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■ REVIEW ARTICLE

The Role of Stress-Induced Inflammation in Schizophrenia

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ABSTRACT: Schizophrenia is a severe mental illness whose onset occurs due to interacting aspects of both nature and nurture. While the epidemiology of schizophrenia is not well understood, there have been multiple models and hypotheses, including the stress-vulnerability-inflammation model and the NMDA receptor hypofunction model, that have inspired new directions for research in schizophrenia. One area of research that has emerged in the hunt for understanding the cause of schizophrenia is neuroimmunology. This review focuses on recent breakthroughs in this field by finding stress as the main agent of immune dysfunction, inflammation, and inflammatory gut alterations in the path to schizophrenia. With these studies, the specific mechanisms of inflammation are highlighted, as well as the role of the gut-brain axis in stress-induced schizophrenia. Furthermore, gaps in available research are addressed and the next areas of research required to one day prevent/delay the onset of schizophrenia are identified.

KEYWORDS: Behavioral and Social Sciences; Neuroscience; Schizophrenia; Stress-Induced Inflammation; Gut-brain axis.

■ Introduction

Schizophrenia is a heterogeneous mental disorder characterized by the presence of two or more defining symptoms over a six-month period. These include positive symptoms like delusions, hallucinations, and paranoia, as well as negative symptoms such as decreased ability to express emotion, impaired thought/speech, and catatonia.[1] The prevalence of schizophrenia internationally is 0.75%, and while this may seem relatively low, schizophrenia represents one of the top 15 causes of disability worldwide.[2] Due to lack of access to treatment, many people with schizophrenia remain undiagnosed and untreated. However, even within those who can access proper care, a significant number suffer from TRS, or treatment resistant schizophrenia, leading to a poor prognosis.[3] Schizophrenia, aside from its defining symptoms, carries increased risk of premature mortality, inflammatory health conditions, and higher rates of suicide, making it a significant burden to those affected by it.[2] Moreover, schizophrenia poses immense economic challenges due to the disproportionately high cost of disease management and the limited upward mobility caused by disease onset.[4] These realities highlight the importance of further research into this complex disorder.

While the epidemiology of schizophrenia is not well understood, recent studies in neuroimmunology have proven promising.[5] Two well-studied models of schizophrenic epidemiology, the stress-vulnerability-inflammation model and the N-methyl D-aspartate (NMDA) receptor hypofunction model, have proven especially useful as the basis for research in neuroimmunology in schizophrenia. The NMDA receptor hypofunction model describes the antagonism of the glutamatergic signaling NMDA receptor in the brain. Antagonism of this receptor by its only known naturally occurring inhibitor, kynurenic acid (KYN-A), causes cognitive dysfunction, depressive symptoms, and other negative symptoms of schizophrenia.[6] Furthermore, controlled studies have showed that inhibition of the NMDA receptor by ketamine and phencyclidine (PCP) have caused positive, negative, cognitive, and physiologic symptoms of schizophrenia (such as eye-movement abnormalities) in healthy patients,[7,8] further highlighting the importance of the proper function of the NMDA receptor. Interestingly, studies have shown a link between NMDA receptor hypofunction and high levels of dopamine in the brain, a mechanism long thought to have been the sole cause of psychosis in schizophrenic individuals.[7] Now, however, through studies in neuroimmunology, it is clear that complex interactions of synergistic factors, rather than one isolated factor, cause onset of schizophrenia. One model that supports this concept is the stress-vulnerability-inflammation model. This model finds that the genetic makeup of a subject predisposes them to inflammation and abnormal immune response later in life,[5] strongly suggesting the roles of both nature and nurture in schizophrenic onset. Indeed, it has been found that schizophrenic patients have mutations on chromosome 6 within the major histocompatibility complex (MHC), a locus heavily associated with autoimmunity and brain development.[9] This implies a role of immune dysfunction in schizophrenia. Moreover, known inflammatory triggers like chronic stress, traumatic events, viral exposure, gut dysbiosis, and chronic inflammatory/autoimmune illnesses have been associated with increased risk of the onset of schizophrenia, further supporting this model of epidemiology.[5,10]

These two models of schizophrenia have prompted novel studies in neuroimmunology and neuroinflammation, allowing for new foundations for possible prevention and treatment for this debilitating disorder. However, due to the complex interaction of multiple social, environmental, and biological factors, the exact mechanisms of schizophrenic onset are difficult to derive from these models alone. To dissect this complex epidemiology, this literature review aims to not only to emphasize the significance of inflammation and NMDA

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receptor hypofunction in schizophrenia, but also highlight a novel mechanism of onset by connecting the impacts of stress on the gut-brain axis to the neuroimmune basis of schizophrenia (Figure 1).

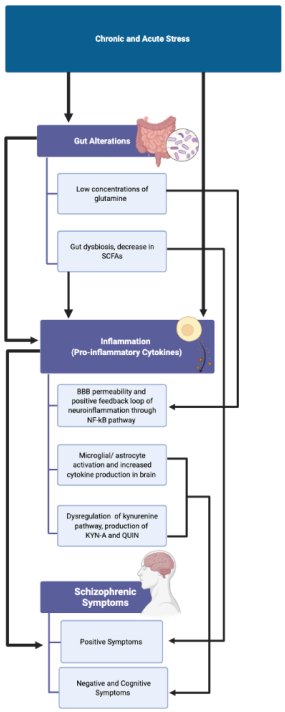

Figure 1: Possible mechanisms in stress-induced schizophrenia. Stress is a driving force in the onset of schizophrenia. In conjunction with genetic and environmental factors, stress may induce inflammation through gut alterations and direct neuroinflammatory pathways. This includes, through gut dysbiosis, decreases in glutamine levels, increases in BBB permeability, microglia/astrocyte activation in the brain, and production of KYN-A/QUIN. These effects collectively lead to inflammation, which has been found to play a significant role in not only symptoms of schizophrenia, but in furthering immune dysregulation characteristic of schizophrenic onset and psychosis. [Figure made in Biorender].

Discussion

Stress-Induced Inflammation in Schizophrenic Epidemiology:

Stress, in its many forms, has a proven role in the epidemiology of schizophrenia. For the purposes of this paper, stress is defined as social or environmental insults that affect the pathogenesis of schizophrenia, either through the stressor itself or the subsequent stress response[11] (e.g., inflammation, increase in cortisol levels, changes in the kynurenine pathway). Evidence shows that mental, physical, and emotional stress in both chronic and acute timeframes is linked to various mechanisms of schizophrenic onset.[12] These forms of stress present themselves in situations related to mental health, immigration, location of upbringing, social support systems, chemical/pathogenic exposure, and physical stress pre- and perinatally.[13] Such acute and chronic stress has been shown to play a consistent role in the onset of schizophrenia.[13] For example, acute stress in the form of emotional, sexual, and physical abuse was associated with an almost seven-fold increase in psychotic symptoms.[13] Additionally, trauma in developmental stages of life was found to affect neurodevelopment and the presentation/severity of schizophrenic symptoms, which collectively affected the cognitive and social functioning of the individual post-onset.[14] In a similar study of genetically vulnerable subjects, those who had experienced more severe and frequent childhood abuse displayed a significant pattern of abnormal anxiety, low stress tolerance, and high cortisol levels, all of which were associated with the portion of subjects who eventually transitioned into psychosis and schizophrenic onset.[11] This suggests that the stress response, such as cortisol level increase, from such socio-environmental stressors may contribute to subsequent mechanisms of onset of schizophrenic psychosis.

One especially consequential mechanism in the epidemiology of stress-induced schizophrenia is inflammation. Inflammation, a response of the immune system to external and internal stressors, can be caused by physical and chronic stress, both of which lead to numerous effects on the immune system, central nervous system, and gastrointestinal tract, creating a positive feedback loop of inflammation. An early determinant of such harmful inflammatory patterns is maternal physical stress, as it puts the offspring at risk for immune dysfunction and eventually schizophrenic onset later in life.[12] This compromise often occurs while the subject's central nervous system (CNS) is developing in the womb; in fact, inflammatory response due to maternal pathogenic exposure (such as influenza, herpes simplex virus, and Toxoplasma gondii)in the second trimester of pregnancy has been shown to significantly increase risk of schizophrenic onset in the offspring later in life.[12,15] Other sources of inflammation in schizophrenia, like illness, environmental factors, and stressors due to economic background,[16] all fall under chronic stress. Chronic stress is known to lower the body's threshold to trigger an immune response; this is due to constant stimulation eventually causing lower-magnitude triggers to set off higher-magnitude immune responses. This induces an increased and prolonged pro-inflammatory response from the body, which directly correlates with psychosis.[12]

The role of inflammatory and autoimmune mechanisms in schizophrenia is further supported by the existence of anti-NMDA receptor encephalitis. This disorder, an autoimmune disorder of the N-methyl D-aspartate receptors in the brain, often presents with both positive and negative psychiatric symptoms.[17,18] Its shared etiology and symptomatic consequences with schizophrenia support the basis for immune-triggered glutamatergic signaling abnormalities in schizophrenic pathogenesis. Furthermore, studies have found that prolonged delivery of NMDA receptor antibodies in mice have resulted in anhedonia, depressive behaviors, and catatonia,[18] all of which are standard negative symptoms of schizophrenia. Further research into the autoimmune basis of schizophrenia is required to further solidify this parallel, but the common ground of an immune response inducing schizophrenia-like heterogeneous symptoms indeed supports the neuroinflammatory basis of schizophrenia. Furthermore, because anti-NMDA receptor encephalitis is treatable by immunotherapies, the possibility for overlapping research of immune treatment in schizophrenia is significant.

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With such evidence of immune mechanisms in schizophrenia, tracing the effects of inflammation is important. Inflammation has been found to increase risk of schizophrenic onset in genetically prone subjects and alters the kynurenine pathway in schizophrenia. Interestingly, low-grade inflammatory markers have been found in postmortem brain studies as well as the blood plasma of almost 40% of schizophrenic patients,[19] supporting evidence of inflammation-driven mechanisms in schizophrenia. An area of interest in this review is the role of cytokines, small inflammatory molecules involved in immune system regulation, which have been found to play multiple significant roles in the pathophysiology of schizophrenia, including in the breakdown of the blood-brain barrier (BBB), production of the NMDA receptor antagonist KYN-A, and upregulation of inflammatory feedback in the central nervous system (CNS).[20-22] Understanding these specific pro-inflammatory cytokines and their effects on the symptoms of schizophrenia has allowed for a more complete picture of both the stress-vulnerability-inflammation and NMDA receptor hypofunction models of schizophrenia mechanisms in schizophrenia.

Cytokines and Blood Brain Barrier Permeability:

Cytokines are able to affect schizophrenia through their actions on the blood brain barrier.[22] The blood brain barrier (BBB) is a system of vasculature of the central nervous system that allows for controlled movement of substances that cross from blood into the brain.[23] In many neuroinflammatory and neurodegenerative diseases like schizophrenia, the BBB plays a role in epidemiology when its structure is compromised.[22] This compromise can occur both pre- and postnatally. For example, physical stress through maternal inflammation from a mutagen, virus, or infection can affect the offspring in the womb despite the central nervous system (CNS) being separated from the peripheral immune system by the BBB. This is because pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6 are able to invade the fetal CNS through the blood brain barrier.[21] This mechanism supports the previously noted role of prenatal environment in the epidemiology of schizophrenia. Furthermore, cytokines can affect and pass through the BBB postnatally as well. In fact, the cytokines IL-6, IFN- γ, and TNF-α have been found to play a direct role in disassembling tight junctions in the BBB, causing decreased regulation of toxins and molecules to the brain, thereby increasing neuroinflammation.[22] Increased BBB permeability due to both chronic-stress-induced alterations and pro-inflammatory cytokines creates a positive feedback loop of immune dysregulation: the increased permeability increases neurotoxic species as well as contributes to ongoing inflammatory response by producing more cytokines.[22] Moreover, the increased inflammation due to cytokine-induced BBB permeability has been found to increase psychotic symptoms and neurodegeneration in schizophrenia.[21,22] Therefore, any stress-induced changes that affect pro-inflammatory cytokine levels or BBB permeability may have direct effects on schizophrenic onset and symptoms (Figure 2).

Cytokines and Kynurenine Pathway in Schizophrenic Symptoms :

Cytokines can also impact schizophrenic etiology through the kynurenine pathway. Cytokines control tryptophan metabolism in the kynurenine pathway in multiple ways, suggesting that studying cytokines may help explain more than one mechanism in schizophrenic epidemiology (Figure 3).[5] First, some cytokines can affect schizophrenic epidemiology through their absence. The cytokine IL-4 is an example of this. IL-4 is known to decrease KYN-A production; therefore, the low levels of IL-4 found in schizophrenic subjects may contribute to high levels of KYN-A.[21]

Name of Cytokine	Evidence for Schizophrenic Epidemiology	Effect of Cytokine	Sources
IL-6 Interleukin-6	• Stimulates hypothalamic cortisol production • Inhibits neurogenesis in hippocampus by up to 50% (along with TNF- α) • Increased activation of IL-6 due to mutation of NRG-1 gene in schizophrenia • Elevated in CSF of first onset and relapse of schizophrenic psychosis • Significant reduction after treatment with certain antipsychotic	• Stimulates production of KYN-A • Disassembles tight junctions in BBB •Can invade fetal CNS • Mediates microglial response	(5,20,21,22)
TNF- α Tumor Necrosis Factor-α	• Increased activation due to mutation NRG-1 gene in schizophrenia • Increases QUIN concentration (negative symptoms) • Elevated consistently in schizophrenic patients • Significant reduction after treatment with certain antipsychotics	• Disassembles tight junctions in BBB • Can invade fetal CNS • Increases death of neural stem cells	(5,22,19)
IL- 1β Interleukin-1β	• Found to be elevated in first-episode psychosis of schizophrenic patients • Higher IL-1β mRNA correlated with a significantly higher KYN-A/TRP ratio • Found to be elevated in CSF studies • Low-grade inflammation associated with increase in IL-1β	• Mediates neurodegeneration (along with IL-6, IL-8, and TNF- α) • Can invade fetal CNS	(5,19,25,26)

Figure 2: Three significant cytokines in schizophrenic epidemiology. Table of cytokines found to impact the inflammatory mechanisms in schizophrenia, including BBB permeability, pre-natal immune compromise, and dysregulation of the kynurenine pathway. [Figure made in Biorender].

Second, some cytokines affect the activity of the enzymes involved in the kynurenine pathway. The cytokines IL-2 and IFN- γ do this by enhancing IDO, an enzyme that, by converting L-kynurenine into KYN-A, increases the concentration of KYN-A.[21] Additionally, both IL-2 and IFN- γ have been associated with acute schizophrenic positive symptoms.[21] Lastly, some cytokines have been found to directly stimulate the production of KYN-A. For example, IL-1β and IL-6 increase the production of KYN-A and are found to be elevated in schizophrenic patients.[21] Studies show that increased levels of KYN-A causes attentional impairment as well as dorsolateral prefrontal cortex (DLPC) volume loss in schizophrenia, which is associated with loss of executive function skills like emotion control and mental organization.[10,19]

Furthermore, as previously discussed, the antagonism of the NMDA receptor directly causes negative, positive, and physiological schizophrenic symptoms; therefore, the regulation of the kynurenine pathway by such cytokines is especially consequential.

The cytokine interleukin-6 (IL-6) is of particular interest, as it affects multiple pro-inflammatory pathways in schizophrenia. In addition to increasing KYN-A in the central nervous system (Figure 3), IL-6 also increases the stress hormone cortisol through stimulation of the hypothalamus,[5] an area of the brain that, in coordination with the pituitary gland, controls significant hormonal activity. This is important because increased levels of cortisol are directly related to schizophrenic symptoms and can occur in response to environmental and physical stress.[5] As mentioned previously, markers of stress response like cortisol are critical to tracing the true effects of

socio-environmental stressors on inflammatory pathways of schizophrenic etiology. Finding ways to prevent the action of cytokines like IL-6, then, may allow for multiple mechanisms of schizophrenic symptoms to be prevented. However, it is important to note the discrepancies in studies involving these cytokines in schizophrenia. For example, IL-6 has been found to be elevated in severely/chronically ill schizophrenic patients when compared to stable subjects, and IL-1β requires more studies to confirm its consistency throughout the entire schizophrenic population.24 Indeed, these studies serve to call for further research into confirming the roles of specific cytokines and their effects not only on KYN-A production in schizophrenia, but through other inflammatory mechanisms as well. Importantly, the origin of pro-inflammatory cytokine release must be identified to prevent inflammation and schizophrenic symptoms at the source; one such source of inflammation has been found in the gut-brain axis..

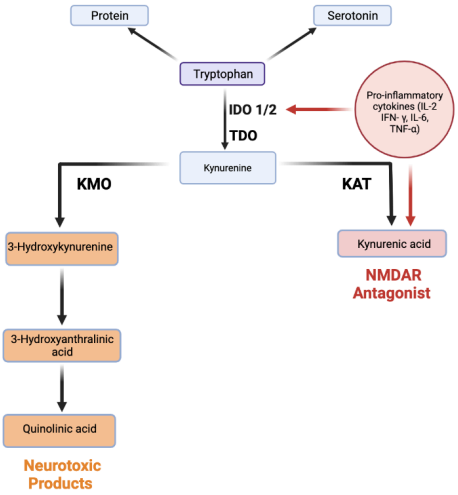

Figure 3: An overview of the kynurenine pathway. The kynurenine pathway has been shown to be regulated by pro-inflammatory cytokines. The pathway involves the substrate tryptophan, an amino acid, being synthesized into protein, or converted into serotonin and L-kynurenine. The enzymes Indoleamine 2,3 Dioxygenase (IDO) as well as Tryptophan 2,3-dioxygenase (TDO) are responsible for the conversion of tryptophan into kynurenine. Kynurenine is then metabolized by enzymes called KATs (kynurenine aminotransferases) to produce kynurenic acid (KYN-A). Kynurenine may also be metabolized into quinolinic acid (QUIN) by a series of reactions that utilize the enzyme kynurenine 3-monooxygenase (KMO) to convert kynurenine into 3-Hydroxykynurenine, then 3-Hydroxyanthranilic acid, and eventually quinolinic acid (QUIN). The two end products of the kynurenine pathway relevant to schizophrenia are KYN-A and QUIN. KYN-A is the only naturally occurring NMDA receptor antagonist, and in high concentrations, cause negative, positive, and physiological symptoms of schizophrenia.

QUIN is a neurotoxic species that causes negative and cognitive symptoms of schizophrenia and has been outlined as a relevant metabolite in other neuropsychiatric disorders as well. The regulation of this pathway by inflammation has shown to induce schizophrenic symptoms. [Figure made in Biorender].

The Gut-Brain Axis in Schizophrenia :

Among the numerous pathways in which stress induces inflammation-driven schizophrenia, a relatively new mechanism that has emerged is through the gut-brain axis. This axis has gained traction in research in recent years due to the emerging evidence that the gut and brain interact through the immune system, nervous system, and metabolic pathways.[27] In fact, stress-induced changes such as gut dysbiosis, gut permeability, and irregular tryptophan metabolism have been found to link directly to depression, anxiety, Parkinson's Disease, and even Alzheimer's disease,suggesting that the gut does indeed play a considerable role in neuropsychiatric epidemiologies. [27,28] Furthermore, there are many consequential pathways of gut alterations that are often overlooked, such as the significant role of the gut mucosal lining in the etiology of depression, showing that the field of gut-brain axis research is one with much potential.[28] This potential has been demonstrated through exciting animal studies in schizophrenia, suggesting the roles of stress-induced gut permeability, glutamine changes, and gut dysbiosis in psychotic symptoms and increased inflammatory mechanisms leading to schizophrenia.[22,29,30] Interestingly, the gut-brain axis may play roles in joining both nature and nurture involved in schizophrenic etiology. These roles may cause changes that are potentially responsible for triggering critical inflammatory pathways involved in disease onset.[29,31] For the purposes of this review, two branches of gut alterations, glutamine changes and gut dysbiosis, will be suggested as possible central mechanisms of promoting inflammatory pathways to induce schizophrenic onset.

The Role of Glutamine in Inflammation:

Glutamine is a conditionally essential amino acid known for its many protective roles in intestinal health, including nucleotide metabolism, intestinal barrier function, inflammatory modulation, and stress response regulation.[30] Furthermore, glutamine prevents inflammatory mechanisms that influence the CNS by promoting cell division in the intestine and supporting tight junction protein function.[22,30] Studies have shown that glutamine protects intestinal barrier function by preventing permeability to toxins and pathogens that could cause inflammation.[32] In fact, in the absence of glutamine, epithelial cell permeability increases; this decreased control on the paracellular pathway is seen in diseases of immune dysregulation, including schizophrenia.[22,30]

Glutamine deficiencies and decreased glutamatergic signaling are seen in the presence of chronic stress in mice studies.[33] This is especially detrimental to schizophrenic etiology because stress-induced glutamine deficiency impacts gut structure and function, and increases proinflammatory cytokines like IL-6 and TNF-α, causing further positive inflammatory feedback and neuroinflammation in schizophrenia.[22] Research has found that glutamine is able to prevent harmful inflammation by inhibiting inflammatory signaling pathways.[30] Specifically, this is seen through the inhibition of the NF-kB transcription pathway. This pathway induces the expression of genes that code for interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α);[30] both cytokines involved in BBB permeability and regulation of the kynurenine pathway in schizophrenic epidemiology. This suggestive evidence of glutamine's role in preventing CNS inflammation is further supported the by the fact that the inhibition of the NF-kB pathway by glutamine prevents a bidirectional immune feedback loop that would otherwise continue neuroinflammation and worsen schizophrenic symptoms.[30]

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In addition to its anti-inflammatory roles, glutamine has been used as a treatment for gastrointestinal inflammatory conditions such as leaky gut syndrome, a condition involving the increased permeability of the intestine due to exposure to pathogens, toxins, or certain types of food antigens, often resulting in autoimmunity and inflammation due to unregulated release of toxins from the gut into the bloodstream.[34] The treatment of this condition with L-glutamine serves to repair tight junctions within the gut and heal the intestinal lining.[34] Interestingly, there have been studies suggesting that immune dysregulation in schizophrenia stems from leaky-gut phenotypes and the sensitivity to certain food antigens, specifically gluten and casein.[35] These studies call for further research into therapeutic use of diet restriction and L-glutamine in repairing gut permeability to prevent continued inflammatory effects.

The Role of Gut Dysbiosis on Inflammation and Schizophrenic Symptoms:

Gut dysbiosis, a change in the bacterial population of the intestine, has also been linked to schizophrenia. Studies have found that stress-induced gut dysbiosis can occur at any point in a person's life, ranging from prenatally to postnatally, making the gut-brain axis an area of interest for studies of schizophrenic onset in both genetically vulnerable and idiopathic patients.[27] Additionally, genetically vulnerable subjects may be predisposed to gut dysbiosis due to the major histocompatibility complex. As previously discussed, the major histocompatibility complex (MHC) is a locus affected in many schizophrenic patients. Interestingly, studies have found that the MHC may control immune response in the gut and induce dysbiosis and inflammation.[36] This immune dysregulation of the microbiome is seen in multiple autoimmune and gastrointestinal diseases, such as celiac disease, Crohn's disease, and ulcerative colitis, all of which have high incidence in the population of schizophrenic patients as well.[36] These changes in the gut population through stress and genetics have also shown their impacts on schizophrenic pathophysiology. For example, it has been shown in multiple studies that there is a notable difference in taxonomy of the gut microbiome in patients with first-episode psychosis versus control subjects.[29]

Furthermore, in studies of chronic schizophrenia, multiple families of gut bacteria were found to be decreased in population,[37] while other studies found increased levels of other families of bacteria, supporting the presence of gut dysbiosis in schizophrenia.[29] Moreover, the composition of the gut microbiome directly correlated to severity of psychotic symptoms,[29,38] suggesting a possible synergistic interaction of stress, gut dysbiosis, and inflammation in psychosis. Additionally, in promising mouse studies, fecal microbiota transplants from mice with schizophrenic endotypes into healthy mice found that the recipient mice formed microbiota and behavior characteristic of mice with schizophrenic endophenotypes, further supporting the role of gut dysbiosis in schizophrenic etiology.[37]

A specific mechanism through which dysbiosis may affect schizophrenia is through metabolic pathways that produce short-chain fatty acids.[39] Short-chain fatty acids (SCFAs) are metabolites formed by the fermentation of fiber by bacteria in the intestine. When gut dysbiosis occurs, the concentration of fiber-fermenting bacteria is decreased, thereby decreasing SCFA levels. Because SCFAs inhibit histone deacetylation, this directly impacts genetic expression in schizophrenia, and may connect back to the previously discussed MHC-controlled immune microbiome dysregulation by affecting expression of the locus, further promoting gut dysbiosis.[36] In fact, studies have found that increased histone deacetylation is associated with schizophrenia; because SCFAs inhibit histone deacetylation, their presence (and lack thereof) may play an important role in the epidemiology of schizophrenia.[39] In addition to their effect on genetic expression in schizophrenia, SCFAs benefit the intestine by decreasing intestinal inflammation and regulating metabolic activity by activating relevant G-protein-coupled receptors.[39] For example, SCFAs like butyric acid decrease inflammation by serving as inhibitors of the NF-kB pathway in a similar way to glutamine, highlighting the importance of maintaining a balanced microbiome in neuropsychiatric disorders.[39] Collectively, there is much evidence on a dynamic interaction of genetics, the environment, stress, and the gut microbiome in regulating inflammation and triggering pathways that lead to disease onset in schizophrenia. These exciting findings demonstrate a need for further research in human subjects on the direct effects of the microbiome on schizophrenic onset and/or prevention.

Conclusion

Based on the known literature, a clear correlation between chronic stress and inflammation-driven schizophrenic symptoms exists. Specifically, the effects of chronic stress, such as gut dysbiosis, changes in glutamine concentrations, and increases in inflammation have been linked to increased BBB permeability, pro-inflammatory cytokine activity, and changes in the kynurenine pathway.

Each of these consequences from stress individually contribute to the neuroinflammation seen in schizophrenia and play possible roles in its onset. The presence of such acute neuroinflammation and pro-inflammatory cytokines has been linked to positive symptoms in schizophrenia, marking this as an area of interest for future studies. Additionally, cytokines have been found to play roles in regulating the kynurenine pathway. Specifically, elevated inflammation increases concentrations of the neurotoxic products KYN-A and QUIN, which causes NMDA receptor hypofunction and furthers cognitive dysfunction in schizophrenia respectively. Existing studies find that inflammation is associated with acute psychotic symptoms, while KYN-A concentrations are mostly associated with negative symptoms; however, the possible source of both positive and negative symptoms has clearly been outlined as chronic stress and inflammation. Therefore, further research in immune-related CNS changes would allow for a more complete picture of the neuroimmune basis of schizophrenia. Examples of such research would include investigating the role of the kynurenine pathway in positive symptoms of schizophrenia and finding preventative genetic therapy or immune-based treatments during neurodevelopment of genetically vulnerable subjects. Additional questions to pursue include the interactions of immune treatments and antipsychotics, and whether controlling neuroinflammation and the kynurenine pathway would allow for more effective results of antipsyho-

tics in treatment-resistant schizophrenia. Additionally, while this review did not focus on the type of schizophrenia studied or comorbid factors, it is important to emphasize the need for considering interference of factors such as sleep, medications, smoking, stress, comorbid health conditions, and medical history, including obstetric complications/compromises in future full-scale clinical studies. With further studies, possible immunosuppressant and gut-supplementary treatments could be developed. These would aim to supplement prevention of psychotic episodes in conjunction with antipsychotics and treatments that focus on BBB and gut permeability to prevent a cytokine-inflammation feedback loop. Moreover, research in this field would allow for hope of treatments that could be used to prevent or delay early onset of schizophrenia in genetically vulnerable patients by manipulating genetic testing, obstetric monitoring, environmental stress, and other compromising triggers as the subject nears typical age range of onset.

With so many possibilities in this emerging field of immune-based schizophrenia, continued research is required to better the prognosis of this debilitating disorder and, one day, prevent onset entirely. In the vast field of medicine, schizophrenia has proven to be a classic example of what can happen in the human body when multiple systems interact with both external and internal environments in self-propagating loops of progression into the illness; in fact, the mere existence of such a complex disorder has allowed for new possibilities and opened minds in medicine through the rise in research on the gut-brain axis and neuroimmunology. With these new attitudes on holistic, rather than strictly systematic, approaches to the human body, there is a better chance of improving not only the prognosis of schizophrenia, but of many other equally devastating illnesses as well.

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