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Section Editors

Endocannabinoids: Stress, Anxiety, and Fear

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Cover and Figure 1. The approximate regional cannabinoid receptor density, based on autoradiographic or immunocytochemical mapping in primate (human and nonhuman) brain, is color-coded on the right side of coronal magnetic resonance images. Results were combined across studies by calculating relative density for each structure as a percentage of the density within the substantia nigra, the area with the highest density of cannabinoid receptors in the human brain.[1–4] There are significant differences across these studies, so these illustrations should be considered a general guide. The laminar distribution of receptors within cortical gray matter is not illustrated. This varies greatly across areas within the cerebral cortex. In the cerebellum, binding is primarily concentrated in the molecular layer of the cortex. Structures involved in the dorsolateral (pink), anterior cingulate (green), and orbitofrontal (blue) prefrontal-subcortical circuits are color-coded onto the left side to provide anatomic orientation.

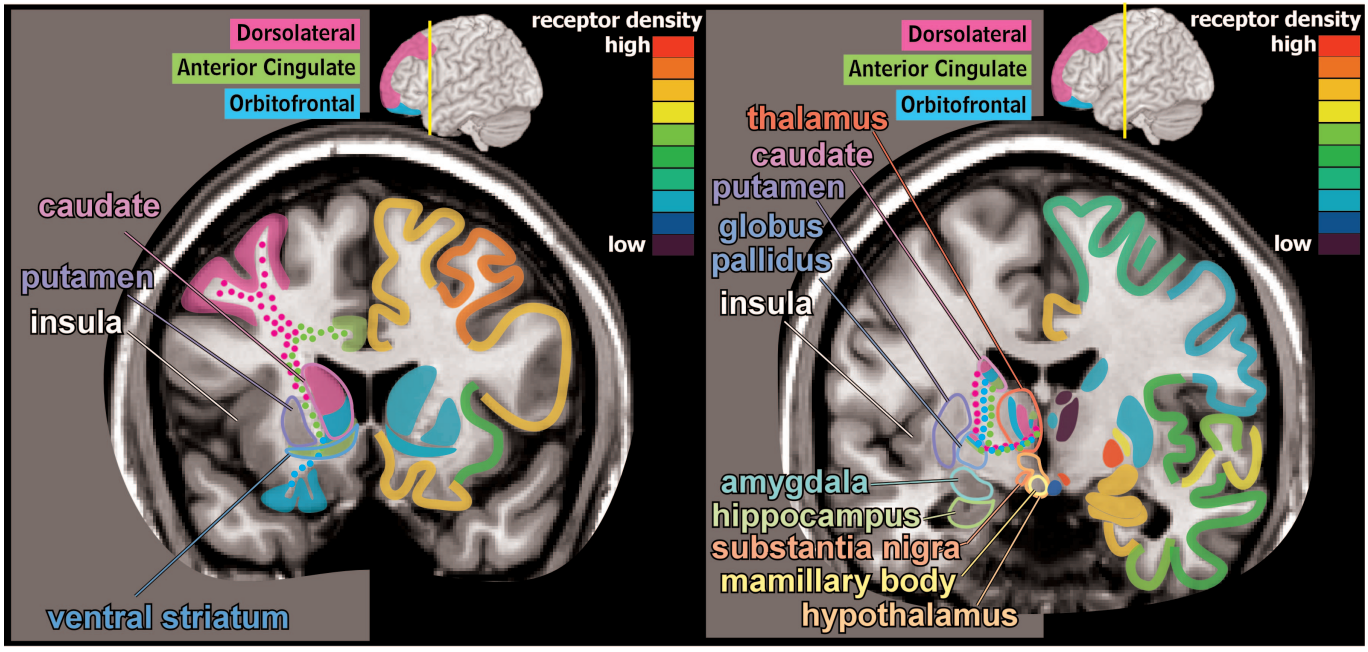
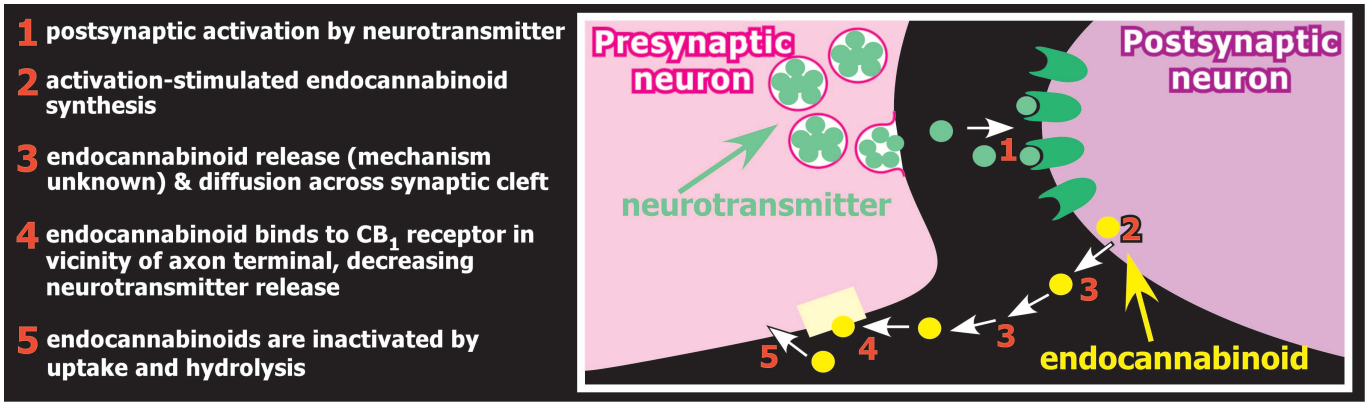


Figure 2. Endogenous ligands (endocannabinoids) for the CB_1 receptor act as retrograde inhibitors of a wide range of neurotransmitters. They are synthesized in the postsynaptic cell in response to depolarization. This is thus an "on-demand" system, activated only when and where needed. Endocannabinoids are released and diffuse across the synapse to activate receptors located on the axon terminal, suppressing neuronal excitability and inhibiting neurotransmission. They are inactivated rapidly by uptake followed by intracellular hydrolysis.



Cannabis sativa (hemp) is a flowering annual that has been in use as a structural material (cordage, cloth, paper) and in medicine for thousands of years.[5–7] Reference to the psychoactive effects of its phytochemical products have been found in writing throughout the ancient world. Cannabis herb (marijuana) is made by drying the leaves and flowering tops. Cannabis resin (hashish) is made by collecting the fluid secreted by the plant during the flowering phase. A recent review indicates that studies of this plant have identified more than 500 compounds within the plant.[6] The principle psychoactive cannabinoids in Cannabis sativa are Δ8 and Δ9 tetrahydrocannabinol (THC).[6,7] Δ9 THC is considered the major psychoactive constituent as it is considerably more abundant in the plant and more potent in effect. The amount of Δ9 THC varies greatly across plant strains and is also affected by farming and preparation techniques.[8] Studies suggest an increasing content of Δ9 THC in street cannabis over the past few decades (e.g., ~1.5% in 1980, 4.47% in 1997, 5.11% in 2002).[8] Δ9 THC is converted to 11-hydroxy-Δ9 THC in the lungs and liver.[7] Onset of action depends on both dose and method of administration. Following ingestion by smoking, initial effects may appear within the first minute, whereas following oral ingestion first effects may appear in 15–30 minutes.[8,9] Onset, duration and nature of action (pleasant versus unpleasant) are affected by other factors, as well, such as individual differences in absorption, method of smoking, previous history, anxiety level, and environmental context.[8,10] Early acute effects commonly include light-headedness and euphoria, with some individuals experiencing tachycardia and hypotension. Later acute effects may include time dilation, relaxation, increased body awareness, increased appetite, sleepiness, impaired memory, and impaired concentration.[7–9,11] Adverse reactions do occur (e.g., anxiety, panic, paranoia, psychotic symptoms), but are much less common.[8,9,11,12] Functional imaging studies indicate that intoxication is associated with increased regional cerebral blood flow and metabolism, particularly in frontal and limbic regions as well as the cerebellum.[8] Both tolerance and dependence can develop with chronic use.[9,11–13] Withdrawal is characterized by nervousness, tension, anxiety, and sleep disturbances. While long-term cognitive impairment has been reported in some studies, the evidence for this is not strong.[7–9,11,12] Some studies support an influence of cannabis use on the development of psychiatric disorders, particularly schizophrenia and mood disorders.[11,12,14]

A surge in research into the mechanism of action for Δ9 THC in the brain followed its isolation and identification in the 1960s.[6] This led to the identification of endogenous cannabinoid (endocannabinoid) receptors in brain tissue. Research intensified following the cloning of these receptors (CB_1 and CB_2) in the early 1990s.[6,7,15,16] Identification of the first endocannabinoid, *N*-arachidonoylethanolamine (anandamide, from the Sanskrit for "eternal bliss") was achieved soon after.[6] A decade later the modulatory action of endocannabinoids at synapses was discovered.[17] Both the CB_1 and CB_2 receptors are cell surface proteins that span the membrane and are coupled intracellularly to one of the G-proteins.[7,16–18] The distributions and actions of the CB_1 and CB_2 receptors are quite different.[6,7,9,15–19] CB_1 receptors are located predominately on axon terminals in both the central and peripheral nervous system and on some peripheral tissues (e.g., liver, gut, adrenal, muscle, fat). CB_2 receptors are found principally peripherally on immune cells (e.g., spleen, macrophages, tonsils, monocytes, neutrophils), and were originally not thought to occur in the brain. More recently they have been identified on both neurons and glial cells, where they may participate in immune functions.[6,7,9,17,20–22] This article will focus on the CB_1 receptor and compounds that interact with it, as this system mediates most or all of the psychotropic actions of cannabinoids.

Studies of the endocannabinoid system support its importance for multiple aspects of brain function including modulation of the hypothalamic-pituitary-adrenal (HPA) axis, regulation of mood, anxiety, and reward, and extinction of fear learning.[10,13] It also participates in the immune, cardiovascular, and gastrointestinal systems.[9,23] Present medicinal uses of compounds that interact with this system include analgesia, suppression of chemotherapy-induced nausea, appetite

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stimulant for illness and medication-related weight loss, reducing motor symptoms (e.g., spasticity, ataxia, weakness) in multiple sclerosis, and reduction of intraocular pressure in glaucoma.[6,9,13,15,19]

CB_1 Receptor Distribution and Actions

A recent meta-analysis of studies related to ligand binding affinity and receptor distribution for the CB_1 receptor indicates important differences between species and among analytic techniques.[24] In vitro binding studies for the CB_1 receptor found differences in binding potential from many factors including tissue state (e.g., brain sections versus brain homogenates), tissue type (e.g., native versus transfected cells), and species. Receptor distribution also varied by method, with in situ hybridization differing considerably from autoradiographic and immunocytochemical studies, which were in rough agreement. Of particular importance, ordering brain structures by receptor density resulted in different rank ordering in human and rat.[24] Maps of the approximate regional cannabinoid receptor density in primate (human and nonhuman) brain is illustrated in the cover art and Figure 1.[1–4] The relative sensitivities of GABA-ergic and glutaminergic neurons may also vary by species.[15] Endogenous ligands (endocannabinoids) for the CB_1 receptor act presynaptically to inhibit release of a wide range of neurotransmitters including glutamate, acetylcholine, norepinephrine, and GABA (Figure 2).[7,15,25] These compounds are not synthesized in advance and stored. Rather, they are synthesized in the postsynaptic cell in response to depolarization. This is thus an "on-demand" system, with synthesis occurring only when and where it is required.[10] Endocannabinoids are released by an unknown mechanism and diffuse across the synapse to activate receptors located on the axon terminal, suppressing neuronal excitability and inhibiting neurotransmission. They are inactivated rapidly by uptake (possibly carrier mediated) followed by intracellular hydrolysis [fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MGL)].[6,7,10,15,18,26] The two most studied endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG). Both anandamide and Δ9 THC are low intrinsic activity (partial) agonists for the CB1 receptor. 2-AG is a high intrinsic activity (full) agonist.[16] Of particular importance, synthetic compounds delivered systemically may not have the same effects as endogenous compounds, as they lack both spatial and temporal specificity.[10,27] This may be one reason why some studies have found a bell-shaped or biphasic relationship between dose and effect, with high doses often having the opposite effect of low doses.[10,14,27,28]

The potential interactions between ligands and receptors are complex.[15,16] Most receptors have both active and inactive conformations. If a particular ligand favors the active conformation of the receptor it is considered to have high intrinsic activity (full agonist). If a ligand does not favor the active conformation then at the same level of receptor occupancy there will be a lower level of activation because some receptors will be in the active state while others will be in the inactive state. Such a ligand is considered to have low intrinsic activity (partial agonist). A third type of interaction is possible in the endocannabinoid system, because at least some portions of it are tonically active. Thus a ligand can actually decrease activity below normal levels (inverse agonist). In addition, particular ligands are able to activate one signaling pathway more than another. This is referred to as agonist-directed trafficking or functional selectivity. Thus, different agonists may favor coupling to different G proteins.

The endocannabinoids are neuromodulatory compounds that provide feedback inhibition via CB_1 receptors and are integral to many types of synaptic plasticity.[10,17,18] The first to be identified were depolarization-induced suppression of inhibition (DSI) in the hippocampus and depolarization-induced suppression of excitation (DSE) in the cerebellum.[17] Endocannabinoid synthesis is stimulated by the increased intracellular calcium that occurs as a result of depolarization of the postsynaptic dendrite for both DSI and DSE, which occur widely in the brain.[18] Activation of metabotropic glutamate or muscarinic receptors can also stimulate endocannabinoid synthesis at both excitatory and inhibitory synapses. These have been termed metabotropic suppression of inhibition (MSI) and metabotropic suppression of excitation (MSE).[18] Although not dependent on a postsynaptic increase in calcium, both MSE and MSI are enhanced by increased calcium and thus may serve as coincidence detectors. An alternative name for this type of plasticity is endocannabinoid-mediated short-term depression (eCB-STD).[17] Endocannabinoids also mediate some types of long-term depression (LTD) in multiple areas, including hippocampus, dorsal striatum, ventral striatum (nucleus accumbens), cerebellum, and prefrontal cortex.[17,18,29] Endocannabinoids can also act on somatic receptors, activating po-

tassium channels, thus depolarizing the neuron and inhibiting action potential generation.[17,18]

Stress, Emotional Regulation, and Homeostasis

> The term 'stress' generally indicates an internal (i.e., infection, psychological condition) or external (i.e., physical danger or damage) circumstance that threatens the homeostasis of the organism. Thus, stress results in a discrepancy, either real or perceived, between the demands of a situation and the organism's resources.[30]

> Fear is an adaptive component of the acute stress response to potentially dangerous stimuli which threaten the integrity of the individual. However, when disproportional in intensity, chronic, irreversible and/or not associated with any actual risk, it constitutes a maladaptive response and may be symptomatic of an anxiety-related neuropsychiatric disorder such as generalized anxiety, phobia, or posttraumatic stress disorder (PTSD), among others.[10]

The endocannabinoid system participates in multiple brain circuits implicated in neuropsychiatric conditions such as those modulating stress reactions, learning, and extinction of fear, emotional regulation, and reward processes.[31,32] CB_1 receptors are found in many areas involved in regulation of the stress response including the paraventricular nucleus (PVN) of the hypothalamus, corticotroph cells in the pituitary, adrenal glands, and limbic-related areas of the brain.[30] Endocannabinoids inhibit the hypothalamic-pituitary-adrenal (HPA) axis and may well provide an ongoing basal level of inhibition. During acute stress, corticotrophin releasing factor is released into the portal system by neurons in the paraventricular nucleus. Corticotrophin releasing factor (CRF) induces release of adrenocorticotrophic hormone from the anterior pituitary. Adrenocorticotrophic hormone stimulates production of glucocorticoids (e.g., corticosterone) in the adrenal gland. Glucocorticoids, in turn, inhibit release of corticotrophin releasing factor in the hypothalamus and adrenocorticotrophic hormone (ACTH) in the pituitary. Negative feedback in the hypothalamus is mediated by glucocorticoid-stimulated synthesis and release of endocannabinoids within the paraventricular nucleus.[10,25,30] Thus, endocannabinoids are released in response to activity in the hypothalamic-pituitary-adrenal axis and serve to bring it back toward its baseline (prestress) state.[10]

Animal studies indicate that neither acute stress nor chronic predictable stress (which will habituate) alter CB_1 receptor density or affinity in the brain.[33] Both chronic unpredictable stress (which does not habituate) and chronic administration of corticosterone, on the other hand, decrease CB_1 receptor density in the hippocampus.[33] These stress conditions also differentially alter the content of 2-AG and anandamide of many brain regions. Some studies support the theory that a progressive increase of 2-AG and decrease of anandamide within limbic-related brain areas (e.g., medial prefrontal cortex, limbic forebrain, amygdala, hypothalamus) may, in part, mediate behavioral habituation to chronic predictable stress.[33] An opposite pattern (increased anandamide, decreased 2-AG) is seen in the ventral striatum, which may have implications for endocannabinoid-mediated facilitation of reward.[33] An antidepressant-like effect (as indicated by enhanced stress-coping behaviors and decreased anhedonic behaviors), has been reported for both compounds that directly activate CB_1 receptors and those that prolong the action of naturally released endocannabinoids (e.g., inhibit uptake, inhibit hydrolysis).[28] Animal studies of social defeat stress (which produces symptoms of anxiety and depression) indicate that it decreases CB_1 receptor-mediated inhibition of GABA (but not glutamate) neurotransmission in the striatum.[34] This change occurs as a result of stress-induced increases in glucocorticoids, and can be reversed by both natural rewards (e.g., access to sucrose) and administration of drugs with rewarding properties (e.g., cocaine).[34] An important role for the endocannabinoid system in reward-related processes is likely. CB_1 receptor-activation modulates dopamine signaling in both the ventral tegmental area and the ventral striatum.[13,29] CB_1 receptors also participate in LTD at glutaminergic synapses in both dorsal and ventral striatum.[29] It has been proposed that the endocannabinoid system provides the common neurobiological mechanism underlying both the rewarding aspects of drugs of abuse and relapse, suggesting that blockade of CB_1 receptors may have therapeutic potential.[13,35] Studies also support the involvement of the endocannabinoid system in extinction of conditioned fear.[10,25,28] Endocannabinoid content of the amygdala is increased following exposure to the conditioned stimulus (e.g., tone previously paired to foot shock).[25,28] Removal of the influence of CB_1 receptors (either by pharmacological blockade or by genetic manipulation) impairs extinction of conditioned fear.[27,28] Extinction is enhanced by administration of compounds that directly activate CB_1 receptors or prolong the ac-

tion of naturally released endocannabinoids (e.g., inhibit uptake, inhibit hydrolysis).[10,27,28]

There is growing evidence that another important function of the endocannabinoid system is regulation of energy balance, both in terms of influencing appetite and by modulating metabolism.[36–39] Both central and peripheral actions are likely to be involved. CB_1 receptors are present in hypothalamic areas (e.g., mediobasal, paraventricular, lateral) integral to balancing energy intake with energy expenditure.[38] Endocannabinoid levels in the hypothalamus are increased by starvation and decreased by food intake.[36] In rats, food intake is increased following administration of endocannabinoids to either the hypothalamus or mesolimbic forebrain.[36] In addition, studies in both humans and animals have found that that blockade of CB_1 receptors normalizes several metabolic parameters that are risk factors for metabolic syndrome (e.g., decreased triglycerides and insulin resistance, increased high-density lipoprotein cholesterol) in excess of what would be expected from weight loss alone, supporting a role in glucose homeostasis and adipose tissue metabolism.[36–40] Research suggests that this system may be overactive in conditions such as obesity and hyperglycemia.[36,38,39,41] CB_1 receptor activation increases fatty acid synthesis in the liver as well as lipid synthesis by adipose tissue, and obesity is associated with increases in CB_1 receptors in both adipose tissue and skeletal muscle.[36]

CONCLUSION

The involvement of the endocannabinoid system in multiple aspects of brain function provides new targets for the development of novel therapeutic agents for a wide range of psychiatric disorders.[9,14] Potential applications include treatment of mood and anxiety disorders, degenerative conditions, and acquired brain injuries.[9,10,14,19,23,25,42–46] In addition to receptor ligands (both agonists and antagonists), a number of compounds have been developed that prolong endocannabinoid action, either by inhibiting uptake or by decreasing hydrolysis.[6,9,15,26] One challenge is to develop agents that are both selective and safe. The difficulty in achieving this has recently been driven home by the European Medicines Agency's decision to suspend sales of rimonabant (CB_1 receptor antagonist/inverse agonist), approved 2 years ago for the treatment of obesity, citing adverse psychiatric effects.[47]

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