepressants
	b. Selective serotonin reuptake inhibitors

Table 2
Paradigms for testing of anxiety-like behaviors in rodents

1	**Unconditioned anxiety**		
	a.	Tests for social anxiety	
		i.	Maternal separation-induced ultrasonic vocalizations (for pups)
		ii.	Social interaction
	b.	Tests based on approach/avoidance conflict	
		i.	Novel open field
		ii.	Defensive withdrawal
		iii.	Elevated plus maze
		iv.	Elevated T-maze
		v.	Zero maze
		vi.	Light/dark box
		vii.	Emergence test
	c.	Tests based on antipredator defensive behavior	
		i.	Mouse defense test battery
		ii.	Predator urine exposure test
		iii.	Predator exposure test
	d.	Other tests	
		i.	Novelty-induced feeding suppression
		ii.	Marble burying
		iii.	Defensive burying
2	**Conditioned anxiety**		
	a.	Tests on conditional fear	
		i.	Fear- conditioned freezing
		ii.	Fear-potentiated startle
		iii.	Conditional fear-induced analgesia
	b.	Operant conflict test	
		i.	Geiller-Seifter test (conditioned suppression of eating)
		ii.	Vogel test (conditioned suppression of drinking)