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Review of the Endocannabinoid System

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Abstract

The endocannabinoid system (ECS) is a widespread neuromodulatory network involved both in the developing CNS as well as playing a major role in tuning many cognitive and physiological processes. The ECS is composed of endogenous cannabinoids, cannabinoid receptors and the enzymes responsible for the synthesis and degradation of endocannabinoids. In addition to its endogenous roles, cannabinoid receptors are the primary target of Δ^9-tetrahydrocannabinol (THC), the intoxicating component of cannabis. In this review, we will summarize our current understanding of the ECS. We will start with a description of ECS components and their role in synaptic plasticity and neurodevelopment, and then discuss how phytocannabinoids and other exogenous compounds may perturb the ECS, emphasizing examples relevant to psychosis.

Keywords

Endocannabinoid; neurodevelopment; psychosis; tetrahydrocannabinol; cannabinoid receptor; synaptic plasticity

Introduction:

The endocannabinoid system (ECS) plays a central role in the developing nervous system while in the mature nervous system it modulates neuronal activity and network function. The ECS is comprised of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the proteins that transport, synthesize and degrade endocannabinoids. It is important to appreciate that most components of the ECS are multifunctional. Thus, rather than being a discrete, isolated system, the ECS influences, and is influenced by, many other signaling pathways. This is especially important to consider when assessing the effects of ECS

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targeting drugs. While cannabis contains many bioactive compounds, most of the psychoactive effects classically associated with cannabis appear to be mediated through the interaction of Δ^9-tetrahydrocannabinol (THC), the major psychotropic constituent of cannabis, with cannabinoid receptors. Cannabidiol (CBD) is another constituent of cannabis, present at variable levels, which interacts with the ECS as well as other neuromodulatory systems. CBD has attracted immense recent interest as a therapeutic agent, including as a treatment for psychosis [1], although the molecular target(s) of CBD remain to be elucidated [2]. The ECS has captured the interest of scientists and physicians studying schizophrenia for several reasons: acute administration of THC recapitulates some symptoms of schizophrenia in a dose-dependent fashion [3, 4], endocannabinoid levels are altered in schizophrenia and change during treatment with antipsychotic drugs [5], and heavy adolescent cannabis use increases the risk to develop schizophrenia, or more severe schizophrenia later in life [6]. In this article we will review key aspects of ECS, with an emphasis on those aspects that are particularly relevant for schizophrenia and psychosis.

Cannabinoid receptors:

CB1 and CB2 are the best-characterized cannabinoid receptors. Both are G protein-coupled receptors (GPCRs), primarily coupling to inhibitory G proteins. They inhibit adenylyl cyclase and certain voltage-sensitive calcium channels, stimulate mitogen-activated proteins kinases (MAP kinases) and inwardly rectifying potassium channels (GIRKs), and recruit beta-arrestins, among other actions [7]. The diversity of CB1 signaling is enhanced by their propensity to heterodimerize with other GPCRs, including D2 dopamine, hypocretin, and opioid receptors (see below[8]). CB1 receptors are particularly enriched in the nervous system, but are also present in diverse organs including liver, adipose tissue, skin, etc. In adult CNS neurons, CB1 is most abundant on certain GABAergic interneurons [9]. However, functional CB1 is found on a wide range of other neurons, including glutamatergic, cholinergic, glycinergic, serotonergic, etc, across the brain (e.g., [10]). In neurons, CB1 receptors are particularly enriched on synaptic terminals [11], reflecting their major role in modulating synaptic transmission, however they are also expressed at functionally important levels on neuronal somata and dendrites [12–14] and some mitochondria [15]. In addition, functional CB1 receptors are expressed by some astrocytes [16]. Expression of CB1 on oligodendrocytes, oligodendrocyte precursors, and microglia, is much less and their physiological role(s) are still being defined [17–19]. CB2 receptors are primarily expressed in cells of immune origin [20, 21] including microglia [22, 23], though they may also be expressed in neurons [24], particularly in pathological states [25]. Microglial CB2 receptor activation is generally anti-inflammatory [26]. Thus, an interesting and unexplored question is if CB2 activation during maternal infection lessens the risk for psychotic disorders in the offspring [27].

Because of the likely association between cannabis use and increased risk for psychosis and schizophrenia [28], substantial efforts have been directed towards identifying genetic polymorphisms in the CB1 gene (*CNR1*) influencing schizophrenia risk, interactions between substance abuse and schizophrenia, and modulation of therapeutic response to antipsychotics. Overall, summarizing a complex literature, no *CNR1* coding polymorphisms have emerged from these studies, and the noncoding polymorphisms reported tend to be

present in subpopulations or have not been robustly repeated in follow up studies. A comprehensive review on the topic was recently published [29].

Signaling:

As mentioned above, CB1 and CB2 receptors primarily couple to inhibitory G proteins (Gi/o) and engage the pathways associated with Gi/o [7]. CB1 and CB2 receptors also recruit beta arrestins and signal through arrestin-dependent pathways [30, 31]. Under some conditions, cannabinoid receptors can also stimulate cAMP formation and engage Gq/11 pathways [32, 33]. Interestingly astrocyte CB1 receptors strongly couple to Gq/11 [16]. Like all GPCRs, CB1 and CB2 receptors show functional selectivity, where different ligands may engage different signaling pathways [8]. Functional selectivity is best visualized by accepting the concept that GPCRs assume multiple conformations, with different conformations coupling with varying efficiencies to distinct intracellular signaling effectors [34, 35]. Different ligands will favor ensembles of distinct conformations, thus structurally dissimilar agonists may stimulate very different signaling pathways, resulting in divergent biological effects [34–36]. In addition, cannabinoid receptor ligands vary in their intrinsic efficacy (maximum activation of a particular signaling pathway). Importantly, THC is a low efficacy CB1 agonist, while 2-arachidonoyl glycerol (an endogenous cannabinoid, see below) and most synthetic CB1 agonists are high efficacy agonists. Thus, functional selectivity as well as the differences in intrinsic efficacy among various cannabinoid receptor ligands emphasizes the importance in preclinical studies of appropriately matching the ligand that will be used with the question being asked. For example, studying the response to a highly efficacious synthetic cannabinoid may not be the proper approach to understanding the consequences of THC, a low efficacy agonist [37, 38]. Conversely, the neuropsychiatric consequences of consumption of “spice” cannabinoids (highly efficacious synthetic cannabinoids) may be very different from those of THC from cannabis [39].

Allosteric modulation:

THC and the endocannabinoids interact with CB1 and CB2 receptors at their orthosteric sites. However, the large size of GPCRs gives ample opportunity for sites where other molecules can bind and, under favorable conditions, modulate the function of the receptor. While not much is known about allosteric modulation of CB2 receptors, several positive and negative allosteric modulators of CB1 receptors have been described. Classically, allosteric modulators may affect the kinetics of orthosteric ligand binding, affect the efficiency of receptor activation, or both. An important feature of allosteric modulators is “probe dependence”. This refers to how an allosteric modulator affects signaling for a specific orthosteric agonist. For example, an allosteric modulator may alter THC signaling, but not endogenous cannabinoid signaling. An important potential endogenous negative allosteric modulator for CB1 is the steroid hormone, pregnenolone [40–42]. Some (though not all [43–45]) investigators have found that pregnenolone decreases signaling of THC via CB1 receptors. It has not been established if pregnenolone modulates CB1 signaling activated by endogenous cannabinoids. A second negative allosteric modulator of CB1 receptors is CBD, which attenuates CB1 activation by THC and endogenous cannabinoids in multiple *in vitro* assays [46, 47]. Negative allosteric modulation of CB1 by CBD may explain why some, but

not all studies ([48–50]), find that CBD-containing strains of cannabis (or co-administration of CBD with THC) may produce less extreme psychoactivity and why frequent consumption of high CBD cannabis may be less detrimental than similar consumption of low CBD cannabis [51, 52].

Multimerization and cannabinoid receptor-interacting proteins:

Like other GPCRs [53], cannabinoid receptors can associate with other GPCRs, a process termed dimerization or multimerization. Association of cannabinoid receptors with other GPCRs has the potential to greatly enrich their signaling repertoire. While both CB1 and CB2 have been found to associate with other GPCRs [54, 55], this has been more widely studied with CB1 receptors. Prominent association partners of CB1 receptors include D2 dopamine receptors [56, 57], orexin A receptors [58], adenosine 2A receptors [59], and delta opioid receptors [60, 61], among others. In addition to other GPCRs, cannabinoid receptors interact with several proteins that may regulate their function. Particularly notable interacting proteins include CRIP1a/b [62, 63], SGIP1 [64], and GASP1 [65]. A major function of CRIP1a appears to be competition with beta-arrestin for binding to the distal C-terminus of CB1. This impairs CB1 signaling and slows CB1 desensitization and internalization [66, 67]. SGIP1 also competes with beta-arrestin binding and in doing so slows desensitization of CB1 receptors and decreases ERK1/2 signaling [64]. GASP1 has been implicated in down regulating CB1 receptors during chronic cannabinoid treatment [68]. It should be noted that while there is firm biochemical and functional evidence that CRIP1a, SGIP1, and GASP1 modulate CB1 receptor function, these are multifunctional proteins with targets other than CB1 receptors [69–71].

Endocannabinoids:

Narrowly defined, endogenous cannabinoids (endocannabinoids, eCBs) are signaling lipids that activate cannabinoid receptors. While 2-arachidonoyl glycerol (2-AG) [72–74] and anandamide (N-arachidonoyl ethanolamine, AEA) [75] are the two best known eCBs, other structurally related lipids also engage cannabinoid receptors (e.g., N-arachidonoyl dopamine [76]). Conversely, 2-AG and AEA have the potential to activate a wide range of GPCRs, nuclear receptors, and ion channels [77–79], although when considering this literature careful examination needs to be given to the experimental design and physiological relevance of the results. In addition, 2-AG is an important intermediate in lipid metabolism, particularly as a source of arachidonic acid for prostaglandin synthesis [80]. Thus, this is another example where maneuvers to increase or decrease eCB levels will have far-reaching effects extending beyond CB1 and CB2 receptors. This is particularly important to keep in mind when interpreting the results of experiments that perturb the synthesis or degradation of eCBs. As discussed below, despite their structural similarity, 2-AG and AEA are synthesized and degraded by different pathways and have distinct physiological roles. Interestingly, of the two eCBs, anandamide appears to be more involved in schizophrenia [1].

eCB synthesis:

Most of what we know about eCB synthesis comes from investigations of mature nervous system and heterologous expression systems. These studies have led to the concept that the dominant form of eCB synthesis is “on demand” [81]. The principal of on demand synthesis is that the eCB exists as a precursor in membrane lipids and is liberated by the activation of enzymes, typically lipases, that are triggered by a specific signal (e.g., G proteins or elevation of intracellular calcium (see below)). This contrasts to classic neurotransmitters that are synthesized and stored in vesicles. The “made on demand” feature of eCBs means that eCBs are released in a very precise temporal and spatial fashion. This contrasts strongly with the administration of exogenous cannabinoid ligands, such as THC or rimonabant, where receptor engagement will be indiscriminate and sustained (minutes or longer for exogenous cannabinoids, seconds or less for eCBs). Thus, it is unsurprising that the effects of systemically administered cannabinoids may differ from the effects of physiologically released eCBs. This is one motivation spurring research into drugs that directly target ongoing eCB signaling, such as inhibitors of eCB transport or degradation or cannabinoid receptor allosteric modulators.

There are multiple synthetic pathways for producing eCBs, with importance of each pathway varying between tissues and across development, as well as potentially in certain pathological states. The canonical pathway for generating 2-AG is a two-step pathway involving removal of the inositol triphosphate from arachidonoyl-containing phosphatidyl inositol *bis* phosphate (PIP2) followed by removal of the acyl group in the 1 position by a diacylglycerol lipase (DAG lipase) [82]. There are two isoforms of diacylglycerol lipase—DAG lipase alpha and DAG lipase beta [83]. Both are abundant in brain, with DAG lipase alpha generally more important for synaptic production of 2-AG and DAG lipase beta more important for microglial formation of 2-AG [84–86]. Precise synaptic localization of DAG lipase alpha appears to involve homer proteins [87] and disrupted synaptic localization of DAG lipase alpha is associated with neurological diseases [88]. Behavioral and physiological deficits associated with mis-targeted DAG lipase alpha often improve after inhibition of 2-AG degradation, highlighting a therapeutic approach that deserves additional investigation [88].

The canonical pathway for AEA production is hydrolysis of N-arachidonoyl phosphatidyl ethanolamine (NAPE) by a NAPE-PLD [89], though additional pathways are well described and may function in a tissue-specific fashion [90–92]. In terms of site of AEA synthesis, NAPE-PLD is predominately a presynaptic protein [93], thus AEA synthesized by NAPE-PLD [94] is unlikely to have a major role as a retrograde neuromodulator (see below).

Most studies measuring eCB synthesis and release rely on tissue disruption, extraction, and chromatography followed by mass spectrometry (e.g., [31]). These techniques are destructive, thus they don’t permit sequential observation of the same tissue over time and are limited in spatial resolution to ~1 mm. The recent development and ongoing optimization of fluorescent cannabinoid-receptor based probes for eCB detection will undoubtedly refine our understanding of the site(s) of eCB synthesis [95].

eCB transport:

Transport of eCBs across the cell membrane is important following their synthesis and in preparation of their degradation. eCBs are synthesized from phospholipids on the inner leaflet of the membrane, thus for eCBs to act on adjacent cells a mechanism for their exit from the cell is necessary [96, 97]. Similarly, eCB degrading enzymes are primarily intracellular, so a process for eCB entry into cells is necessary to terminate their action. The polar nature of eCBs prevents their passage across cell membranes by simple diffusion and there is little evidence for ATP- or Na^{2+}-requiring eCB transporters, suggesting that carrier-mediated facilitated diffusion as the likely mechanism for transmembrane eCB transport (reviewed by [98]). Substantial evidence suggests that both anandamide and 2-AG are transported by the same endocannabinoid membrane transporter (EMT) [99]. The notion that inhibiting eCB uptake as a strategy for prolonging eCB action for therapeutic gain has motivated the development of EMT inhibitors. Since eCB transport is driven by the concentration gradient, a drug that inhibits eCB degradation will also inhibit uptake. This is especially evident for anandamide [99], and less so for 2-AG [99], perhaps reflecting distinct short-term fates of transported anandamide and 2-AG (e.g., different intracellular sequestering mechanisms). Thus, careful experimentation is necessary (e.g., examining initial rates of uptake and inhibition of eCB degrading enzymes, conducting experiments in cells lacking eCB degradative enzymes, determining inhibition of eCB efflux, etc.) to identify authentic EMT inhibitors. Taking these considerations into account several series of EMT inhibitors have been developed and tested in a variety of physiological and behavioral systems. Generally, EMT inhibitors increase eCB levels, potentiate eCB actions and produce cannabimimetic effects (e.g., [100–102]). Progress in this field will be greatly aided by the identification of the EMT.

eCB degradation:

eCB signaling is frequently terminated by hydrolysis of the arachidonic group from either the glycerol (2-AG) or ethanolamine (AEA). 2-AG hydrolysis is primarily carried out in the CNS by monoacyl glycerol lipase (MAGL) or ABDH6 [103, 104], while fatty acid amino hydrolase (FAAH) primarily terminates AEA action [105]. MAGL is found at the highest levels presynaptically [106], while ABHD6 is mostly found in dendrites [104] suggesting the two different 2-AG degrading enzymes have fundamentally different functions. Importantly, the arachidonic acid liberated by the hydrolysis of AEA or 2-AG can serve as a substrate for cyclooxygenases to produce prostaglandins and related molecules [80]. Another route of transformation of eCBs is their direct metabolism by COX-2 to produce prostamides (from AEA) [107] or prostaglandin glycerol esters (2-AG) [107–109]. Thus, degradation of eCBs is not simply the termination of signaling but may be a transition to a new type of signaling.

eCB’s as retrograde messengers:

A major function of the ECS in the mature nervous system is as a retrograde messenger mediating several forms of eCB-mediated synaptic plasticity [110]. Here, eCBs synthesized by the post-synaptic cell travel retrogradely across the synapse to activate presynaptic

cannabinoid receptors, suppressing neurotransmission from CB1-expressing terminals. There are both transient and long-lasting forms of eCB-mediated synaptic plasticity. Both forms involve stimulation of the post-synaptic neuron (either by depolarization and calcium influx or activation of a Gq/11-linked GPCR). The two transient forms are denoted depolarization-stimulated suppression of excitation (DSE, if excitatory transmission is suppressed) or depolarization-stimulated suppression of inhibition (DSI, if inhibitory transmission is suppressed) and metabotropic-stimulated suppression of excitation (MSE, if excitatory transmission is suppressed) or metabotropic-stimulated suppression of inhibition (MSI, if inhibitory transmission is suppressed). These processes act on a time scale of tens of seconds [111]. Certain repetitive forms of low frequency stimulation of excitatory synapses lead to a persistent eCB-mediated long-term depression (LTD) [112, 113]. In this case, LTD induction depends on sustained eCB production. However, once LTD is established, it is independent of eCBs or CB1 receptors. The implications of eCB-mediated synaptic plasticity are dependent on the activity of the CB1-expressing synapse (e.g., if the synapse is not active, there will be little effect) and the relationship between the inputs driving eCB synthesis and the presynaptic terminals expressing CB1 receptors [114].

Non-retrograde effects of eCB's on neuronal excitability:

While much attention is paid to the role of eCBs as retrograde messengers, it is important to appreciate eCBs modify neuronal excitability in other ways. These can be summarized as (1) direct modulation of ion channels, (2) activation of GIRK channels, and (3) enhancement of a hyperpolarization-activated cation channels (I_h). eCBs also modulate several important ion channels, including 5HT3 [115], TRPV1 [116], GABA-A [79], glycine [117] and many others [118]. As always, it is important to establish the parameters under which such modulation is relevant *in vivo* as some of these effects require high eCB concentrations. Activation of GIRK channels by CB1 receptors is a well-described signaling pathway (e.g., [119]). Thus, it is not surprising that eCBs produced by high levels of neuronal activity activate somatic CB1 receptors to open GIRK channels [12, 13]. This may function in a cell autonomous [12] (i.e., slow-self inhibition) or non-cell autonomous [13] fashion. I_h is a dendritically enriched cation channel that regulates dendritic excitability and plays a central role in synaptic plasticity and learning [120] and enhancing its activity impairs learning. I_h activation by CB1 receptors has been proposed as a possible mechanism for THC-impaired learning [14]. Coupling of I_h to dendritic CB1 receptors involves a signaling cascade consisting of c-Jun-N-terminal kinase 1 (JNK1), guanylyl cyclase, cGMP, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels to enhance I_h [14].

Interactions between eCBs and exogenous cannabinoids (THC and spice compounds):

The varying efficacies of 2-AG, AEA, THC, and the synthetic cannabinoids used recreationally ("spice") gives rise to several potentially important and interesting interactions. For example, THC is a fairly potent, low efficacy agonist while 2-AG is less potent, but a highly efficacious agonist [121]. Thus, under conditions where either CB1 receptor density or post-receptor coupling is limited, THC may antagonize endogenous 2-

AG signaling e.g., [97]. This THC/ 2-AG interaction may explain some interesting human behavioral data where even very high doses of the CB1 antagonist rimonabant weakly antagonize the subjective effects of THC [122]. Conversely, rimonabant may have profound effects on THC-induced physiological changes (e.g., heart rate) at considerably lower doses [123]. This likely varies across synapses as sometimes THC mimics 2-AG effects [124]. On the other hand, spice compounds are high efficacy agonists, fully and indiscriminately activating CB1 receptors and countering AEA signaling (AEA is a low efficacy agonist) [125, 126].

Dynamic expression of ECS during brain development:

ECS is present from the earliest stage of pregnancy, in the preimplantation embryo and uterus [127], placenta [128] and in the developing fetal brain [129]. In human fetal brains, CB1Rs can be detected at week 14 of gestation, with preferential expression in the cerebral cortex, hippocampus, caudate nucleus, putamen and cerebellar cortex, mirroring their adult distribution. By week 20, intense expression is evident in CA2–CA3 of hippocampus and in the basal nuclear group of the amygdala [130, 131]. While there are differences according to brain region, generally, AEA is present at low concentrations in the brain at mid-gestation and gradually increases through the perinatal period and into adolescence, until adult levels are reached [132]. On the other hand, fetal 2-AG levels gradually increase through the prenatal period, surging at birth [132, 133]. Notably, 2-AG concentrations (2–8 nmol/g tissue) are approximately 1000-fold higher than those of AEA (3–6 pmol/g tissue) throughout brain development [102]. The mechanisms regulating 2-AG and AEA synthesis in the developing prenatal brain remain to be defined.

The dynamic expression of the ECS and its roles in various aspects of neural development have been summarized in several comprehensive reviews [134–136]. Here we will focus on recent mechanistic insights on how eCBs influence growth cone behaviors during axonal pathfinding [137–139]. CB1 receptor activation induces growth cone collapse in developing GABAergic neurons [138], as well as in cortical excitatory neurons [140]. After post-mitotic glutamatergic neurons become polarized and their projecting axons reach their target zones, CB1R is enriched in long-range axonal tracts including the corticothalamic and corticospinal tracts [141–143]. This ‘atypical’ (versus the adult situation) CB1R expression pattern in long-range glutamatergic axons disappears after birth. Constitutive genetic deletion of CB1R or prenatal CB1R pharmacological blockade in mice increases the number of axons with aberrant trajectories in the corpus callosum and leads to abnormal fasciculation of long-range axons [141, 142]. Similar to CB1R, the prenatal distributions of DAGLalpha/beta and MAGL are localized to long-range glutamatergic axons [133, 142]. While MAGL is co-expressed with both CB1R and DAGLalpha in cultured cortical neurons, MAGL is differentially recruited to the consolidated axon shaft [133]. Thus, CB1Rs, transported by Kinesin 1-mediated axonal transport [144], are maintained inactive by the absence of 2-AG (owing to the presence of active MAGL) while undergoing vesicular transport along the consolidated axon. The absence of MAGL at the growth cones lifts the restriction on CB1R signaling, allowing CB1R to be activated by cell autonomous 2-AG production. Taken together, the subcellular localization of ECS components are well positioned to modulate the process of neural circuit wiring. An open question is how THC or synthetic cannabinoids

consumed by the mother affects these CB1Rs and the long-term consequences of their engagement by THC.

CB1R activation induces retraction of actin-rich growth cones and results in aberrant projections [138–140]. Non-muscle myosin II (NM II) is molecular motor protein linked to actin filaments and has the contractile properties to dynamically control the actomyosin network and thus cell morphology [145]. NMII is an ATPase and is activated by the phosphorylation of its regulatory light chain to enable actomyosin contractility. The rapid remodeling of axon morphology by eCBs involves atypical coupling of activated CB1Rs to heterotrimeric G_{12}/G_{13} proteins. G_{12}/G_{13} then activate Rho-GTPase and Rho-associated kinase (ROCK) to phosphorylate NM II, triggering rapid contraction of the actomyosin cytoskeleton [139]. Furthermore, Njoo et al. [146] found that CB1R complexes with several members of the Wiskott-Aldrich syndrome protein family verprolin homologous protein 1 (WAVE1) complex and the Rho-GTPase Rac1. WAVE1-complex is known to be involved in actin nucleation. Through this complex, eCBs directly impact actin polymerization and stability by functionally modulating Rac1 and WAVE1 activity, leading to growth cone collapse, as well as retraction of synaptic spines of mature neurons. In addition, CB1R can act in concert with the adhesion molecule deleted in colorectal cancer (DCC; a receptor for the axonal guidance molecule, netrin-1) influencing axonal growth cone behavior [140]. Slits, a family of secreted chemorepellent proteins, and their receptors, Roundabout (Robo), play critical roles in axonal guidance [147, 148]. eCBs can configure Slit2/Robo1 signaling to modulate axon patterns. Pharmacologically increasing 2AG via a selective MAGL inhibitor JZL184 [149], increases Slit2 levels in oligodendrocytes and Robo1 in axonal growth cones. The neuronal increase of Robo1 depends on CB1R activating ERK1/2 and JNK pathways. Taken together, the ECS is dynamically and spatially posited to regulate axon outgrowth, navigation, and synaptogenesis by modulating cytoskeleton stability and levels of axon guidance/adhesion molecules. While the above discussion focuses on the effects of cannabinoids on early CNS development, it is likely several of the same principals underlie potential detrimental effects of adolescent cannabinoid exposure in specific brain regions such as the prefrontal cortex (e.g., [150]).

Summary:

The ECS has been implicated in the risk for developing schizophrenia, perturbing the ECS (i.e., through cannabis use) may influence the course of psychoses, and acute intoxication with natural or synthetic cannabinoids can induce transient psychotic symptoms. Through the ECS's role in the developing nervous system, it is well positioned to interact with factors that may predispose an individual to developing psychotic disease and the course of that disease. The ECS's involvement in multiple aspects of neuronal function provides a means by which its disruption will alter sensory processing and may predispose to psychotic symptoms. An important unresolved question is whether manipulating ECS will be beneficial in treating psychiatric diseases where psychosis is a prominent feature.

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