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The endocannabinoid signaling system: a potential target for next-generation therapeutics for alcoholism

Balapal S. Basavarajappa[1,2,3,*]

1 *Division of Analytical Psychopharmacology, New York State Psychiatric Institute*

2 *Department of Psychiatry, College of Physicians & Surgeons, Columbia University, New York, NY 10032, USA*

3 *Nathan Kline Institute for Psychiatric Research, Orangeburg, Orangeburg, NY 10962, USA*

Abstract

Research into the endocannabinoid signaling system has grown exponentially in recent years following the discovery of cannabinoid receptors (CB) and their endogenous ligands, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Important advances have been made in our understanding of the endocannabinoid signaling system in various aspects of alcoholism, including alcohol-seeking behavior. **Alcohol increases** the synthesis or impairs the degradation of endocannabinoids, leading to a locally elevated endocannabinoid tone within the brain. Elevated endocannabinoid tone might be expected to result in compensatory down-regulation of CB1 receptors or dampened signal transduction. Following release, endocannabinoids diffuse back to the presynaptic neuron where they act as short-range modulators of synaptic activity by altering neurotransmitter release and synaptic plasticity. Mice treated with the CB1 receptor antagonist SR141716A (rimonabant) or homozygous for a deletion of the CB1 receptor gene exhibit reduced voluntary alcohol intake. CB1 knockout mice also show increased alcohol sensitivity, withdrawal, and reduced conditioned place preference. Conversely, activation of CB1 receptor promotes alcohol intake. Recent studies also suggest that elevated endocannabinoid tone due to impaired degradation contributes to high alcohol preference and self-administration. These effects are reversed by local administration of rimonabant, suggesting the participation of the endocannabinoid signaling system in high alcohol preference and self-administration. These recent advances will be reviewed with an emphasis on the endocannabinoid signaling system for possible therapeutic interventions of alcoholism.

Keywords

Alcoholism; endocannabinoids; synaptic plasticity; reward; FAAH; CB1 receptors; alcohol-drinking behavior; therapy

INTRODUCTION

Alcoholism is a complex disorder affecting modern society in many ways, yet there are few effective treatment strategies currently available. Almost 19 million Americans have an “alcohol problem”; however, only 2.4 million have been diagnosed and just 139,000 receive medication to treat it [1]. It is estimated that in the United States alone, taxpayers spend over $180 billion annually to deal with alcohol-related problems [2]. Alcohol abuse contributes to

*Corresponding address: Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd, Orangeburg, NY-10962, Tel: 845-398-3234 or 5454; Fax: 845-398-5451; E-mail: Basavaraj@nki.rfmh.org

cardiovascular illnesses, liver disease, cancer, and psychiatric disorders. Alcohol produces several physiological effects in human [3]. Imaging studies demonstrate structural changes in the human brain with prolonged exposure to alcohol. Although its effects on the CNS are dramatic, alcohol is not a potent drug. Alcoholism represents one of the most widespread addictions and is characterized by the phenomena of alcohol tolerance and dependence. Many different biological systems in the brain influence the response to alcohol, and chronic, heavy exposure results in brain adaptations that form the underpinnings of alcoholism. Alcohol is believed to interact with manifold components of the cell membrane, probably exerting effects on membrane receptors and ion channels besides modulating neurotransmitter release. Indeed, there is a vast literature showing that alcohol-induced intoxication is correlated with alcohol's interaction with a variety of receptors that are coupled to neurotransmission and second-messenger systems, leading to changes in regulation of cellular functions [4–6]. Such neuroadaptive changes occur as a consequence of the continuous presence of alcohol in the brain and probably bring about many of the neurobiological events in alcoholism. Despite this knowledge of the mechanisms of alcohol action, little is known about the chronic adaptations that alcohol produces in the brain after prolonged exposure, which lead to long-term alcohol abuse and alcohol addiction. It is now clear that there is no single neurotransmitter system that can be regarded as being responsible for mediating all the central effects of alcohol (for a recent review see [7]). Further research is essential for understanding the biological basis of alcohol-related behaviors and for identifying molecular targets for therapeutic compounds that can alter alcohol's actions in the brain.

Overwhelmingly, recent studies suggest that cannabinoids and alcohol activate similar reward pathways. The CB1 receptors also seem to regulate the reinforcing properties of alcohol[8–12] [13,14]. The discovery of cannabinoid receptors and their endogenous ligands set a landmark in cannabinoid research. These discoveries impacted significantly on alcohol research, too, since there is now considerable evidence that endocannabinoid signaling plays a key role in alcohol addiction, and this has promising clinical consequences. The purpose of this article is to analyze the interaction between alcohol and endocannabinoid signaling, paying particular attention to the reward mechanism. Therapeutic aspects driving from these new insights are also discussed.

THE ENDOCANNABINOID SIGNALING SYSTEM

Tremendous progress has been made in understanding the endocannabinoid system since the cloning in 1990 of the CB1 receptor, which is activated by Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive component of *Cannabis sativa.* The endocannabinoid signaling system consists of: the endocannabinoids; the enzymes and proteins responsible for their synthesis, transport and degradation; the cannabinoid receptors; and the downstream signaling molecules (Table 1). So far, two cannabinoid receptor subtypes have been cloned and characterized; these are named CB1 and CB2. They belong to the large super family of G protein-coupled receptors (GPCRs). GPCR comprises seven transmembrane domains, an extracellular N-terminal tail, three extracellular and three intracellular loops that link the transmembrane domains, and an intracellular C-terminal tail. The CB1 receptor is mainly expressed in the brain and spinal cord and thus is often referred to as the *brain cannabinoid receptor*. The CB1 receptor is expressed at rather high levels in brain regions such as the hippocampus, basal ganglia, and cerebellum and expressed at low levels in peripheral tissues, including the spleen, testis, and leucocytes [7,15]. The CB2 receptor is sometimes referred to as the *peripheral cannabinoid receptor* because of its largely peripheral expression in immune cells, including the white blood cells; CB2 is not expressed even moderately in any brain region [16,17]*. Evidence for another G-

*Note: Recent studies suggested that CB2 cannabinoid receptors are functionally expressed in neurons in the brain (For references see Onaivi et. al. Ann. N.Y. Acad. Sci, 2007, 1074, 514-536).

protein-coupled cannabinoid receptor ("CB3" or "anandamide receptor") in the brain as well as in endothelial tissues is mounting [18–21]. However, the cloning and characterization of this new cannabinoid receptor is yet to come.

The identification of cannabinoid receptors suggested that the brain produces its own chemicals that interact with the CB1 receptor during normal brain function. Thus, an endogenous *cannabinoid-signaling* pathway exists in the brain. Beginning in 1992, two endogenous ligands for mammalian cannabinoid receptors were discovered and characterized. These are N-arachidonylethanolamine—termed anandamide (AEA), from *ananda*, the Sanskrit word for *bliss*—and 2-arachidonylglycerol (2-AG) (Fig. 1) [22–24]. A third, ether-type endocannabinoid, 2-AG ether (noladin ether) (Fig. 1), was isolated from the CNS and shown to display pharmacological properties similar to AEA [25]. A fourth type of endocannabinoid, virodhamine (Fig. 1), in contrast to the previously described endocannabinoids, is a partial agonist with in vivo antagonist activity at the CB1 receptor [26]. Endocannabinoids are present in peripheral tissues as well as in the brain, and recently they were found to be present in breast milk[27]. Brain tissue concentrations of 2-AG are approximately 200-fold higher than those of AEA [28]. The distribution of both endocannabinoids in different brain regions is similar. The highest concentrations are found in the brain stem, striatum and hippocampus, and the lowest in the cortex, diencephalons and cerebellum. However, there is no correlation between endocannabinoid concentration and CB1 receptor distribution. Unlike classical neurotransmitters and neuropeptides, endocannabinoids are not stored in intracellular compartments; rather, they are produced on demand by receptor-stimulated cleavage of lipid precursors [29–34] and released from neurons immediately afterwards [29,31–35].

Endocannabinoids are inactivated by reuptake via a membrane transport molecule, the AEA membrane transporter (AMT) [34,36–41], and subsequent intracellular degradation [29,42, 43] by fatty acid amide hydrolase (FAAH) [38,43–47]. The distribution of FAAH in the brain is similar to that of the CB1 receptor; high concentrations are found in the hippocampus, cerebellum and cerebral cortex [41,46,48–50]. CB1 receptors couple to a variety of signaling pathways through G_i or G_o protein (Table 1), including inhibition of adenylate cyclase [51–53], activation of p42/p44 MAPK [54] [55,56] [57], activation of PI3 kinase [54,57], and activation of c-Jun N-terminal kinase (JNK1 and JNK2) [58]. Endocannabinoids and Δ^9-THC stimulated tyrosine phosphorylation of the FAK+6,7 neuronal splice isoforms on several residues, including Tyr-397, in hippocampal slices [59,60]. Endocannabinoids increased the association of Fyn, but not Src, with FAK+6,7. These effects were sensitive to manipulation of cAMP-dependent protein kinase, suggesting that they were mediated by inhibition of a cAMP pathway [60]. Δ^9-THC promoted phosphorylation of Raf-1 and recruited it to the membrane in cortical astrocytes [55]. MAPK, which is activated by stimulation of CB1 receptors, was shown to activate the Na^+/H^+ exchanger [61]. AEA-stimulated activation of MAPK activity was shown to phosphorylate cytoplasmic phospholipase A_2 ($cPLA_2$) [57]. CB1 receptor agonists induce the early gene expression of Krox-24 [62], c-fos and c-Jun in the brain [63–65], but whether this is mediated by CB1 receptor-activated MAPK is not known. Δ^9-THC-induced phosphorylation of the transcription factor Elk-1 is mediated by MAPK/ERK [66]. Activation of protein kinase B/Akt (isoform IB) by cannabinoid agonists is mediated by Gi/o and PI3K [67].

L-type Ca^{2+} channels are inhibited by CB1 receptor agonist [68]. CB1 receptors activate A-type and inwardly rectifying potassium channels and inhibit N-type and P/Q-type calcium channels and D-type potassium channels [15,53]. In addition, cannabinoids can close sodium channels, but whether this effect is receptor-mediated has yet to be proved. There is also evidence from experiments with rat hippocampal CA1 pyramidal neurons that CB1 receptors inhibit M-type potassium channels [69]. CB1 receptors have also been reported to activate phospholipase C through G proteins [70]. Based on these findings, it has been suggested that

targeting of specific CB1 receptors or their downstream signaling pathway will be an essential consideration in drug development (Table 1).

Endocannabinoids were shown to act as retrograde messengers in the CNS [71] and behave as neuromodulators in many physiological processes. Endocannabinoids released from postsynaptic neurons upon depolarization activate presynaptic CB1 receptors, resulting in inhibition of the release of both excitatory and inhibitory neurotransmitters (depolarization-induced suppression of inhibition, DSI, or depolarization-induced suppression of excitation, DSE) (Fig. 2). This endocannabinoid retrograde messenger activity was also recently found to occur after synaptic activation of group 1 metabotropic glutamate receptors [72] and D2 dopamine (DA) receptors [73]. It remains to be investigated whether endocannabinoid-mediated DSI exists in other brain regions such as ventromedial medulla [74], amygdala [75], substantia nigra [76], and striatum [77] in which exogenously applied CB1 receptor agonists are known to suppress inhibitory postsynaptic currents (IPSCs). DSE was reported in the ventral tegamental area (VTA) as a Ca^{2+}-dependent phenomenon, blocked by CB1 receptor antagonists and enhanced by CB1 receptor agonist [73]. Importantly, DSE was partially blocked by the D_2 DA antagonist and enhanced by the D_2 DA agonist without changing the presynaptic cannabinoid activity [73]. These observations indicate that activation of D_2 DA receptors in the VTA significantly enhances the depolarization-induced release of endocannabinoids, which are responsible for the inhibition of glutamate transmission in the VTA [73]. A synchronous release of miniature excitatory postsynaptic currents (mEPSCs) in Sr^{2+}-substituted extracellular solution was reduced by endocannabinoids in the prefrontal cortex and striatum [78,79]. It remains to be demonstrated whether or not DSE is present in the striatum [79], substantia nigra [80], periaqueductal gray [81] and spinal cord [82]. Furthermore, it is unclear how this endocannabinoid makes its way to the presynaptic nerve terminal or if it is produced there by the action of another unknown signaling molecule.

ENDOCANNABINOIDS AND SYNAPTIC PLASTICITY

AEA was demonstrated to be an effective inhibitor of new synapse formation, raising the interesting possibility that the endocannabinoid system may regulate the number of functional synapses [83–85]. Long-term potentiation (LTP) and long-term depression (LTD) of CA3-CA1 synaptic transmission are two widely accepted models for learning and memory. It was observed that striatal and nucleus accumbens (NAc) LTD were absent in CB1 receptor knockout mice, reduced or eliminated by treatment with rimonabant, and enhanced by the HU-210, suggesting that striatal and NAc LTD are mediated by an endocannabinoid [86] [87]. The endocannabinoid that mediated LTD was evidently released as a retrograde messenger, because LTD was prevented by chelating postsynaptic Ca^{2+} (with 20mM BAPTA) in the recorded cell [87]. CB1 receptors are present on glutamatergic terminals in the prefrontal cortex [88], and activation of CB1 receptor by agonists suppresses glutamate EPSCs in layer V slices of rat cortex, evidently by acting at a presynaptic site [78]; it remains to be determined whether CB1 receptors mediate LTD in the cortex as well. CB1 receptor activation inhibits both LTP and LTD induction in the hippocampus [89,90]. These early investigations are just beginning to address the effects of endocannabinoids on the neurophysiology of the brain, and further studies are needed before the roles of these molecules are fully elucidated.

THE ENDOCANNABINOID SIGNALING SYSTEM IN ALCOHOL ACTION

The presence of endocannabinoid signaling in the thalamus, hippocampus, and cortex, and in the striatum, substantia nigra, and cerebellum supports a role for this pathway in both cognitive and motor responses. This anatomical distribution and the actions of endocannabinoids are consistent with the behavioral effects of alcohol, including memory disruption, impaired motor activity, catalepsy, antinociception, and hypothermia [13,91–96]. Adaptation at several steps

of the endocannabinoid signaling pathway in the brain may play an important role in the development of alcohol addiction [7].

In recent years, several studies provided evidence for the participation of endocannabinoid signaling in the pharmacological actions of alcohol. Earlier studies have demonstrated that chronic alcohol exposure leads to activation of Ca^{2+}-dependent and arachidonic acid-specific PLA_2 in neuronal cells and the brain [97,98]. In recent investigations, it was examined whether the increased arachidonic acid (AA) levels due to PLA_2 activation in alcohol-exposed tissue may be diverted to the synthesis of endocannabinoids. Indeed, it was found that the exposure of SK-N-SH cells or cerebellar granular neurons (CGNs) to chronic alcohol resulted in an increased accumulation of endocannabinoids [32–34] (Table 2). In these studies, it was demonstrated that endocannabinoid synthesis increased with the experimental condition known to cause cellular tolerance to and dependence on alcohol in neurons [99–102]. A similar increase in brain AEA levels also was shown in mice exposed to chronic alcohol [103]. Another study demonstrated that chronic exposure of rats to alcohol caused a decrease in the level of endocannabinoids in the mid-brain, while AEA content increased in the limbic forebrain, a key area for the reinforcing properties of habit-forming drugs, including alcohol (Table 2) [104]. These observations indicate the possible involvement of the endocannabinoids in alcohol-induced neuroadaptive changes in the brain and that activation of endocannabinoid signaling and endocannabinoid-mediated neurotransmission may be responsible for activation of the limbic system by alcohol. The mechanism by which chronic alcohol exposure leads to selective increases in the levels of endocannabinoids remains to be established and such an investigation will be of great utility in formulating therapeutic strategies to treat problems associated with alcohol abuse.

The mechanism (s) involved in the inactivation of endocannabinoids in vivo is not completely understood. However, functional studies indicate that AEA signaling at the cannabinoid CB1 receptor is terminated through an uptake mechanism that transports AEA into the cell where it subsequently undergoes rapid degradation by FAAH [36,37,44,105]. Thus, chronic alcohol-induced increases in extracellular AEA could result from a decrease in AEA influx, an increase in AEA efflux from the cell, and/or altered intracellular metabolism [34]. In fact, it was found that the elevated levels of extracellular AEA from neuronal cells exposed to chronic alcohol resulted from inhibition of the uptake of AEA (Table 2). This effect is apparently independent of the CB1 receptor since alcohol inhibited the uptake of AEA in both wild-type and CB1 receptor knockout mice equally [34]. After prolonged exposure to alcohol, cells become tolerant of these effects such that AEA uptake is no longer inhibited by acute alcohol exposure (Table 2) [34]. These observations suggest that alcohol-induced inhibition of AEA uptake may, in part, be responsible for the alcohol-induced increase in extracellular AEA.

Alcohol and AEA inhibit luteinizing hormone-releasing hormone (LHRH) in medial basal hypothalamic explants by activating CB1 receptors located on GABAergic neurons. Therefore, these studies indicate that alcohol and AEA act through CB1 receptors to inhibit adenylate cyclase activity, preventing the inhibition of basal GABA release by cAMP [106]. In vitro, electrophysiological recordings demonstrated that endocannabinoids and alcohol share a similar pattern in the inhibition of kainate-activated currents in *Xenopus* oocytes expressing the AMPA glutamate receptor, although AEA was a 100-fold more potent at inhibiting AMPA receptor function than was alcohol [107]. This is in agreement with reports that ethanol inhibits the function of both NMDA and non-NMDA glutamate receptors [108]. Furthermore, it was previously shown that AEA inhibition of kainate-activated homomeric and heteromeric glutamate receptor subunits, which was specific and voltage-independent, may underlie the involvement of endocannabinoids in the modulation of fast synaptic transmission in the CNS [107]. Therefore, the long-lasting consequences of compulsive, uncontrollable drug and alcohol use may be associated with memory formation during long-term ingestion of drugs

and/or alcohol [109]. If the memory of drug use, the effects of the drug, and dependency are associated with alcohol and drug addiction, then it remains to be determined if short-term memory disruption by cannabis use, which is involved in glutamatergic transmission, can be exploited in the treatment of drug and alcohol addiction. All these observations suggest the physiological significance of the endocannabinoid signaling system and its role in the modulation of brain function. Thus, an understanding of the physiological mechanisms of endocannabinoid-mediated signaling is crucial to be able to unravel the pathways involved in alcohol action, including alcohol abuse.

Overwhelming evidence suggests that the CB1 receptor mediates some of the pharmacological and behavioral effects of alcohol, including alcohol-drinking behavior in the CNS (Table 2) [8–12,110–113]. CB1 receptor number and function were found to be downregulated in chronic alcohol-exposed mouse brain [114,115]. Similarly, the forced consumption of high levels of alcohol led to significantly reduced CB1 receptor gene expression in the caudate-putamen (CPu), the ventromedial nucleus of the hypothalamus (VMN), and the CA1 and CA2 fields of the hippocampus [116]. These results strongly support the participation of the endocannabinoid signaling system in mediating some of the pharmacological and behavioral effects of alcohol, and hence the CB1 receptor may constitute an important target for therapeutic intervention in alcohol-related behaviors. The precise mechanism by which chronic alcohol exposure leads to a reduction in the levels of CB1 receptor remains to be elucidated; however, it is possible that increased endocannabinoid synthesis or impaired endocannabinoid uptake and degradation [32–34], leading to a locally elevated endocannabinoid tone, could result in a compensatory down- regulation of CB1 receptor levels.

THE ENDOCANNABINOID SIGNALING SYSTEM, BRAIN REWARD CIRCUITRY AND ALCOHOL DRINKING BEHAVIOR

There is strong evidence that the dopaminergic system that projects from the VTA of the midbrain to the NAc as well as to other forebrain sites, including the dorsal striatum, is the major substrate of reward and reinforcement produced by most drugs of abuse (Fig. 3), including alcohol [117–120]. CB1 receptors are present in the different regions of the brain reward circuitry, including the VTA and the NAc, and also in several areas projecting to these two structures, such as the prefrontal cortex, the central amygdale and the hippocampus [121]. It is well established that cannabinoids activate dopaminergic neurons in the VTA [117–120,122,123] resulting in the release of DA in the NAc [124]. Acting as a retrograde messenger, endocannabinoids that activate CB1 receptors present on axon terminals of GABAergic neurons in the VTA could inhibit GABA synaptic transmission, thus removing this inhibitory input on dopaminergic neurons [125]. Glutamate transmission from neurons of the prefrontal cortex in the VTA and NAc is similarly modulated by the activation of CB1 receptors [73,126]. Furthermore, a D2 receptor antagonist has been shown to attenuate the alcohol-induced formation of 2-AG in cerebellar granular neurons [33]. In addition, the hyperactivity associated with post-synaptic D2 receptor activation is accompanied by a dramatic increase in AEA output within the striatum and this effect is potentiated by the CB1 receptor antagonist SR141716A [35]. Acute alcohol-induced DA release in the NAc is in fact mediated by CB1 receptors [112]. The acute alcohol-induced increase in DA in NAc dialysates in C57BL/6 mice was completely inhibited by pretreatment with SR141716A or deletion of the CB1 receptors (CB1 receptor knockout)[112,127]. Thus, the endocannabinoid system appears to be involved in the primary rewarding effects of alcohol because alcohol increases dopaminergic neuron firing rates, thus making possible the release of endocannabinoids in the VTA. Therefore, the endocannabinoid signaling system represents a key component in the neurobiological substrate of alcohol addiction, and the CB1 receptor is a possible candidate target to explain genetic variations in human alcohol vulnerability [128].

Several studies have shown that voluntary alcohol intake is inhibited by CB1 receptor blockade in rodents (Table 3). Rimonabant has been shown to decrease voluntary alcohol intake in alcohol-preferring C57BL/6 mice [8], in Sardinian alcohol-preferring (sP) rats [10], in alcohol self-administering Long Evans rats [129], and in alcohol-preferring congenic B6.Cb4i5-β/13C/Vad and B6.Cb4i5-β14/Vad mouse strains [103]. The acute administration of rimonabant suppressed alcohol self-administration in chronic alcohol-exposed Wistar rats [130]. A significant increase in alcohol preference (free-choice) was observed when Wistar rats were treated with an acute dose of rimonabant during chronic alcohol treatment [131]. The administration of rimonabant after chronic alcoholization significantly decreased the preference for alcohol. Alcohol withdrawal signs were also decreased by administration of rimonabant in these studies[131]. Furthermore, acute administration of CP55, 940 increased the motivation of Wistar rats to consume alcohol and this effect was completely prevented by pretreatment with the rimonabant [11,132]. An acute dose of rimonabant completely abolished the alcohol deprivation effect (i.e. the temporary increase in alcohol intake after a period of alcohol withdrawal) in sP rats [133]. In agreement, acute administration of WIN 55,212-2 and CP55, 940 significantly stimulated voluntary alcohol consumption in alcohol-preferring sP rats and this was completely prevented by rimonabant [134]. However, none of these studies demonstrated any involvement of DA in CB1 receptor-regulated voluntary alcohol intake in these animals. Nonetheless, existing evidence suggests that activation of the CB1 receptor by an agonist may involve the release of DA in NAc and inactivation by rimonabant may inhibit the DA release [112]; this in turn may regulate the voluntary intake of alcohol in these animals.

Predisposition to excessive alcohol consumption and development of alcoholism has been linked to genetic factors. Large, well-constructed, population-based twin studies have shown that the heritability of alcoholism is around 50–60% [135,136]. Evidence to show the participation of the cannabinoidergic system in alcohol drinking behavior is derived from the observed differences in CB1 receptor function in two genetic strains of mice: alcohol-preferring C57BL/6 and alcohol-avoiding DBA/2. In these studies, it was found that C57BL/6 mice have a significantly lower level of CB1 receptor binding sites and higher affinity for [^{3}H] CP-55, 940 than do DBA/2 mice [137]. Interestingly, although they are more numerous, the CB1 receptors of DBA/2 mice are less often coupled to G-proteins compared to the CB1 receptors of C57BL/6 mice, as shown by a GTPγS binding assay [138], which further suggests the participation of these receptors in controlling voluntary alcohol consumption. A recent study showed lower regional levels of CB1 receptor function and lower CB1 receptor gene expression in the brains of Fawn Hooded (alcohol-preferring) rats versus Wistar rats (alcohol-non-preferring) [139]. This was further examined using genetically modified CB1 receptor knockout mice, which exhibited dramatically reduced voluntary alcohol consumption (Table 3). For example, young CB1 receptor wild-type mice exhibited a significantly higher alcohol preference and voluntary alcohol intake compared to their CB1 knockout littermates [113]. Furthermore, rimonabant has been shown to reduce voluntary alcohol intake in CB1 receptor wild-type but not in knockout mice [113]. Similarly, administration of rimonabant significantly reduced alcohol and sucrose intake in C57BL/6x129/Ola mice and had no effect in CB1 receptor knockout C57BL/6x129/Ola mice [140]. Another recent study also provides evidence for participation of the CB1 receptor in the regulation of voluntary alcohol consumption and in some of the acute intoxicating effects caused by administration of alcohol [12]. Alcohol consumption and preference are decreased, whereas alcohol sensitivity and withdrawal severity are increased in CB1 knockout mice (Table 3). Consistent with previous data, female mice consumed more alcohol than did male mice [12]. CB1 receptor knockout mice showed an increase in alcohol withdrawal-induced convulsions, suggesting that alcohol consumption is also inversely related to alcohol withdrawal severity. Alcohol produced a similar reduction in body temperature in CB1 knockout and wild-type mice [141]. Motor coordination on a rotarod was reduced in both CB1 knockout and wild-type mice [141]. In another study, CB1 knockout mice (CD1 background) were more sensitive to the hypothermic and sedative/hypnotic effects

of alcohol than wild-type mice [12]. CB1 knockout mice displayed a significant decrease in locomotor activity following injection of alcohol (1–2.5g/kg) [12]. Importantly, the analysis of recombinant inbred strains for alcohol withdrawal severity led to identification of a quantitative trait locus on chromosome 4 in close proximity to the CB1 receptor gene [142, 143]. Alcohol withdrawal signs observed in CB1 receptor wild-type mice were not observed in CB1 receptor knockout mice [141]. A decreased expression and activity of FAAH was found in the prefrontal cortex (PFC) of alcohol-preferring rats with a compensatory down-regulation of CB1 signaling [144]. Furthermore, intra-PFC injections of the FAAH inhibitor URB597 increased alcohol self-administration in Wistar rats [144]. Recently, increased alcohol consumption and preference and decreased alcohol sensitivity were observed in female but not in male FAAH knockout mice [111]. These results suggest that impaired FAAH function may present a phenotype of high voluntary alcohol consumption, and identify FAAH both as a regulator of endocannabinoid function and a possible therapeutic target for alcohol-related disorders. These data taken together indicate that the endocannabinoid signaling system could be important for alcohol reinforcing effects. These findings are significant for the development of potential therapeutic strategies for the treatment of alcoholism and addiction in general.

THERAPEUTIC OPPORTUNITY

Although the detailed physiology, biochemistry and pathophysiology of the endocannabinoid signaling system have not been fully investigated, there is already overwhelming evidence to indicate that pharmacological modulation of the endocannabinoid signaling system could provide new treatments for a number of disease states, including alcohol addiction. Recently it was reported that rimonabant holds an important therapeutic role in treating liver fibrosis [145] and alcohol abuse accounts for more than half of the prevalence of liver fibrosis and cirrhosis in the western world [146]. Therefore, it is important to examine whether alcohol-induced liver fibrosis and cirrhosis results in increased endocannabinoid levels and rimonabant reverses alcohol-induced liver fibrosis/cirrhosis. In terms of drug development, the CB1 receptor antagonist rimonabant has progressed furthest and is in late phase III trials for the treatment of obesity and as an aid for smoking cessation [147,148]. An NIAAA clinical study of the effectiveness of rimonabant to reduce voluntary alcohol drinking has progressed to phase I trials. Pending results of the clinical trials, rimonabant could become an important addition to the limited arsenal of effective treatments for alcoholism. During drug abuse there are changes in endocannabinoid levels in various brain regions [13,149–151]. Therefore, drugs which regulate the level of endocannabinoids by inhibiting their metabolism (FAAH inhibitors such as URB597) or uptake (AM404) could locally target sites while limiting effects in uninvolved cognitive areas to produce a higher therapeutic value [111,144]. Cannabinoid interactions with the dopamine system have been offered as a possible mechanism for some of the therapeutic potential of cannabinoid-based drugs in alcoholism. A recent study provides evidence of the ability of CB1 receptor antagonist to mitigate alcohol-withdrawal symptoms, and block the formation of physical dependency by inhibiting alcohol intake. Recent data on the role of CB1 receptors in alcohol drinking behavior, including alcohol tolerance as discussed in the earlier sections, clearly suggest that agents such as CB1 receptor antagonists, including rimonabant, will be promising therapeutic agents for the treatment of alcoholism.

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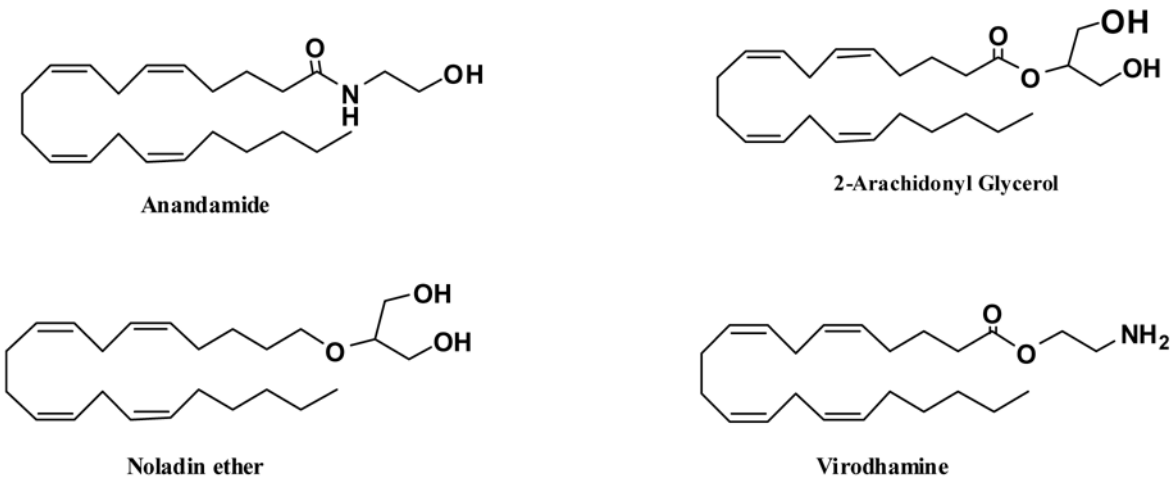

Fig (1). Molecular structures of endocannabinoids that are known to bind to brain cannabinoid receptors

These endocannabinoids share a polyunsaturated fatty acid moiety (arachidonic acid) and a polar head group consisting of ethanolamine or glycerol.

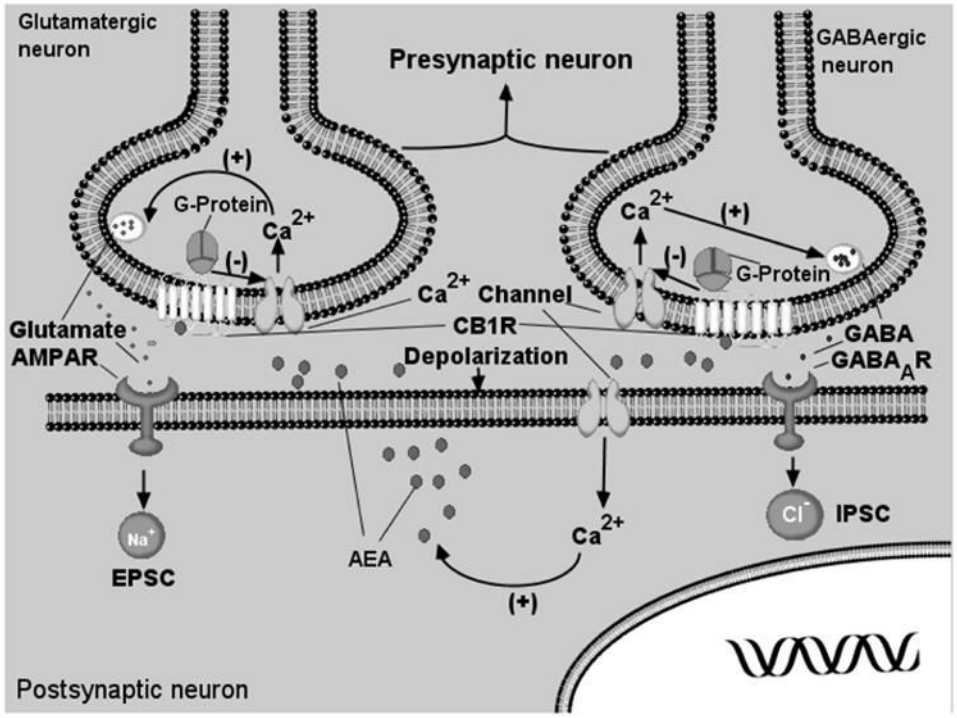

Fig (2). A hypothetical model for the action of endocannabinoids on excitatory and inhibitory neurotransmission through retrograde messenger activity

Depolarization of postsynaptic neuron causes the generation and release of endocannabinoids such as anandamide (AEA). The released endocannabinoids then activate the CB1 receptors (CB1R) at presynaptic terminals and suppress the release of glutamate (left) or GABA (right) by inhibiting Ca^{2+} channels.

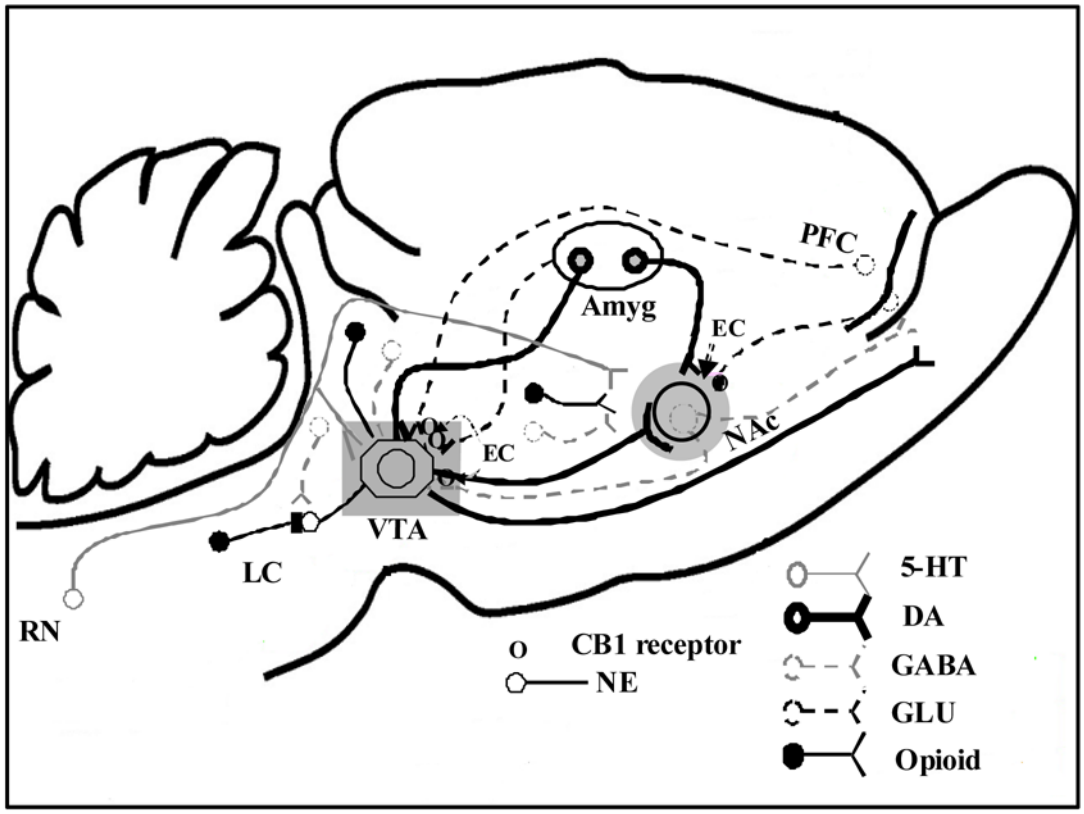

Fig 3. Neural reward circuits important in endocannabinoid action in modulation of the addiction-related effects of drugs of abuse including alcohol

The ventral tegamental area (VTA) contains both dopamine (DA) and γ-aminobutyric acid (GABA) neurons that innervate the nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala (Amyg), and other forebrain targets not shown in the diagram. The glutamatergic (GLU) projections from the PFC to the NAc and the VTA are shown. In the VTA, glutamate inputs from the PFC synapse on mesoaccumbens GABA neurons and mesoprefrontal DA neurons. CB1 receptors are located on presynaptic glutamatergic and GABAergic neurons but not on dopaminergic neurons in the VTA. Activation of CB1 receptors in the VTA by endocannabinoids (EC; broken arrows) produces inhibition of GABA release and removes the inhibitory effect of these GABAergic cells on dopaminergic neurons. The activation of dopaminergic neurons facilitates the release of EC from dopaminergic cells. These EC acting in a retrograde manner on presynaptic CB1 receptors, inhibit both inhibitory (GABA) and excitatory inputs to VTA dopaminergic neurons. In the NAc, EC inhibit glutamatergic neurons through a retrograde manner acting mainly on CB1 receptors on the axon terminals of glutamatergic neurons. This inhibition of glutamate release results in activation of VTA dopaminergic neurons by indirectly inhibiting the GABAergic neurons that originate in the NAc and project to the VTA. CB1 receptors on the glutamatergic projections from the PFC would be important to modulate motivation to seek the drug, including alcohol. Opioid interneurons modulate GABA-inhibitory action on the VTA and influence the firing of norepinephrine (NE) neurons in the locus ceruleus (LC). Serotonergic (5-HT) projections from the raphe nucleus (RN) extend to the VTA and the NAc.

Table 1

The pharmacology of the endocannabinoid signaling system

		Ref (recent reviews)
CB1 receptors		
Localization	Mainly neurons in the CNS and periphery	[7,15,152]
Function in the CNS	Inhibit transmitter release	[71]
	Inhibit adenylate cyclase and cAMP	[7,152,153]
	Inhibit protein kinase A	[15]
	A-type and inwardly rectifying K^+ channels activation	[15]
	Inhibit N-type, P/Q-type $Ca2^+$channels	[15]
	Inhibit D-type and M-type K^+ channels	[7,15,69]
	MAPK activation	[57]
	PI3K activation	[55,152]
	Raf-1 activation	[55,152]
	Protein kinase B/Akt activation	[67]
	cPLA2 activation	[57]
	PLC activation	[70]
	FAK+6,7 activation	[60]
	Elk-1 activation	[66]
	c-fos and c-Jun activation	[63,64]
Selective agonists	CP-55940, ACEA, WIN 55,212-2, HU-210, Arvanil, Δ^9-THC, MetAEA, Nabilone, 0-1812	
Selective antagonists/ inverse agonist	Rimonabant, AM251, AM 281, O-2050, LY320135,	
Endogenous agonists	Arachidonyl ethanolamine (AEA)	[7]
	2-Arachidonyl glycerol (2-AG)	
	2- Arachidonyl glycerol ether (Nolandin ether)	
	N- Arachidonyl dopamine	
	O- Arachidonyl ethanolamine (Virodhamine)	

Table 2

Effects of alcohol on the endocannabinoid signaling system

Endocannabinoid system	Effects	Animal and Tissue	Ref
CB1 receptors	Decreased	Mouse, WB	[114]
	No Change	Rat	[154]
	Decreased	Mouse, LFB	[111]
	Decreased	Mouse, CT, HP ST, CB	[155]
CB1 receptor-G-protein activation	Decreased	Mouse, WB	[114]
	Decreased	Mouse, CT, HP ST, CB	[155]
CB1 receptors mRNA	Decreased	Rat, CPu, VMN CA1 and CA2	[116]
	Increased	Rat, DG	[116]
	No change	Rat	[154]
AEA	Increased	SK-N-SH cells	[32]
	Increased	Rat, CG neurons	[34]
	Increased	Rat, LFB	[104]
	Increased	Rat, LFB	[156]
	Decreased	Rat, midbrain	[104]
	Decreased	Rat, midbrain	[156]
	Increased	Mouse, WB	[103,155]
2-AG	Increased	Rat, CG neurons	[33]
	Decreased	Rat, LFB	[104]
AEA uptake	Decreased	Rat, CG neurons	[34]
FAAH	No Change	Rat, CG neurons	[34]
	Decreased	Mouse, WB	[155]

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonylglycerol; FAAH, fatty acid amidohydrolase; WB, whole brain; LFB, limbic forebrain; CT, cortex; HP, hippocampus; ST, striatum; CB, cerebellum; CPu, caudate-putamen; VMN, ventromedial nucleus of the hypothalamus; CA1 and CA2 fields of hippocampus; DG, dentate gyrus; CG neurons, cerebellar granular neurons

Table 3

Changes to the addictive properties of alcohol by rimonabant or in CB1 receptor or FAAH knockout mice

Model	Dose (mg kg^{-1})[a]	Effect	Animal	Ref
Rimonabant				
Two-bottle choice (voluntary consumption)	0.3–3.0 (sc)	Attenuation	Rat, Mouse	[8]
	2.5–10.0 (ip)	Attenuation	Rat	[10]
	0.3–3.0 (ip)	Attenuation	Rat	[129]
	3.0 (ip)	Attenuation	Mouse	[113]
	3.0–10.0 (ip)	Attenuation	Mouse	[140]
	5.0 (ip)	Attenuation	Mouse	[157]
	3.0 (ip)	Attenuation	Mouse	[158]
Two-bottle choice (acquisition)	0.3–3.0 (ip)	Attenuation	Rat	[159]
Beer-consumption (lick-based)	0.3–3.0 (ip)	Attenuation	Rat	[11,132]
Two-bottle choice (deprivation effect)	0.3–3.0 (ip)	Attenuation	Rat	[133]
Self-administration	0.3–3.0 (ip)	Attenuation	Rat	[9]
	0.3–3.0 (ip)	Attenuation	Rat	[160]
Self-administration (relapse)	1.0 and 3.0 (ip)	Attenuation	Rat	[9]
Extracellular dopamine levels (microdialysis)	3.0 (ip)	Attenuation	Rat	[127]
	3.0 (ip)	Attenuation	Mouse	[112]
Alcohol-withdrawal signs	10.0 (ip)	Attenuation	Rat	[131]
CB1 receptor knockout mice				
Two-bottle choice (voluntary consumption)		Attenuation		[112]
		Attenuation		[113]
		No change		[141]
		Attenuation		[12]
		Attenuation		[157]
Conditioned place preference		Attenuation		[161]
		Attenuation		[157]
Withdrawal signs		Suppression		[141]
		Increase		[12]
FAAH knockout mice				
Two-bottle choice (voluntary consumption)		Increase		[111]

[a] Abbreviations: ip, intraperitoneal; sc, subcutaneous.