Mini-review

Animal research highlights a therapeutic potential of cannabinoids for the treatment of depression

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Abstract

Long known for their mood altering effects, cannabinoids are currently under investigation for their therapeutic potential in the treatment of depression. Findings from multiple areas of basic research indicate that this system is indeed a viable target for novel antidepressant drugs. Rodent models of depression have been shown to alter levels of the endogenous cannabinoids and the cannabinoid CB_1 receptor, implicating this system in the etiology of depression. Additionally, cannabinoid drugs have demonstrated efficacy in rodent tests for antidepressant drug-like activity, and these effects appear to share common mechanisms of action with current antidepressant drugs, such as the selective-serotonin reuptake inhibitors. Thus, although the effects of cannabinoids on depression in humans remain to be elucidated, animal studies have provided impetus to further pursue this line of clinical research.
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Introduction

Cannabinoid drugs, well known for their effects on mood, are currently being tested clinically for the treatment of depression. In humans, depression is characterized by the core symptoms of depressed mood and/or loss of pleasure or interest in most activities (anhedonia) [1]. Other signs of depression include changes in body weight, sleeping patterns, psychomotor behavior, energy level, and cognitive functioning [1]. Interestingly, activation of cannabinoid CB_1 receptors has been shown to affect pain perception, food intake, locomotor activity, cognition, and mood-related behaviors (for review, see Piomelli, 2003 [2]). This striking overlap between the physiological functions altered by depression and those modulated by cannabinoid receptor signaling has implicated this system as a likely target for the treatment of mood disorders. Although the effects of cannabis use on mood disorders in humans is still a matter of debate [3], recent studies in animals provide support for the suggestion that activa-

tion of the cannabinoid system might indeed be a useful therapy for depression. Findings from several areas of basic research substantiate this notion. First, in animal models of depression (described below), there appears to be a down-regulation of endogenous cannabinoid signaling in specific brain regions. Secondly, a number of groups have found cannabinoid drugs to be effective in rodent models of depression and tests for antidepressant-like activity. Finally, treatment with these drugs appears to share common mechanisms of action with traditional antidepressant treatments. Together, these lines of evidence provide a strong rationale for the use of cannabinoids in the pharmacotherapy of depression.

Studying depression in rodents

While mood is often thought to be a uniquely human quality, depression can in fact be modeled in rodents using a chronic mild and/or unpredictable stress (CMS/CUS) protocol. In this model, a random se-

quence of mild stressors (such as food or water deprivation, changes in light cycle, crowded housing, physical restraint) presented daily over the course of several weeks, produces a number of physiological and behavioral alterations reminiscent of those seen in humans with depression, including changes in body weight, cognitive functioning, and responsiveness to rewards [4]. Furthermore, as in humans, these changes are sensitive to chronic, but not acute, treatment with antidepressant drugs, thus making this a highly valid model of depression. This model can be used both to examine the effects of chronic stress on the brain and to identify treatments that confer antidepressant-like activity. Another test used to study antidepressant-like treatments in rodents, which has good predictive validity, but less face validity than the CMS model, is the forced swim test. This test does not model features of depression, but rather is a useful tool for identifying antidepressant-like treatments. Most antidepressant treatments – for example, those modulating monoaminergic systems (i.e., serotonin- or norepinephrine- reuptake inhibitors) – decrease the time an animal spends immobile and increase the amount of time a rodent spends swimming or struggling while in a cylinder of water from which it has learned it cannot escape. Thus, this test also may be used to identify new drugs that might possess antidepressant-like activity in humans. Both of these tests have been used by several groups to study the relationship between cannabinoid receptor signaling and mood-related behaviors in rodents.

Endocannabinoid alterations by chronic stress

There is a paucity of research on the effects of chronic stress on endogenous cannabinoid signaling, but recent findings suggest that this system is altered by chronic stress models of depression in rodents. In rats subjected to 3 weeks of CUS, Hill and colleagues found a significant reduction in the levels of the endocannabinoid 2-AG and CB_1 receptor protein in the hippocampus [5]. A similar study by Bortolato and colleagues reported that after 10 weeks of CMS, CB_1 receptor mRNA was increased in the prefrontal cortex and decreased in the rat midbrain, and 2-AG levels were decreased in the thalamus [6] These alterations observed in the hippocampus, prefrontal cortex, midbrain, and thalamus are particularly interesting, given the involvement of these neural structures in the regulation of emotion [7]. Additionally, in the study by Bortolato and colleagues, 5 weeks of treatment with URB597 (an inhibitor of the hydrolysis of the endocannabinoid anandamide; 0.3 mg/kg, i.p.) elevated levels of anandamide in the midbrain, thalamus, and striatum, while reversing chronic stress-induced reductions in body weight gain and consumption of a palatable sucrose solution [6] – further suggesting deficient endocannabinoid signaling as a factor in some of the depression-like symptoms induced by chronic stress.

These basic research results implicating endocannabinoid signaling in the modulation of affect are compli-

mented by findings from human studies. In clinical trials of the CB_1 receptor antagonist rimonabant for the treatment of obesity, anxiety and depression are among the most frequent adverse events reported [8-12]. Additionally, human studies suggest that the endocannabinoid system is altered during depression. Hungund and colleagues reported an increase in both CB_1 receptor mRNA and CB_1 receptor-stimulated [35S]GTPγS binding in the dorsolateral prefrontal cortex of subjects with a life-time diagnosis of major depression who committed suicide, compared to normal controls (matched by age, sex, and postmortem interval) who died by accident or natural causes [13]. In another study, Hill and colleagues reported reduced serum 2-AG levels in drug-free females diagnosed with major depression compared to demographically-matched controls, with levels of 2-AG negatively correlated to the duration of the depressive episode [14]. In the latter study, serum anandamide was not associated with major depression, but was negatively correlated with measures of anxiety. Overall, these studies in both rodents and suggest that endocannabinoid signaling is altered – in specific brain regions and, perhaps, in the periphery – during depression or negative affective states. Although the relationship between chronic stress and endocannabinoid signaling remains to be explored further, this limited, but compelling evidence indicates there is an alteration of the activity of this system during chronic-stress related states, such as depression.

Cannabinoids and modulation of mood-related behaviors in rodents

Recent research from several groups has afforded significant preclinical evidence for the utility of cannabinoids in the treatment of depression. Overall, the evidence indicates that low doses of cannabinoid agonists exert anti-anxiety and antidepressant effects in rodents; however, these dose-dependent effects can be modulated by other factors, such as previous experience with the drug or environmental manipulations that alter the level of stress experienced by the animal [15]. For example, the synthetic CB_1 receptor agonist HU210 (0.1 mg/kg, i.p.) has been reported to increase anxiety-like behaviors after acute administration [16], but, at the same dose administered twice daily for 10 days, exerted antidepressant-like effects in the forced swim test, and reduced anxiety-like behavior in another rodent test for stress-related behaviors [17]. Other groups also have found antidepressant-like effects of this cannabinoid agonist. Recently, McLaughlin et al reported that when HU210 (1 and 2.5 µg) was infused directly into the dentate gyrus of the dorsal hippocampus of rats, animals showed an increase in swimming time and a reduction in the amount of time spent immobile during the forced swim test [18]. Similarly Bambico et al recently reported that another cannabinoid agonist, WIN55,212-2, given in low doses (0.1 and 0.2 mg/kg, i.p.) also decreased immobility by increasing swim-

ming in the forced swim test, but was ineffective at higher doses (1 and 2 mg/kg, i.p.) [19]. Furthermore, in the previously described CUS study by Hill and colleagues, stressed animals demonstrated impairments in reversal learning in the Morris water maze that were corrected by administration of HU210 (0.01 mg/kg, i.p.) [5]. The findings from these studies highlight the ability of cannabinoid agonists to exert behavioral effects similar to known antidepressant compounds, and to correct stress-induced disruptions in cognitive functioning, a symptom of depression also observed in humans.

Cannabinoids and traditional antidepressants: common effects

Although the mechanism(s) by which cannabinoids modulate mood-related behavior is not entirely elucidated at present, administration of cannabinoids appears to produce effects similar to those observed following other antidepressant treatments, namely enhancement of serotonergic signaling and hippocampal neurogenesis. In the study by Bambico et al, the antidepressant-like effects of treatment with WIN55,212-2 were paralleled by increases in the firing rate of serotonergic neurons of the dorsal raphe nucleus, and were prevented by preadministration of a serotonin synthesis inhibitor [19]. Additionally, the behavioral profile in the forced swim test following cannabinoid treatment – increases in swimming, but no change in struggling – resembles that produced by selective serotonin-reuptake inhibitors (SSRIs) [20], further suggesting these compounds may act by an enhancement of serotonergic signaling. Enhancement of hippocampal neurogenesis may be another common feature of cannabinoids and current antidepressant treatments. Hippocampal neurogenesis is an important, if not necessary event [21], for the effects of antidepressant treatments on behavior (reviewed in [22]), and, interestingly, a number of groups have implicated cannabinoids in the regulation of cell proliferation and differentiation (for review, see [23]). Indeed, Jiang and colleagues reported that treatment with HU210 enhanced proliferation of cultured embryonic hippocampal neural stem/progenitor cells, as well as adult hippocampal cells, and that the effects of HU210 on mood-related behaviors (described in the previous section) were abolished when animals were subjected to x-ray irradiation of the hippocampus (destroying neural stem cells) during HU210 treatment. Thus, similar to some other known antidepressant treatments (such as SSRIs), the effects of cannabinoids appear to depend on an enhancement of serotonergic activity and hippocampal neurogenesis.

Conclusions

In conclusion, several lines of basic research have lent credence to the idea that cannabinoid drugs have thera-peutic potential for the treatment of depression. A rodent model of depression, the CMS/CUS protocol, appears to induce a deficiency in endocannabinoid signaling, and enhancement of cannabinoid receptor signaling reverses depression-like symptoms induced by this protocol. Furthermore, several cannabinoid receptor agonists also have demonstrated efficacy in the forced swim test – a test with high predictive validity for the identification of antidepressant compounds. Finally, treatment with cannabinoid drugs produces effects that appear to be common to current antidepressant treatments. Overall, recent findings from multiple areas of basic research have implicated the cannabinoid system in the etiology and treatment of depression, thus providing solid justification for investigation of these drugs as novel pharmacotherapeutic agents for the treatment of depression.

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