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Are CB_1 Receptor Antagonists Nootropic or Cognitive Impairing Agents?

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Abstract

For more than a decade, a considerable amount of research has examined the effects of rimonabant (SR 141716) and other CB_1 receptor antagonists in both in vivo and in vitro models of learning and memory. In addition to its utility in determining whether the effects of drugs are mediated though a CB_1 receptor mechanism of action, these antagonists are useful in providing insight into the physiological function of the endogenous cannabinoid system. Several groups have reported that CB_1 receptor antagonists enhance memory duration in a variety of spatial and operant paradigms, but not in all paradigms. Conversely, disruption of CB_1 receptor signaling also impairs extinction learning in which the animal actively suppresses a learned response when reinforcement has been withheld. These extinction deficits occur in aversively motivated tasks, such as in fear conditioning or escape behavior in the Morris water maze task, but not in appetitively motivated tasks. Similarly, in electrophysiological models, CB_1 receptor antagonists elicit a variety of effects, including enhancement of long-term potentiation (LTP), while disrupting long-term depression (LTD) and interfering with transient forms of plasticity, including depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). The collective results of the in vivo and in vitro studies employing CB_1 receptor antagonists, demonstrate that these receptors play integral roles in different components of cognitive processing. Functionally, pharmacological blockade of CB_1 receptors may strengthen memory duration, but interferes with extinction of learned behaviors that are associated with traumatic or aversive memories.

Keywords

cannabinoid; learning and memory; cognition; rimonabant (SR 141716); marijuana

INTRODUCTION

The primary active constituent of marijuana, Δ^9-tetrahyrocannabinol, and other cannabinoids have long been known to produce a wide range of pharmacological effects, including impairment of learning and memory in humans and in laboratory animals [Ranganathan and D'Souza, 2006; Varvel et al., 2005]. These drugs bind to and activate CB_1 and CB_2 cannabinoid receptors, each of which have been cloned and characterized [Gerard et al., 1991; Matsuda et al., 1990]. Virtually all the behavioral effects of cannabinoids are mediated through the CB_1 receptor. Rimonabant [Rinaldi-Carmona et al., 1994] and other CB_1 receptor antagonists have been very useful tools for basic biomedical research and, until recently, represented a novel class of potential pharmacotherapeutic agents for the treatment of obesity. Although rimonabant possesses efficacy in treating disorders associated with obesity (e.g., the metabolic

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syndrome [Despres et al., 2005] and type 2 diabetes [Scheen et al., 2006]) and tobacco addiction [Rigotti et al., 2009], concerns related to its safety have thwarted clinical development of this class of drugs [Doggrell, 2008]. Nevertheless, CB_1 receptor antagonists have been instrumental for investigating the pharmacology of cannabinoid receptor agonists and elucidating the physiological function of the endogenous cannabinoid system.

It is well established that the administration of cannabinoid receptor agonists impairs memory in a wide range of animal models of learning and memory. Similarly, administration of the endogenous cannabinoid, anandamide [Devane et al., 1992], to mice lacking fatty acid amide hydrolase (FAAH), the enzyme responsible anandamide metabolism [Cravatt et al., 2001], leads to impaired performance in a working memory version of the Morris water maze [Varvel et al., 2005]. Collectively, these actions of exogenous and endogenous cannabinoids, the presence of endogenous cannabinoids in brain (e.g., anandamide and 2-arachidonoylglycerol (2-AG)), and the high density of CB_1 receptors in the hippocampus and other brain regions associated with learning and memory [Herkenham et al., 1991] suggest the possibility that blocking endocannabinoid signaling could elicit nootropic effects. Here, we review the scientific literature that has examined the effects of CB_1 receptor antagonists in preclinical and in vitro models of learning and memory. Although rimonabant has been the CB_1 receptor antagonist of choice in the vast majority of published literature, several other antagonists have been employed in learning and memory studies, including AM251 [Gatley et al., 1996], AM281 [Gatley et al., 1998], SR147778 [Rinaldi-Carmona et al., 2004], and CE [Cao et al., 2007].

RIMONABANT-INDUCED MEMORY ENHANCEMENT

In this section, we will review research that has evaluated the effects of CB_1 receptor antagonists in rodent models of learning and memory. As most of these studies have employed rimonabant, much of this discussion will be on this drug. In general, the nootropic effects of rimonabant in whole animals are highly dependent on the demands of the task employed and occur in some, but certainly not all, models of learning and memory.

Terranova and colleagues [1995] were the first to report that rimonabant has memory-enhancing effects. Using a rodent social recognition task, subjects were presented with a juvenile conspecific on two trials separated by an inter-trial interval (ITI) of various durations [Terranova et al., 1996]. In this paradigm, the difference in the amount of time spent investigating the juvenile between the first and second trials is used to infer memory. Accordingly, a decrease in the amount of investigative time during the second trial compared to the first trial indicates that the subject remembers the juvenile, while increasing the ITI leads to a concomitant increase in trial 2 investigation time, signifying that the test subject has forgotten the conspecific. Administration of rimonabant to healthy rats immediately after the original encounter, but not when administered just prior to the recall session enhanced memory duration [Terranova et al., 1996]. Likewise, rimonabant attenuated memory deficits of aged mice and rats in this task as well as prevented performance deficits produced by presenting the test subject with a different juvenile between the two encounters with conspecific subject.

Rimonabant has also been found to improve memory in radial arm maze and elevated T-maze spatial memory tasks. In one radial arm maze task, rats were given a two-phase test in which they were first allowed access to seven of the eight arms, each of which was baited with food. During the second phase, all eight arms were available, but only the previously blocked arm was baited with food. Increasing the ITI increases the difficulty of the task and causes a concomitant increase in the number of errors (i.e., entries into previously available arms). Rimonabant (1 or 3 mg/kg) significantly prolonged memory duration when given before the first phase [Lichtman, 2000; Wise et al., 2007]. However, rimonabant was without effect when administered immediately after the acquisition phase or 20 min before the second phase. In a

different version of the radial arm task in which four arms were blocked, rimonabant given immediately after the acquisition phase enhanced performance during the retrieval test [Wolff and Leander, 2003]. However, only 1 mg/kg of rimonabant was effective, while the 0.3 and 3.0 mg/kg doses failed to elicit significant effects. Similarly, the CB_1 receptor antagonist developed by Pfizer, CE, enhanced memory duration in the rat radial arm maze delay task [Wise et al., 2008]. In the elevated T-maze task, subjects are placed on the apparatus that consists of two open and two closed arms. After being given multiple exposures, the subjects spend significantly more time in the closed arms compared to the amount of time spent in the open arms. Rimonabant administered before or immediately after training, enhanced avoidance performance [Takahashi et al., 2005]. Again, only a single dose of drug was effective (i.e., 1.0-mg/kg, but not 0.5- or 2.0-mg/kg doses), and it was ineffective if given only before the retention test. While no direct anxiogenic effects of rimonabant were found in this study, other reports have shown that rimonabant can produce such effects [Patel and Hillard, 2006], thus complicating interpretation of these results. However, these findings are generally consistent with the above observations that rimonabant treatment before or immediately following training can enhance memory duration in some paradigms.

A few studies have examined whether rimonabant can ameliorate chemical-induced memory impairment. Drago's group has reported that rimonabant can ameliorate memory deficits in a murine model of Alzheimer's disease [Mazzola et al., 2003]. Specifically, they gave mice intracerebroventricular injections of β-amyloid fragments or vehicle 1 week before training in a passive-avoidance task. The subjects were then evaluated for retention 1 and 7 days after acquisition. Rimonabant (1 mg/kg) given 30 min before the second retention session normalized performance in the mice infused with β-amyloid fragments to the same level as the control animals. However, rimonabant did not enhance performance in control mice given intracerebroventricular injections of vehicle. Moreover, rimonabant was ineffective when given before the acquisition session, suggesting that its effects were on retrieval processes [Mazzola et al., 2003].

In contrast, there are conflicting results in experiments that have examined whether rimonabant can block scopolamine-induced memory deficits. Rimonabant (3 mg/kg) failed to block the memory disruptive effects of scopolamine (0.5 mg/kg) in a rat radial arm maze task [Lichtman and Martin, 1996]. However, rimonabant (1 mg/kg) partially attenuated the deficits elicited by 0.06 mg/kg in the rat social recognition task [Terranova et al., 1996]. Similarly, in the elevated T-maze task described above in which control mice typically exhibit significant increases in the amount of time spent in the closed arms compared to the open arms over trials, rimonabant at 1 mg/kg, but not at 0.5 or 2 mg/kg, blocked the disruptive effects of scopolamine (1 mg/kg) on performance [Takahashi et al., 2005]. There are considerable procedural differences among these studies, which could account for the different results, including species (mice vs. rats), task (spatial memory vs. avoidance learning), and doses of rimonabant as well as scopolamine. However, in a recent study, the disruptive effects of scopolamine in acquisition of active avoidance learning were not ameliorated in CB_1 (−/−) mice [Bura et al., 2007], supporting the view that the effects of scopolamine are not mediated through CB_1 receptors.

Until recently, rimonabant was not thought to enhance memory in operant paradigms. It failed to improve performance in delayed match to sample, delayed non-match to sample, and fixed consecutive number and fixed ratio operant tasks [Brodkin and Moerschbaecher, 1997; Hampson and Deadwyler, 2000; Mallet and Beninger, 1998; Mansbach et al., 1996]. Given that these operant tasks are heavily dependent on working or short-term memory, it was initially thought that the CB_1 receptor plays a functional role in memories that persist for longer periods of time (i.e., minutes or hours) than memories that decay on the order of seconds. However, Deadwyler and Hampson's groups demonstrated that rimonabant significantly improved performance on a delayed non-match to sample task that was strongly associated with increased

the strength in firing pattern ensembles of CA1 and CA3 hippocampal neurons, in trials with delay intervals of >10 s [Deadwyler et al., 2007].

In addition to a lack of apparent effect of rimonabant in operant memory paradigms, blocking CB_1 receptor signaling has been found to either not affect or impair acquisition in a variety of tasks. Rimonabant had no effect on the number of trials required to achieve criteria in a T-maze avoidance task [Takahashi et al., 2005] or in an active avoidance paradigm in mice [Bura et al., 2007]. Intra-hippocampal administration of rimonabant in food-storing black-capped chickadees before training had no effect on acquisition in locating a hidden food reward [Shiflett et al., 2004]. Similarly, there were no differences in acquisition rates between rimonabant-treated mice and vehicle-treated mice or between CB_1 (−/−) mice and wild-type mice in a fixed platform Morris water maze task [Varvel et al., 2005; Varvel and Lichtman, 2002]. However, other studies have reported that disruption of CB_1 receptor signaling can impair learning. First, Zimmer and colleagues found that while young CB_1 (−/−) mice (i.e., 6–7 weeks) on a C57BL/6 background display as good as or better learning than wild-type mice, mature CB_1 (−/−) mice (i.e., >3 months) showed poor learning in a battery of tests [Bilkei-Gorzo et al., 2005]. The poor performance in the mature CB_1 (−/−) mice was accompanied by a loss of CB_1 receptors in the CA1 and CA3 regions of the hippocampus. Similarly, CB_1 (−/−) mice on a CD1 background strain showed dramatically impaired acquisition of a contextually conditioned fear response, and AM251 treatment produced a more modest impairment [Mikics et al., 2006]. Finally, CB_1 (−/−) mice as well as rimonabant-treated mice displayed selective impairments in a cerebellar-dependent eye-blink conditioning task [Kishimoto and Kano, 2006]. Disruption of CB_1 receptor signaling led to a failure of mice to acquire eye-blink conditioning in cerebellar-dependent delay procedure in which there is a temporal overlap of the unconditioned stimulus (US; i.e., shock to the eyelid) with the preceding tone conditioned stimulus (CS). Remarkably, CB_1 (−/−) mice and rimonabant-treated mice displayed normal acquisition in the cerebellar-independent trace conditioning procedure in which there is a stimulus free interval of time between presentation of the CS and US. Clearly, the role that CB_1 receptors play in learning and memory is highly dependent on several components, including the type of task, specific methodological considerations, neural substrates that underlie the plasticity, species, and age of the animal. Nevertheless, CB_1 receptor antagonists have been demonstrated to enhance memory duration in spatial memory, social recognition, and operant tasks.

CB_1 RECEPTOR ANTAGONISM AND EXTINCTION

The studies discussed above in which blockade of CB_1 receptor signaling enhanced performance in radial arm maze, social recognition, and delayed non-match to sample tasks support the hypothesis that rimonabant may potentially serve as a memory-enhancing agent. Conversely, disruption of CB_1 receptor signaling has also been shown to impair an important component of cognition known as extinction, which requires the suppression a learned response when reinforcement is withheld [Myers and Davis, 2002; Rescorla, 2001]. As discussed below, several studies have demonstrated that rimonabant disrupts extinction of fear-conditioned and spatial navigation tasks, but this effect does not appear to occur in appetitively motivated tasks.

A commonly used behavioral paradigm to study extinction is fear conditioning, which pairs a neutral CS, such as an auditory tone or contextual cues, with an aversive US (typically electric foot shock). Following acquisition, exposure to the CS alone elicits a conditioned fear response (CR), such as freezing behavior. Subsequent exposures to the CS alone, in the absence of foot shock, lead to progressive decreases in freezing (i.e., extinction). Several reports have shown impaired extinction, but not acquisition, of conditioned fear responses in rimonabant-treated mice and/or CB_1 (−/−) mice [Cannich et al., 2004; Kamprath et al., 2006; Marsicano et al., 2002; Niyuhire et al., 2007; Suzuki et al., 2004]. In the first such report, CB_1 (−/−) mice and

rimonabant-treated wild-type mice displayed impaired short-term (within-session) and long-term (across days) extinction of conditioned freezing to a tone that had been paired with foot shock, without showing any evidence of impaired acquisition, locomotion, or shock sensitivity [Marsicano et al., 2002]. This effect has since been replicated by several other laboratories [Cannich et al., 2004; Kamprath et al., 2006; Niyuhire et al., 2007]. Importantly, presentation of the tone during extinction (i.e, in the absence of shock) was found to increase endogenous cannabinoid levels in the amygdala, a brain area associated with fear [Marsicano et al., 2002]. Moreover, differences between CB_1 (+/+) and (−/−) mice were observed on the activation of extracellular signal-regulated kinases (ERKs), their downstream effector AKT, and the phosphatase calcineurin in different aspects of the amygdala and hippocampus in response to non-reinforced presentation of the tone following fear conditioning, indicating a functional relevance for extinction-stimulated release of endocannabinoids [Cannich et al., 2004]. These findings are consistent with the notion that the release of endocannabinoids may play a critical role in extinction learning. An alternative explanation for some of these results is that disruption of CB_1 receptor signaling may lead to non-associative sensitized fear responses induced by electric shock. In support of the latter hypothesis, foot shock delivered to mice in one context sensitized the fear responses of mice subjected to a subsequent tone delivered the next day in a different context [Kamprath et al., 2006]. This effect dissipated in wild-type mice after repeated exposures to the tone, presumably due to habituation processes. However, CB_1 (−/−) mice and rimonabant-treated mice continued to display this sensitized response. This effect could contribute to or even possibly account for the extinction deficits described above. On the other hand, chemical blockade or genetic deletion of CB_1 receptors failed to impair extinction in an eye-blink conditioning task in which subjects received 100 extinction trials per day across four days [Kishimoto and Kano, 2006].

In addition to cued conditioning paradigms, fear responses (e.g., freezing) can also be conditioned to the environmental context in which the shock occurred, absent of any discrete CS temporally paired with the shock. Of consequence, conditioned freezing to a context is believed to involve hippocampal processes, while the hippocampus is not believed to play a major role in conditioned freezing to a tone [Phillips and LeDoux, 1992]. In one series of experiments, rimonabant was found to impair extinction of conditioned freezing to the test chamber (i.e., contextual conditioning) in which mice had received the shock [Suzuki et al., 2004]. In this contextual conditioning paradigm rimonabant failed to disrupt the within-session (short-term) extinction of conditioned freezing, but did disrupt extinction when the mice were tested 24 h later, suggesting that consolidation of the extinction learning was impaired. Similarly, the CB_1 receptor antagonist SR147778 impaired short-term extinction of freezing to a context that had been paired with foot shock [Pamplona et al., 2006]. This pattern of results differs from results in the cued-fear conditioning experiments discussed above in which both within-session and long-term extinction were impaired, suggesting that the role of endocannabinoids in extinction may differ between the hippocampus and amygdala. Another fear conditioning task is the passive avoidance task in which mice are trained to avoid a context paired with shock. As described in most of the conditioned freezing studies, rimonabant disrupted extinction of avoidance behavior in a two-chamber passive avoidance task [Niyuhire et al., 2007]. This experiment shows that the effects of rimonabant in the classically conditioned fear responses described above can be generalized to other types of fear conditioning tasks.

Blockade of CB_1 receptors also impairs extinction in the Morris water maze task [Varvel et al., 2005]. In this model, mice were trained in a fixed platform procedure and were subjected to either a spaced extinction procedure (i.e., a single 60-s extinction trial given every two to four weeks) or a massed extinction procedure (i.e., four daily 120-s trials given on 5 consecutive days). In the massed procedure, disruption of CB_1 receptor signaling did not alter the rate of extinction. In the spaced extinction procedure, the control mice exhibited extinction across the probe trials, while rimonabant-treated mice and CB_1 (−/−) mice continued to return to where

the platform had been located, indicating extinction deficits. Importantly, an additional group of wild-type mice that was given only a single-probe trial 9 weeks after acquisition exhibited near-perfect performance, indicating that performance reflected extinction and not merely time-dependent forgetting. This dependency of the extinction-impairing effects of CB_1 blockade on the inter-trial interval resembles the profile of rimonabant observed in the contextual conditioning task described above, where long-term, but not short-term extinction was impaired [Suzuki et al., 2004]. This phenomenon may reflect the hippocampal-dependency of these tasks (as opposed to cued fear conditioning), as early work showed that hippocampal lesions produced extinction deficits when long inter-trial intervals were used, but not with shorter ones [O'Keefe and Conway, 1978]. This effect of rimonabant impairing extinction was subsequently replicated using a protocol in which extinction trials were performed once per week [Varvel et al., 2005].

An important implication of rimonabant-induced extinction deficits is that subsequent learning may be adversely affected. For example, CB_1 (−/−) mice as well as rimonabant-treated mice learn the location of the fixed platform Morris water maze task at identical rates as wild-type mice [Varvel et al., 2005; Varvel and Lichtman, 2002]. However, CB_1 (−/−) mice exhibit a significant impairment in learning to a new location of the platform, such as in a reversal task in which the location of the hidden platform was moved to the opposite side of the tank [Varvel and Lichtman, 2002]. While wild-type mice readily learned the new platform location, CB_1 (−/−) mice continued to swim to the original platform location, despite being repeatedly shown the new platform location. A similar phenomenon was reported in an experiment evaluating place-learning in food-storing birds, where intrahippocampal infusion of rimonabant during initial acquisition enhanced retention of the food location, but interfered with their ability to learn a subsequent location [Shiflett et al., 2004]. Curiously, a low dose of either AM251 or the potent CB_1 receptor agonist HU-210 increased behavioral flexibility (i.e., reduced perseverative errors) in a set-shifting four arm maze task in which rats received food reinforcement [Hill et al., 2006]. Consistent with the notion that behavioral flexibility can be regulated by cannabinoids, SR147778 retarded and WIN55,212-2 facilitated reversal learning in a rat Morris water maze task [Pamplona et al., 2006].

A common feature of the tasks discussed above is that each paradigm employs aversive unconditioned stimuli. Conversely, several reports found that rimonabant did not affect extinction in appetitive learning paradigms. For example, CB_1 (−/−) mice acquired and extinguished an operant nose-poke task comparably to controls, though overall response rates were reduced in the CB_1 (−/−) mice [Holter et al., 2005]. The observation that CB_1 (−/−) mice undergo equivalent rates of extinction in an operant tasks for palatable food was subsequently replicated [Ward et al., 2007]. Similarly, rimonabant-treated mice in an operant lever-pressing task for sweetened condense milk displayed an equivalent rate of extinction as vehicle-treated mice, though the characteristic extinction burst was completely abolished and baseline response rates were reduced [Niyuhire et al., 2007]. An alternative explanation for the discrepant results of CB_1 receptor blockade on extinction in aversively and appetitively motivated behaviors is that the nature of the task determines whether CB_1 receptors play a role in extinction. Specifically, studies examining appetitively motivated behavior employed operant procedures, which certainly have distinct behavioral demands than conditioned fear paradigms or the Morris water maze. In order to test this hypothesis, Harloe et al. [2008] employed a modified Barnes maze task in which the behavioral demands of the task (i.e., locating and entering the hidden compartment) were kept constant, but the nature of the reinforcer varied. In aversive version of the task, subjects entered the hidden compartment to escape from aversive stimuli (i.e., bright lights and air turbulence). In the appetitive procedure, the mice were water restricted and access to water served as the reinforcer. Strikingly, rimonabant treatment disrupted extinction learning in the Barnes maze under aversive, but not under appetitive, conditions. These findings support the hypothesis of Holter et al. [2005] that

the endocannabinoid system modulates the extinction of learned behavior that is associated with aversive memories, leaving extinction of learned behaviors from appetitively reinforced tasks intact. Accordingly, these findings raise additional safety concerns related to the development of CB_1 receptor antagonists for therapeutic applications.

EFFECTS OF CB_1 ANTAGONISTS ON SYNAPTIC PLASTICITY

The behavioral effects of CB_1 antagonists in the learning and memory tasks discussed above are most likely mediated by effects on synaptic plasticity, the general process by which functional connections between neurons are altered in response to particular patterns of activation. Electrophysiological approaches have been used to characterize several distinct forms of plasticity, ranging from long-lasting changes in the responsivity of neurons such as long-term potentiation (LTP) and long-term depression (LTD) to transient forms such as depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). A large body of evidence primarily from studies that have used CB_1 receptor antagonists or CB_1 (−/−) mice suggests that endocannabinoids play important physiological roles in mediating or modulating different types of plasticity.

LTP refers to the phenomenon in which brief electrical stimulation applied to afferent pathways results in an increase in the resulting excitatory synaptic potentials of postsynaptic neurons, which can last from hours to weeks. This phenomenon was first observed in the hippocampus [Bliss and Lomo, 1973], where it has been most extensively characterized, but has since been demonstrated in many other brain areas. Several studies examining the effects of a variety of cannabinoids in this paradigm have demonstrated that exogenous cannabinoid receptor agonists disrupt LTP in the hippocampus [Collins et al., 1994; Nowicky et al., 1987; Terranova et al., 1995]. Similarly exogenous administration of anandamide [Terranova et al., 1995] or 2-AG [Stella et al., 1997] also disrupts LTP. The effects of these agonists have been blocked by rimonabant or AM-251, which supports CB_1 receptor involvement in these effects [Collins et al., 1995; Lees and Dougalis, 2004; Misner and Sullivan, 1999; Paton et al., 1998; Stella et al., 1997; Terranova et al., 1995].

Interestingly, rimonabant administered alone has been reported to promote the induction of LTP in prefrontal cortex slices [Auclair et al., 2000], and CB_1 (−/−) mice have been found to exhibit enhanced hippocampal LTP induced by moderate stimulation of the Shaffer collaterals [Bohme et al., 2000]. Similarly, both rimonabant and AM251 facilitated LTP elicited by theta burst stimulation (but not by higher frequency stimulations) in the hippocampus [Slanina et al., 2005], while seven daily treatments of AM251 also enhanced induction of LTP [Hoffman et al., 2007]. A proposed mechanism given for cannabinoid agonist-induced disruption of LTP is that presynaptic CB_1 receptors appear to inhibit release of the glutamate necessary to depolarize the postsynaptic cell and initiate the induction of LTP [Sullivan, 2000]. Consistent with this, the application of CB_1 receptor antagonists has been shown to increase glutamatergic transmission in the hippocampus [Auclair et al., 2000], as well as other brain areas such as the ventral tegmental area (VTA) [Melis et al., 2004], implying that release of glutamate is tonically inhibited by endocannabinoids [Auclair et al., 2000]. However, the role of CB_1 receptors in this effect is still controversial [Al-Hayani and Davies, 2000; Paton et al., 1998; Terranova et al., 1995], and appears to depend on a number of factors such as species, strain, and age of the subject. There is evidence that this inhibition of hippocampal glutamate release is mediated by a novel, non-CB_1 receptor that is sensitive to both WIN 55212 and rimonabant [Hajos and Freund, 2002; Hajos et al., 2001; Hoffman and Lupica, 2000].

A complementary mechanism by which CB_1 antagonists could enhance LTP has been suggested by the characterization of another form of inhibitory plasticity, long-term depression of inhibitory transmission (LTD_i), where the inhibitory influence of GABA release is

depressed, thus promoting the induction of LTP. The suppression of inhibitory transmission by CB_1 agonists has been well characterized [Riedel and Davies, 2005; Szabo and Schlicker, 2005]. LTD_i, i.e., it can facilitate subsequent induction of LTP and is dependent on CB_1 receptors [Chevaleyre and Castillo, 2003]. Specifically, LTD_i is not observed in tissue from CB_1 (−/−) mice and is prevented by AM251 [Mato et al., 2004].

In contrast to the strengthening of synaptic strengths accomplished with LTP, another form of long-term synaptic plasticity known as long-term depression (LTD) results in a persistent weakening of synaptic strength. LTD has been demonstrated in several brain areas, including the hippocampus, striatum, cerebellum, and various parts of the cortex [Gaiarsa et al., 2002; Kemp and Bashir, 2001]. Over the past few years, the endocannabinoid system has been proposed to be a crucial component of LTD in several brain areas, including the striatum, amygdala, frontal cortex, and nucleus accumbens. In the striatum, LTD was absent in CB_1 (−/−) mice and greatly reduced in slices preincubated with rimonabant, while it was potentiated by AM404, a nonselective inhibitor of both FAAH and the putative anandamide transporter [Gerdeman et al., 2002]. In slice preparations containing prelimbic cortex-NAc synapses, stimulation of the prelimbic cortex afferents for 10 min was found to induce LTD of evoked excitatory transmission. Induction of this LTD was completely blocked by rimonabant or AM251, and was absent in CB_1 (−/−) mice. Once established, rimonabant had no effect on the late-phase of this LTD [Robbe et al., 2002]. A similar facilitative role of endocannabinoids on LTD has been proposed in the amygdala, where LTD induced by WIN55212-2 or amphetamine was blocked by AM251, and the amphetamine-induced LTD was facilitated by AM404 [Chu et al., 2003]. Additionally, LTD in the neocortex [Sjostrom et al., 2003] as well as in the nucleus accumbens [Hoffman et al., 2003; Robbe et al., 2003] has been shown to be dependent on presynaptic activation of CB_1 receptors. These findings support the notion that endocannabinoids serve as retrograde messengers to reduce excitatory inputs to output neurons in a variety of brain areas.

This hypothesized role of endocannabinoids is also consistent with a series of experiments examining the effects of cannabinoid agonists and CB_1 antagonists on synaptic plasticity in the prefrontal cortex [Auclair et al., 2000]. Tetanic stimulation induced plasticity in slightly more than half of the neurons examined, with approximately equal numbers of cells developing LTP and LTD. However, in the presence of WIN55212-2 almost all the plastic synapses showed LTD, while in the presence of rimonabant almost all the plastic synapses developed LTP. The consequences of such a shift on learning are unclear, though it may suggest that forms of learning heavily dependent on LTP could be enhanced by CB_1 antagonists, while forms of learning heavily dependent on LTD could be impaired.

In addition to their effects on forms of long-term plasticity discussed above, CB_1 receptor antagonists have been shown to block the occurrence of transient forms of plasticity, such as depolarization-induced suppression of inhibition (DSI) and its corollary depolarization-induced suppression of excitation (DSE). DSI involves GABAergic transmission and has been demonstrated in hippocampal CA1 pyramidal cells [Pitler and Alger, 1992, 1994] as well as in the cerebellum [Llano et al., 1991; Vincent et al., 1992]. Depolarization of the postsynaptic cell results in the release of a retrograde messenger which diffuses back across the synapse and inhibits further GABA release, thus diminishing inhibitory tone for a brief period of a few seconds. Conversely, DSE involves the short-term inhibition of glutamate release, and has also been demonstrated in several brain areas including the VTA [Melis et al., 2004]. Wilson and Nicoll as well as Ohno-Shosaku and colleagues independently provided the first evidence that endogenous cannabinoids may play a critical role in DSI. Supporting such a role for endocannabinoids are the findings that DSI in the hippocampus is completely blocked by CB_1 receptor antagonists [Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001] and is absent in CB_1 (−/−) mice [Wilson et al., 2001]. In addition, DSI observed in cerebellar Purkinje cells

is mediated by CB_1 receptors located on presynaptic neurons [Diana et al., 2002; Kreitzer and Regehr, 2001; Yoshida et al., 2002]. Based on these findings, it has been hypothesized that endocannabinoids are released from the postsynaptic neuron, travel retrogradely to presynaptically located CB_1 receptors where they inhibit GABA release. Similarly, AM251 prevented DSE in cerebellar Purkinje cells [Kreitzer and Regehr, 2001]. Clearly, it will be important to determine whether endogenous cannabinoids are actually released during DSI. Despite the potential importance of these phenomena, their physiological significance remains to be established. Intriguingly, attempts to induce DSI using pulse trains that mimic the much lower firing rates of hippocampal cell-firing patterns observed in vivo found DSI most often when synaptic inputs from multiple neurons converged temporally, allowing the summation of postsynaptic membrane events to exceed the threshold for calcium entry [Hampson et al., 2003; Zhuang et al., 2005].

DISTINGUISHING BETWEEN CB_1 RECEPTOR ANTAGONISM AND INVERSE AGONISM

Findings in which CB_1 receptor antagonists alter behavior may implicate the involvement of endogenous cannabinoids; however, these drugs are also known to have inverse agonist properties in which they exert opposite pharmacological effects from CB_1 receptor agonists [Landsman et al., 1997]. Whereas cannabinoid receptor agonists stimulate [^{35}S]guanosine-5′-(gamma-O-thio) triphosphate (GTPγS) binding [Burkey et al., 1997; Sim et al., 1996], rimonabant decreases GTPγS binding in membranes isolated from human cannabinoid CB_1 receptor-transfected CHO cells [Landsman et al., 1997; Pan et al., 1998], suggesting inverse agonist activity. Consequently, as an inverse agonist, rimonabant would be expected to elicit the opposite effects of cannabinoid agonists at the receptor. Since cannabinoid agonists impair memory, a cannabinoid inverse agonist might be expected to enhance memory, without invoking a role for endocannabinoids. However, Sim-Selley and colleagues [2001] have demonstrated that rimonabant is ~7,000-fold more selective as a CB_1 receptor antagonist than as an inverse agonist. In rat cerebellar membranes, it competitively antagonized WIN 55,212-2-stimulated GTPγS binding at nM concentrations, but inhibited basal receptor-mediated G-protein activity at μM concentrations [Sim-Selley et al., 2001]. While emerging research is directed on developing a neutral CB_1 receptor antagonist [Hurst et al., 2006; Thomas et al., 2004], at the present time one cannot distinguish between endogenous cannabinoid tone and inverse agonist activity when observing a pharmacological effect of rimonabant alone.

Another explanation for intrinsic effects of rimonabant is that this drug may act at noncannabinoid sites of action, although it does not bind to CB_2, histamine, dopamine, opioid, 5-HT, adenosine, and several other receptors and ion channels [Compton et al., 1996; Rinaldi-Carmona et al., 1994]. The extent to which similar phenotypes are observed in rimonabant-treated mice and CB_1 (−/−) mice tends to provide converging lines of evidence implicating the involvement of endogenous cannabinoids. However, even this indirect approach can present significant challenges, as mature (i.e., 3–5 months of age) CB_1 (−/−) mice, display significant learning deficits that are accompanied by a decrease of neurons in the CA1 and CA3 regions of the hippocampus [Bilkei-Gorzo et al., 2005].

CONCLUSIONS

The collective results of the research investigating CB_1 receptor antagonists on learning and memory reveal a complex array of effects that are highly dependent on the particular model employed as well as other important procedural aspects (e.g., species, strain, dose of antagonist). In many behavioral tasks, performance is near flawless, which precludes the possibility of detecting drug-induced enhancements. Most of this research has employed the CB_1 receptor antagonist/inverse agonist, rimonabant. Thus, the question of whether the

behavioral effects of rimonabant reflect a blockade of endogenous cannabinoid tone or inverse agonism activity at the CB_1 receptor remains unanswered. The capability of quantifying endogenous cannabinoid levels in the synapse will help answer this question. Nonetheless, the results of in vitro and in vivo studies are consistent with the notion that these drugs may possess utility as nootropic agents in disease states in which cognitive processes have been compromised. For example, rimonabant has been demonstrated to enhance memory duration in several rodent models of learning and memory. Additionally, CB_1 receptor antagonists have positive effects on LTP. On the other hand, the findings that these drugs impair short-term models of extinction learning in aversively motivated tasks, reversal learning, and acquisition, indicate that caution should be exercised in treating patients who possess anxiety-related disorders. Additional research is needed to ascertain whether rimonabant's effects on cognitive processes related to memory duration and extinction can be separated.

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