The Endocannabinoid System and Schizophrenia: Links to the Underlying Pathophysiology and to Novel Treatment Approaches

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Six decades after the introduction of dopamine D_2-receptor–based antipsychotics, schizophrenia remains one of the most severe and difficult-to-treat mental disorders. While a range of alternative therapeutic targets, such as the glutamatergic system, have attracted attention for negative symptoms and cognitive dysfunction,[1] novel treatments for the core symptoms of schizophrenia remain unproven.[2]

The Endocannabinoid System

The endocannabinoid system (ECS) is a largely overlooked brain homeostatic system that is relevant to both the pathophysiology and treatment of schizophrenia. It centers on 2 G-protein–coupled receptors, cannabinoid-1 receptor[3] and cannabinoid-2 receptor[4]; lipid ligands or endocannabinoids[5,6] including anandamide and 2-arachidonoylglycerol; and enzymes involved in endocannabinoid biosynthesis (diacylglycerol lipase) and degradation (fatty acid amide hydrolase [FAAH] and monoacylglycerol lipase).[7,8] Cannabinoid-1 receptors are highly expressed in the brain regions implicated in the putative neural circuitry of schizophrenia, including the cerebral cortex, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum,[9] where they modulate presynaptic glutamate and GABA release.[10,11] Furthermore, endocannabinoids enhance dopaminergic function in the prefrontal cortex and hippocampus while providing inhibitory feedback on mesolimbic dopamine neurotransmission.[12–14] Finally, endocannabinoids are increased in response to stress, possess intrinsic antioxidant properties, and are precursors of membrane lipids, leukotrienes, and prostaglandins.[15]

The Endocannabinoid System and Schizophrenia

Anandamide levels, increased in acute schizophrenia, may represent a compensatory mechanism, specifically in early illness. Cerebrospinal fluid and plasma levels of anandamide were noted to be significantly increased in acutely ill, antipsychotic-naive, first-episode schizophrenia patients compared to controls.[16,17] Increased levels negatively correlated with psychotic symptoms and normalized with antipsychotic response.[17] Furthermore, in prodromal individuals, elevated anandamide levels were associated with lower risk of conversion to schizophrenia,[18] suggesting that anandamide increases could be compensatory in this context.

Studies of cannabinoid-1 receptor densities in schizophrenia show mixed results. Postmortem studies of cannabinoid-1 receptors in schizophrenia have found alterations in the anterior[19] and posterior[20] cingulate cortices, but 1 study[21] found no changes. The availability of positron emission tomography (PET) ligands for in vivo imaging techniques shows promise for future studies.[22] In a preliminary PET study in schizophrenia

patients, Wong et al[23] found that elevated cannabinoid-1 receptor density in the frontal, middle, and posterior cingulate regions correlated with psychopathology.

Cannabinoid-1 receptor gene polymorphisms may be associated with schizophrenia. Cannabinoid-1 receptor gene[3] (*CNR1*) polymorphisms have been associated with schizophrenia in some studies,[24,25] but not in others.[26,27] While this inconsistency might reflect demographic differences in the study populations, another possibility is the heterogeneity of the illness.

Exogenous Cannabinoids and Schizophrenia

Epidemiologic studies have linked both onset and extent of cannabis use with the development and severity of schizophrenia. A number of longitudinal studies have found that earlier onset of cannabis use, especially before 18 years of age, was associated with an increased incidence of psychotic symptoms or disorder later in life.[28–31] For instance, a study of Swedish military conscripts (N = 45,570) showed a significant dose-response relationship between self-reported cannabis use at enrollment and psychiatric hospitalization for schizophrenia in the ensuing 15 years.[28] Heavy cannabis users by 18 years of age were 6.7 times more likely than nonusers to be hospitalized for schizophrenia later in life.[29] Similarly, a birth-cohort study of 1,037 people born in Dunedin, New Zealand,[30] found that, compared to nonusers, individuals with cannabis use at ages 15 and 18 years had higher rates of psychotic symptoms and schizophreniform disorder at age 26. Consistent with these studies, a systematic review[32] of 35 studies demonstrated an increased risk of psychosis in individuals who had ever used cannabis and the existence of a dose-response effect, with greater risk in people who used cannabis most frequently. Meta-analyses of studies of cannabis use and psychosis suggest that cannabis is a component cause in the development and prognosis of psychosis[33] and that the age at onset of psychosis was 2.7 years earlier among cannabis users compared with non–substance-using controls.[34] Finally, in a recent nationwide Finnish study,[35] the 8-year rate of ultimate conversion to schizophrenia in 18,478 patients with substance-induced psychotic disorders was highest in cannabis users (46%), followed by amphetamine (30%) and alcohol (5%) users. Moreover, the risk was highest in the first 3 years, especially in cannabis users.

Δ^9-tetrahydrocannabinol, a partial cannabinoid-1 receptor agonist, produces psychotomimetic effects, whereas cannabidiol, a putative FAAH inhibitor, may attenuate them. Cannabis contains a number of constituent cannabinoids of which Δ^9-tetrahydrocannabinol (THC) is the main psychoactive component. In psychopharmacologic challenge studies, the acute administration of THC has been shown to transiently induce a range of positive, negative, cognitive, and psychophysiologic

abnormalities in healthy people, comparable to those observed in schizophrenia.[36] THC similarly induced an increase in psychotic symptoms in stable, antipsychotic-treated schizophrenia patients, who were more sensitive to THC-induced positive symptoms and cognitive deficits as compared to healthy controls.[37]

In contrast to THC, cannabidiol, another component of cannabis, does not appear to have psychotomimetic effects, instead producing hypnotic, anticonvulsive, anxiolytic, and neuroprotective effects.[38] In healthy subjects, cannabidiol pretreatment reduced the psychotomimetic effects of THC[39] and attenuated ketamine-induced depersonalization.[40] Furthermore, chronic cannabis users with evidence (per hair analyses) of significant cannabidiol exposure showed lesser positive schizophrenia-like symptoms than those without.[41]

Conversely, a subgroup of schizophrenia patients may derive benefit from exogenous cannabinoid-1 receptor agonism. Despite the above evidence, cannabis continues to be the most-abused illicit substance in schizophrenia.[42] In 1 open-label study,[43] treatment with dronabinol resulted in symptomatic improvement in 4 of 6 treatment-resistant patients who had a self-reported history of benefits from cannabis use. Additionally, meta-analysis revealed that in a subgroup of patients, cannabis use is associated with improved cognition,[44] further pointing to a significant heterogeneity in the interaction between the disease and cannabis.

In summary, the ECS is implicated in the major pathophysiologic hypotheses for schizophrenia: mesolimbic hyperdopaminergia (and dopaminergic hypofrontality), glutamate/GABA disruptions, oxidative stress, deficiency of membrane lipids, and neuroinflammation. Its involvement is supported by alterations in the ECS in patients with schizophrenia and further by epidemiologic and laboratory data supporting the role of exogenous cannabinoids in psychosis and schizophrenia. Given the pleiotropism of the ECS and heterogeneity of the evidence, the nature of the link between the ECS and schizophrenia is complex, requiring further study.[45]

Novel Treatment Strategies Based on the Endocannabinoid System

Cannabinoid-1 receptor antagonism has demonstrated anxiolytic but no clear antipsychotic effects. Alternatively, novel therapeutic targets focused on boosting endogenous anandamide levels may show greater promise.[46] Such targets may have most utility in acute, early-phase schizophrenia via their ability to increase prefrontal and decrease mesolimbic dopamine. Elevating anandamide levels has been shown to ameliorate symptoms in animal models of schizophrenia; for example, hyperlocomotion in dopamine transporter knockout mice[12] and PCP-induced social withdrawal.[47] Anandamide itself has poor bioavailability, but drugs exist that reduce its deactivation via inhibition of FAAH and blocking reuptake into the neuron.[48] In a 4-week trial of 42 acute schizophrenia patients, cannabidiol showed comparable efficacy to amisulpride for positive and negative symptoms, while being better tolerated.[49] Moreover, symptom improvement correlated with increases in anandamide, suggesting that cannabidiol may mediate its effect via FAAH inhibition. Synthetic FAAH inhibitors increase anandamide over 2-arachidonoylglycerol levels, the latter of which may be implicated in cannabinoid-1 receptor–mediated psychotic effects. A range of synthetic anandamide-boosting drugs promise efficacy and tolerability in mood and anxiety disorders,[50,51] but these have not yet been tested in schizophrenia.

Future Directions

In vivo cannabinoid-1 receptor imaging. Availability of several cannabinoid-1 receptor PET ligands now permits in vivo imaging in patients at every stage of psychotic illness.[23] Future studies may disambiguate the effects of antipsychotic medications, stage of illness, and cannabis use (among other factors) from schizophrenia-related changes in cannabinoid-1 receptor availability.

Preclinical and clinical studies examining the role of the cannabinoid-2 receptor in schizophrenia. Initial genetic linkage studies associated cannabinoid-2 receptor gene hypofunction with an increased risk of schizophrenia,[52] warranting further study of this association and treatments directed at this receptor.

Acute psychopharmacologic challenge studies in healthy humans. The controlled, acute administration of THC in a laboratory serves to probe the ECS and characterize its role in psychosis. Further, putative therapeutic drugs can be tested against THC in this laboratory model. Finally, characterizing the relative contributions of the principal constituents of cannabis on psychotomimetic effects may have important public health implications.

Clinical trials of novel ECS agents in schizophrenia. Novel antipsychotic drugs targeting the ECS may best focus on early-phase schizophrenia given a preponderance of clinical evidence in this population. On the basis of the hypothesis that the ECS (perhaps via increases in anandamide) plays a compensatory role in early psychosis, treatment with a FAAH inhibitor could decrease conversion to schizophrenia in prodromal patients or improve prognosis in first-episode psychosis patients.

Conclusions

There are substantial preclinical, clinical, and epidemiologic data supporting the involvement of the ECS in schizophrenia. The ECS hypothesis unifies other major pathophysiologic hypotheses of schizophrenia. Further studies are warranted to further probe the exact nature of ECS abnormalities in schizophrenia. Consideration of stage and heterogeneity of the illness is vital. Further exploration of the potential benefit of cannabidiol and other anandamide-boosting agents may lead to novel treatments.

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