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RESEARCH REVIEW

Endocannabinoids modulate mood

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Mood disorders, depressive episodes, and other negative mood disturbances are highly prevalent forms of mental illness that can lead to suicide, especially in the absence of psychotherapy and/or pharmacotherapy. Current pharmacotherapeutic options for mood disorders are unimpressive in clinical practice, promoting only minor improvement in affective symptoms while resulting in often intolerable cognitive and somatic side effects, leading to poor patient adherence to drug regimens. Currently, commonly-prescribed antidepressants manipulate the same neurotransmitter systems (dopamine, norepinephrine, and serotonin) targeted by earlier generations of these drugs (e.g., monoamine oxidase inhibitors, monoamine and indoleamine reuptake inhibitors, tricyclic antidepressants) only with improved system specificity. However, there exists a clear need to explore alternative neurochemical systems for use in the pharmacotherapy of mood disorders. One such system is the endogenous cannabinoid system, whose role in mood modulation is explored in this review.

INTRODUCTION

Unified perception across sensory modalities is colored by core affect: the sensations, feelings, emotions, moods, and motivations that constitute experience. These affective states are a complex function of multiple systems interacting across various levels of organization (Scherer, 2000). Any particular affective state, however, may be quantified along two fundamental dimensions: arousal and valence (Posner, Russell, & Peterson, 2005). For example, the emotions "fear" and "sadness" are affective states that may occur with similar magnitudes of negative valence, but be distinguished by amount of accompanying arousal. Emotions are fleeting states for which there are often identifiable causal antecedents. In contrast, moods are ambiguous and enduring states. Moods, however, are similarly distinguishable by arousal and valence. For example, "anxiety" is a negative valence, high arousal "background" state, while "depression" is a background state commonly characterized by negative valence but minimal arousal.

Moods may ensure that the organism is physiologically prepared to respond to environmental stimuli that are anticipated based on its recent affective history (Mendl, Burman, & Paul, 2010). Additionally, moods may be indicators of internal resource availability and sufficiency to meet environmental demands—that is, secondary appraisal mechanisms (Larsen, 2000). As such, much like physical pain, negative emotions and moods are unpleasant yet useful perceptions, signaling that "something is wrong," and motivating appropriate behavioral responses that are facilitated by concurrent alterations in physiology. While neural systems putatively responsible for different dimensions of core affect have been identified (Posner et al., 2005), the mechanisms by which the experience of affective states (and mood states in particular) are modulated remain obscure, especially at the neurochemical level.

A confluence of psychological and physiological vulnerabilities is implicated in the etiology of mood disorders; however, it is believed that deficient and/or dysregulated neurochemical modulation may underlie and/or subserve disordered mood states. Although mood disorders are serious neuropsychiatric diseases that not only erode quality of life, but also potentially threaten it, their prevalence is underestimated by popular misconception. In the United States, 17.5% of the general population suffers from a mood disorder, and 30.7% is at risk for one during a lifetime (Kessler, Petukhova, Sampson, & Zaslavsky, 2012). Approximately 13%, 4%, and 4% of people in the general U.S. population think about, plan, or attempt suicide in their lifetimes, respectively, with the odds of lifetime ideation or attempts for mood-disordered individuals being 10.7 to 1 and 12.9 to 1, respectively (Kessler, Borges, & Walters, 1999). Affective disturbance in mood-disordered individuals follows an agonizing, recurrent course that is difficult to cope with. Unsurprisingly, there exists a link between intensity, instability, and variability of negative mood and suicidality (Palmier-Claus, Taylor, Varese, & Pratt, 2012). Indeed, the presence and severity of suicidal ideation are linked to the severity of negative mood disturbance, and in particular, to symptoms such as anhedonia, loss of interest and motivation, persistent sadness, and pessimism (Keilp et al., 2012).

Although a cornucopia of chemicals is available for the treatment of mood disorders, including antidepressants, anxiolytics, and mood stabilizers, most of these are unimpressive in clinical practice. In fact, after accounting for initial differences in the severity of symptoms, one naturalistic study found that depressed persons treated with psychotropic drugs fared worse than those treated without (Ronalds, Creed, Stone, Webb, & Tomenson, 1997). Beyond bountiful somatic side effects (e.g., hyperglycemia, dyslipidemia, hepatotoxicity), many of these medications bear black box warnings—paradoxically—about an increased risk of suicidal ideation with use. As a drug side effect, increased suicidal ideation is troubling, but whether it translates to an increased risk of suicide (and thus, a "real" cause for concern) has been debat-

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ed between pharmaceutical developers and regulators. However, Robertson et al. (2009) showed that in the Food and Drug Administration (FDA) Adverse Event Reporting System data from 2004 to 2008, all drugs associated with increased suicidal ideation were also associated with an increase in attempted or committed suicide rates. Sometimes psychiatric side effects and complications such as these are sufficiently adverse or prevalent during clinical trials that regulators (e.g., in the US, the FDA) refuse to approve a drug for clinical use altogether, and yet other drugs go to market before their potential harms become apparent.

Of course, psychiatric side effects are not limited to drugs intended to treat psychiatric symptoms. Federal regulatory agencies in various countries were justifiably concerned with the increased incidence of psychiatric complications associated with use of the cannabinoid antagonist, "rimonabant," intended to treat obesity, despite stellar performance on the primary endpoints of its clinical trials. In the 1-year follow-up to the rimonabant in obesity (RIO)-Europe study group clinical trial, Van Gaal and colleagues report greater weight loss and reduced cardiovascular risk factors in overweight, dyslipidemic patients assigned daily rimonabant (20mg) compared to those on placebo (2005). Rimonabant treatment effected continued weight loss and improved fasting serum high-density lipoprotein (HDL), cholesterol, triglycerides, glucose, and insulin, compared to placebo at the 2-year follow-up as well (Van Gaal et al., 2008). At the 1-year follow-up for the RIO-Lipids study group, Després and colleagues (2005) reported that improved cholesterol, HDL, triglycerides, and weight-loss occurred with rimonabant treatment, as in RIO-Europe, but that patients' anxiety and depression frequently led to discontinuation of the drug. According to Van Gaal, in RIO-Europe, incidence of depressed mood was not different between treatment groups. However, meta-analysis of the RIO trials (-Europe, North America, Lipids, Diabetes) by Christensen and colleagues (2007) revealed that while rimonabant did result in more weight-loss, it also caused more adverse side effects than placebo, and participants receiving rimonabant were more likely than those receiving placebo to discontinue treatment due to anxiety and depression.

Notably, shortly after its 1-year follow-up, the clinical trial of rimonabant for the prevention of cardiovascular events (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes, CRESCENDO), which sought to test whether the cardiovascular and metabolic improvements observed in the RIO studies translated to reduced prevalence of heart attack and stroke, was terminated prematurely for increased incidence of adverse neuropsychiatric side effects, including depressed mood and major depressive disorder (MDD), in the drug-group compared to placebo (Topol et al., 2008). Federal regulators were alarmed: 4 individuals taking rimonabant (20 mg) committed suicide. Investigators in both the RIO and CRESCENDO clinical trials rigorously screened and excluded subjects for prior and/or pre-existing psychiatric conditions. As such, chronic antagonism of the endogenous cannabinoid system was capable of effecting clinically relevant mood disturbances in (formerly or ordinarily) mentally healthy individuals. Concerned about lax screening in clinical practice, federal regulatory agency banned rimonabant. Pharmaceutical companies have since aborted clinical trials for other cannabinoid antagonists (otenabant and taranabant for obesity, surinabant for smoking cessation).

While the influence of daily rimonabant on subjective mood state takes longer than 2 weeks to manifest, Horder, Cowen, Di Simplicio, Browning, and Harmer (2009) found that a single 20-mg dose of rimonabant was able to reduce incidental recall of positive, self-relevant words. After 7 days of such doses, a reduction was also observed in the number of positive, self-relevant words mistakenly recognized as previously seen during a word categorization and memory task (Horder, Browning, Di Simplicio, Cowen, & Harmer, 2012). Capable of diminishing dispositional optimism and positive emotional memory, even short-term blockade of the endogenous cannabinoid system has affective consequences that are distinct from and precede (yet may subserve) the mood disturbance associated with long-term blockade. The tragedy of rimonabant in clinical trials, then, is a testament to the role of the endogenous cannabinoid system in core affect, and why its manipulation holds promise for the pharmacotherapy of mood disorders.

THE ECB SYSTEM

Two arachidonate-derived ligands, the enzymes responsible for their synthesis and degradation, and two G-protein-coupled receptors constitute the endogenous cannabinoid system. Two different genes, CNR1 and CNR2, on human chromosomes 6 and 1, encode the cannabinoid receptor proteins, CB1 and CB2, respectively, which suggests differences not only in expression and regulation, but also function. Originally, CB2 was found mainly in peripheral tissues, particularly in the immune system, while CB1 was observed primarily in the central nervous system (Devane, Howlett, & Melvin, 1988; Herkenham et al., 1990). Since then, it has been shown that there is remarkable, albeit incomplete, overlap in the expression profile of the cannabinoid receptors at the tissue, but not subcellular, level extending support for differences in the function of each. In the central and peripheral nervous system (e.g., enteric, sensory, sympathetic), neurons may express both CB1 and CB2, but only CB1 is expressed pre-synaptically at the axon terminal button. Neuroglia—astrocytes, oligodendrocytes, and microglia—may also express both receptors. While putatively distinct in function, CB1 and CB2 share not only inhibitory G-protein coupling, but also ligands.

The endogenous cannabinoid ligands, N-arachidonoylethanolamide (AEA; anandamide) (Devane et al., 1992) and sn-2-arachidonoylglycerol (2-AG) (Sugiura et al., 1995), are synthesized through unique metabolic pathways initiated by distinct signaling cascades. Unlike neurotransmitters, which are stored in vesicles upon synthesis, the endocannabinoids, AEA and 2-AG, are synthesized on demand from their arachidonate precursor in membrane phospholipids. Both endocannabinoids exhibit a short half-life in vivo (on the order of minutes) due to dense and widespread expression of their degradative enzymes, fatty acid amide hydrolase

(FAAH) and monoacylglycerol lipase (MGL).

Originally, it was believed that both AEA and 2-AG were released from the post-synaptic density of the dendritic spine by the post-synaptic neuron to act on pre-synaptically located CB1 (Egertová, Giang, Cravatt, & Elphick, 1998), effecting activity-dependent inhibition of neurotransmission (Piomelli, 2003). However, since then, research has corroborated retrograde paracrine signaling for 2-AG alone (Mátyás et al., 2008). AEA is now believed to be an autocrine-signaling molecule, released by the axon terminal button to act on its own CB1. In either case, endocannabinoid signaling via CB1 still (generally) inhibits neurotransmission in an activity-dependent manner.

CB1 IN THE BRAIN

Based on its expression in the brain alone, a role for CB1-mediated endocannabinoid signaling in core affect may not only be suspected, but expected.

In an early publication in the endocannabinoid niche, Herkenham and colleagues (1990) used tritiated CP-55, 940 (a CB1 agonist) to autoradiographically map cannabinoid receptor expression and distribution at the protein level across the brains of different species (e.g., dog, human, rhesus monkey, rat). All species exhibited very dense binding in the globus pallidus (the in/out-put loop of the basal ganglia), substantia nigra, hippocampus, and cerebellum, and dense binding across the cerebral cortex and striatum (nucleus accumbens, caudate nucleus, putamen). The nucleus accumbens is a subcortical structure involved in reward and ultimately, pleasure. Drug abuse, food, friends, sex, and associated stimuli are all capable of eliciting the release of dopamine at the nucleus accumbens by dopaminergic neurons in the ventral tegmental area of the midbrain. In these densely labeled areas, the amount of cannabinoid receptor protein exceeded 1pmol/mg total protein, placing its density on the order of glutamate and gamma-amino-butyric acid (GABA) receptors in brain.

Herkenham also found sparse but high binding in the amygdala, hypothalamus, and spinal cord, while only diffuse binding the midbrain and brainstem. Popularly regarded as the "fear center" of the brain, the amygdala is actually a heterogeneous subcortical structure involved in the processing the affective salience of stimuli and events, including instances of reward and punishment. In turn, the hypothalamus not only oversees the endocrine system, but also orchestrates organismal homeostasis at the behavioral and physiological level, mediating most, if not all, drives including affiliation, feeding, and mating, as well as the response to stressors.

Dense binding across the cerebral cortex was also reported in Herkenham's study, but the resolution of autoradiography is poor, so the exact location of CB1 in the cortex remained obscured. Immunohistochemistry has a greater resolution than autoradiography, allowing identification of not only which, but also where on or in, cells express a protein of interest. Tsou and colleagues (1998) were the first to map CB1 in the rat brain by directing an antibody at the amino-terminus of CB1, which would be expected to be exposed on the extracellular surface owing to CB1 being a G-protein coupled receptor. Moldrich & Wenger (2000) followed up shortly thereafter with a better-resolved immunohistochemical map. Among the cortical areas for which they both detailed pre-synaptic CB1 immunoreactivity are the cingulate, claustrum, hippocampus, insula, and somatosensory cortex. The hippocampus is famously involved in the consolidation of episodic or autobiographical memory, while the somatosensory cortex is involved in the sense of touch. The cingulate cortex, especially the ventral anterior cingulate, appears to be involved in affective (and motivational) information processing. The insula may not only be involved in the integration of salient internal bodily sensations and signals (i.e., interoception), but also affective rendering of the internal state into consciousness awareness (Herbert & Pollatos, 2012). Based on its structure and connectivity, the current hypothesis holds that the claustrum may be involved in the integration of information across sensory modalities to produce a unified, conscious perception of the external world (Crick & Koch, 2005).

As previously mentioned, glia may also express CB1. Astrocytic feet span the length of the apical capillary endothelium, forming the glial limiting membrane at the blood-brain barrier, which spans nearly all capillaries perfusing the brain. These perivascular astrocytes regulate neuronal metabolic flux, and consequently, activity. As such, CB1 expression at perivascular glial fibers should not be dismissed, especially since there exists a pool of each endocannabinoid ligand in circulation. Unlike perivascular astrocytes, cortical astrocytes modulate neuronal activity more directly via peri-synaptic glutamate uptake. While Moldrich & Wenger (2000) observed no specific immunoreactivity in rat cortical astrocytes or oligodendrocytes (the myelinating glia of the central nervous system, which modulate the activity of entire collections of neurons at the level of the axon), CB1 was observed in the perivascular glial fibers of limbic brain areas such as the amygdala, cingulate cortex, medial forebrain bundle, and olfactory bulb and cortex. It is possible that endocannabinoid activity at perivascular astrocytes in the limbic areas may affect perisynaptic cortical astrocytes in these limbic areas (and in turn, neuronal activity) since all astrocytes are electrically coupled (via gap junctions) and communicate with each other through intracellular Ca2+ waves.

Consequently, CB1 in the brain is positioned to modulate activity in neural circuits responsible for not only motivating our most basic wants and needs, but also enjoyment of their fulfillment. Moreover, the endocannabinoid system may modulate circuits whose concerted activity may be generating our seamless subjective experience of the milieu externe and interne. In depression, it is the inability to experience pleasure, loss of interest and motivation, persistent sadness, and pervasive pessimism—affective symptoms in which many of the same neural systems documented to express CB1 are implicated—that erode the quality of life, leading to suicidal ideation, attempts, and not infrequently, death.

ALTERED BRAIN CB1 IN HUMANS WITH NEGATIVE MOOD DISTURBANCE

Further supporting a role for endocannabinoids in the modulation of negative affect, in post-mortem examination, the brains of individuals who suffered from depression and those who committed suicide show alterations in the endogenous cannabinoid system relative to controls, namely: increased CB1 density in the dorsolateral prefrontal cortex (Hugund et al., 2004; Vinod et al., 2005), a brain region involved in manipulating the contents of working memory. Given its role in selective attention, hyperactivity in the dorsolateral prefrontal cortex may promote pessimistic biases in depressed persons such as the tendency to recall and fixate on negative emotional memories. Consequently, upregulation of CB1-mediated endocannabinoid signaling in the region may be a protective response. Unfortunately, it is virtually impossible to establish whether post-mortem alterations observed in humans indeed resulted from negative mood disturbance throughout life, much less ascertain their nature—are these alterations protective or part of the problem? Some insight, however, can be gained by use of rodent models, which are highly amenable to experimental manipulation.

THE ECB SYSTEM IN RAT MODELS OF NEGATIVE MOOD DISTURBANCE

Using the chronic unpredictable or mild stress (CUS) protocol, which involves daily administration of various stressors (e.g., restraint, forced swim, cage rotations, social isolation, water deprivation) for at least 3 weeks, it is possible to induce behavior in rats that bears an uncanny resemblance to melancholic depression in humans. By 3 weeks of CUS, for example, rats lose interest in sex, although sexual performance is unimpaired, suggesting a loss of motivation (Hill et al., 2008). Over 5 weeks of CUS, rats lose weight and interest in sucrose, both absolutely and relative to bodyweight, suggesting reduced reward sensitivity or anhedonia (Bortolato et al., 2007). Additionally, physiological alterations observed in depressed humans, such as increased secretion of corticosteroids and pro-inflammatory chemo/cytokines, are also observed in rats subjected to CUS (Grippo, Francis, Beltz, Felder, & Johnson, 2005).

Commonly prescribed antidepressants rescue CUS-treated rats from depressive phenotype, but can manipulations of the endocannabinoid system? In behavioral tests classically employed by pharmacologists for screening and developing new pharmacotherapies, low doses of drugs that activate CB1 (agonists) tend to have antidepressant and anxiolytic effects, while high doses tend to register strong anxiogenic effects. After 3 weeks of CUS, however, even low doses are anxiogenic (Hill & Gorzalka, 2004). Indirect enhancers of CB1 signaling (inhibitors of AEA & 2-AG degradative enzymes, FAAH and MGL) also have antidepressant and anxiolytic effects in classic behavioral tests. After 5 weeks of CUS, the bodyweight of both rats treated daily for 5 weeks with imipramine (an antidepressant) and those similarly treated with URB597 (a FAAH inhibitor) was restored to normal. More importantly, both drugs were able to raise sucrose intake (absolutely and relative to bodyweight) in stressed rats to the level of intake seen in non-stressed rats, suggesting reversal of CUS-induced anhedonia. Indirect enhancement of CB1-mediated signaling, then, shows promise as a potential new pharmacotherapy for depression.

Does CUS induce alterations of the endocannabinoid system in the brains of rats? If so, do antidepressants treat these alterations? A 2008 study by Hill, Carrier, and McLaughlin, et al. addresses these questions. In it, 3 weeks of CUS increased CB1 density in the rat prefrontal cortex, but decreased CB1 density in the hypothalamus and the ventral striatum. Concurrent treatment with the antidepressant imipramine prevented the development of these alterations, but not a CUS-induced decrease in hippocampal CB1 density that replicated previous findings (Hill, Patel, Carrier et al., 2005). Both receptor down-regulation in mature hippocampal neurons and reduced hippocampal neurogenesis may be involved in the observed loss of CB1 density.

Reduced hippocampal neurogenesis has been observed in both individuals suffering from depression and rats undergoing CUS, and many drugs used to treat depression in humans such as tranylcypromine, reboxtine, and fluoxetine, are known to promote hippocampal neurogenesis in rats by promoting the proliferation of progenitor cells (Malberg, Eisch, Nestler, & Duman, 2000). Not only do neural progenitor cells in the hippocampus show CB1 immunoreactivity in both embryonic and adult rats, but chronic treatment with HU210 (a CB1 agonist) has been shown to result in their proliferation, suggesting that this drug's anxiolytic and antidepressant effects in the Novelty Suppressed Feeding and Forced Swim Test, respectively, are mediated by its ability to promote hippocampal neurogenesis, much like traditional pharmacotherapies for depression in humans (Jiang, Zhang, Xiao, & van Cleemput, 2005). Although CUS-induced reductions in tissue endocannabinoid content are inconsistent, the fact that 3 weeks of CUS are sufficient to reduce hippocampal 2-AG content (Hill, Patel, Carrier et al., 2005) or global AEA content in an imipramine-insensitive manner (Hill et al., 2008) could support the idea that chronic unpredictable stress leading to depression may induce a deficiency in CB1-mediated endocannabinoid signaling in the hippocampus that ultimately leads to less neurogenesis.

Thus, CUS induces not only depression-like behavior in rats, but also regionally specific alterations in their brains' endocannabinoid systems that are consistent with those observed post-mortem in depressed humans. However, are these alterations promoting or responding to the development of negative mood disturbance? In order to address this question, McLaughlin, Hill, Dang, et al. (2012) looked more closely at the prefrontocortical endocannabinoid system in rats exposed to CUS. Here, the prefrontal cortex (PFC) was subdivided into dorsomedial PFC, which included the anterior cingulate and motor cortices, and ventromedial PFC, which included pre- and infra-limbic cortices. Following CUS, increased CB1 density without a change in the receptor's affinity for its ligands was observed in the ventromedial PFC. Based on

this, McLaughlin et al. decided to test the effects of local CB1 antagonism on rat behavior in the forced swim test (FST). If endocannabinoid signaling in the ventromedial PFC were involved in pathogenesis or maintenance of depression, then local blockade should ameliorate CUS-induced depressive phenotype and produce an antidepressant effect in the FST.

In the FST, stressed rats given a microinjection of AM251 (a selective CB1 antagonist) into the ventromedial prefrontal cortex actually spent more time immobile and less time swimming than both stressed rats given vehicle (1 part dimethyl sulfoxide to 9 parts 0.9% saline) and non-stressed rats given either vehicle or AM251. Clearly, local CB1 antagonism did not have an antidepressant effect. Local CB1 blockade decreased what little proactive coping rats were capable of after CUS. As such, up-regulation of the endocannabinoid system in the ventromedial PFC (pre- and/or infra-limbic cortex) following CUS could very well be protective, and endocannabinoid signaling in either the pre- and/or infralimbic cortex may facilitate proactive coping behaviors.

Furthermore, in a separate set of experiments (McLaughlin et al., 2012), McLaughlin and colleagues observed sharp reductions in the AEA content of the ventromedial PFC of non-stressed rats immediately following FST. It seems that proactive coping behavior acutely depletes AEA in either the pre- and/or infralimbic cortex of non-stressed rats. Additionally, indirect local enhancement of endocannabinoid signaling via microinjection of URB597 (a FAAH inhibitor) prior to the FST reduced the amount of time rats spent immobile and increased the amount of time spent swimming and struggling. This effect was blocked by local preadministration of AM251, confirming CB1-dependency. Proactive coping responses to an unpredictable acute stressor cause a drop in local AEA content, possibly explaining reduced AEA content in the prefrontal cortex of rats following 3 weeks of CUS (Hill et al., 2008). Indeed, CUS may result in reduction of ventromedial PFC AEA content to a level insufficient for sustained facilitation of proactive coping, prompting local up-regulation of functional receptors. Taken together, McLaughlin's findings strongly suggest that CB1-mediated endocannabinoid signaling in the ventromedial PFC supports proactive responses to distress.

In humans, proactive coping strategies are a protective cognitive factor in the etiology of negative mood disturbances. Depression, for example, is often marked by helplessness—passive acceptance of defeat in the face of chronic, unpredictable, and seemingly insurmountable perceived challenges or threats. Curiously, the concentration of AEA in systemic circulation may act as an indicator of internal resource availability and sufficiency to face challenges and threats in the environment. In rats, the pool of the AEA in circulation was increased in an imipramine-insensitive manner following 3 weeks of CUS (Hill et al., 2008). In humans, the amount of AEA in circulation briefly increases following acute psychological distress (Dlugos Childs, Stuhr, Hillard, & de Wit, 2012), a response that is possibly blunted in individuals suffering from depression (Hill, Miller, Carrier, Gorzalka, & Hillard, 2009). Additionally, the baseline concentration of AEA in circulation is inversely related to both cortisol secretion during the acute stress response and negative affective symptoms such as anxiety, anhedonia, and indifference (Dlugos et al., 2012; Giuffrida et al., 2004).

DISTRESS AND THE ECB SYSTEM

Behavioral responses to any stressor, including unpredictable challenges or threats in the environment, are facilitated by the acute stress response, a pattern of physiological activation organized by the hypothalamus that includes adrenal secretion of catecholamines and corticosteroids as well as the activation of the sympathetic peripheral nervous system. Experience of the acute stress response—viz., distress—is an affective phenomenon marked by high arousal and negative valence. As mentioned earlier, individuals suffering from depression show altered hypothalamic-pituitary-adrenal (HPA) axis activity. Successful treatment of depression not only restores normalcy to the HPA axis, but also activity in the prefrontal cortex and hippocampus (Aihara, Ida, Yuuki, et al., 2007)—all three of which are subject to endocannabinoid modulation.

Interestingly, a 2009 study on rats by Hill and colleagues showed that acute stress causes a drop in amygdalar AEA, but not 2-AG content, possibly via induction of FAAH activity. It was also found that the anticipated increase in serum corticosterone following acute stress was strongly and inversely related to amygdalar AEA content. Importantly, microinjection of URB597 into the basolateral amygdala reduced stress-induced corticosterone secretion in a CB1-dependent manner, but neither central nor medial nucleus of the amygdala did. As such, the tone of CB1-mediated endocannabinoid signaling in the basolateral amygdala seems to modulate activation of the HPA axis in response to acute stress. However, microinjection of AM281 (a CB1 antagonist) into the dorsal periaqueductal gray (dPAG) will block increased sympathetic nervous system activation and arterial blood pressure, whisker twitching, and limb movement resulting from electrical stimulation of the hypothalamic defense area (Dean, 2011), while in the absence of the latter, microinjection of AEA into the dPAG can reproduce this acute stress response-like pattern in a CB1-dependent manner.

Taken together, these findings suggest that endocannabinoid signaling facilitates some of the rapid changes in physiology that constitute the acute stress response, while also negatively modulating its extent and duration. When perceived challenges or threats (viz., stressors) are chronic and unpredictable, the hypothalamus may trigger acute stress responses before previous ones have terminated, effectively ignoring negative feedback, such as that provided by increased corticosteroid concentration in circulation, which in vulnerable individuals may ultimately result in altered HPA axis activity.

CONCLUSION

Sustained alterations in the physiology of various neural structures including the amygdala, prefrontal cortex, hippocampus, hypothalamus, and ventral striatum, such as those that can be induced by chronic unpredictable stress, may help explain negative mood

disturbances. These disturbances may involve either arousal or valence or both, a view which agrees with the subjective experience of individuals suffering from mood disorders and speaks to the observed frequency of co-morbid anxiety disorders. Beyond underlying vulnerabilities in physiology that augment risk for the development of affective and somatic symptoms that characterize negative mood disturbances, neither concurrent cognitive-affective appraisal and analysis by individuals nor sociocultural factors (e.g., social support) can or should be ignored, especially in the development of hopelessness, a cognitive factor known to mediate risk for suicidality, and the quality of life eroding course of mood disorders.

Importantly, CB1-mediated endocannabinoid signaling in the brain is positioned to modulate cognitive-affective circuitry and respond to dysregulation. Negative mood disturbance alters the endocannabinoid system in human and rat brains, and augmentation of endocannabinoid signaling in rat models of human depression rescues both affective and somatic symptoms. Although pre-clinical evidence points toward indirect enhancement of endocannabinoid signaling as a promising potential new pharmacotherapy for mood disorders, whether it will be pursued in human clinical trials remains to be seen.

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