The Endocannabinoid System and the Brain

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Annu. Rev. Psychol. 2013. 64:21–47

First published online as a Review in Advance on July 12, 2012

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi: 10.1146/annurev-psych-113011-143739

Keywords

Δ^9-tetrahydrocannabinol (THC), anandamide, anxiety, 2-arachidonoyl glycerol (2-AG), cannabidiol, cannabinoid receptors, cognition, depression, memory, neurogenesis, reward

Abstract

The psychoactive constituent in cannabis, Δ^9-tetrahydrocannabinol (THC), was isolated in the mid-1960s, but the cannabinoid receptors, CB1 and CB2, and the major endogenous cannabinoids (anandamide and 2-arachidonoyl glycerol) were identified only 20 to 25 years later. The cannabinoid system affects both central nervous system (CNS) and peripheral processes. In this review, we have tried to summarize research—with an emphasis on recent publications—on the actions of the endocannabinoid system on anxiety, depression, neurogenesis, reward, cognition, learning, and memory. The effects are at times biphasic—lower doses causing effects opposite to those seen at high doses. Recently, numerous endocannabinoid-like compounds have been identified in the brain. Only a few have been investigated for their CNS activity, and future investigations on their action may throw light on a wide spectrum of brain functions.

Contents

INTRODUCTION: CANNABIS AND THE BRAIN

Cannabis Use Over Millennia: A Bird's-Eye View

The Assyrians (about second millennium BC to sixth century BC) used cannabis for its psychoactive, mind-altering effects as well as for its medical properties. It was named either *ganzi-gun-nu* ("the drug that takes away the mind") or *azzalu*, which was apparently a drug for "depression of spirits," for a female ailment (possibly amenorrhea), or even for annulment of witchcraft (Campbell Thomson 1949). The importance of cannabis intoxication seems to have been central in early Zoroastrian shamanic ecstasy (Mechoulam 1986). Its wide use in the Middle East has continued ever since. Indeed, it was a central theme in Arab poetry of the Middle Ages (Rosenthal 1971). In China and India it was known for the dual nature of its effects. In the Chinese classic medical pharmacopeia Ben Ts'ao, originally compiled around the first century AD, cannabis was recommended for numerous maladies, "but when taken in excess it could cause seeing devils" (Mechoulam 1986, p. 9).

In Europe, cannabis was introduced by the Napoleonic soldiers returning from Egypt and by British physicians returning from India. Industrial hemp, which contains negligible amounts of psychoactive material, was of course grown previously, but the psychoactive variety was unknown. The psychological effects caused by cannabis preparations—presumably North African hashish—became known in Europe mostly through the writings of members of the Parisian *Le Club des Hachichins* in the mid-nineteenth century, particularly Baudelaire, Gautier, and Moreau (Mechoulam 1986). Baudelaire, a major literary figure at the time, emphasized the "groundless gaiety" and "the distortion of sounds and colours" following cannabis use. Moreau, a psychiatrist, in his 1845 book, *Hashish and Mental Illness* (Moreau 1973), described in detail numerous psychological phenomenon noted in experimental subjects: feeling of happiness, excitement and dissociation of ideas, errors of time and space, enhancement of the sense of hearing, delusions, fluctuations of emotions, irresistible impulses, and illusions and hallucinations. This diversity of actions—some of them opposite to each other—has confounded cannabis research ever since. Indeed, Moreau reported that some of

his volunteers experienced "...occurrences of delirium or of actual madness". He concluded, "There is not a single, elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish..." (Moreau 1973, p. 18). But today few marijuana users will reach a state of "delirium or of actual madness." In most cases, they will report an increase in relaxation and euphoria and possibly enhancement of their senses, but an impairment of memory. These striking differences are probably due to the well-known biphasic activity of Δ^9-tetrahydrocannabinol (THC)—the psychoactive constituent—whose effects at low doses may be opposite to those produced by high doses. Moreau's volunteers presumably orally consumed large amounts of hashish, whereas today North Americans and Europeans usually smoke cannabis, and most users adjust their dose to achieve the desired effects.

Surprisingly, research on cannabis advanced slowly. A major reason for the neglect was the lack of knowledge of its basic chemistry. Modern research—namely research over the past 150 years—is based on quantitative data. Unlike morphine and cocaine, which had been isolated and made available in the nineteenth century and thus could be quantitatively investigated in vitro, in animals, and in humans, the psychoactive constituent(s) of cannabis were not isolated and their structures were not elucidated until the 1960s; hence quantitative research was not possible before then.

It is conceivable that the material reaching Europe in the past varied widely in its contents; thus its medical use also was not reliable, and research with it was of little value. Indeed, around the beginning of the twentieth century cannabis almost disappeared, both as a medicinal agent and for recreational purposes in Europe and in North America. In addition, the anti-cannabis laws made research on it, particularly in academic institutions, very difficult. Indeed, from the early 1940s until the mid-1960s, research on cannabis was limited to a few scattered groups. This paucity of early research has now been more than compensated for by the avalanche of papers on the plant cannabinoids and on the endogenous cannabinoids. Not surprisingly, the burst of recreational marijuana use, in the mid-1960s in the United States and later in Europe, coincided with the new wave of research on cannabis.

Δ^9-Tetrahydrocannabinol and Cannabidiol

Over nearly a century, numerous attempts were made to isolate in pure form the active marijuana constituent(s) and to elucidate its (or their) structure(s), but these attempts were unsuccessful (Mechoulam & Hanus 2000). Now we can understand the reason for this lack of success. There are more than 60 cannabis constituents, with closely related structures and physical properties, making their separation difficult. With the advance of modern separation techniques, the isolation and the structure elucidation of the active principle, THC, was finally achieved in 1964 (Gaoni & Mechoulam 1964). Shortly thereafter, THC was synthesized (Mechoulam et al. 1967). Thus, THC became widely available for research, and several thousand papers have been published on it. Surprisingly, although most of the plant cannabinoids have now been identified—and their structures are related chemically—the only major mood-altering constituent is THC.

Another major plant cannabinoid is cannabidiol (CBD), which was isolated during the late 1930s, but its structure was elucidated only in 1963 (Mechoulam & Shvo 1963). As it does not parallel THC in its central nervous system (CNS) effects, initially only a limited amount of research was focused on it. However, over the past two decades CBD was found to be a potent anti-inflammatory agent, to attenuate the memory-impairing effects produced by THC, and to cause a plethora of other effects. Hundreds of publications have addressed its various actions (for a review, see Mechoulam et al. 2009). Both THC and CBD are present in the plant mainly as their nonpsychoactive carboxylic precursors (THC-acid and CBD-acid), which slowly lose their acidic function (decarboxylate) in the

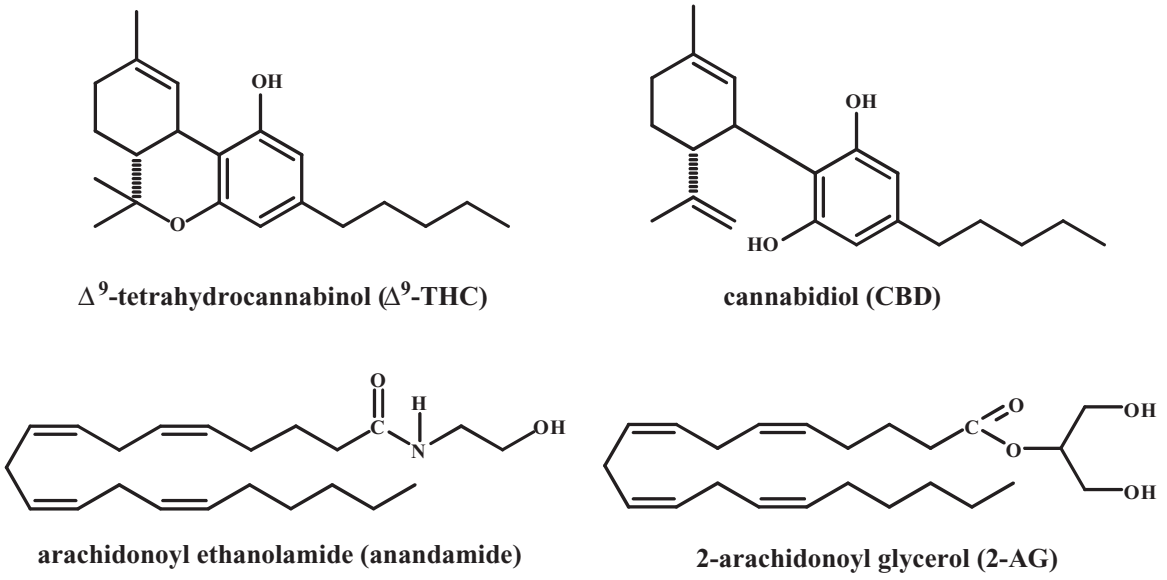

Figure 1

Structures of the plant cannabinoids Δ^9-tetrahydrocannabinol and cannabidiol and of the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol.

plant on heating. The structures of THC and CBD are presented in **Figure 1**.

The cannabis plant varieties differ tremendously in their contents. In industrial hemp the concentration of THC is less than 0.3%, in hashish in the 1960s it was about 5%, whereas in marijuana it was about 2% to 3%, but nowadays strains have been developed—mostly for illegal use—that contain up to 25%.

The Endocannabinoid Receptors

Originally it was assumed that cannabinoids act through a nonspecific membrane-associated mechanism; however, the very high stereospecificity of the action of some synthetic cannabinoids pointed to a more specific mechanism (Mechoulam et al. 1988). The first data indicating that cannabinoids may act through receptors were published by Howlett, who showed that cannabinoids inhibit adenylate cyclase formation, and the potency of the cannabinoids examined paralleled the level of their pharmacological action (Howlett et al. 1986). The same group shortly thereafter indeed reported the existence of binding sites in the brain (Devane et al. 1988). Their distribution was found to be consistent with the pharmacological properties of psychotropic cannabinoids (Herkenham et al. 1990), and the receptor was cloned (Matsuda et al. 1990). A second, peripheral receptor, CB2, was later identified in the spleen (Munro et al. 1993). Both CB1 and CB2 receptors belong to the superfamily of G protein–coupled receptors (GPCRs). The two cannabinoid receptors exhibit 48% amino acid sequence identity. Both receptor types are coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase (for a detailed review on the pharmacology of cannabinoids, see Howlett et al. 2002).

The CB1 Receptor

It was originally believed that the CB1 receptor was expressed mainly in the CNS, and hence it was considered a brain cannabinoid receptor. We are now aware that it is present in numerous peripheral organs, although in some of them the receptor levels are low. CB1 receptors are

among the most abundant GPCRs in the brain. The highest densities of CB1 receptors, in the rodent brain, are noted in the basal ganglia, substantia nigra, globus pallidus, cerebellum, and hippocampus, but not in the brainstem. The high CB1 levels in the sensory and motor regions are consistent with the important role of CB1 receptors in motivation and cognition. CB1 receptors appear to be involved in γ-aminobutyric acid (GABA) and glutamate neurotransmission, as they are found on GABAergic and glutamatergic neurons (Howlett et al. 2002). The CB1 receptor is present and active from the earliest phases of ontogenetic development, including during the embryonal stages, which indicates that it is of importance in neuronal development and newborn suckling (Fride et al. 2009). Surprisingly the CB1 receptor levels in rats are increased on transition from adolescence [postnatal days (PND) 35–37] to adulthood (PND 70–72), a pattern that is opposite to that of other neuroreceptor systems (Verdurand et al. 2012). Also, unexpectedly, ligands that interact similarly with CB1 receptors may have significantly different pharmacological profiles. This may be due to the ability of CB1 receptors to form heteromeric complexes with other GPCRs (Pertwee et al. 2010).

The distribution of CB1 receptors differs in neonatal brain and adult brain. It is abundant in white matter areas at the early age but is much less abundant later (Romero et al. 1997). It is of interest to determine whether this difference has anything to do with the behavioral landmarks associated with different ages.

The CB1 receptors are found primarily on central and peripheral neurons in the presynapse. These locations facilitate their inhibition of neurotransmitter release, which is one of the major functions of the endocannabinoid system. Activation of CB1 receptors leads to a decrease in cyclic adenosine monophosphate (cAMP) accumulation and hence to inhibition of cAMP-dependent protein kinase (PKA). CB1 receptor activation leads to stimulation of mitogen-activated protein (MAP) kinase activity, which is a mechanism by which cannabinoids affect synaptic plasticity, cell migration, and possibly neuronal growth (Howlett et al. 2002). CB1 receptors are also coupled, again through G proteins, to several types of calcium and potassium channels.

Several types of CB1 receptor gene knockout mice are available and are widely used (Zimmer et al. 1999). CB1 receptor gene polymorphisms have been observed, and their importance is yet unknown, although susceptibility to addiction and neuropsychiatric conditions has been suggested (Zhang et al. 2004).

The CB2 Receptor

It was originally assumed that CB2 receptors were present only in cells of the immune system; however, they have now been identified throughout the CNS (Ashton et al. 2006, Onaivi et al. 2008a, van Sickle et al. 2005), particularly in microglial cells (Nunez et al. 2004, Stella 2004), though at lower levels than those of the CB1 receptors. Under some pathological conditions, CB2 receptor expression is enhanced in the CNS as well as in other tissues. It seems possible that the CB2 receptor is part of a general protective system (for a review, see Pacher & Mechoulam 2011). In that review, we speculated that "The mammalian body has a highly developed immune system which guards against continuous invading protein attacks and aims at preventing, attenuating or repairing the inflicted damage. It is conceivable that through evolution analogous biological protective systems have evolved against nonprotein attacks. There is emerging evidence that lipid endocannabinoid signaling through CB2 receptors may represent an example/part of such a protective system" (Pacher & Mechoulam 2011, p. 194). In view of the various protective effects associated with the CB2 receptor, several synthetic CB2-specific receptor agonists, which do not bind to the CB1 receptor, have been synthesized. HU-308 was one of the first such compounds reported (Hanus et al. 1999); however, numerous additional ones are now known, and since they do not cause the psychoactive effects associated with CB1 agonists, several pharmaceutical firms are presently active in the field.

CB2 receptor agonists might be expected to become drugs in various fields, including neuropsychiatric, cardiovascular, and liver disease.

Endogenous Cannabinoid Agonists

The discovery of the cannabinoid receptors suggested that endogenous molecules, which may stimulate (or inhibit) the receptors, are presumably present in the mammalian body. The plant constituent THC, which, apparently by a quirk of nature, binds to these receptors, is a lipid compound; hence it was assumed that any possible endogenous cannabinoid molecules (endocannabinoids) would also be lipids. Indeed, we were able to isolate and identify two compounds, one from brain—which we named anandamide, based on the Sanskrit word *ananda* ("supreme joy")—and a second one [2-arachidonoyl glycerol (2-AG)] from peripheral tissues (Devane et al. 1992, Mechoulam et al. 1995). Their structures are presented in **Figure 1**. These two endogenous cannabinoids have been investigated in great detail (for a review, see Howlett et al. 2002). Additional endogenous molecules that bind to the cannabinoid receptors have been identified, but some of them may be artifacts, and interest in them is negligible.

Unlike most neurotransmitters (e.g., acetylcholine, dopamine, and serotonin), anandamide and 2-AG are not stored in vesicles but rather are synthesized when and where they are needed. Again, unlike most neurotransmitters, their action is not postsynaptic but rather mostly presynaptic, i.e., they serve as fast retrograde synaptic messengers (Howlett et al. 2002). However, whether both endocannabinoids, or only 2-AG, serve as fast retrograde synaptic messengers remains to be established. Thus 2-AG, after its postsynaptic synthesis, crosses the synapse and activates the cannabinoid presynaptic receptor, which makes possible the inhibition of various neurotransmitter systems that are present there. This is a primary activity of the endocannabinoids.

Contrary to THC, which is metabolized over several hours and excreted (or stored as one of its metabolites), endocannabinoids are rapidly removed by a membrane transport process yet to be fully characterized (Fu et al. 2011). In the cell, anandamide is hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH). 2-AG is also hydrolyzed enzymatically, both by FAAH and by monoacyl hydrolases. Suppression of these enzymes prolongs the activity of the endocannabinoids (Gaetani et al. 2009).

Although there is solid evidence that the activation of presynaptic CB1 receptors can lead to inhibition of the release of a number of different excitatory or inhibitory neurotransmitters both in the brain and in the peripheral nervous system, there is also in vivo evidence that CB1 receptor agonists can stimulate dopamine (DA) release in the nucleus accumbens (Gardner 2005). This effect apparently stems from a cannabinoid receptor-mediated inhibition of glutamate release. Indeed, many of the actions of cannabinoid receptor agonists (including endocannabinoids) are dose-dependently biphasic (Sulcova et al. 1998). Endocannabinoids also exhibit an "entourage effect"—namely enhancement of their activity by structurally related, biologically inactive, endogenous constituents (Ben-Shabat et al. 1988). The multiple functions of endocannabinoid signaling in the brain have recently been very well reviewed (Katona & Freund 2012).

In the following review of the effects of brain endocannabinoids and related fatty acid amides of amino acids (FAAAs) and closely related compounds on emotions and cognition, we summarize the large number of published observations. It seems that many of the FAAAs in the CNS that have been investigated—and most have not been investigated yet—have significant effects. If we assume that the dozens of compounds of this type present in the brain are not biosynthesized by mistake but rather play some physiological role, it is tempting to speculate that their levels and their interactions may be of importance in the profile of emotions and possibly of individual personalities. This topic is further discussed in the Conclusions section of this review.

THE CANNABINOID SYSTEM IN ANXIETY AND DEPRESSION

Freud considered the problem of anxiety a "nodal point, linking up all kinds of most important questions; a riddle, of which the solution must cast a flood of light upon our whole mental life" (Freud 1920). We have made some progress since Freud's time, but according to the National Institute of Mental Health, anxiety disorders still affect about 40 million people in the United States alone, and antianxiety drugs are among the top prescription drugs.

Cannabis has been used for millennia as a medicinal agent (Mechoulam 1986). In India, bangue (the local name for cannabis at the time) was believed to help the user to be "delivered from all worries and care" (Da Orta 1563), and its extensive present-day use throughout the world is presumably due, in part at least, to the same effects. For recent reviews on cannabis and anxiety, see Gaetani et al. (2009), Moreira & Wotjak (2010), Parolaro et al. (2010), and Zanettini et al. (2012). For general reviews on the endocannabinoid system, including detailed data on anxiety and depression and emerging pharmacotherapy, see Pacher et al. (2006) and Pertwee (2009).

A few years ago the major pharmaceutical firm Sanofi-Aventis developed and initiated marketing for an antagonist (or more precisely an inverse agonist) of the CB1 receptor. Because CB1 agonists enhance appetite, such a drug could become a major weapon against obesity. Many other companies had related compounds in various stages of development. The Sanofi compound, named rimonabant, indeed affected obesity and even blocked the psychoactive effects of THC, including short-term memory and lowered cocaine-seeking responses to suitable cues (in animals). However, although psychiatric disorders were indicated as exclusion criteria, rimonabant-treated patients had enhanced anxiety problems and suicidal tendencies (Christensen et al. 2007), and the drug had to be withdrawn from the market. This rather expensive proof is a further addition to previous evidence, indicating the importance of the CB1 cannabinoid system in anxiety. Interestingly, Lazary et al. (2011) have recently suggested that as some variants of the CB1 receptor gene contribute more significantly than others to the development of anxiety and depression, by genomic screening—possibly in combination with the gene of the serotonin transporter—high-risk individuals could be identified and excluded from the treatment population and thus CB1 antagonists could still be useful. Such screening and treatment would represent a model for modern personalized medicine.

As mentioned previously, many of the psychological effects of cannabis, as well as of THC, are biphasic, depending principally on the dose level and to a certain extent upon the personality of the user. In normal subjects, THC may cause either euphoria and relaxation or dysphoria and anxiety (D'Souza et al. 2004, Wade et al. 2003). Pure THC may not entirely mimic the effects of cannabis, which contains additional cannabinoid constituents, such as CBD, that modulate the effect of THC. Besides, CB1 receptors rapidly desensitize following the administration of agonists, further diminishing the effect of agonists.

Cannabidiol, which does not bind to either CB1 or CB2, possesses anxiolytic and antipsychotic properties (Mechoulam et al. 2002) both in animals and in humans. It shows anxiolytic-like effects with mice in the elevated plus maze and in the Vogel conflict test (Guimarães et al. 1990, Moreira et al. 2006). In humans it was found to lower anxiety in stressful situations (Bergamaschi et al. 2011). The mode of action of CBD as an anxiolytic molecule is not well understood. Most probably it involves action as a serotonin receptor 1A (5-HT_{1A}) agonist (Campos & Guimaraes 2008), enhancement of adenosine signaling through inhibition of uptake (Carrier et al. 2006), or inhibition of the GPR55 receptor (Sharir & Abood 2010).

Endocannabinoids and Anxiety

There are no direct experimental data on the role of endocannabinoids on anxiety in

humans. To our knowledge neither anandamide nor 2-AG has ever been administered to human subjects. This is an absurd situation, presumably a result of regulatory limitations. By contrast, when insulin was discovered in the 1920s, it became an available drug within a year. We can only assume that, because many of the physiological systems are regulated through checks and balances by a variety of endogenous molecules, the endocannabinoids, which affect neurotransmitter release, apparently exert such an action on anxiety, which is a normal human reaction to a variety of stressful conditions.

Considerable data exist on the direct effects of endocannabinoids on anxiety in animals. Rubino et al. (2008) have shown that methanandamide (a stable analog of anandamide) injected into the prefrontal cortex of rats leads to an anxiolytic response. However, large increases of the dose administered led to an anxiogenic response due to TRPV1 stimulation.

An indirect pathway for enhancement of endocannabinoid levels is by blocking their enzymatic hydrolysis. The Piomelli group (Kathuria et al. 2003) reported a novel class of potent, selective, and systemically active carbamate-based inhibitors of FAAH, the enzyme responsible for the degradation of anandamide. The best inhibitors in this series (URB532 and URB597) had anxiolytic properties in rats in the elevated zero-maze test and suppressed isolation-induced vocalizations due to augmented brain levels of anandamide. These effects could be prevented by blockage of the CB1 receptor. These results indirectly confirmed that anandamide has antianxiety properties. The rationale behind this approach is based on the mechanism of anandamide formation and release, which is known to take place when and where needed. As mentioned above, contrary to the classical neurotransmitters, anandamide is not stored in synaptic vesicles but rather is synthesized and released in the synaptic cleft following neuronal activation. Presumably its levels and those of FAAH in anxiety and depression will be highest in the brain areas involved in the regulation of mood and emotions. Therefore, inhibition of anandamide metabolism would enhance CB1 activation mainly where anandamide levels are highest. Following the same experimental rationale, Moise et al. (2008) confirmed that URB597 inhibited FAAH activity and led to elevated levels of additional fatty acid amides (N-palmitoyl ethanolamine and N-oleoyl ethanolamine), but not of anandamide itself, in hamster brain. However, Cippitelli et al. (2008) have reported an elevation of anandamide levels in rats with URB597, which was found to reduce anxiety associated with alcohol withdrawal. Blockade of the CB1 receptor with rimonabant induced anxiogenic-like behavior in the elevated plus maze; URB597 induced anxiolytic-like effects in this assay. URB597 did not alter unconditioned or conditioned social defeat or rotarod performance.

Enhancement of 2-AG levels produces similar effects. Sciolino et al. (2011) have shown that enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-AG-hydrolyzing enzyme monoacylglycerol lipase (MGL), produces anxiolytic effects under conditions of high environmental aversiveness in rats.

Recently, two parallel publications indicated that the CB2 receptor is also involved in endogenous antianxiolytic activity. García-Gutiérrez & Manzanares (2011) reported that mice overexpressing the CB2 receptor showed lower anxiety-like behaviors in the open field, the light-dark box, and the elevated plus maze tests, indicating that increased expression of the CB2 receptor significantly modifies the response to stress in these tests. Busquets-Garcia et al. (2011), using doses of URB597 and JZL184 that selectively modulated the concentrations of anandamide and 2-AG, respectively, recorded similar anxiolytic-like effects in two behavioral paradigms. However, whereas the anxiolytic-like effects of URB597 were mediated through a CB1-dependent mechanism, the anxiolytic-like effects of JZL184 were CB1 independent. The anxiolytic-like effects of JZL184 were absent in CB2 knockout mice and were prevented by pretreatment with selective CB2 antagonists. These two

publications indicate the crucial role of the CB2 receptor on the modulation of anxiety. As activation of the CB2 receptor does not lead to undesirable psychoactivity, these observations may be of significant clinical importance, and therefore the CB2 receptor represents a novel target to modulate anxiety-like responses. The protective effect of the CB2 receptor is in line with our previous suggestion that this receptor is part of a general protective mechanism (Pacher & Mechoulam 2011).

The molecular mechanism of the effect of endocannabinoids on anxiety is still to be fully clarified. Andó et al. (2012) have confirmed considerable involvement of CB1 receptors in the effect of exo- and endocannabinoids on GABA efflux. However, they also found that CB2-like receptors are likely involved. Hofmann et al. (2011) have described a new form of cannabinoid-mediated modulation of synaptic transmission, so far in the dentate gyrus only. They report that anandamide action under certain conditions is not mediated by CB1 receptors, CB2 receptors, or vanilloid type I receptors, and is still present in $CB1^{-/-}$ animals. It would be of interest to determine whether this new pathway (through a receptor?) is involved in anxiety and depression.

The endocannabinoid system plays a gatekeeper role with regard to activation of the hormonal hypothalamic-pituitary-adrenal (HPA) axis. Tonic endocannabinoid signaling constrains HPA axis activity, ultimately habituating the stress response and restoring homeostasis. Specifically, glucocorticoids produced in response to stress recruit endocannabinoids to increase the excitability of principal neurons in the prelimbic region of the medial prefrontal cortex; the principal neurons initiate inhibitory relays terminating HPA axis activation (Hill et al. 2011). However, following chronic stress, endocannabinoid signaling downregulation is implicated in the overload of hormonal signaling that can result in anxiety and depression in humans. For an excellent review of this literature, see Riebe & Wotjak (2011).

The Endocannabinoid System, Neurogenesis, and Depression

Hill et al. (2008) have summarized the results of the experimental work done on the endocannabinoid system and depression and have concluded that research so far supports the assumption that hypofunctional endocannabinoid signaling contributes to depressive illness and that enhanced endocannabinoid signaling is associated with antidepressant efficacy. However, a hyperfunctional endocannabinoid system contributes to depression. This discrepancy was explained by showing that in the animal model of depression that was used, endocannabinoid signaling was differentially altered in various brain areas. The antidepressive drug imipramine affected some, though not all, of these changes.

In view of the excellent existing summary by Hill et al. (2008), in the present review we discuss mainly the relation between cannabinoids, their two known receptors, and neurogenesis. A leading current hypothesis of depression is that is it is linked with neurogenesis. This hypothesis is based on the downregulation of neurogenesis in depressive-like behaviors in animals and on its upregulation by antidepressant treatments.

Over the past few years, considerable data have indicated that the endocannabinoid system plays a central role in neurogenesis (for reviews, see Galve-Roperh et al. 2009, Oudin et al. 2011). It is established that CB1 mRNA is expressed in many regions of the developing brain (Buckley et al. 1998), activation of CB1 is required for the axonal growth response (Williams et al. 2003), the endocannabinoid system drives neural progenitor cell proliferation (Aguado et al. 2006), and cannabinoids actually promote neurogenesis (Berghuis et al. 2007). Reductions in adult neurogenesis were noted in CB1- and CB2-knockout mice (Aguado et al. 2006, Palazuelos et al. 2006). Jin et al. (2004) have reported that both CB1 and VR1 receptors are involved in adult neurogenesis.

Endocannabinoids, particularly 2-AG and diacylglycerol lipases (DAGLs), which are

involved in 2-AG synthesis, play a major role in axonal growth and guidance during development (Oudin et al. 2011). Harkany and colleagues (Keimpema et al. 2010) have shown that the synthesizing enzymes (the DAGLs) alone are not sufficient to account for the growth effect of 2-AG, but both the DAGLs and the degradation enzyme, MGL, play a role. However, MGL is temporally and spatially restricted from the neurite tip, thus enhancing 2-AG activity during axonal growth. The CB2 receptor has recently been shown to promote neural progenitor cell proliferation via mTORC1 signaling (Palazuelos et al. 2012).

Because depression decreases neurogenesis, the findings summarized above are particularly exciting, as they not only help us understand the role of endocannabinoids as endogenous antidepressants but also suggest that synthetic endocannabinoid-like compounds may be developed as a novel type of antidepressive drug.

Onaivi et al. (2008a) and van Sickle et al. (2005) have reported that, contrary to previous reports, CB2 receptors are present in the brain. This unexpected discovery led several groups to investigate the relevance of this receptor in various brain pathological states. Thus, transgenic mice overexpressing the CB2 receptor showed decreased depressive-like behaviors in several relevant assays. Also, contrary to wild-type mice, these transgenic mice showed no changes in BDNF gene and protein expression under stress (García-Gutiérrez et al. 2010). The Onaivi group reported that in Japanese depressed subjects there is high incidence of a certain polymorphism in the CB2 gene (Onaivi et al. 2008b). Hu et al. (2009) compared the antidepressant action of the CB2 agonist GW405833 with the action of desipramine in two antidepressive rodent assays—the time of immobility and a swimming assay. Although both desipramine and GW405833 significantly reduced immobility, contrary to desipramine, GW405833 had no effect in the swimming test. These results indicate that desipramine and cannabinoid drugs have different mechanisms in their antidepressive action.

These results together indicate that as increased CB2 receptor expression reduces depressive-related behaviors, apparently via a mechanism that differs from the mode of action of most antidepressants used at present, the CB2 receptor could be a novel therapeutic target for depression. It will be of interest to establish whether the activity of the CB2 receptor in depression is related to neurogenesis.

CANNABINOIDS AND REWARD SYSTEMS

Although the conditions under which cannabinoid drugs have rewarding effects are more restricted than with other drugs of abuse (such as cocaine and heroin), when they produce reward-related behavior, similar brain structures are involved (for an excellent recent review, see Serrano & Parsons 2011).

Rewarding/Aversive Effects of Cannabinoids

In humans, marijuana produces euphoria, but dysphoria, dizziness, and anxiety are also reported, probably the result of the previously mentioned biphasic effects of THC. Following administration of THC to humans, some studies have shown increased dopamine transmission (Bossong et al. 2009) but others have shown no change in dopamine transmission (Barkus et al. 2011) as measured by positron emission tomography. The endocannabinoid system may play a specific role in appreciation of rewards, as THC pretreatment attenuated the brain response to feedback of monetary rewards as measured by functional magnetic resonance imaging (fMRI) (van Hell et al. 2012).

In animal models, early research suggested that THC was not rewarding to monkeys (Harris et al. 1974) when assessed in the drug self-administration paradigm. In rodents, some investigators have reported that THC (as well as other abused drugs such as cocaine) reduces the threshold for electrical brain stimulation reward (Gardner et al. 1988), but other investigators report that it increases the

threshold (Vlachou et al. 2007). Unlike the self-administration paradigm, the conditioned place preference (CPP) paradigm can be used to assess both the rewarding and the aversive effects of drugs. Conflicting findings were reported in studies using the CPP paradigm with rodents. Early reports revealed that THC produced CPPs (Lepore et al. 1995), but other reports showed conditioned place aversions (e.g., Mallet & Beninger 1998a, Parker & Gillies 1995) due to differing CPP procedures. Indeed, unlike other rewarding drugs, such as cocaine or heroin, low-dose pre-exposure to the effects of THC is necessary to establish a CPP in rodents (Valjent & Maldonado 2000).

More recently, Tanda et al. (2000) have developed a very sensitive and reliable method of establishing self-administration in monkeys, which relies on the use of very low doses of THC but does not require pre-exposure to the drug. In addition, both anandamide (Justinova et al. 2005) and 2-AG (Justinova et al. 2011) are self-administered by monkeys with or without a cannabinoid self-administration history, and both effects are prevented by pretreatment with rimonabant, indicating that the rewarding effect is CB1 receptor mediated. Treatment with the FAAH inhibitor, URB597, shifts the anandamide self-administration dose-response curve to the left, such that anandamide has rewarding effects at lower doses (Justinova et al. 2008). However, URB597 is not self-administered by monkeys (Justinova et al. 2008) and does not produce a CPP in rats (Gobbi et al. 2005), possibly because it neither causes THC-like effects nor increases extracellular mesolimbic DA levels in rats (Justinova et al. 2008, Solinas et al. 2007). In contrast, DA is known to be released in the striatum by THC (Bossong et al. 2009). Cues associated with marijuana use also activate the reward neurocircuitry associated with addiction in humans (Filbey et al. 2009). Indeed, microinjections of THC into the posterior ventral tegmental area (VTA) and into the posterior shell of the nucleus accumbens (NAcc) serve as rewards for both self-administration and CPP in rats (Zangen et al. 2006).

Cannabinoids and Relapse

Treatment of addiction is often hindered by the high rate of relapse following abstinence from the addicting drug. Multiple factors such as exposure to drug-associated stimuli, drug priming, and stress can precipitate drug craving and relapse in humans. In humans, alterations in the CB1 receptor gene and in the FAAH gene have been shown to enhance fMRI activity in reward-related areas of the brain during exposure to marijuana cues (Filbey et al. 2010).

Considerable recent research suggests that CB1 receptor antagonism (or inverse agonism) interferes with drug- and cue-induced relapse in animal models. Relapse is characterized by drug-seeking behavior in extinction triggered by renewed exposure to drug-associated cues or a priming dose of a drug itself (Everitt & Robbins 2005). Such drug-seeking behavior contrasts with actual drug-taking behavior during the self-administration session. Rimonabant prevents drug-associated cues from producing relapse following extinction training in rats and mice (De Vries & Schoffelmeer 2005). Recent evidence suggests that rimonabant is relatively more effective in interfering with drug-seeking behavior than drug-taking behavior (De Vries & Schoffelmeer 2005). In an early report, the CB1 receptor agonist, HU-210, was shown to reinstate cocaine seeking following long-term extinction of cocaine self-administration (De Vries et al. 2001), an effect that was prevented by rimonabant. Of most therapeutic importance, however, was that rimonabant alone blocked drug seeking evoked by the cocaine-paired cues and by a priming injection of cocaine, as well as seeking of heroin (De Vries et al. 2005, Fattore et al. 2003), methamphetamine (Anggadiredja et al. 2004), and nicotine (De Vries et al. 2005) evoked by drug-associated cues and by a priming injection of the drug itself. Therefore, blockade (or inverse agonism) of the CB1 receptor interferes generally with drug-seeking behavior.

Drug-seeking behavior represents the incentive motivational effects of addictive drugs under control of the mesolimbic DA system.

The regulation of the primary rewarding effects of drugs of abuse may be in part controlled by endocannabinoid release in the VTA, which produces inhibition of the release of GABA, thus removing the inhibitory effect of GABA on dopaminergic neurons (Maldonado et al. 2006). In the NAcc, released endocannabinoids act on CB1 receptors on axon terminals of glutamatergic neurons. The resulting reduction in the release of glutamate on GABA neurons that project to the VTA results in disinhibition of the VTA dopamine neurons. Blockade of CB1 receptors attenuates the release of DA in the NAcc in response to rewarding medial forebrain bundle electrical stimulation (Trujillo-Pisanty et al. 2011). The prefrontal cortex and NAcc appear to play a primary role in the prevention of cue-induced reinstatement of heroin (Alvarez-Jaimes et al. 2008) and cocaine (Xi et al. 2006) seeking by CB1 antagonism.

Although blockade of CB1 receptors affects cue- and drug-induced relapse, it does not appear to affect cocaine seeking that is reinstated by exposure to mild footshock stress (De Vries et al. 2001). Indeed, stress-induced relapse to heroin or cocaine seeking is much more sensitive to manipulations of the corticotrophin-releasing factor and noradrenaline systems than the DA system (Shaham et al. 2000). For instance, infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala prevents footshock-induced but not cocaine-induced reinstatement of cocaine seeking (Leri et al. 2002).

Rimonabant showed great promise as an antirelapse treatment; however, as mentioned above, it was removed from the European market as a treatment for obesity because of the undesirable side effects of anxiety. The generality of the effects of cannabinoids on motivational processes may explain these undesirable side effects. Given that rimonabant not only acts as a CB1 antagonist but is also a CB1 inverse agonist, the relapse-preventing properties, and potentially the adverse side effects, may also be mediated by its inverse cannabimimetic effects that are opposite in direction from those produced by cannabinoid receptor agonists (Pertwee 2005). Recent evidence suggests that at least some adverse side effects of CB1 receptor antagonists/inverse agonists seen in clinical trials (e.g., nausea) may reflect their inverse agonist properties (Bergman et al. 2008). It will be of interest to evaluate the potential of more newly developed CB1 receptor neutral antagonists, such as AM4113 (Sink et al. 2008), to prevent drug-seeking behavior.

Recently, selective CB2 receptor agonists were shown to inhibit intravenous cocaine self-administration, cocaine-enhanced locomotion, and cocaine-enhanced accumbens extracellular dopamine in wild-type and CB1 receptor knockout mice but not in CB2 knockout mice. This effect was blocked by a selective CB2 receptor antagonist. These findings suggest that brain CB2 receptors also modulate cocaine's effects (Xi et al. 2011). Again, as mentioned above, the CB2 receptor seems to have general protective properties (Pacher & Mechoulam 2011).

Although considerable evidence indicates that antagonism of the CB1 receptor interferes with cue- and drug-induced relapse, there is a growing literature suggesting that FAAH inhibition and cannabidiol also prevent relapse to drug seeking. FAAH inhibition has been selectively evaluated for prevention of nicotine seeking (Forget et al. 2009, Scherma et al. 2008). However, it is not clear if these effects are mediated by the action of anandamide or other fatty acids [oleoylethanalamide (OEA) and palmitoylethanalamide (PEA)], which act on peroxisome proliferator-activated receptor-α (PPAR-α) receptors, because Mascia and colleagues (2011) recently showed that selective PPAR-α agonists also counteract the reinstatement of nicotine seeking in rats and monkeys. Thus, elevations in fatty acids produced by blockade of FAAH may have potential in treating relapse. Most recently, Cippitelli et al. (2011) found that FAAH inhibition reduced anxiety produced by nicotine withdrawal. Cannabidiol, the nonpsychoactive compound in marijuana, also attenuated cue-induced reinstatement of heroin seeking as well as restored disturbances of glutamatergic and endocannabinoid systems

in the accumbens produced by heroin seeking (Ren et al. 2009). Apparently, in addition to the many other ailments that cannabidiol improves (Mechoulam et al. 2002), it may also be a potential treatment for heroin craving and relapse.

CANNABINOIDS AND COGNITION

Cognition involves the ability to acquire, store, and later retrieve new information. Several recent reviews are available on the effects of cannabis on cognition in humans and other animals (Akirav 2011, Marsicano & Lafenetre 2009, Ranganathan & D'Souza 2006, Riedel & Davies 2005). Clearly, the chief psychoactive component in cannabis, THC, produces acute cognitive disturbances in humans and animals, more profoundly affecting short-term than long-term memory.

Effects of Cannabis on Cognition in Humans

When under the influence of THC, humans demonstrate transient impairment in short-term episodic and working memory and consolidation of these short-term memories into long-term memory, but no impairment in retrieval of information once it has been previously encoded into long-term storage (Ranganathan & D'Souza 2006). However, a recent naturalistic study revealed that cannabidiol prevented the memory-impairing effects of acute THC in humans (Morgan et al. 2010). Therefore, the relative THC/cannabidiol ratio in cannabis will profoundly modify the effects of cannabis on memory in human marijuana smokers.

The effect of chronic cannabis exposure on cognitive abilities of abstinent individuals is, however, controversial and fraught with contradictions in the literature. Polydrug abuse and pre-existing cognitive and emotional differences between cannabis users and nonusers make interpretation of the human literature problematical. In a review of the literature, Solowij & Battisti (2008) conclude that chronic exposure to marijuana is associated with dose-related cognitive impairments, most consistently in attention and working memory functions—not dissimilar to those observed under acute intoxication. On the other hand, several reports indicate that few, if any, cognitive impairments are produced by heavy cannabis use over several years (e.g., Dregan & Gulliford 2012, Lyketsos et al. 1999). More recently, a thorough review of the specific versus generalized effects of drugs of abuse on cognition (Fernandez-Serrano et al. 2011) reported that there has been only one study (Fried et al. 2005) of "pure" cannabis users. Fried et al. (2005) conducted a longitudinal examination of young adults using neurocognitive tests that had been administered prior to the first experience with marijuana smoke. Individuals were defined (by urination samples and self-reports) as light (fewer than five times a week) or heavy (greater than five times a week) current or former (abstinent for at least three months) users. Current heavy users performed worse than nonusers in overall IQ, processing speed, and immediate and delayed memory tests. In contrast, former heavy marijuana smokers did not show any cognitive impairment. Fernandez-Serrano et al. (2011) conclude that the acute effects of cannabis on prospective memory are attenuated in long-term abstinence (at least three months).

Drawing conclusions from the human literature is challenging (Ranganathan & D'Souza 2006) because of widely differing methodologies, including different tasks, lack of sufficient controls, participant selection strategies (only experienced cannabis users included in samples), different routes of administration, different doses administered, often small sample sizes, tolerance of and dependence on cannabinoids, and the timing of the test (given the long half-life of THC). In addition, factors such as a predisposition to substance use in general may confer greater vulnerability to cannabis-related cognitive effects. Therefore, experimental investigation of the effects of cannabinoids on various processes involved in learning and memory rely heavily upon animal models. These models provide insights into the critical role of the

endocannabinoid system in the physiology of learning and memory.

Effects of CB1 Agonists on Learning and Memory in Nonhumans

Consistent with the human literature, most reports using animal models suggest that acute administration of CB1 agonists selectively disrupts aspects of short-term or working memory while leaving retrieval of previously learned memory (long-term or reference memory) largely intact. A common behavioral paradigm designed to evaluate these different aspects of memory is the delayed matching (or nonmatching) to sample (DMS) task. Once the animal has learned to perform this operant task (reference memory), it must then indicate (usually by pressing a bar) which test sample matches (or does not match) the original sample stimulus presented several seconds earlier (working memory). CB1 agonists (THC and WIN-55,212) disrupt accuracy of such performance in a delay-dependent manner, consistent with a selective disruption of working memory (Heyser et al. 1993). These effects are blocked by the CB_1 antagonist rimonabant. It is important to note that these effects occur at doses that do not interfere with the acquisition of the original reference memory of the task. A simpler variant of the DMS procedure used in rodents, the spontaneous object recognition task, does not rely upon prior operant training, but instead relies upon a rodent's natural preference to explore novel objects. In this task, a rat or mouse is allowed to spontaneously explore two identical objects, then after a delay is given a choice to explore a novel object or the previously presented sample object. In this measure of short-term memory, CB1 agonists (WIN-55,212 and CP55,940) produced a delay-dependent deficit in discrimination between the novel and familiar objects in the choice task (O'Shea et al. 2004, Schneider & Koch 2002), with the disruptive effect enhanced 21 days after chronic pretreatment in adolescents but not adults (O'Shea et al. 2004).

Spatial memory tasks also rely upon accurate working memory. A demanding spatial memory task is the 8-arm radial maze, which requires rats to first learn which arms contain food rewards (reference memory) and then to remember which arms have already been visited in a test session (working memory) after an imposed delay. THC increases the number of working memory errors (re-entries) at low doses, and these effects are blocked by rimonabant (Lichtman & Martin 1996). The impairment of working memory by THC (5 mg/kg) in adult rats is enhanced following chronic exposure (once a day for 90 days), but disappears following 30 days of abstinence from the drug (Nakamura et al. 1991). On the other hand, adolescent rats treated with very high escalating doses of THC (2.5–10 mg/kg) chronically for 10 days and left undisturbed for 30 days until their adulthood exhibited greater impairment in spatial working memory on the radial arm maze than did vehicle controls. The working memory deficit was also accompanied by a decrease in hippocampal dendritic spine density and length (Rubino et al. 2009).

The commonly employed spatial memory task, the Morris water maze, requires animals to navigate in a pool of water to locate a hidden platform by learning its location relative to salient visual cues. The water maze task can be used to evaluate the effect of cannabinoid agonists on reference memory (location of the platform remaining fixed across days and on trials within a day) and working memory (location of platform is changed each day, but remains constant across trials within a day). In the water maze task, THC disrupts working memory at much lower doses than those that disrupt reference memory; in fact, doses sufficient to disrupt working memory are below those that produce other effects characteristic of CB1 agonism, including antinociception, hypothermia, catalepsy, or hypomotility (Varvel et al. 2001). Vaporized marijuana smoke produces a similar effect (Niyuhire et al. 2007a).

Although exogenous CB1 agonists consistently suppress working memory in these models, manipulations that elevate endogenous cannabinoids do not consistently produce such an impairment. On the one hand, elevation

of anandamide (by FAAH inhibition), but not 2-AG (by MGL inhibition), interfered with the consolidation of contextual conditioned fear and object recognition memory (Busquets-Garcia et al. 2001); on the other hand, several other studies have reported facilitation of working memory by FAAH inhibition (Campolongo et al. 2009a, Mazzola et al. 2009, Varvel et al. 2007). Likewise, FAAH-deficient mice (with tenfold increases in brain levels of anandamide) also showed improved rather than impaired performance in this task. Therefore, the effects of exogenously administered CB1 agonists are not always consistent with the effects of manipulations that elevate the natural ligands for the receptors. However, FAAH inhibition also elevates several other fatty acids, including OEA and PEA, which are ligands for PPAR-α. Mazzola et al. (2009) recently found that the enhanced acquisition of a passive avoidance task by the FAAH inhibitor, URB597, was not only reversed by a CB1 antagonist, but also by a PPAR-α antagonist (MK 886). The PPAR-α agonist (WAY1463) also enhanced passive avoidance performance, and this effect was blocked by a PPAR-α antagonist (Campolongo et al. 2009a). Therefore, FAAH inhibition may enhance memory not only by increasing anandamide, but also by elevating OEA and PEA. Most recently, Pan et al. (2011) reported that MGL knockout mice, with elevated levels of 2-AG, show improved learning in an object recognition and water maze task. Thus, there is evidence that both anandamide and 2-AG enhance learning and memory under some conditions.

Effects of CB1 Antagonists on Learning and Memory in Nonhumans

The findings that CB1 agonists produce working memory deficits suggest that inhibition of these receptors may lead to enhancement of short-term memory. However, the literature is replete with mixed findings. CB1 antagonist administration produces memory enhancement in mice in an olfactory recognition task (Terranova et al. 1996) and a spatial memory task in an 8-arm radial maze (Lichtman 2000). In addition, CB_1-/- mice are able to retain memory in an object recognition test for at least 48 hours after the first trial, whereas wild-type controls lose their capacity to retain memory after 24 hours (Reibaud et al. 1999). In contrast, studies using other paradigms, such as the DMS, have shown no benefits of rimonabant on learning or memory (e.g., Hampson & Deadwyler 2000, Mallet & Beninger 1998b). One explanation (Varvel et al. 2009) for the mixed findings is that the temporal requirements of the task predict the potential of CB1 antagonism to facilitate or not facilitate performance. Studies showing enhancement of memory generally require memory processes lasting minutes or hours, whereas studies showing that rimonabant is ineffective generally require retention of information lasting for only seconds, suggesting that blockade of CB1 receptors may prolong the duration of a memory rather than facilitate learning. If this is the case, then rimonabant may facilitate retention of memories tested after long intervals but may have no benefits in tasks such as DMS and repeated acquisition that require rapid relearning of new information (for review, see Varvel et al. 2009).

Role of Endocannabinoids in the Hippocampus in Learning and Memory

The decrement in working memory by cannabinoids appears to involve their action at the hippocampus. The hippocampus is one of the areas of the brain with the highest density of CB1 receptors, and large amounts of anandamide are found in the rodent hippocampus. Interestingly, the selective detrimental effect of CB1 agonists on working memory (but not reference memory) resembles the effects of hippocampal lesions on these two forms of memory (Hampson & Deadwyler 2000, Heyser et al. 1993). Furthermore, THC-induced deficits in the DMS paradigm are associated with specific decreases in firing of individual hippocampal neurons during the sample but not the match part of the experiment (Heyser et al. 1993). Intracranial administration of the CB1 agonists

directly into the hippocampus also disrupts working memory performance in an 8-arm radial maze (Lichtman et al. 1995, Wegener et al. 2008), water maze spatial learning (Abush & Akirav 2010), and object recognition memory (Clarke et al. 2008). In contrast, intrahippocampal AM251 also has been shown to disrupt memory consolidation of an inhibitory avoidance task (de Oliveira et al. 2005). Recent work suggests that the cannabinoid and the cholinergic systems in the hippocampus interact during performance of a short-term memory task in the rat (Goonawardena et al. 2010). These effects may be mediated by cannabinoid-induced decreases in acetylcholine release in the hippocampus. Acetylcholine is also implicated in the pathophysiology of Alzheimer's disease and other disorders associated with declined cognitive function.

Overall, the literature implicates changes in hippocampal functioning as the source of working memory deficits produced by THC, although other brain regions are currently being investigated as well (Marsicano & Lafenetre 2009). Cannabinoid receptors localized to different brain regions modulate distinct learning and memory processes, such that the role of endocannabinoids in other regions may be different than their role in the hippocampus. In fact, Campolongo et al. (2009b) showed that infusion of CB1 agonist WIN 55,212,2 into the basolateral amygdala actually enhanced consolidation of inhibitory avoidance learning by enhancing the action of glucocorticoids in this region. Consistently, Tan et al. (2011) found that delivery of a CB1 antagonist to this region interferes with olfactory fear conditioning. The differential effects of CB1 agonists on different brain regions may account for different findings reported between systemic and localized administration of cannabinoid agonists.

Long-term changes in synaptic strength are believed to underlie associative memory formation in the hippocampus and amygdala. The impairments in working memory produced by CB1 agonists may be the result of the suppression of glutamate release in the hippocampus, which is responsible for the establishment of long-term potentiation, a putative mechanism for synaptic plasticity (Abush & Akirav 2010, Shen et al. 1996). Retrograde signaling by endocannabinoids results in suppression of neurotransmitter release at both excitatory (glutamatergic) and inhibitory (GABAergic) synapses in the hippocampus in a short- and a long-term manner. Endocannabinoid-induced long-term depression (LTD) is one of the best examples of presynaptic forms of long-term plasticity. Recent evidence indicates that presynaptic activity coincident with CB1 receptor activation and NMDA receptor activation is required for some forms of endocannabinoid LTD. The long-lasting effects of LTD appear to be mediated by a CB1 receptor–induced reduction of cAMP/PKA activity in the hippocampus (Heifets & Castillo 2009).

Endocannabinoid Modulation of Extinction of Aversive Memory

Avoidance of aversive stimuli is crucial for survival of all animals and is highly resistant to extinction. Considerable evidence indicates that the endogenous cannabinoid system is specifically involved in extinction learning of aversively motivated learned behaviors (Marsicano et al. 2002, Varvel & Lichtman 2002). A seminal paper by Marsicano et al. (2002) reported that CB1 knockout mice and wild-type mice administered the CB1 antagonist rimonabant showed impaired extinction in classical auditory fear-conditioning tests, with unaffected memory acquisition and consolidation. This effect appeared to be mediated by blockade of elevated anandamide in the basolateral amygdala during extinction (Marsicano et al. 2002). Using the Morris water maze task, Varvel & Lichtman (2002) reported that CB1 knockout mice and wild-type mice exhibited identical acquisition rates in learning to swim to a fixed platform; however, the CB1-deficient mice demonstrated impaired extinction of the originally learned task when the location of the hidden platform was moved to the opposite side of the tank. Because animals deficient in CB1 receptor activity show impairments

in suppressing previously learned behaviors, CB1 agonists would be expected to facilitate extinction of learned behaviors in nondeficient animals. Indeed, WIN-55,212 facilitated extinction of contextual fear memory and spatial memory in rats (Pamplona et al. 2006).

The effect of enhancing the endogenous levels of anandamide by blocking its reuptake or by inhibiting FAAH during extinction learning has also recently been investigated. Chhatwal et al. (2005) reported that the reuptake blocker (and FAAH inhibitor) AM404 selectively facilitated extinction of fear-potentiated startle in rats, an effect that was reversed by rimonabant pretreatment. Varvel et al. (2007) reported that mice deficient in FAAH, either by genetic deletion ($FAAH^{-/-}$) or by pharmacological inhibition, displayed both faster acquisition and extinction of spatial memory tested in the Morris water maze; rimonabant reversed the effect of FAAH inhibition during both task phases. These effects appear to be specific to extinction of aversively motivated behavior, because neither CB1-deficient mice (Holter et al. 2005) nor wild-type mice treated with rimonabant (Niyuhire et al. 2007b) displayed a deficit in extinction of operant responding reinforced with food. Most recently, Manwell et al. (2009) found that the FAAH inhibitor URB597 promoted extinction of a conditioned place aversion produced by naloxone-precipitated morphine withdrawal but did not promote extinction of a morphine-induced or amphetamine-induced CPP.

It has been well established that extinction is not unlearning, but instead is new inhibitory learning that interferes with the originally learned response (Bouton 2002). The new learning responsible for extinction of aversive learning appears to be facilitated by activation of the endocannabinoid system and prevented by inhibition of the endocannabinoid system. More recent work has suggested that the apparent effects of manipulation of the endocannabinoids on extinction may actually reflect its effects on reconsolidation of the memory that requires reactivation (Lin et al. 2006, Suzuki et al. 2008). That is, every time a consolidated memory is recalled it switches to a labile state and is subject to being disrupted. Depending upon the conditions of retrieval and the strength of the original trace, these reactivated memories can undergo two opposing processes: reconsolidation, when the conditions favor the permanence of the trace, or extinction, when the conditions indicate that the memory has no reason to persist. Suzuki et al. (2008) have proposed that the endocannabinoid system is important for the destabilization of reactivated contextual fear memories; that is, reconsolidation or extinction relies on a molecular cascade (protein synthesis and cAMP response element-binding-dependent transcription) that is impeded by prior blockade of the CB1 receptors. Fear memory cannot be altered during restabilization if it was not previously destabilized via activation of the CB1 receptor. Whatever the actual mechanism for facilitated extinction of aversive memories with activation of the endocannabinoid system and inhibited extinction with inhibition of the endocannabinoid system, these results have considerable implications for the treatment of posttraumatic stress disorder. Progress in enhancing endocannabinoid signaling will be of great benefit in the treatment of this distressing disorder.

CONCLUSIONS

Cannabinoid research was originally initiated with the limited aim of understanding the action of an illicit drug. After the chemistry of the plant and the pharmacological and psychological actions of THC were elucidated—or actually only assumed to be elucidated—in the 1960s and early 1970s, research in the field waned. However, over a decade starting from the mid-1980s, two specific receptors and their ligands—the bases of the endocannabinoid system—were found to be involved in a wide spectrum of biological processes. This endocannabinoid system has opened new vistas in the life sciences, particularly in aspects associated with the CNS.

One of the main results of activation of the presynaptic CB1 receptor is inhibition of neurotransmitter release. By this mechanism the

endocannabinoids reduce excitability of presynaptic neurons. CB1 receptors are responsible for the well-known marijuana effects as well as for effects on cognition, reward, and anxiety. In contrast, a major consequence of CB2 receptor activation is immunosuppression, which limits inflammation and associated tissue injury. Enhancement of CB2 receptor expression and/or of endocannabinoid levels has been noted in numerous diseases, including CNS-related ones. Thus, a main result of CB2 receptor activation seems to be a protective effect in a large number of physiological systems.

In the present review we have summarized evidence that cannabinoids modulate anxiety, brain reward function, and cognition by acting at CB1 (and possibly CB2) receptors in distinct brain regions. The effects of cannabis on anxiety appear to relate to the dose of THC and are modulated by the anxiolytic action of cannabidiol (if present in the plant material). A major function of the endocannabinoid system is the homeostatic regulation of the HPA axis in response to stressors. Although THC does not appear to be as rewarding as other drugs of abuse (cocaine, heroin, amphetamine) in animal models of drug abuse, recent work suggests that under optimal conditions, animals do self-administer THC. The rewarding effects of THC are mediated by elevation of DA in the mesolimbic DA system. Blockade of CB1 receptors in this system interferes with the potential of drugs or drug-related cues (but not stress) to produce relapse in animal models.

Both the animal and human literatures suggest that CB1 agonists interfere with short-term working memory and may interfere with consolidation of these memories into long-term memories while leaving previously learned long-term reference memory intact. In cannabis, these effects of THC may be prevented by a sufficiently high dose of cannabidiol. In addition, the memory-impairing effects of THC are usually limited to the acute effects of the drug itself. Recent literature suggests that the endocannabinoid system may play an especially important role in the extinction of aversively motivated learning. Treatments that amplify the action of endocannabinoids may play a critical role in treating posttraumatic stress disorder in the future. Memory decline in aging may also be protected by the action of the endocannabinoid system. Mice lacking CB1 receptors showed accelerated age-dependent deficits in spatial learning as well as a loss of principal neurons in the hippocampus, which was accomplished by neuroinflammation (Albayram et al. 2011). These exciting findings suggest that CB1 receptors on hippocampal GABAergic neurons protect against age-dependent cognitive declines. In addition, interesting recent work suggests that cannabidiol reduces microglial activity after β-amyloid administration in mice and prevents the subsequent spatial learning impairment (Martin-Moreno et al. 2011), suggesting that this nonpsychoactive compound in marijuana may be useful in treating Alzheimer's disease. Cannabidiol has also been shown to recover memory loss in iron-deficient mice, a model of neurogenerative disorders (Fagherazzi et al. 2012).

A very large number of anandamide-like compounds, namely FAAAs or chemically related entities, have been found in the brain (Tan et al. 2010). The action of very few of them has been evaluated. However, those that have been investigated show a variety of effects. Arachidonoyl serine has vasodilator activity—an important protective property in some brain diseases—and lowers the damage caused by head injury (Cohen-Yeshurun et al. 2011). Surprisingly, this effect is blocked by CB2 antagonists, although this compound does not bind to the CB2 receptor. Apparently, its action is indirectly CB2 related. Oleoyl serine, which is antiosteoporotic, is also found in the brain (Smoum et al. 2010); oleoylethanolamide regulates feeding and body weight (Fu et al. 2005); stearoylethanolamide shows apoptotic activity (Maccarrone et al. 2002); the anti-inflammatory palmitoylethanolamide may also be protective in human stroke (Naccarato et al. 2010); arachidonoyl glycine is antinociceptive (Bradshaw et al. 2009); and arachidonoyl dopamine affects synaptic transmission in dopaminergic neurons

by activating both cannabinoid and vanilloid receptors (Marinelli et al. 2007). Presumably, the additional many dozens of related endogenous molecules found in the brain will also exhibit a wide spectrum of activities. Why does the brain invest so much synthetic endeavor (and energy) to prepare such a large cluster of related molecules rather than just a few of them?

If subtle chemical disparity is one of the causes for the variability in personality—an area in psychology that is yet to be fully understood—we may have to look for a large catalog of compounds in the brain with distinct CNS effects. Is it possible that the above-described large cluster of chemically related anandamide-type compounds in the brain is related to the chemistry of the human personality and the individual temperamental differences? It is tempting to assume that the huge possible variability of the levels and ratios of substances in such a cluster of compounds may allow an infinite number of individual differences, the raw substance which of course is sculpted by experience. The known variants of CB1 and FAAH genes (Filbey et al. 2010, Lazary et al. 2010) may also play a role in these differences. If this intellectual speculation is shown to have some factual basis, it may lead to major advances in molecular psychology.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors would like to thank Erin Rock for editorial help. The authors were supported by a grant from the National Institute of Drug Abuse (U.S.) to R.M. (DA-9789) and from the Natural Sciences and Engineering Research Council of Canada (92057) to L.A.P.

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Annual Review of Psychology
Volume 64, 2013

Contents

Indexes

Errata

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