Review

Biological Psychiatry

The Role of Endocannabinoid Signaling in Cortical Inhibitory Neuron Dysfunction in Schizophrenia

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ABSTRACT

Cannabis use has been reported to increase the risk of developing schizophrenia and to worsen symptoms of the illness. Both of these outcomes might be attributable to the disruption by cannabis of the endogenous cannabinoid system's spatiotemporal regulation of the inhibitory circuitry in the prefrontal cortex that is essential for core cognitive processes, such as working memory, which are impaired in schizophrenia. In the healthy brain, the endocannabinoid 2-arachidonylglycerol 1) is synthesized by diacylglycerol lipase in pyramidal neurons; 2) travels retrogradely to nearby inhibitory axon terminals that express the primary type 1 cannabinoid receptor (CB_1R); 3) binds to CB_1R, which inhibits gamma-aminobutyric acid release from the cholecystokinin-containing population of interneurons; and 4) is metabolized by either monoglyceride lipase, which is located in the inhibitory axon terminal, or by α-β-hydrolase domain 6, which is co-localized presynaptically with diacylglycerol lipase. Investigations of the endogenous cannabinoid system in the prefrontal cortex of subjects with schizophrenia have found evidence of higher metabolism of 2-arachidonylglycerol, as well as both greater CB_1R receptor binding and lower levels of CB_1R messenger RNA and protein. Current views on the potential pathogenesis of these alterations, including disturbances in the development of the endogenous cannabinoid system, are discussed. In addition, how interactions between these alterations in the endocannabinoid system and those in other inhibitory neurons in the prefrontal cortex in subjects with schizophrenia might increase the liability to adverse outcomes with cannabis use is considered.

Keywords: Cannabinoid, Cannabis, CB_1R, Cognitive, Inhibitory, Prefrontal cortex

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In recent years, cannabis use has increased in prevalence in parallel with an earlier age of onset of cannabis use during adolescence and a greater content of Δ9-tetrahydrocannabinol, the major psychoactive component of cannabis (1). These trends raise the question of whether the higher rates and earlier onset of use of more potent cannabis may lead to potentially deleterious societal health consequences. One area of potential concern arises from evidence of a relationship between cannabis use and schizophrenia.

Schizophrenia is a serious psychiatric illness associated with high levels of disability and morbidity, elevated rates of suicide, and early mortality (2). The disorder is typically characterized by the triad of 1) psychotic symptoms, such as hallucinations and delusions; 2) negative symptoms, such as alogia and avolition; and 3) impairments in cognitive functions such as working memory and cognitive control. Multiple lines of evidence suggest that cannabis use worsens the course of schizophrenia and may be a risk factor for development of the illness. First, intravenous administration of Δ9-tetrahydrocannabinol has been reported to transiently worsen or induce psychotic symptoms and cognitive deficits in individuals with or without schizophrenia, respectively (3,4). Second, a large number of studies have identified cannabis use as a risk factor for developing schizophrenia (1,5–12). This elevated risk has been reported to remain significant, though may be attenuated, after correcting for confounding variables such as psychotic symptoms preceding cannabis use, familial risk, parental factors, other psychiatric illness, social background, affiliation with deviant peers, socioeconomic status, trauma, baseline IQ, substance use, and level of education (1,5–12). In addition, this risk is inversely related to the age of onset of cannabis use and directly related to the amount of cannabis use. For example, onset of cannabis use at age 15 relative to age 18 was associated with a higher risk of a psychotic disorder at age 26 (6). Third, cannabis use is associated with an earlier age of onset of schizophrenia (13–15), particularly with higher levels of daily cannabis consumption and when the onset of cannabis use begins before age 15 (16,17). Fourth, individuals with schizophrenia who use cannabis have longer durations of hospital stays and more frequent readmissions (18). However, these lines of evidence do not demonstrate that cannabis use is either necessary or sufficient to develop schizophrenia.

Cannabis use in healthy subjects has been reported to result in deficits in the same cognitive domains that are disturbed in schizophrenia and that have the strongest association with poor functioning and long-term outcomes (19–21). For example, otherwise healthy individuals with prolonged

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exposure to high levels of cannabis have performance deficits on neuropsychological tests that persist into periods of abstinence and are more severe in individuals who began using cannabis in adolescence (22). A prospective cohort study found a decline in cognitive function that only occurred in adolescent-onset cannabis users and that did not recover with cessation of cannabis use in adulthood (23). Paradoxically, schizophrenia subjects with a prior history of cannabis use have been reported to have higher performance on multiple cognitive tasks relative to schizophrenia subjects without a cannabis use history (24,25). However, this finding may be explained by the observation that individuals with schizophrenia who have a history of cannabis use have a higher premorbid IQ than those without a history of cannabis use (26). Indeed, higher neurocognitive functioning is also seen in individuals with schizophrenia who abuse other substances (27–29), suggesting that individuals with a more severe course of schizophrenia may lack the cognitive and social capacities to obtain and use illicit substances (27), while a subgroup of schizophrenia subjects with less cognitive impairments may be capable of abusing substances. Alternatively, given the evidence of cannabis use as a risk factor for developing schizophrenia, a subset of individuals at risk for schizophrenia who have relatively normal cognitive functioning may have developed schizophrenia after exposure to cannabis and consequently may have otherwise higher cognitive performance relative to individuals who develop schizophrenia regardless of exposure to cannabis use. However, while epidemiologic studies do not present a fully clear picture of the relationship between cannabis use and cognitive functioning in schizophrenia, direct administration of Δ9-tetrahydrocannabinol to individuals with schizophrenia has been reported to transiently worsen cognitive deficits (4).

Experimental studies in animals have provided more direct evidence of a causal relationship between cannabis use and cognitive impairments. For example, administration of Δ9-tetrahydrocannabinol or other cannabinoid-1 receptor (CB_1R) agonists produced cognitive deficits in adolescent, but not adult, rats (30–32). Similarly, regular administration of Δ9-tetrahydrocannabinol to adolescent monkeys altered the trajectory of developmental improvements in spatial working memory (33). These findings suggest that the long-lasting deleterious effects of Δ9-tetrahydrocannabinol on cognitive function may be more prominent when the exposure occurs during periods of neural circuitry development, such as adolescence, which is also the time period when the symptoms of schizophrenia become clinically apparent.

CORTICAL CIRCUITRY AND COGNITIVE PROCESSES IN SCHIZOPHRENIA

Understanding the mechanisms by which cannabis may disrupt the cognitive functions that are also impaired in schizophrenia requires knowledge of aspects of the cortical circuitry that supports cognitive processes such as working memory. For example, spatial working memory, which is altered in adolescent monkeys by persistent exposure to Δ9-tetrahydrocannabinol (33), depends on a distributed neural circuit that includes the dorsolateral prefrontal cortex (DLPFC) (34). In the DLPFC, layer 3 pyramidal neurons provide reciprocal excitatory connections to other layer 3 pyramidal neurons that sustain circuitry activity during the delay period of working memory tasks (35). In addition, the subpopulation of cortical inhibitory (gamma-aminobutyric acid [GABA]) basket neurons that express the calcium-binding protein parvalbumin provide inhibitory input that tunes pyramidal neuron firing (36). The interaction between layer 3 pyramidal neurons and parvalbumin basket neurons generates gamma frequency (30–80 Hz) oscillations whose power scales with the demands of working memory tasks (37,38). In schizophrenia, DLPFC layer 3 pyramidal neurons and parvalbumin basket neurons are altered. For example, the density of dendritic spines, the postsynaptic targets of excitatory inputs from other pyramidal neurons, are lower on layer 3 pyramidal neurons in schizophrenia (39,40). Furthermore, deficits in messenger RNA (mRNA) levels for parvalbumin (41–45) and in parvalbumin protein levels in basket cell axon terminals (46) are present in the DLPFC in schizophrenia. In addition, deficits in mRNA levels for the GABA synthesizing enzyme glutamic acid decarboxylase 67 (GAD67) (47–52) are particularly prominent in parvalbumin neurons (41), and GAD67 protein levels are lower in parvalbumin neuron axon terminals (52). Thus, the connectivity among pyramidal neurons and parvalbumin basket neurons appears to be impaired in the DLPFC in schizophrenia and could contribute to the alterations in gamma oscillations that underlie working memory deficits (53,54).

Active cannabis use may affect cognitive functioning in schizophrenia by further interfering with the regulation of the already dysfunctional interaction between DLPFC pyramidal neurons and parvalbumin basket neurons. For example, in the primate neocortex, the principal receptor for cannabinoids, CB_1R, is strongly expressed in the DLPFC (55). In the neocortex, CB_1Rs are preferentially localized to the axon terminals of GABA-containing basket neurons that contain the neuropeptide cholecystokinin (CCK) and, to a lesser extent, of some pyramidal neurons (56–58). In fact, the density of CB_1Rs is much higher in the axon terminals of CCK basket cells than of pyramidal cells (59–61). The inhibitory axon terminals from CCK basket neurons target both pyramidal neurons and parvalbumin neurons (56,57). Activation of CB_1Rs suppresses GABA release from CCK neuron axon terminals onto pyramidal neurons (62), and CCK basket neurons also regulate pyramidal neuron activity (56,63,64). Thus, exogenous cannabinoids such as cannabis broadly suppress CCK neuron-mediated inhibition of pyramidal neurons and parvalbumin neurons without the tightly regulated, spatiotemporal selectivity of endocannabinoids.

THE ENDOCANNABINOID SYSTEM

Further exploration of the relationship between cannabis use, cortical circuitry disturbances, and cognitive impairments in schizophrenia also requires knowledge of the endocannabinoid system. The primary endocannabinoid ligands in the brain include anandamide and 2-arachidonylglycerol (2-AG) (65). Anandamide is a partial CB_1R agonist and is found at relatively low concentrations in the brain (65,66). In contrast, 2-AG is a full CB_1R agonist and is found at much higher concentrations than anandamide in the brain (67).