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Parasitic brain infection, endocannabinoids, and schizophrenia

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SUMMARY

Cannabis use has often been associated with various forms of psychosis. Today it is well established that everyone produces marijuana-like compounds known as endocannabinoids. The endocannabinoid system is a homeostatic regulator of all body systems including the nervous system. As a result, imbalances in the endocannabinoid system have been considered as possible causes of various forms of mental illness and abnormal behavior. In this paper, a novel hypothesis is presented that suggests that an as yet undefined subset of schizophrenia is caused by an excess of endocannabinoids that are produced to protect the brain in response to infections by agents such as *Toxoplasma gondii*.

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1. Introduction

Schizophrenia is a chronic debilitating condition affecting approximately 1% of the population [1]. It is characterized by disorganized thoughts, hallucinations, and delusions (positive form), and apathy and avolution (negative form). Similar symptoms result from cannabis use, which has often been associated with psychosis (Greek meaning diseased soul), and specifically schizophrenia [2] However, it is only in recent times that tools have become available to properly, scientifically evaluate whether or not there is a cause-and-effect relationship between cannabis use and schizophrenia in a susceptible population, such as potentially found in adolescents [3]. Thus far, these studies have produced conflicting results regarding the etiological role of cannabis and schizophrenia [4]. This manuscript will examine brain infection-induced immune imbalance as a possible cause for a subset of schizophrenia cases.

Over the past two decades, there has been an explosion of research into the endocannabinoids system. It is well documented that the endocannabinoid system is a master regulator of homeostasis [5]. All body systems, cardiovascular, digestive, endocrine, excretory, immune, musculo-skeletal, are homeostatically regulated by endocannabinoids. With the discovery of the endocannabinoids system, the biology of an individual's internal endocannabinoid activity could be linked with behavioral abnormalities [6].

1.1. Genetics

Currently, DNA sequence analysis has revealed a number of genetic changes in components of the endocannabinoid system that could be potentially be associated with a variety of illnesses, including schizophrenia. For example, there are triple repeats in the CB1 receptor [7], which is located in the vicinity of the schizophrenia susceptibility locus [8], as well as a polymorphism in the catechol-*O*-methyltransferase (COMT) gene [9]. However, a recent study examining these genetic variations in a case controlled study found no evidence for an association with schizophrenia [10].

1.2. Measuring endocannabinoids

Another important tool for determining the endocannabinoids system's involvement in illness has been the use of NMR to actually measure the levels of endocannabinoids in individuals. For example, higher than normal levels of endocannabinoids have been found in the blood of individuals with a variety of psychological abnormalities including anorexia nervosa [11], and schizophrenia [12,13].

1.3. Cannabinoid receptors

The CB1 receptor was the first cannabinoid receptor to be identified [14] and cloned [15]. This receptor is predominantly responsible for the psychological affects of marijuana. Subsequently, the CB1 receptor was shown to have been important neuroprotective properties [16]. The CB2 receptor was identified and cloned from the spleen [17]. While the CB2 receptor has recently been shown to regulate numerous tissues [18], in particular under conditions of pathology [19], its primary function appears to be in regulating the immune system, where it typically turns down the inflammatory responses.

1.4. Immune balance

Balances between pro-inflammatory and anti- inflammatory activities characterize the immune response. The pro-inflammatory arm of the immune system is driven by Th1 and Th17 cytokines including IL-1 and TNF. In contrast, the anti-inflammatory

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arm of the immune system is driven by Th2 cytokines, including IL-4 and IL-10. An unbalanced immune response can have severe consequences. Using malaria as an example, a weak TH1 response promotes a fulminate parasitic infection [20], whereas, an excessive TH1 response leads to TNF mediated autoimmune pathologies, specifically with cerebral malaria [21]. Immune response in the brain are typically mediated by microglial cells [22]and astrocytes [23]. Microglial cells, as well as most other cells, express toll-like receptors that activate the innate immune response to a variety of pathogens. TRL 11 specifically responds to *Toxoplasma gondii* [24]. These responses are typically pro-inflammatory in nature. However, neurons and glial cells also express cannabinoid receptors. CB2 receptors turn down the pro-inflammatory immune response by promoting a Th2 cytokines [25]. Furthermore, there is a negative association between schizophrenia and arthritis [26], thus implying that the immune system of these individuals has a reduced level of pro-inflammatory activity than is found in the population at large.

2. Hypothesis

There are a number of disparate observations regarding schizophrenia that may be integrated into a cohesive model based on immune imbalance. Firstly, there is a strong negative correlation between rheumatoid arthritis and schizophrenia [26], yet, a number of similarities between these diseases have been indicated [27]. Secondly, rheumatoid arthritis is associated with a Th1/17 pro-inflammatory cytokine bias [28]. The negative correlation between arthritis and schizophrenia implies that schizophrenics may exhibit an excessive Th2 immune imbalance. Support for this suggestion comes from studies that examined endocannabinoid levels in schizophrenics, where high levels were found in the serum, especially during schizophrenic episodes [12]. Cannabinoids limit the pro-inflammatory immune response in the nervous system [29] by increasing Th2 cytokines [25]. Thirdly, for many years there has been suggested link between schizophrenia and *T. gondii* [30], as well as other pathogens such as HIV.

Putting these three observations together leads to the hypothesis that a chronic *T. gondii* infection, or other brain infections, may result in brain inflammation to which the body responds by increasing neuroprotective endocannabinoid levels [31]. These psychoactive molecules may in turn promote the psychological manifestations of schizophrenia. Considering that a three fold higher level of anandamide is found systemically during schizophrenic episodes, the local levels at the site of synthesis must be extremely high.

3. Discussion

For decades marijuana consumption has remained the center of controversy. The discovery of the endocannabinoid system now provides a scientific foundation for examining this topic. A possible link between cannabis consumption and schizophrenia continues to fuel the controversy. Numerous hypotheses have been proposed in an effort to explain schizophrenia. Proposals regarding genetic and environmental factors, as well as age remain inconclusive. This paper presents a novel hypothesis that suggests that a high level of endocannabinoid activity in the brain is produced in response to brain infections, and high levels of these psychoactive compounds maybe crucial for the development of schizophrenia. This suggestion is consistent with other possible causes of schizophrenia.

Current cannabinoid research indicates an important role played by endo and exo-cannabinoids in promoting the survival of nerve cells, largely through the CB1 receptor, and in down regulating potentially dangerous pro-inflammatory immune responses, through the CB2 receptor. The latter activity, while on the surface appearing to be beneficial, may have serious negative consequences with respect to schizophrenia, which is hypothesized to result from parasitic brain infections as exemplified by *T. gondii*. In view of the psychoactive properties of endocannabinoids, a high local concentration of these otherwise protective molecules could be responsible for schizophrenic symptomology.

This hypothesis predicts that there is a subset of schizophrenics for whom an appropriate antibiotic regime might control the inflammatory infection to the degree that the brain would produce lower levels of endocannabinoids, and hence provide symptomatic relief. An additional therapeutic strategy that might reduce the probability of future schizophrenic episodes could include treatment with a CB2 receptor-specific antagonist to facilitate the immune system's capacity to control this type of infection.

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