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Endocannabinoid Signaling in the Etiology and Treatment of Major Depressive Illness

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Abstract

The purpose of this review is to examine human and preclinical data that are relevant to the following hypotheses. The first hypothesis is that deficient CB1R-mediated signaling results in symptoms that mimic those seen in depression. The second hypothesis is that activation of CB1R-mediated signaling results in behavioral, endocrine and other effects that are similar to those produced by currently used antidepressants. The third hypothesis is that conventional antidepressant therapies act through enhanced CB1R mediated signaling. Together the available data indicate that activators of CB1R signaling, particularly inhibitors of fatty acid amide hydrolase, should be considered for clinical trials for the treatment of depression.

Keywords

CB1 receptor; 2-arachidonoylglycerol; fatty acid amide hydrolase; URB597; tetrahydrocannabinol; genetics; circulation

1. Introduction

The endocannabinoid signaling (ECS) system has emerged over the last 20 years as an extremely important mechanism for the regulation of long and short term synaptic plasticity. ECS is particularly important in the CNS processing of reward, fear, memory extinction and stress. As all of these fundamental processes are dysregulated in major depression, better understanding of ECS holds great potential for improved understanding of the biology of depression. A large body of preclinical evidence demonstrates that loss of ECS results in phenotypic changes that mimic symptoms of human depression while manipulations that increase ECS produce anti-depressant effects in depression models. Studies of genetic polymorphisms in humans suggest that genetic differences in the ECS can confer resistance or vulnerability to depression. These and other data offer strong support for the hypothesis that drugs or other manipulations that enhance ECS could be effective treatments for depression in a subset affected individuals. As modern therapy moves towards personalized medicine, drugs that target the ECS could be important additions to the pharmacotherapy of psychiatric disorders in general and of depression in specific.

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1.1. Endocannabinoid Signaling

Although there are more than 60 unique chemicals in the cannabis sativa plant, only one of them, Δ^9-tetrahydrocannabinol (THC), has been shown to produce psychoactive effects in humans [1]. THC exerts its effects on the body because it is a partial agonist of two G protein coupled receptors (GPCRs), cannabinoid receptors types 1 and 2 (CB1R and CB2R, respectively) [2, 3]. The psychoactive effects of THC are the result of activation of CB1R [4]. Both CB1R and CB2R couple to G proteins in the $G_{i/o}$ family and their cellular effects are blocked by pertussis toxin treatment [5]. CB2R couple to G_i but not G_o proteins and exert their cellular effects via inhibition of adenylyl cyclase and regulation of transcription factors [6]. CB1R regulate the activities of adenylyl cyclase, ERK, glycogen synthase kinase 3; and the open probability of calcium and potassium channels [7]. In addition, CB1R can signal an increase in cAMP through G_s [8] and can increase intracellular calcium concentrations through $G_{q/11}$ proteins [9]. CB1R are very highly expressed in the brain, particularly in regions involved in motivated behavior and emotional processing [10]. CB2R are primarily expressed in cells of myeloid and splenic lineage, including microglial cells in the brain [11]. CB2R are also expressed in neurons of some species, including the ferret [12].

In 1992, Devane, Mechoulam and colleagues identified *N*-arachidonylethanolamine (AEA) as an endogenous agonist of the CB1R [13]. The family of *N*-acylethanolamines (NAE) had been identified and studied earlier, although AEA was considered a minor member of the family because of its very low concentrations in healthy tissues [14]. AEA is a partial agonist of CB1R [15] and has very low efficacy at CB2R [16]. A second endogenous arachidonate, 2-arachidonoylglycerol (2-AG), is a full agonist of both CB1R and CB2R [17]. There is no evidence that the endocannabinoids (eCBs) are stored in vesicles; instead they are likely synthesized and released in an “on-demand” manner.

The mechanisms for biosynthesis of AEA are not completely understood; early studies demonstrated that members of the NAE family were synthesized from *N*-acyl-phosphatidylethanolamine (NAPE) precursors via the action of a NAPE-selective phospholipase D (NAPE-PLD) [14]. However, NAPE-PLD knock out mice have normal concentrations of brain AEA [18], suggesting that other enzymatic pathways contribute to the production of AEA. Indeed, a second pathway has been identified in brain by which NAPE is converted to glycerophospho-NAE through the actions of alpha, beta hydrolase 4 (ABH4), followed by hydrolysis of glycerophospho-NAE to NAE via glycerophosphodiesterase 1 (GDE1) [19]. However, mice in which both NAPE-PLD and GDE1 are both genetically deleted also have normal AEA concentrations [20]. Two other pathways have been identified in peripheral tissues; one in which phospholipase C converts NAPE into phosphorylated NAE, followed by the actions of a phosphatase to complete the NAE synthesis [21]. In injured liver, AEA concentrations rise as a result of fatty acid amide hydrolase (FAAH) acting as a synthase in the presence of high concentrations of free arachidonic acid [22]. Triggers for the synthesis of AEA include high concentrations of intracellular calcium [23] which could activate phospholipase A_2 and increase free arachidonic acid.

2-AG is synthesized from diacylglycerol through the actions of diacylglycerol lipase (DGL) [24]. DGL is present in neurons that are synaptically related to neurons expressing the CB1R [25], which offers support for the hypothesis that 2-AG is an endocannabinoid. Diacylglycerol is a product of phospholipase C (PLC) activation; PLC beta activity is triggered by GPCRs that activate G_q and PLC gamma is activated by receptor tyrosine kinases. Of particular importance in brain are the metabotropic glutamate receptors (mGluRs) that couple to Gq and link glutamatergic signaling to recruitment of ECS [26].

AEA is catabolized by two amidohydrolases: FAAH [27] and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) [28]. Of the two, FAAH is a more important regulator of AEA in brain [28]. FAAH is an intracellular enzyme that is constitutively active [29]. FAAH activity plays a very important role in the regulation of AEA concentrations in brain; inhibition of FAAH results in a significant increase in AEA concentrations in most brain regions [30, 31]. URB597 is a well characterized and selective inhibitor of FAAH that has very interesting effects on emotional processing that will be discussed further below.

More than 80% of 2-AG hydrolytic activity in the brain is accomplished by monoacylglycerol lipase (MGL) [32]; other enzymes that can hydrolyze 2-AG include FAAH [33] and ABHD6 [34]. MGL is often found in the same neurons as those expressing the CB1R [35] and across the synapse from neurons expressing DGL [36]. Interestingly, MGL is present in both cytosol and membrane subcellular fractions (Hillard and Shrestha, unpublished data), leading to the possibility that its function is regulated by translocation from cytosol to the membrane, where its substrates, the monoacylglycerols, would be present [37]. MGL is inhibited selectively by JZL184 [38] although this inhibitor has greater efficacy in mouse than in rat [39].

Both AEA and 2-AG are substrates for several enzymes that oxidize arachidonic acid, including cyclooxygenases and lipoxygenases [40]. Of particular note is the data demonstrating that cyclooxygenase type 2 contributes functionally to the inactivation of eCB-mediated signaling in the brain [41–43].

CB1R are expressed at very high density in the brain and are found on presynaptic terminals in many brain regions [44]. It is well accepted that eCB-CB1R signalling underlies many forms of retrograde, activity dependent suppression of neurotransmitter release [45]. The eCBs, particularly 2-AG, are synthesized in post-synaptic neurons in response to increased excitatory activity. The process by which the eCBs are released from synthetic cells is not understood, but they activate CB1R on the presynaptic terminals to inhibit neurotransmitter release on short (via inhibition of calcium channel opening) and long (via kinase cascades) time scales. CB1R are present on glutamatergic [46], GABAergic [47], serotonergic [48] and noradrenergic [49] axon terminals in the brain. Functional evidence indicates that the activation of CB1R at all of these receptors results in inhibition of transmitter release [44]. Therefore, ECS is positioned to regulate activity of the neurotransmitters that are known to be involved in emotional processing.

2. Cannabis, ECS and Depression: Human Studies

2.1. Cannabis Use and Depression: Is There a Causal Relationship?

Cannabis sativa has been cultivated by humans for thousands of years as a therapeutic agent [50]. Many cannabis users use the drug because of its ability to elevate mood. In a study of young users, 69% reported that they used cannabis to "…feel better when down or depressed" [51]. Self-reports of cannabis use and mood find that individuals who report regular use of cannabis also report less depressed mood and greater positive affect than non-users [52]. These data suggest a 'self-medication' hypothesis of cannabis use in depression. However, several clinical trials in the 1970s designed to determine the anti-depressant efficacy of THC failed to find any benefits in the treatment of depression and that THC produced unacceptable adverse effects [53, 54]. However, THC is not the only component of cannabis, and is a partial agonist of CB1R [15].

An alternative hypothesis is that cannabis use predisposes individuals to depression. A small study using validated questionnaires found that individuals diagnosed with depression experience more depressive symptoms, aggression and sadness when intoxicated with cannabis than when not [55]. In another study, cannabis use was identified as a significant predictor of suicidal behaviors in high school students even after adjustment for depressive symptoms [56]. Several prospective studies have found evidence that cannabis use precedes the diagnosis of depression [57–59]. However, a large longitudinal study did not find that past cannabis use significantly predicted future depression when baseline differences between users and nonusers were carefully controlled [60].

It is possible that acute use of cannabis in non-depressed individuals elevates mood but that long term cannabis use promotes depressive symptoms, perhaps as a result of down-regulation of CB1R. In any case, the evidence for a causal relationship in humans between cannabis use and depression is equivocal at this time.

It has been suggested that a shared genetic predisposition could underlie the association between depression and cannabis use [60]. Both cannabis abuse and depression are moderately heritable [61] and cannabis dependence and depression are co-morbid diagnoses more often than would be expected by chance [62, 63]. Twin studies suggest that shared environmental factors also contribute significantly to the co-morbidity of cannabis dependence and depression [63]. There are very interesting polymorphisms in several genes encoding proteins of the ECS that could contribute to vulnerability to depression, particularly depression that is triggered by stress (section 2.6).

2.2. Human Imaging Studies

The acute effects of THC and chronic effects of cannabis use have been examined in humans using imaging modalities. The location of CB1R in human brain suggests that the ECS is involved in reward processing [64, 65], a hypothesis that is supported by some preclinical data (section 5.3.). Reward anticipation and reward feedback can be examined in human brain using a monetary incentive delay (MID) task as the brain is examined using functional magnetic resonance imaging (fMRI) [66]. Neural activity evoked by reward anticipation is not different between vehicle and THC treatment trials in occasional cannabis

users [67]. However, THC produced a widespread reduction of brain activity in response to receipt of reward, suggesting that it dampened the appreciation of reward. In particular, THC reduced neural activity in the inferior parietal cortex, a brain region associated with salience representation [68]. Overall, these data suggest that THC reduces appreciation of the monetary reward of the study, perhaps because it increases reward threshold (section 5.3.). Positron emission tomography studies that assess dopamine release have not shown a clear ability of THC to increase striatal dopaminergic neurotransmission [69–71]. Thus, acute THC does not produce an increase in reward-related neural activity and could dampen responsivity.

However, both chronic cannabis use and chronic CB1R antagonist treatment decrease striatal responses. In particular, 7 day treatment with the CB1R antagonist rimonabant results in decreased striatal responses to pictures of highly palatable food [72]. Chronic cannabis users exhibit a blunted nucleus accumbens and caudate neural responses to anticipation of reward, suggesting dampened reward sensitivity [73]. These data are in accord with epidemiological studies that chronic cannabis users exhibit more depressive symptoms than nonusers (section 2.1).

BOLD fMRI has been used together with presentation of validated pictures of angry and fearful faces to assess amygdalar reactivity in humans [74]. Treatment of healthy, casual cannabis users with oral THC results in a decrease in the activation of the amygdala in response to threatening faces, which supports a role for ECS in the regulation of anxiety [75]. A second study of smoked cannabis also found reduced amygdalar activation to threat and, in addition, demonstrated in a small sample that cannabis use was inversely related to amygdalar reactivity [76]. An imaging genetics study discovered that carriers of a polymorphic version of the gene for FAAH that results in decreased enzymatic activity found that amygdalar reactivity is decreased in individuals with increased AEA-mediated signaling [77]. Together, these studies are in accord with considerable human and preclinical data that activation of ECS can be anxiolytic [78].

2.3. CB1R Antagonism Increases Depressive Symptoms in Humans

Pharmacological, biochemical and genetic evidence support the hypothesis that hypoactive ECS, particularly reduced CB1R activity, contribute to depression in humans. The CB1R inverse agonist/antagonist, rimonabant was examined in a series of clinical trials in Europe for the treatment of obesity, insulin resistance and metabolic disorder. A meta-analysis of the randomised trial data found that rimonabant caused significantly more adverse effects than placebo; in particular, rimonabant-treated individuals were 2.5 times more likely than placebo-treated to discontinue the drug because of depressive mood disorders [79]. The data included in this analysis were solely from trials in which depressed mood was an exclusion criteria. The CRESCENDO trial of rimonabant efficacy, powered to detect cardiovascular endpoints, did not include depressed mood as an exclusion and more than 15% of the individuals enrolled in this trial had a history of depression [80]. CRESCENDO revealed no significant reduction in adverse cardiovascular events when it was prematurely ended at 13.8 months; however, there were significantly more adverse neuropsychiatric and serious psychiatric events in the rimonabant treated group than placebo. Among these were an

increase in depressive symptoms; and four rimonabant-treated and one placebo-treated individuals committed suicide during the trial [80]. These data indicate that pharmacological blockade of CB1R signaling can predispose humans to depression, particularly those with previous depressive episodes.

2.4. Evidence of Changes in ECS in Postmortem Brain

Post-mortem studies have compared CB1R expression in groups who have died with depression or by suicide. CB1R mRNA in the prefrontal cortex (PFC) of depressed individuals is significantly increased compared to controls [81]. Similarly, depressed suicides have 24% greater CB1R agonist binding site density and more CB1R protein in the dorsolateral prefrontal cortex (DLPFC) than matched controls [82]. Furthermore, CB1R agonist-induced GDP/GTP exchange was also increased in DLPFC membranes from suicides compared to controls, evidence that the increased CB1R density represents functional receptors [82, 83]. Another study found that neuronal CB1R density in the anterior cingulate cortex (ACC) was not different between patients with major depression and controls but that CB1R density was significantly decreased in depressed individuals taking selective serotonin reuptake inhibitors (SSRIs) compared with patients who were not [84]. Tissue contents of AEA and 2-AG in the DLPFC are increased in alcoholic patients with depression compared to alcoholics without depression [83]. Together, these studies suggest that ECS in the frontal cortex is hyperactive in depressed individuals.

One study has examined subcortical ECS in postmortem samples and found that ventral striatal FAAH activity is higher in alcoholic suicides than alcoholics [85]. This finding suggests that AEA content would be reduced in this brain region, resulting in decreased ECS. Therefore, it is possible (and supported by preclinical studies discussed in section 4) that ECS is altered in a brain-regional manner in depressed individuals. Further studies are needed to clarify the mechanism for the changes in ECS components and the roles of these changes in depression and suicide.

2.5. Circulating eCBs, Stress and Depression

The eCBs can be measured in both plasma and serum (see [86] for a recent review). Macrophages [87–89] and platelets [87] synthesize eCBs and several inflammatory conditions are accompanied by significantly elevated circulating eCBs [90–92]. Both CB1R [93] and CB2R [6] are expressed by circulating immune cells and activation of the CB2R exerts anti-inflammatory effects [6]. Thus, circulating eCBs could contribute to the regulation of inflammation through effects on immune cells in the blood.

Physiological stress increases eCB concentrations in the circulation. For example, circulating 2-AG concentrations are increased significantly in patients undergoing cardiopulmonary bypass [92]. Parabolic flight maneuvers that produce a significant physiological stress increase both AEA and 2-AG concentrations in the circulation with different time courses [89]. Intense exercise produces a significant increase in plasma AEA [94]. The role of the eCBs in the context of physiological stress could be to dampen stress-induced inflammation. In addition, circulating cortisol concentrations were inversely related to AEA concentrations in the flight study [89] and positively correlated with orthostatic

tolerance in a head-up tilt study [95], suggesting that eCBs might buffer endocrine and neuronal responses to stress as well.

Of more significance for the topic of depression, psychological stress also alters eCBs in the circulation. The Trier Social Stress Test (TSST) is a validated method for inducing psychological stress in human subjects. In one study, a seventeen minute version of the TSST resulted in a significant increase in circulating 2-AG at the end of the test compared to pre-test values in healthy women [96]. No differences in AEA were detected. A second study using a 6 min version of the TSST found that serum concentrations of AEA and two other NAEs, oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), were increased immediately after the test [97]. 2-AG concentrations tended to increase after both stress and nonstress (control) sessions compared to baseline values obtained before either session. The nonstress control session in this study was a friendly discussion that did not evoke changes in heart rate, cortisol or reported anxiety compared to baseline. The change in AEA did not correlate with either sympathetic nervous system activation or changes in glucocorticoids in the circulation; however, the change in PEA was positively correlated with serum cortisol [97]. Subanalyses of this study found that AEA increased significantly in men but not women; and in Caucasians but not African American or Asian participants, suggesting that the eCB response to stress is not a consistent response in all demographic groups. Thus, physical and psychological stress exposure alters eCB concentrations in the circulation.

A study of circulating eCBs in women viewing erotic films found that AEA concentrations were inversely related to both physiological and subjective indices of arousal while 2-AG was inversely related to only subjective indices [98], suggesting that circulating AEA and 2-AG concentrations are responsive to different aspects of the stimulus.

Interestingly, several studies suggest that stress exposure results in a “rebound” decrease in circulating NAEs. Women exposed to the TSST exhibit significantly lower concentrations of PEA and OEA 30 min after the end of the test [96]. Similarly, imagery of a stressful experience produced a slow decrease in circulating AEA that became significantly lower than baseline at 75 min after the stress [99]. Since the non-cannabinoid NAEs reduce IL-6 expression [100], it is possible that stress-induced decreases in NAEs could contribute to a delayed increase in IL-6 that occurs following stress exposure [101] through dysinhibition of its expression [96].

Taken together, these studies demonstrate that psychological and physiological stresses induce changes in circulating eCBs that are sensitive to the specifics of the stressor. There is clearly much work to be done to understand both the sources of circulating eCBs and their purpose. One hypothesis is that elevations in circulating eCBs buffer immune and endocrine stress responses. Another possibility is that eCBs in the circulation contribute to energy balance regulation during stress as activation of CB1R increases food consumption and fuel storage in fat and liver [102].

Since repeated exposure to stress is a contributing factor for the development of depression, our group tested the hypothesis that circulating eCBs are dysregulated in depression. Serum 2-AG concentrations have been found in two studies to be significantly reduced in depressed

women compared to matched controls [96, 103]; one study also found a significant decrease in AEA [96]. 2-AG concentrations were correlated with the length of the depressive episode: the longer the duration, the lower the 2-AG concentrations [103]. Interestingly, depressed women had intact 2-AG and NAE responses to the TSST [96], suggesting that the mechanisms that regulate 2-AG and NAEs during an acute stress exposure and the process by which 2-AG becomes suppressed in major depression are not the same.

Depression is accompanied by increased inflammation [104], leading to the hypothesis that suppressed 2-AG could contribute to an increased inflammatory state seen in depression. Another possible role for the eCBs is as a mediator of the coincidence between cardiovascular morbidity and major depression [105]. In a study of depressed women, we found that both diastolic and mean arterial blood pressures were positively correlated with serum contents of AEA and 2-AG, an association that did not occur in controls [106]. Whether or not the deficit in circulating 2-AG could contribute to the emotional and behavioral symptoms associated with depression is unknown at this time.

These data suggest that measurement of circulating eCBs could provide a useful biomarker for depression in general, but more importantly, could be used in a personalized medicine approach to diagnose “low eCB” depression as a subtype that might be more amenable to an ECS-mediated therapies.

2.6. Genetic Studies Support a Role for ECS in Vulnerability to Depression

The CB1R is encoded by the *CNR1* gene and this gene exhibits multiple forms of genetic heterogeneity in humans (see [86] for review). The first heterogeneity described is a microsatellite polymorphism in the 3' untranslated region (UTR) in which the trinucleotide, AAT, is repeated multiple times [107]. Many single nucleotide polymorphisms (SNP) are in the region of the *CNR1* gene. Only one SNP, rs1049353, is within the coding region of the gene and this mutation does not alter the amino acid sequence of the CB1R protein [108]. Other SNPs have been identified that are in putative regulatory regions of *CNR1* that exhibit interesting associations with variations in the processing of reward and fear; and in psychiatric disease occurrence and severity [86].

FAAH, the primary protein responsible for the degradation of AEA and the other NAEs in the brain, also has an important heterogeneity in humans. A SNP in the human *FAAH* gene (rs324420) occurs in the coding region of the gene [109]. The common nucleotide at this position is C and the rare nucleotide is A; and the combined genotype distribution among all races is 67% CC, 30% AC and 3% AA [86]. This change in nucleotide results in a change in amino acid at position 129 in the FAAH protein from proline to threonine [109]. Interestingly, this amino acid change does not alter the catalytic activity of FAAH but makes the enzyme more susceptible to proteolysis. T lymphocytes from individuals with the AA genotype have approximately 50% of the FAAH protein as individuals with the CC genotype [110]. As expected, AA individuals also have significantly higher concentrations of AEA and the other NAEs in their circulation compared to CC homozygotes [111]. This leads to the hypothesis that individuals with an A allele at rs324420 have increased AEA/CB1R signaling.

There is evidence that genetic heterogeneity in both *CNR1* and *FAAH* contribute to several emotional traits that are important for vulnerability to stress and/or mood dysregulation. For example, an imaging genetic study found that subjects with AC or AA genotypes in *FAAH* exhibit significantly greater activation of the ventral striatum in response to a reward than individuals homozygous for C [77]. Individuals with an A allele also exhibited increased impulsivity and reduced reactivity to fearful facial expressions in the same study. These findings suggest that individuals with increased AEA signaling (as a result of reduced FAAH expression) have heightened sensitivity to reward, are more impulsive, and are less fearful.

Although these data obtained in healthy individuals indicate a role for *FAAH* genotype in the regulation of reward, genetic association studies available currently do not support a role for *FAAH* genotype in susceptibility to depression. One study found no significant association of rs324420 with depressive symptoms in a cohort of about 200 individuals [109]. A second study found a small, non-significant increase in the odds ratio for depression in individuals with an A allele at position 385 [112], which is opposite of what would be predicted by the imaging genetic studies described above. This issue likely will require large population studies to answer.

The impact of *CNR1* genotype on personality and mood has been examined in imaging genetic studies. Four SNPs in the *CNR1* gene were significantly associated with neuronal responses to happy faces measured in the ventral striatum of healthy volunteers [113]. Interestingly, no associations with disgusted faces was found. Since happy faces are socially rewarding, these results suggest that genetic variation in *CNR1* could play a role in the differences among individuals in responsivity to social reward and thereby contribute to depression and perhaps also to autism.

The role for *CNR1* genetic variability in depression has been examined in multiple studies. The length of the AAT trinucleotide repeat was significantly associated with depression in a small, case control study of Parkinson patients [114] but not in a large population study [115]. A study comparing control and depressed Caucasians found that the depression group was significantly enriched in the A allele at rs1049353 [112]. These investigators estimated an odds ratio of 2.46 for the contribution of this SNP to the probability of having depression. However, another population study found that any association between *CNR1* genotype and depression diminished when covariation for negative life events was included in the analysis [116]. These data suggest that *CNR1* genotype and negative life events exhibit a gene x environment interaction; for example, *CNR1* genotype could influence vulnerability to negative life events by affecting the response of the individual to negative events or by regulating choices. In agreement with this hypothesis, a significant contribution of *CNR1* genotype to the personality characteristics of neuroticism and agreeableness was uncovered. In particular, neuroticism, which is the ease with which emotions are aroused, magnifies the significance of negative life events and is a well-known predictor of depression [117]. Less is known about the contribution of the personality trait agreeableness to depression, but it could affect the likelihood of the depressed individual to benefit from social interaction or support.

Another very interesting study examined the role of *CNR1* genotype in vulnerability to anhedonia in individuals that experienced early life physical abuse [118]. Data from two cohorts demonstrated that genotype at this SNP did not affect anhedonia in non-abused individuals, but exerted a very large effect on anhedonia in those who had experienced early life abuse. In particular, individuals with at least one copy A at rs1049353 were significantly less likely to exhibit anhedonia than individuals with the more common G nucleotide at this position. Another study compared three SNPs in *CNR1* (rs6454674, rs806368 and rs6801844) in a case control study in which the cases were suicide attempters [119]. Two of these SNPs (rs6454674 and rs806368) have been reported to form haplotype blocks with rs1049353 [86]. There was no association of genotype at any of these SNPs with suicidality in the study. According to current theories regarding suicidal behaviour, risk of suicide is determined by both psychiatric illness and illness-independent, genetically mediated predisposition towards suicidal ideation [120]. Thus, these data suggest that *CNR1* genotype does not contribute specifically to predisposition for attempting suicide. Together, the results of these studies support the hypothesis that *CNR1* genotype modulates the effects of negative life experience, perhaps through effects on personality, and could be involved in vulnerability to specific depressive symptoms.

A recent study found that having a GG genotype at rs1049353 conferred a better long-term anti-depressant response to treatment with the SSRI, citalopram, in males [121]. This is a very interesting result that is consistent with the hypothesis that interactions between ECS and serotonergic signaling could be important in the control of mood. They suggest further than knowledge of *CNR1* genotype could be used in a personalized medicine approach to guide antidepressant therapy choices.

Thus, the studies of the genetic association of *CNR1* and *FAAH* with the occurrence and vulnerability to depression are beginning to paint a picture that *CNR1* genotype can, as a result of determination of personality and/or susceptibility to severe stress, influence the occurrence of depression and depressive symptoms. It is clear that more work needs to be done in this area, particularly to further clarify gene x environment interactions.

3. Suppressed ECS and the Etiology of Depression: Preclinical Studies

In this section, we turn our attention to preclinical studies. We will first review studies demonstrating that suppression of ECS produces symptoms that recapitulate human depression.

3.1. Behavioral Studies

There is considerable evidence in rodent models that pharmacological inhibition and genetic disruption of ECS produce symptoms in rodents that recapitulate human depression [122]. Blockade of CB1R signaling results in impairments in reward sensitivity [123–125]. CB1R hypofunction is associated with reduced drive for natural rewards, including sex [126] and food [127]. CB1R null mice and those treated with CB1R antagonists exhibit increased basal anxiety [128–130] and increased vigilance and arousal [131]. Reduced CB1R signaling and chronic CB1R antagonist treatment result in inappropriate extinction of aversive memories [132, 133] and increased likelihood that passive coping strategies will be used in the face of

inescapable stress [125, 134, 135]. Other common symptoms of depression include sleep disturbances and decreased food consumption, both of which also occur when CB1R signaling is inhibited [127, 131].

Together, these data provide compelling evidence that reduced CB1R-mediated, ECS reduces drive toward reward, increases anxiety and decreases extinction of aversive memories, all hallmarks of human depression.

3.2. HPA axis

HPA axis dysfunction is present in many individuals with major depression and has been hypothesized to contribute to its etiology and symptomatology [136]. For example, corticotropin releasing factor (CRF) concentrations are increased in the CSF of depressed patients compared to controls [137]. Receptors for CRF (CRHR1) are decreased in number in the prefrontal cortex of individuals who died by suicide [138], which is consistent with hyperactive CRF secretion and subsequent down-regulation of receptors. Basal cortisol concentrations are elevated in approximately 66% of depressed individuals, particularly those with the most severe depressive symptoms [136]. Inability of patients to suppress cortisol release following dexamethasone challenge is considered diagnostic of depressive mood disorders [139]. Finally, long term treatment with all of the effective antidepressant drugs and electroconvulsive shock therapy (ECT) result in reductions in basal and stress-induced activation of the HPA axis [122]. Thus, hyperactivity of the HPA axis accompanies depression in many individuals, and attenuation of hyperactive HPA axis activity is a common feature of effective anti-depressant therapies.

CB1R null mice exhibit hyperactive HPA axis activity at baseline [140] and in response to stress [130, 140]. Similarly, administration of CB1R antagonists systemically [141], and directly into the amygdala [142] and PFC [130] produce hyperactive HPA axis responses. Rats chronically treated with high doses of a CB1R agonist exhibit increased sensitivity to activation of the HPA axis by stress [143]. Deficient CB1R-mediated signaling results in prolonged return to baseline circulating corticosterone concentrations following restraint stress due to impaired glucocorticoid negative feedback [130]. ECS is also required for adaptation (habituation) of the HPA axis [144] and neural response [145] to repeated exposures to the same stress.

3.3. Hippocampal Neurogenesis

Hippocampal atrophy occurs in unmedicated individuals suffering from recurrent major depression [146] and it has been hypothesized, based on preclinical models of depression, that this is the result of reduced neurogenesis in the subgranular zone of the adult dentate gyrus [147]. Chronic treatment with effective anti-depressant drugs, repeated ECT and voluntary exercise all increase neurogenesis in the hippocampus, evidence that reduced neurogenesis could contribute to depression [148]. Brain derived growth factor (BDNF) is a critical mediator of hippocampal neurogenesis, and its hippocampal concentration is reduced in preclinical models of depression [149] and increased by anti-depressant therapies [150]. These and other data have led to the neurotrophic hypothesis of depression, which is that loss of hippocampal BDNF results in neuroanatomical and functional alterations that

contribute to depression-related behavior, while antidepressants are therapeutically effective because they increase concentrations of hippocampal BDNF [151].

Several studies indicating that hippocampal progenitor proliferation and neurogenesis require intact ECS. Chronic CB1R blockade in otherwise untreated mice inhibits cell proliferation in the dentate gyrus, evidence that tonic ECS is required for appropriate neuroprogenitor cell turnover [125, 152]. An earlier study found that chronic THC treatment, which is known to decrease CB1R density in the hippocampus [153], decreased the number of neurons in the hippocampus [154]. Although this could be the result of increased neuronal loss, these data are also consistent with reduced neurogenesis caused by decreased CB1R function. Since chronic CB1R blockade also results in decreased BDNF concentrations in the hippocampus [125], it is possible that ECS is required for basal BDNF secretion. CB1R deficiency also impairs glutamate-induced increases in hippocampal neuroprogenitor cell turnover [155] and the neurogenic effects of environmental enrichment and wheel running [156, 157]. Thus, tonic activity at CB1R appears to be required for both basal and stimulated adult hippocampal neurogenesis.

3.4. Dendritic Complexity

Preclinical studies have found that stress exposure decreases dendritic complexity in several stress-responsive brain regions, including the PFC [158] and hippocampus [159] while complexity in the amygdala is increased [160]. It is thought that this bi-directional change in dendritic complexity results in amygdalar dominance, favoring the expression of fear and anxiety [161]. CB1R null mice exhibit reduced apical dendritic length and branching in layer II/III of the prelimbic region of the PFC [130]. In addition, exposure of CB1R null mice to chronic stress produces no further decrease in PFC dendritic complexity compared to either condition alone, suggesting that stress-induced loss of dendritic length and branching in the PFC result from decreased ECS [130]. On the other hand, chronic stress increases amygdalar dendritic length in both wild type and CB1R null mice [130]. Thus, reduced ECS increases susceptibility to stress-induced reductions in PFC dendritic complexity, resulting in an even greater imbalance between PFC and amygdalar influences on behavior than occurs in the presence of normal ECS.

3.5. Summary

Taken together, these data strongly suggest that reduced ECS in preclinical models recapitulates the majority of measurable behavioral, endocrine and morphological changes that are seen in humans with depression. As such, these data provide strong support for the hypothesis that dysregulated ECS contributes to depression and, further, that increased ECS would be an effective treatment for mood disorders.

4. ECS is Altered in Preclinical Models of Depression

In the preceding section, we presented evidence that loss of ECS results in symptoms of depression in preclinical models. In this section, we consider evidence that preclinical models of depression include alterations in ECS.

Chronic exposure to unpredictable stress (CUS) is used in rodents to evoke symptoms that mimic human depression, including anxiety, anhedonia, passive coping and learned helplessness [162]. CUS exposure results in decreased CB1R density in the hippocampus, hypothalamus and ventral striatum of male rats [163–165]. This response to CUS is sexually dimorphic as female rats exhibit a significant increase in CB1R density in the hippocampus following 21 days of CUS, in spite of the fact that they exhibit the same physiological signs of stress exposure as male rats [165]. The male-female differences seen in this study were also observed in gonadectomized animals. Further evidence for reduced CB1R function in CUS treated rodents come from data that exogenous CB1R agonists lose effectiveness in CUS treated rats [166, 167]. Furthermore, CUS in mice impairs eCB-mediated retrograde synaptic depression in the nucleus accumbens due to a decrease in CB1R function [168]. Similarly, chronic restraint stress in juvenile male rats decreases ECS in the paraventricular nucleus of the hypothalamus [169] while chronic social defeat stress decreases ECS-mediated regulation of GABA release in the striatum [170].

It is possible that sustained elevation of glucocorticoids in the brain of chronically stressed rodents is the mechanism by which CB1R function is reduced. For example, chronic treatment of rats with corticosterone in the drinking water decreases CB1R density in hippocampus and amygdala [171] and chronic corticosterone injections decrease CB1R density in the hippocampus [172]. Similarly, functional studies demonstrate that the effects of stress to reduce hypothalamic [169] and striatal [170] ECS require genomic glucocorticoid receptor (GR) activation. These data suggest that hyperactive HPA axis activity, as occurs in chronic stress, results in increased GR activation in the CNS which decreases CB1R density. Adrenalectomy, which reduces circulating glucocorticoids, increases expression of CB1R mRNA in the striatum [173]. Thus, we could hypothesize further that GR exerts an inhibitory effect on CB1R gene translation and so reduces CB1R protein expression. An alternative hypothesis is that chronic GR activation increases eCB tone at the CB1R, resulting in agonist-induced down-regulation of CB1R signaling. Some support for this hypothesis comes from the finding that chronic corticosterone administration increases amygdalar 2-AG concentrations [171].

Interestingly, CUS increases CB1R protein, binding site density and mRNA expression in the PFC [31, 164, 174]. Similarly, bilateral removal of the olfactory bulbs (OBX), which produces behavioral and biochemical changes consistent with depression in humans [175], also results in significant increases in CB1R density and coupling to GDP/GTP exchange in PFC [176]. Thus, two rodent models of depression exhibit increased CB1R density in the PFC, a change that is also observed in the frontal cortex of depressed suicides [82]. The mechanism for this change is not completely clear. However, treatment of rats with imipramine throughout stress exposure abolishes the CUS-induced increase in PFC CB1R density [164], suggesting that CUS-induced deficits in serotonergic or noradrenergic signaling could contribute to the increase in PFC CB1R density.

An important question raised by these studies is whether the increased CB1R signaling contributes to the development or symptoms of depression or is a compensatory change which dampens the consequences of chronic stress. A recent paper found that CUS increases immobility in the forced swim test in rats and that this was exacerbated by administration of

a CB1R antagonist into the ventromedial PFC [174], evidence that increased CB1R density opposes the effect of CUS to increase passive coping. These data suggest that increased CB1R expression in the PFC opposes rather than contributes to the effects of CUS and so is a compensatory not causative change.

CUS exposure alters the brain regional concentrations of the eCBs. AEA content is decreased following 21 days of CUS in PFC, hippocampus, hypothalamus, amygdala, midbrain, and ventral striatum without a concomitant change in the activity of FAAH, suggesting that synthesis of AEA is reduced [164]. The effects of CUS on 2-AG contents are more variable. 2-AG content is increased in the hypothalamus and midbrain [164]; one study found a significant reduction of 2-AG content in the hippocampus [163] while another found no change [164]. CUS has no significant effect on either AEA or 2-AG concentrations in the nucleus accumbens [168].

Thus, depression models exhibit decreased CB1R-mediated signaling in subcortical regions and increased CB1R density in the PFC. Decreased subcortical ECS is likely due to glucocorticoid-induced reductions in CB1R density while the increase in PFC CB1R density could be due to reduced serotonergic signaling and could oppose the effects of CUS and OBX to produce depression-like behaviors. These data add support to the hypothesis that ECS has been changed in depression and, together with the evidence described earlier, adds support to the hypothesis that therapies designed to increase ECS could be beneficial in the treatment of depression.

5. Mechanistic Support for Anti-Depressant Efficacy of ECS

In this section, we will summarize data from preclinical studies that direct and indirect activation of ECS can produce behavioral and biochemical effects that are similar to those of conventional antidepressants. Available evidence demonstrates that increased ECS shares each of the currently accepted mechanisms for antidepressant efficacy. ECS increases serotonergic and noradrenergic signaling, dampens HPA axis activity and increases neurogenesis and cellular resilience in the hippocampus. In addition, ECS enhances reward and so can be considered a “pro-hedonic” system. Data to support these conclusions are discussed individually below.

5.1. ECS-serotonin interactions

A large body of evidence supports the hypothesis that alterations in serotonin (5-HT) signaling play a pivotal role in the mechanism of action of anti-depressant drugs [177]. Drugs such as the SSRIs increase 5-HT concentrations in the synapse and eventually down-regulate release-inhibitory autoreceptors (5-$HT_{2A/2C}$ receptors) on serotonergic axon terminals. Three mechanisms have been described by which ECS modulates the activity and/or release of 5-HT.

First, CB1R agonists can regulate the firing of serotonergic neurons in the dorsal raphe nucleus (DRN) through effects directly in the DRN [178–180]. ECS within the DRN can have both excitatory and inhibitory effects on serotonergic neuronal firing, so the net effect

of ECS will depend on synaptic strength, endogenous eCB tone and relative CB1R density on terminals impinging on DRN serotonergic neurons [181].

Second, CB1R are present on axon terminals of serotonergic neurons in projection areas, including the hippocampus and amygdala [182, 183]. In parallel with its effects in other transmitter systems [44], activation of CB1R on serotonergic axon terminals inhibits 5-HT release [184–188], which could produce “pro-depressant” effects according to the monoamine hypothesis. Blockade of CB1R increases basal extracellular concentrations of 5-HT in mPFC [189, 190], indicating ECS exerts tonic inhibition of 5-HT release through receptors present on CB1R terminals.

Third, ECS indirectly increases DRN neuronal activity through effects in the PFC. Exogenous administration of CB1R agonists increases firing of serotonergic neurons in the DRN when PFC-DRN neuronal circuits are intact [191]. Endogenous activation of CB1R through systemic and intra-PFC inhibition of the AEA catabolic enzyme, FAAH, also increase firing of neurons in the DRN in a CB1R-dependent manner [192–194]. FAAH null mice exhibit reduced responsiveness of mPFC pyramidal cells to $5\text{-HT}_{2A/2C}$ agonist treatment, suggesting that a sustained increase in AEA down-regulates PFC $5\text{-HT}_{2A/2C}$ receptors [193]. Taken together, these studies indicate that enhanced ECS in the PFC increases excitatory drive on serotonergic neurons in the DRN [191]. In further support of this notion, systemic administration of CB1R agonists increases 5-HT concentrations in the nucleus accumbens [195]. These studies support the hypothesis that CB1R share the ability of SSRIs to enhance synaptic concentrations of 5-HT, albeit through an alternative mechanism.

Thus, the available data do not paint a consistent picture for the regulation of 5-HT signaling by the ECS. However, behavioral data (discussed below) indicate that the predominant effect of ECS activation in stressed rats is to increase 5-HT signaling in the PFC.

Although weeks of treatment with SSRIs are required to produce anti-depressant efficacy in humans, acute treatment of rodents with clinically effective anti-depressants of multiple drug classes produce immediate changes in behavior in inescapable and stressful situations, usually either a period of forced swim (FST) or suspension by the tail [196]. Effective anti-depressants decrease passive coping (i.e. immobility) and increase active coping behaviors; serotonergic enhancers increase swimming while noradrenergic enhancers increase struggling behaviors.

Treatment of rats with CB1R agonists and indirect agonists produce antidepressant-like effects in the FST that are dependent upon intact serotonergic signaling and can be mimicked by administration of FAAH inhibitors into the PFC [191, 192, 194, 197, 198]. A recent biochemical study has found that PFC AEA content is decreased and FAAH activity increased immediately following exposure to FST, leading to the hypothesis that exposure to an inescapable stress decreases ECS through reduced AEA [194]. In agreement with this hypothesis, FAAH null mice exhibit decreased responses to stress and increased basal serotonergic tone in the frontal cortex [199]. PEA decreases immobility in both the FST and tail suspension tests after oral administration to mice [200]. Although this study did not

examine the mechanism, it has been suggested that exogenously administered NAEs can increase the functional activity of endogenous AEA because they compete for binding to FAAH and thereby reduce AEA catabolism [201]. These data suggest that inhibition of the overactive FAAH could provide a selective and mechanistically sound method to enhance ECS in the context of depression.

Interestingly, treatment of rats with a single dose of THC does not alter FST behavior and exerts complex effects on DRN firing [202]. THC is a partial agonist of CB1R [15] which could contribute to its lower effectiveness. These findings are particularly interesting in light of the lack of reproducible anti-depressant effects of THC in humans discussed above. We suggest that the lack of effectiveness of THC does not preclude the possibility that other activators of ECS could be useful anti-depressants.

It is interesting in this regard that cannabidiol, a component of cannabis sativa with low affinity for CB1R [2], binds to heterologously expressed, human $5HT_{1A}$ receptors and exhibits agonist-like effects at this receptor subtype [203, 204]. Although the affinity of cannabidiol for these receptors is moderate (mid-micromolar), there is evidence that this mechanism underlies several of the pharmacological effects of cannabidiol, including attenuation of nausea and vomiting [204] and attenuation of autonomic and behavioral responses to restraint stress [205]. These data lead to the hypothesis that cannabidiol could exert antidepressant effects via activation of $5HT_{1A}$ receptors. Indeed, a recent study in male mice demonstrated that 30 mg/kg cannabidiol (but not higher or lower doses) decreases immobility in the FST through a $5HT_{1A}$ receptor-dependent mechanism [206]. These data are particularly intriguing in light of the information discussed in section 2.1 that cannabis has better anti-derpessant efficacy than THC alone. Other cannabis constituents, including cannabidiol, likely contribute to the pharmacological effects of the cannabis plant.

The role of the CB1R in the regulation of FST behavior is less clear in mice both activation and inhibition of ECS can both increase and decrease immobility [207–209]. A recent study indicates that ECS affects behavior in the FST through both 5-HT and noradrenergic mechanisms in mice [210].

Taken together, these data indicate that ECS can modulate 5-HT signaling and FST behaviors through multiple mechanisms that seem to exhibit species differences. However, studies in both rats and mice indicate that anti-depressant effects of acute treatment with CB1R direct and indirect agonists are likely mediated through increased 5-HT signaling. While this behavioral pattern mimics that of SSRI class anti-depressants, it is likely that ECS increases 5-HT release rather than inhibits 5-HT reuptake and so could represent an alternative mechanism for the treatment of depression.

5.2. ECS-norepinephrine interactions

Several classes of effective anti-depressants act through increased norepinephrine signaling, including the tricyclic antidepressants that inhibit NE reuptake and monoamine oxidase (MAO) inhibitors that inhibit NE catabolism. There is considerable evidence that ECS modulates NE signaling and some evidence that this modulation can result in antidepressant effects.

CB1R protein and mRNA can be detected in the locus coeruleus (LC) and nucleus of the tractus solitarius (NTS), the two important clusters of noradrenergic cell bodies [211–214]. CB1R protein in the LC is presynaptic at symmetrical synapses, suggesting that ECS can inhibit GABA-mediated suppression of noradrenergic neurons [215]. Indeed, CB1R agonist treatment suppresses the inhibition of LC firing induced by activation of the major GABAergic afferent to the LC [216]. In addition, systemic administration of CB1R agonists [216] and FAAH inhibitors [192] increase the firing rate of noradrenergic neurons in the LC in a CB1R-dependent manner. CB1R agonists also increase c fos expression in the LC [217, 218] and increase norepinephrine (NE) synthesis [187] and release [218] in terminal regions. Taken together, these results are consistent with increased firing of LC neurons, although there are conflicting data regarding the site of action [219].

Consistent with increased LC firing, systemic administration of CB1R agonists increase the release of NE in frontal cortex and nucleus accumbens [218, 220] and increase tyrosine hydroxylase (TH) activity in LC, hippocampus and cortex [186]. Since TH activity is tightly coupled to NE release, these data support the hypothesis that CB1R activation increases NE release. Chronic activation of CB1R by agonist treatment down-regulates NE binding site densities and function [221–224], findings consistent with a sustained increase in NE release which induces down-regulation of adrenergic receptors.

On the other hand, there is evidence that CB1R are present on noradrenergic terminals [49] and that activation of this receptor pool can suppress NE release [225]. Consistent with these data, CB1R antagonist treatment increases microdialysate NE concentrations in anterior hypothalamus and mPFC in male rats [190, 226] and increases electrically-evoked release of NE from human and guinea pig hippocampal slices [227].

Therefore, ECS can modulate NE signaling through two opposing mechanisms: increased activity in LC neurons and inhibition of NE release from terminals. There is evidence that stress exposure influences which of these processes predominates. Although CB1R agonists increase NE release in the PFC in unstressed rodents, they suppress stress-induced NE release [224], suggesting that ECS drive on LC neuronal activity predominates under normal conditions while inhibition of NE release at terminal regions predominates during stress. In support of this idea, CB1R agonists increase immobility and decrease climbing in the FST in rats previously exposed to stress [224], behavioral effects that are consistent with decreased NE release in the PFC [228]. These studies indicate that ECS regulation of NE signaling is context-dependent and suggest the intriguing possibility that ECS is a pivot point with regard to the effects of stress on NE signaling.

In a preceding section, data that CB1R agonists exert antidepressant-like effects in the FST through increased 5-HT signaling in rats were presented. Like 5-HT, elevations in NE also produce antidepressant effects in the FST. Acute treatment of rodents with antidepressants that inhibit NE uptake, such as desipramine, reduce immobility and promote the active coping behavior of struggling and climbing rather than swimming in the FST [228]. Chronic treatment of rats with a synthetic CB1R agonist reduces immobility and increases struggling in the FST; effects that were attenuated by β-adrenergic receptor blockade [229]. Since chronic CB1R agonist up-regulates NE signaling [230], a possible mechanism is that

repeated exposure to CB1R agonists increases NE transmission in the behavioral coping circuit. An alternative mechanism is that chronic CB1R agonist treatment results in down-regulation of CB1R on NE terminals [221, 222], resulting in dysinhibition of NE release. The second possibility is supported by CB1R antagonist inhibition of immobility in the FST through a mechanism that requires catecholamines [210]. If a subset of tonically active CB1R inhibit NE release, both acute CB1R antagonism and chronic treatment with agonists (which down-regulate CB1R at this site) could enhance NE release and thereby increase active coping in FST.

In summary, ECS regulates NE signaling in both positive and negative ways through effects on LC activation and NE release in terminal regions. Importantly, ECS appears to have an important role in the regulation of NE during stress and chronic activation of CB1R in rodent models produces NE-dependent increases in active coping behavior in the FST. However, data are presented in section 7 which indicate that CB1R-mediated increases in NE signaling can increase HPA axis reactivity and conditioned place aversion, which, if paralleled in humans, would have pro-depressive rather than anti-depressive consequences.

5.3. ECS and Reward

Most depressive disorders in humans include anhedonia or decreased incentive to seek positive reinforcers as a core symptom [231]. There are conflicting data regarding the effects of CB1R agonists on reward seeking and reward thresholds. The “gold-standard” assay for the effects of drugs on reward is to examine the thresholds for activation of intracranial self-stimulation (ICSS) [232]. One study reported that THC administration lowers ICSS thresholds, which is consistent with increased sensitivity to reward [233]. However, studies using fully efficacious direct agonists [234] and indirect agonists [235] reveal that high doses of these agents increase the threshold frequency for ICSS in rats in a CB1R-dependent manner. These latter studies suggest that activation of ECS dampens reward sensitivity. One study examined ICSS responses in rats exposed to CUS for 10 days and found no effects of THC on thresholds in either normal or CUS rats; however, this study also failed to demonstrate an effect of CUS on ICSS thresholds, suggesting that the stress period might have been too short [167].

Another commonly employed method for determining reward sensitivity is the sucrose consumption test. Although there are a large number of reports that CB1R inhibition or deletion decrease sucrose consumption (reviewed in [122]), there is conflicting evidence regarding the ability of CB1R activation to increase consumption of sucrose-containing water in unstressed rodents [236, 237]. Thus, this could be an ECS-mediated function that is maximally activated under normal conditions so that exogenous agonist treatment cannot increase it further. An alternative explanation, supported by the ICSS studies described above, is that CB1R in different brain regions act in opposing ways to regulate reward.

While CB1R activation does not have consistent effects on sucrose consumption in normal mice, both direct agonist treatment and FAAH inhibition reverse the effect of chronic restraint stress to reduce sucrose consumption [237]. Similarly, FAAH inhibition reverses the effects of CUS [31] and adolescent THC exposure in females [238] to reduce sucrose consumption. Taken together, these data indicate that high ECS is required for proper

reward sensitivity such that increased CB1R activity cannot increase sensitivity in healthy animals. However, since a consequence of chronic stress is to decrease ECS tone (discussed in section 3.2 above), maintaining ECS through CB1R direct and indirect agonists maintains hedonic behaviors in the context of chronic stress. Further evidence for this hypothesis comes from the finding that CB1R antagonism blocks stress-induced but not cocaine-induced reinstatement of cocaine place preference in mice [239]. These data suggest that ECS is required for stress-induced relapse to drug seeking, possibly through effects on reward sensitivity.

5.4. ECS and HPA Axis Regulation

Considerable evidence has accumulated to support the hypothesis that ECS is altered by glucocorticoid exposure and modulates stress responses through effects on synaptic activity. Exogenous administration of glucocorticoids to rats results in a rapid increase in eCB contents in several limbic structures [240]. Multiple studies indicate that ECS is an effector of glucocorticoids in the brain [241]. In the hypothalamus, glucocorticoids act through a membrane receptor to rapidly mobilize eCBs that, through CB1R on glutamatergic axons, inhibit excitatory drive onto corticotropes in the paraventricular nucleus (PVN) [242, 243]. Glucocorticoid infusion into the PVN rapidly inhibits HPA axis activation, an effect that is blocked by the CB1R antagonist, AM-251 [244]. In agreement with these data, increased ECS suppresses stress-induced activation of the HPA axis [141].

Both the hippocampus [245] and medial PFC (mPFC) [246] are responsive to glucocorticoids and participate in long-loop feedback regulation of the HPA axis and recent evidence indicates that these effects of glucocorticoids also require ECS [130, 247]. ECS signaling is also involved in the behavioral effects of glucocorticoids, including enhancement of memory consolidation [248] and stress-induced reinstatement of cocaine seeking behavior in mice [239].

In spite of the evidence discussed above that acute stress and glucocorticoid treatment increase eCB-mediated signaling in hypothalamus, hippocampus and PFC, acute stress exposure in rodents results in decreased amygdalar and PFC AEA concentrations [142, 145, 194, 249]. The reduction in AEA content is accompanied by an increase in the activity of FAAH [142, 194]. If the decline in amygdalar AEA is prevented, HPA axis activation by stress is reduced [142]; evidence that tonic CB1R signaling in the amygdala opposes stress-induced HPA axis activation and must be inhibited in order for the HPA stress response to occur. In other words, AEA functions as a gatekeeper for the stress response [141]. Importantly for depression, inhibition of FAAH mediated hydrolysis of AEA during exposure to chronic stress prevents the development of glucocorticoid hypersecretion [144].

Overall, the available data regarding the interaction of ECS and the HPA axis indicates that increased ECS dampens the initial activation of the HPA axis and also is required for an appropriate and timely return to basal levels of activity following stress offset. As such, a testable hypothesis is that pharmacological activators of ECS could reduce HPA axis hyperactivity in humans with depression.

5.5. ECS Regulation of Adult Hippocampal Neurogenesis

Antidepressant therapies increase signaling pathways and transcriptional regulators that promote cellular resilience and synaptic plasticity in the hippocampus [250, 251]. In particular, all forms of conventional antidepressant therapies increase production of BDNF and increase cell proliferation and neurogenesis in the hippocampus [148]. These changes occur at the same time as the clinical benefit of antidepressants and are not seen with acute treatments [148]. Similarly, the behavioral efficacy of antidepressants in preclinical models require increased BDNF expression and hippocampal neurogenesis [150, 252]. Antidepressant treatment normalizes alterations in hippocampal plasticity in rodent models and individuals on long-term antidepressant medication do not exhibit the hippocampal atrophy seen in non-medicated depressives [122].

Increased ECS also produces many of the effects on hippocampal plasticity seen following conventional antidepressant treatment. Cannabinoids increase the expression of hippocampal BDNF [253, 254] and chronic cannabinoid treatment of both adult and aged rats increases neurogenesis in the hippocampus [255, 256]. FAAH null mice exhibit increased cell proliferation in the hippocampus [257]. Obese animals exhibit increased neurogenesis that is inhibited by CB1R blockade [258]. Interestingly, the non-psychoactive phytocannabinoid, cannabidiol, also increases hippocampal neurogenesis through an ECS-requiring mechanism [259]. The mechanism could be related to AEA synthesis since the effect of CBD was opposed by high FAAH activity. Importantly, activation of ECS reverses the effects of chronic stress to reduce hippocampal neurogenesis [260].

5.6. Summary

The data summarized in this section support the hypothesis that increased ECS can mimic the effects of conventional antidepressants to enhance serotonergic and noradrenergic signaling; maintain hedonia during chronic stress; suppress hyperactivity of the HPA axis; and increase hippocampal BDNF expression and neurogenesis. Thus, these data suggest that cannabinoid-based antidepressants could be at least as efficacious as conventional therapies.

6. Regulation of ECS by Conventional Antidepressants and Other Therapies

Since increased ECS has many characteristics that mimic those of antidepressant therapies, several studies have explored the concept that currently used antidepressant therapies produce their antidepressant effects via changes in ECS.

Prolonged treatment of rodents with the SSRI fluoxetine results in increased CB1R mRNA, protein and signaling in frontal cortex [261, 262], while another SSRI, citalopram, was reported to decrease CB1R signaling in hippocampus and PVN [263]. These data are reminiscent of the differential effects of CUS on CB1R expression discussed in section 4. The MAO inhibitor, tranylcypromine, increases CB1R binding site density in PFC and hippocampus but concurrently reduced tissue AEA concentrations in the same regions, making assessment of the impact on CB1R signaling difficult [261]. Chronic treatment with the tricyclic antidepressant, desipramine, increased CB1R density in hippocampus and

hypothalamus without affecting eCB contents [264]. Conversely, imipramine, increased CB1R density in the amygdala and decreased binding in the hypothalamus, midbrain and ventral striatum [261]. ECT was found to increase CB1R signaling in the amygdala and reduced both CB1R density and AEA content in the PFC [265]. There are no commonalities in these data, leading to the conclusion that ECS changes do not universally contribute to the efficacy of these drugs to treat depression. However, it is likely that ECS is upstream of both 5-HT and NE signaling (sections 5.1 and 5.2), thus might not be expected to be altered consistently by drugs that modify these signaling circuits.

Although there are no commonalities among the classes of antidepressants to alter ECS, it is possible that changes in ECS could contribute more selectively to the beneficial effects of antidepressants. For example, desipramine and other tricyclics that act through increased NE signaling are particularly effective at reducing hyperactive HPA axis activity in depression. The HPA dampening effects of desipramine are accompanied by increased CB1R signaling in the hypothalamus and are antagonized by inhibition of CB1R signaling [264]. These data indicate that increased hypothalamic ECS could be a mechanism by which chronic antidepressants suppress HPA axis hyperactivity.

Non-drug therapies are also used with varying effectiveness to treat depression. Although insomnia is highly prevalent in patients with depression and is an important diagnostic criterion and risk factor for depression [266], sleep deprivation (wake therapy) provides rapid clinical relief in many patients [267, 268]. Deprivation specifically from rapid eye movement (REM) sleep increases the expression of CB1R in the thalamus, brain stem and spinal cord and decreases expression of both FAAH and the 2-AG catabolic enzyme, MGL [269]. Sleep deprivation increases 2-AG concentrations in the hippocampus [270] and increases circulating eCBs in humans [271].

Exercise, which is antidepressant in humans, increases CB1R mRNA, binding site density and signaling in the hippocampus [156, 157]. Similarly, both voluntary exercise and the opportunity to consume sucrose solutions increase ECS in the striatum and, importantly, provide resilience against stress-induced changes in synaptic activity [272]. These data are particularly important because they indicate that up-regulation of ECS is possible and that, as expected, it results in stress-resilience. Intense exercise increases both AEA and BDNF in the circulation of humans; in fact the two mediators were found to be positively correlated with one another [94].

ECT is a reliable and effective treatment for depression in humans. ECT exposure to rats increases CB1R density in the amygdala and reduces CB1R density and AEA concentrations in the PFC [265]. Whether these changes in ECS contribute to the antidepressant efficacy of ECT is not known.

Thus, the available data indicate that ECS is very plastic and is altered by multiple therapies that can reduce depression in humans. However, these data do not support an “endocannabinoid signature” for these therapies and indicate that the interactions are likely to be modality/drug specific. Furthermore, it is possible that changes in ECS can contribute to the beneficial and adverse effects of antidepressant therapies.

7. Evidence that activation of ECS could exacerbate depression

The emphasis in the sections above was to present evidence supporting the hypothesis that enhancers of ECS would be useful antidepressants. However, there are data supporting the opposite hypothesis, that inhibition of ECS could be beneficial. In addition, ECS mediates several glucocorticoid effects in the CNS that could be considered as detrimental. As a result, it is possible that ECS activation could have troubling adverse effects that would hamper usefulness as an antidepressant.

It should not be surprising that activation of CB1R-mediated signaling in the brain can have opposing effects. Although CB1R are very highly expressed and found in virtually every brain region [10], the characteristics of CB1R-ECS indicate that it is designed to modulate synaptic plasticity at a very local level. Therefore, global activation and inhibition of ECS can easily be imagined to produce a myriad of effects that will be determined by receptor density at a synapses, prevailing eCB tone, pharmacokinetic effects and likely many other factors.

In support of this argument, cannabinoid agonists have long been known to produce biphasic effects in many *in vivo* assays. This extends to some effects relevant to mood regulation, such as HPA axis regulation [141] and anxiety-like behaviors [129]. Studies in mice with neuronal-selective deletion of CB1R indicate that the biphasic effects of cannabinoid agonists on anxiety are due to dose-dependent activation of CB1R on GABA and glutamatergic terminals that exert opposite effects on behavior [273]. In particular, the anxiolytic effects of CB1R agonists occur at low doses and are mediated by CB1R on glutamatergic terminals while the anxiogenic effects occur at higher doses and are mediated by CB1R on GABAergic terminals. Earlier studies from our laboratory found that restraint stress and CB1R agonist activation synergized to activate amygdalar neuronal activity, measured using c fos [274], further evidence that CB1R activation can produce effects that could worsen some of the symptoms of depression.

ECS can have opposite effects in the FST, the classical assay for antidepressant efficacy. In section 5.1., we presented data that CB1R agonists produce antidepressant effects in the rat FST. However, CB1R antagonists can also have antidepressant effects in the FST [208, 209, 275]. Similarly, rimonabant reduces hyperactivity in OBX rats, a hallmark of antidepressant efficacy [254]. On the other hand, chronic rimonabant does not increase hippocampal BDNF in normal rats, while CB1R agonists do [254] suggesting that CB1R blockade is not as robust an antidepressant therapy as CB1R activation.

A recent study from Lutz and colleagues provides some insight into the ability of CB1R antagonists to produce antidepressant effects [210]. They found that the ability of the CB1R antagonist, rimonabant, to decrease immobility was unaffected by suppression of 5-HT signaling, instead, was reversed by inhibition of catecholamine synthesis. This finding suggests that ECS-mediated activation of catecholamine signaling exerts pro-depressive effects in the FST.

These data are consistent with other studies that some of the negative consequences of stress are mediated by ECS-NE interactions. For example, high doses of CB1R agonists increase

HPA axis responsivity to stress [141, 276] and pretreatment of rats with antagonists of either β-adrenergic or alpha1-adrenergic receptors significantly attenuate this response [277]. While NE signaling is not the only process involved, these data are consistent with ECS acting up-stream of noradrenergic signaling to potentiate stress-induced HPA axis activation. Similarly, high doses of CB1R agonists induce conditioned place aversion in rodents [278–281], an effect that is abolished by depletion of NE [282] and β-adrenergic blockade [283] in nucleus accumbens. It has been argued that stress-induced increases in ECS potentiate stress-induced memory consolidation through increased NE signaling [248]. Although interactions between ECS and noradrenergic signaling in this context have not been demonstrated directly, ECS inhibits GABA signaling in the basolateral amygdala (BLA) during stress [37] and inhibition of GABAergic activity in the BLA enhances memory consolidation by increasing NE signaling [284]. These and other observations [248] are consistent with a model in which stress produces behavioral changes through recruitment of both ECS and NE signaling.

9. Summary

The potential role for ECS-based therapies must be explored with a clear and complete picture of the potential beneficial and adverse effects that will occur from exogenous activation (or inhibition) of ECS. However, several preclinical studies suggest that FAAH inhibitors could have fewer adverse effects than direct CB1R agonists. For example, the FAAH inhibitor URB597 does not increase HPA axis reactivity [145], produce anxiogenic effects in the elevated plus maze [129] or synergize with stress to activate the amygdala [274]. Furthermore, chronic treatment with URB597 normalizes multiple depressive symptoms caused by adolescent THC exposure, indicating that it has broad antidepressant efficacy [238]. A recent study found that URB597 and an SSRI could exert synergistic effects in the FST [285]. This suggests that FAAH inhibition might improve efficacy of conventional therapies, which could result in reduced doses and adverse effects.

Finally, depression is a multi-factorial disorder that can manifest with different symptoms. It is very likely a disorder with both genetic and environmental causes. Better understanding of the roles of all candidate systems in the etiology and symptoms of depression is the only way to inform treatment approaches that are evidence-based and personalized. This will lead to better outcomes for people with this debilitating disease.

Abbreviations

2-AG	2-arachidonoylglycerol
5-HT	serotonin
ABH4	alpha, beta hydrolase type 4
ABHD6	alpha, beta hydrolase domain 6
ACC	anterior cingulate cortex
AEA	*N*-arachidonylethanolamine

BDNF	brain derived neurotrophic factor
CB1R	cannabinoid receptor type 1
CB2R	cannabinoid receptor type 2
CUS	chronic unpredictable stress
DGL	diacylglycerol lipase
DRN	dorsal raphe nucleus
DLPFC	dorsolateral prefrontal cortex
ECS	endocannabinoid signaling
ECT	electroconvulsive shock therapy
FAAH	fatty acid amide hydrolase
fMRI	functional magnetic resonance imaging
FST	forced swim test
GDE1	glycerophosphodiesterase 1
GPCR	G protein coupled receptor
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenal
ICSS	intracranial self-stimulation
MAO	monoamine oxidase
MGL	monoacylglycerol lipase
MID	monetary incentive delay
mGluR	metabotropic glutamate receptor
LC	locus coeruleus
NAAA	*N*-acylethanolamine-hydrolyzing acid amidase
NAE	*N*-acylethanolamine
NAPE	*N*-acyl-phosphatidylethanolamine
NAPE-PLD	*N*-acyl-phosphatidylethanolamine selective phospholipase D
NE	norepinephrine
OBX	olfactory bulbectomy
OEA	oleolyethanolamide
PEA	palmitoylethanolamide
PFC	prefrontal cortex
PLC	phospholipase C

PPAR	peroxisome proliferator activated receptor
PVN	paraventricular nucleus
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
TH	tyrosine hydroxylase
THC	Δ^9-tetrahydrocannabinol
TSST	Trier social stress test
UTR	untranslated region

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