ABSTRACT

This paper was written prompted by a poignant film about adolescent girl with schizophrenia who babysits for a younger girl in an isolated cabin. Schizophrenia is an illness that both authors are fascinated with and that they continue to study and investigate. There is now compelling evidence that schizophrenia is a very complex syndrome that involves numerous neural pathways in the brain, far more than just dopaminergic and serotonergic systems. One of the more popular theories in recent literature is that it represents a hypoglutaminergic deficiency of certain pathways, including thalamic ones. After much review of research and study in this area, we have concluded that most such theories contain a number of shortcomings. Most are based on clinical responses to certain drugs, particularly antipsychotic drugs affecting the dopaminergic neurotransmitters: thus, assuming dopamine release was the central cause of the psychotic symptoms of schizophrenia. The theory was limited in that dopamine excess could only explain the positive symptoms of the disorder. Antipsychotic medications have minimal effectiveness for the negative and cognitive symptoms associated with schizophrenia. It has been estimated that 20–30% of patients show either a partial or no response to antipsychotic medications. In addition, the dopamine hypothesis does not explain the neuroanatomic findings in schizophrenia.

Keywords: Glutamate receptors, Immunoexcitotoxicity, Microglia, Pro-inflammatory cytokines

HISTORICAL BACKGROUND AND CLINICAL PRESENTATION

The following is a short introduction to the historical background of this disease and its clinical symptomatology. Schizophrenia was originally named *dementia praecox* for "premature dementia." In 1893, the German psychiatrist Emil Kraepelin separated the two psychoses with which this disorder had been confused: *dementia praecox* and manic depression. It was renamed schizophrenia by the Swiss psychiatrist Eugen Bleuler in 1908, meaning in Latin "split mind or split personality." It was not until the mid-20th century that true schizophrenia was further separated from split (or multiple) personality hysteria — the latter, subsequently categorized as either a conversion reaction or a dissociative, identity disorder. Hollywood, though, continues
to confuse the two disorders — that is schizophrenia and hysteria — in their films.[41]

As one of us has written elsewhere, the two of the leading lights of psychiatry at the turn of the century, Austrian psychoanalyst Sigmund Freud (1856–1939) and German psychiatrist Emil Kraepelin (1856–1926) had conflicting approaches to mental illness, including schizophrenia. Freud recommended psychotherapy, which was almost always unsuccessful and ineffective in severely mentally ill patients. Kraepelin, in contrast, preferred more aggressive intervention with electroconvulsive therapy and insulin shock therapy, the former often ineffective, the latter dangerous and no longer used. Thus, psychosurgery came into vogue; fortunately, it was soon supplanted by psychotherapy, which has proven much safer and more efficacious effective in Schizophrenia in at least 75% of patients.[42]

Necessarily in the original descriptions of the disease, the behavioral and sociological aspects of schizophrenia have been emphasized, but not it's anatomic, biochemical, or pathophysiological substrates. For example, schizophrenia has been described as a functional mental illness that begins gradually, occasionally almost suddenly, striking in adolescence or young adulthood. No standard neuroimaging techniques disclosed any definitive pathological abnormalities in these patients. Moreover, there was no objective pathognomonic test that would confirm the illness, which is still diagnosed on the clinical symptomatology and observed behavior.

In his autobiography, Nobel-prize winner Eric R Kandel explains how, as a psychiatrist and research neuroscientist, he had attempted to apply the scientific method to psychiatry as a new “science of the mind.” He asserts that the human mind can be studied with biological tools to create this new science. He further asserts that in time all mental disorders, including those categorized as “functional” (or psychological, including schizophrenia by implication), will be found to have a structural, biochemical, and/or molecular basis, and that the old subjective criteria for psychiatric illnesses will completely give way to the new biological and scientific "science of the mind.”[8] We do not agree with this viewpoint, rather we agree with Sir John Eccles that the mind is a separate metaphysical entity from the material brain. This does not negate the idea that dysfunction of the brain can result in abnormal behavior and thought patterns of a psychological nature. The analogy of a radio fits here perfectly. The radio represents the brain with its complex of circuits, transistors, and other electronic components, while the mind would represent the invisible radio waves giving activity to the electronic contraption. Any abnormality of the “radio” would be manifested as a garbled radio message or static.

In medical school and in our psychiatry rotations, we learn about the four fundamental symptomatologies of schizophrenia, originally described by Dr. Bleuler as the four as of schizophrenia: (1) looseness of associations, or disordered associations with a loss of contact with reality; (2) autism, a disordered conception of the world with a preference for fantasy rather than reality; (3) a disorder of affect, or an abnormal emotional state or mood; (4) ambivalence, a mixed feeling about a subject matter — one may be unconscious, but the contradictory attitudes may be indirectly expressed. Schizophrenia is also characterized by cognitive impairments, delusions, and hallucinations that are most frequently auditory.[91]

Neurophysiological disorders of the central nervous system neurotransmission and biochemical defects of neurotransmitters production, transport, reuptake, blockage, and degradation have provided the best theories for explaining the good to excellent responses in schizophrenic patients to a variety of neuropharmacological agents. In addition, defects in working memory associated with disconnection of the hippocampal formation with the prefrontal cortex and in neurotransmission in the dorsolateral prefrontal cortex and frontotemporal disconnection have implicated both the frontal and temporal lobes in the neuropathology of schizophrenia.[94,95]

**IMMUNOECCITOTOXICITY IN NEURODEGENERATIVE DISEASES AND SCHIZOPHRENIA**

The leading author has written a number of papers on a newer hypothesis of neurodegenerative disease, of which schizophrenia is one.[14-16] This involves what he has described as immunoeccitotoxicity — that is an interaction between immune factors and glutamate receptors that leads to degeneration of specific groups of neurons and neural pathways. Central to this mechanism is prolonged or intermittent activation of the brain's microglia, a major source of immune cytokines, chemokines, and other immune factors as well as the excitotoxins, glutamate, aspartate, and quinolinic acid.[14,15,13,58]

Inflammation in the brain, especially if prolonged, triggers excitotoxicity, which over time destroys, first synaptic connections, axons, and then eventually neuronal cell bodies — something seen in postmortem examinations of autistic brains.[14] Because microglia are the source of both immune cytokines and other mediators as well as excitotoxins one may conclude that inflammation within the brain is always accompanied by excitotoxicity.[14,33] Associated with immunoeccitotoxicity one also witnesses, as an intimate part of the process, high levels of reactive oxygen species (ROS) and reactive nitrogen species and lipid peroxidation products accumulating within these affected brain areas.[81] This has also been confirmed in cases of schizophrenia.[90]
Both postmortem and most in vivo positron emission tomography (PET) scanning have demonstrated microglial activation in the affected areas of the brain of schizophrenia patients and autism spectrum disorder (ASD) patients. Some PET scans for microglial activation did not show activation in unmedicated schizophrenia patients. It has been suggested that in the case of medicated schizophrenic patients this may be because most scanned patients where on antipsychotic medications, but not all, and atypical forms of antipsychotic medications have been shown, in particular, to suppress microglial activation.

Interestingly, the areas of the brain most affected in schizophrenia have been shown to have higher densities of microglia than are normally seen in healthy brains (28% higher in frontal cortex and 57% higher in temporal area). The highest concentration of activated microglia occurred in Broadman area 9 an area characteristically affected in schizophrenia. We see this same finding in Parkinson’s disease, with the substantia nigra naturally having the highest density of microglia in the brain. In the normal brain, there are relatively high concentrations of microglia in the limbic areas of the brain and prefrontal cortex as well. In this study, the researchers also found that the highest microglial density occurred in the gray matter of the frontal, temporal and cingulate cortex, whereas in the subcortical white matter microglial density was only increased in the frontal and temporal area, concentrated mostly at the junction with the gray matter. No microglial density concentration was seen in the cingulate and corpus collosum subcortical white matter areas. No clustering of the microglia was observed, suggesting a lack of microglial proliferation or recruitment. This would indicate microglial density occurring during early neurodevelopmental stages.

Microglial activation and resulting immunoexcitotoxicity, especially with priming, would explain the dysfunctional behavioral control and cognitive deficiency seen in schizophrenia as this process would alter dendritic and synaptic pruning, and also interfere with later plasticity. The studies of first episode schizophrenia patients have shown extensive network damage in drug treatment naïve patients, which is also seen despite antipsychotic drug treatment.

Microglia priming is also a critical process in this disorder and most neurodegenerative diseases. Priming is a state where microglia have a dramatic increase in the enzyme systems and cellular signaling responsible for producing the destructive elements released by fully active microglia, such as the excitotoxins and immune mediators (proinflammatory cytokines, interferons and chemokines). Despite priming of the microglia, these destructive elements are not released by the primed microglia at that time. A subsequent immune challenge, either locally or systemically, will initiate full microglial activation and release of much higher levels of destructive elements than with unprimed microglia. Systemic inflammation is a major factor in microglial priming, but a number of environmental factors, both internal and external, can also prime microglia. Aging itself primes microglia. Fully activated microglia experience induction of neuronal and inducible nitric oxide synthetase as well as COX-2 production of proinflammatory prostaglandins.

Activation of microglia in schizophrenia was first reported in 1999, where microglial activation was seen in the frontal cortex and hippocampus in 14 patients. Since then, this has been confirmed in a number of studies. The hypo glutaminergic theory of schizophrenia is based largely on the findings that many of the positive symptoms of schizophrenia improve significantly following stimulation by NMDA receptor agonist and that specific glutamate blocking drugs (phencyclidine [PCP] and ketamine) can induce a schizophrenia-like condition in normal volunteers. Dopamine receptor stimulation does not improve the negative symptoms or cognitive deficits. In addition, 20–30% of schizophrenia patients show only partial or no response to antipsychotic treatment.

One of the main problems we find with this theory is that there is compelling evidence that immune/inflammatory events occurring in utero and during early postnatal development can increase the risk of schizophrenia later in life, usually around adolescence. Thus, early in the course of the disorder, even before the obvious symptoms develop, one may see subtle psychological changes, indicating that the process begins much earlier and is not fully manifest until a great deal of destructions occurs in brain connectivity and neuronal loss. We hypothesize that early in the course of the disease one witnesses immunoexcitotoxicity, which as the disease progresses we see a progressive loss of neurons and their connections in selected areas of the brain. A loss of these neural pathways leads to further brain dysfunction, especially in memory and behavior. It should be kept in mind that glutamate is the major transmitter for over 50% of the brain and 90% of the cortex.

ASDS AND SCHIZOPHRENIA: A POSSIBLE LINK

It is also important to appreciate that schizophrenia and ASDs share core symptoms and overlap in many ways pathologically, mainly by extensive microglial activation, anatomical changes, and similar behavioral attributes. Common to both conditions are deficits in social interaction and cognition. In both conditions one sees disruption of cognitive processing, disruption of emotional processing and abnormalities in sensory gating functions of the brain. Anatomically, they also share abnormalities
in the cerebellum, insular cortex, right parahippocampus, posterior cingulate, putamen, claustrum, left thalamus, and fusiform gyrus. Pinket al. also noted the two conditions also share a deficit pattern during neuronal activation triggered during social cognition task, specifically within the amygdala, fusiform gyrus, and ventrolateral prefrontal cortex. In addition, there appears to be a strong genetic link associated with both, and interestingly, a number of these genes have to do with control of microglial function (TREM2, TLRs, TYRO proteins, etc.). Despite the genetic link, an environmental trigger appears to be essential in both disorders.

Research has clearly shown that early life events can have lasting impacts in the brain and behavioral function throughout life. The strongest link to schizophrenia has been the observation that prenatal infections increase the risk of both autism and schizophrenia. It has been shown that cytokines play an important role in brain development. While it was first assumed that the infectious organisms were responsible for the increased incidence of schizophrenia in the offspring, subsequent studies demonstrated that the responsible factors were immune mediators. This was demonstrated by the use of non-infectious immune stimulators such as lipopolysaccharide (LPS) and Poly I: C (double stranded RNA molecule). Both LPS and Poly I: C have been shown to elevate the levels of cytokines in the placenta, amniotic fluid, fetus, and fetal brain.

Of the pro-inflammatory cytokines involved, IL-6 appears to play the major role. The studies have shown that blocking IL-6, using genetic or pharmacologic methods, prevented the long-term anatomical, and behavioral consequences of exposure to Poly I: C.

It has also been shown that animals born to mothers who sustained an immune challenge during gestation demonstrated a specific set of abnormalities in brain function, such as deficits in working memory, abnormal executive function, impaired discrimination, and deficits in both spatial and non-spatial information processing. While there are many similarities between autism and schizophrenia, there are also major differences, such as excessive brain growth in the early stages of ASDs. This tends to disappear over time as the disorder progresses. One major difference is that with ASDs the brain inflammation is long-term and continuous, extending into adulthood. One sees a 50-fold increase in TNF-alpha levels in cases of autism, far higher than we see in schizophrenia. Data from autopsy studies and microglial scanning studies suggest that in the schizophrenia the brain inflammation is more intermittent throughout the disease process. More recent studies suggest that in schizophrenia we are seeing inflammation beginning in prenatal life extending even into adulthood. Despite this, chronic inflammation is less often seen with schizophrenia and IL-6 levels are only modestly elevated, as opposed to what is seen in ASDs. Experimentally, a single dose of Poly I: C only produces acute inflammation in the fetus rather than extending into adulthood.

### INFLAMMATION AND SCHIZOPHRENIA

The studies have shown that patients with recent onset schizophrenia demonstrate activation of pro-inflammatory networks and inflammatory mediators. Rather than continuous immune activation we may be seeing multiple hits throughout early years of the person's life occurring during development and during the long phase of progression. This would constitute a priming effect. Evidence for a priming effect comes from the observation that early life (prenatal or neonatal) exposure to immune stimulants cause an excessively vigorous immune reaction in the infant when stimulated. For example, we see higher levels of IL-6 and TNF following immune stimulation by phytohemagglutinin and LPS in schizophrenic patients than with normal controls.

It has also been shown that success in treatment parallels lowering of these inflammatory cytokines. Progressive brain atrophy occurs during the course of the disorder associated with either multiple hits or a lower grade, but continuous level of inflammation, less intense than we see with ASDs. Inflammation is also associated with childhood traumas and are associated with a proinflammatory phenotype and a higher incidence of adolescent onset schizophrenia.

We have seen that experimental studies support the link between inflammation, elevated cytokines (especially IL-6) and the development of schizophrenia, including the anatomical and pathological changes seen in the disorder. The source of the pro-inflammatory cytokines appears to be mainly from activated and or primed microglia and invading macrophages, which once in the brain take on the appearance and function of microglia. The question that remains would be—what is the ability of proinflammatory cytokines alone to cause neurodegeneration? For example, it has been shown that TNF-alpha alone in the CNS cannot destroy neurons, despite the presence of very high levels in the extraneuronal space.

### THE GLUTAMATE HYPOTHESIS FOR SCHIZOPHRENIA

Stone et al. noted that the dopaminergic hypothesis did not adequately explain all the neuroanatomical and clinical
findings in schizophrenia patients.\textsuperscript{104} The glutamate hypothesis of schizophrenia causation began with the observation that specific NMDA receptor blockers, such as PCP and ketamine could transiently induce symptoms very similar to schizophrenia.\textsuperscript{50} Unlike the antipsychotic medication targeting only the dopamine receptors, which only reduced the positive symptoms, glutamate blockers also improved the negative symptoms of schizophrenia as well as the cogitative problems.\textsuperscript{57} Further evidence came from the finding that glutamate antagonists (NMDA receptor blockers) worsened the symptoms in schizophrenic patients.\textsuperscript{2,65}

Initially, it was assumed that schizophrenia was a disorder of deficient glutamate receptor function universally. Subsequent studies came to a different conclusion. Most important, it was observed that both phencyclidine and ketamine were selective NMDA receptor blockers. Further studies also demonstrated that rather than low levels of glutamate in the brain, one sees elevated levels, particularly in the striatum and prefrontal cortex (especially anterior cingulate) following NMDA receptor blockade.\textsuperscript{23,53,72,75,93} Clearly defined evidence of the effects of ketamine increasing anterior cingulate glutamate levels in humans was demonstrated by Rowland \textit{et al.} in a study using healthy subjects.\textsuperscript{93} We see similar elevations in brain glutamate following other agents known to inhibit glutamate release from specific areas of the brain, if confined to the NMDA receptors.\textsuperscript{1} \textsuperscript{1}H-MRS studies have demonstrated increased glutamate brain levels in antipsychotic free and naive subjects during their first episode of psychosis, including subjects with ultra-high risk for psychosis.\textsuperscript{34}

Additional evidence comes from treatment studies which have shown that unmedicated schizophrenia patients have elevated brain glutamate levels and that once successfully treated the glutamate levels return to normal. Clinical improvement parallels the fall in striatal glutamate levels.\textsuperscript{33} In essence, treatment response seems to follow lowering of the brain glutamate levels in specific brain areas. A recent study found higher glutamate levels in the anterior cingulate cortex in antipsychotic treated patients who were unresponsive to the treatment drugs.\textsuperscript{33}

That is, higher glutamate levels were seen in treatment resistant patients than in those who responded well to treatment.

The activated microglia are the main source of elevated glutamate. Inflammatory activation of microglia is accompanied by the release of excitotoxic levels of glutamate and other excitotoxic molecules such as quinolinic acid and aspartate.\textsuperscript{14,66,107} Howes and McCutcheon have proposed that microglial activation during neurodevelopment may cause dopamine excess by reducing cortical inhibitory inputs to subcortical dopamine neurons.\textsuperscript{52} This would sensitize the dopaminergic neurons to various stresses throughout early life, leading to dopaminergic initiated positive schizophrenic symptoms.\textsuperscript{78} It is also known that dopaminergic neurons are influenced by glutamatergic neurons.\textsuperscript{43,44} Prenatal activation of microglia has been shown to result in a delayed impairment of glutamatergic synaptic function, which would explain the behavioral and cognitive dysfunction which arises during postnatal development.\textsuperscript{92}

**HOW NMDA RECEPTOR UNDERACTIVATION RESULTS IN IMMUNOEXCITOTOXICITY AND ELEVATED BRAIN GLUTAMATE LEVELS**

Initially, when impaired NMDA receptor function was discovered in schizophrenia, it was assumed that reduced overall glutaminergic function was responsible for the negative symptoms. Recent studies have demonstrated another mechanism. Rather than a general reduction in NMDA receptor function, new studies suggest the thalamus is the main site of NMDA receptor hypofunction.\textsuperscript{98} These special NMDA receptor neurons synapse with thalamic GABAergic inter-neurons. A reduction in NMDA receptor function would reduce GABA production, leading to a disinhibition of excitatory downstream neurons. These excitatory neurons synapse with glutamergic neurons across multiple brain areas known to be hyperactive in schizophrenia.\textsuperscript{98,110} Injection of NMDA antagonist into the anterior nucleus of the thalamus results in cortical degeneration, but direct injections of these antagonists into the cortex has no degenerative effects.\textsuperscript{98}

The extraneuronal surge of glutamate occurring with NMDA receptor antagonism causes neurodegeneration most likely by acting through AMPA/kainate receptors, in particular, the calcium sensitive GluR2-lacking AMPA receptors.\textsuperscript{37,54} Additional evidence comes from the observation that minocycline, by suppressing microglial activation, has been effective in treating the negative symptoms of schizophrenia in antipsychotic refractory cases.\textsuperscript{60}

**IMMUNOEXCITOTOXIC NEURODEGENERATION IN SCHIZOPHRENIA**

A combination of microglial activation and suppression of GABAergic activity by NMDA receptor suppression, leads to a significant elevation in extraneuronal glutamate levels\textsuperscript{34,60} [Figure 1]. Further, the evidence of the critical role being played by associated glutamate elevation was demonstrated in a study using healthy human volunteers in which agents that inhibited glutamate release reversed behavioral and cognitive changes induced by NMDA receptor antagonists.\textsuperscript{3}
It has been hypothesized that the excitotoxicity occurs through excessive activation of AMPA/kainate receptors by the elevated extraneuronal glutamate[1]. Elevation of quinolinic acid (QUIN) occurs in the face of CNS inflammation as well by shifting the metabolism of tryptophan toward QUIN formation. Elevation of QUIN has been associated with major depression by immune modulation of glutamatergic neurotransmission.[101]

**INTERACTION BETWEEN THE IMMUNE SYSTEM AND GLUTAMATE RECEPTORS: MECHANISM OF IMMUNOEXCITOTOXICITY**

The earliest reports demonstrating an enhancement of excitotoxicity by TNF-alpha were by Gelbard et al. in which they used human neuronal cultures exposed to subtoxic dose of TNF-alpha and AMPA.[45] When exposed individually to these compounds no toxicity was seen but when combined, full excitotoxic neuronal injury was observed. Later this synergistic effect of combining TNF-alpha and an excitotoxic amino acid was shown in an in vivo model in which subtoxic doses of either substance alone had no significant toxic effect but when combined produced a large area of tissue necrosis.[49] It was further shown that TNF-alpha, by stimulating TNFR1 pathway, induced excitotoxicity by stimulating the release of high levels of glutamate from the microglia through hemichannels into the extraneuronal space.[106] [Figure 3]. It was also shown that stimulation of group 2 metabotropic glutamate receptors (mGluRs) induces TNF-alpha release from microglia. Olmos and Llado proposed that excitotoxicity was enhanced by the ability of autocrine enhancement of TNF-alpha release from microglia which stimulated inflammatory pathways in the microglia, enhancing the release of glutamate into the extracellular space.[83]

It has also been shown that elevation of proinflammatory cytokines, especially TNF-alpha, inhibits the glutamate reuptake transporters GLAST and GLT-1, which raises extracellular glutamate levels to neurotoxic levels and prevents lowering of extracellular glutamate during activity of the cystine-glutamate antiporter.[19,61,69,108] TNF-alpha also stimulates the up-regulation of glutaminase, the enzyme that converts glutamine to glutamate within astrocytes and microglia.[13,14] Glutamine synthetase, the enzyme responsible for converting glutamate into glutamine, is also suppressed by elevated levels of TNF-alpha.[13,14] TNF-alpha acts through its receptor TNFRI on microglia to stimulate trafficking of GluR2-lacking AMPA receptors to the neuronal synaptic membrane.[87] These special AMPA receptors, because they are calcium permeable and increase intraneuronal calcium levels, are more prone to inducing excitotoxicity. In addition, TNF-alpha stimulates internal trafficking of GABA receptors. Together, these TNF-alpha related effects on glutamate receptors, enzymes and trafficking enhance excitotoxicity.
and intimately link inflammatory mediaters to excitotoxicity. Because activated microglia are the principal source of both excitotoxins and inflammatory mediators, it becomes difficult to determine exactly how much each contributes to neurodegeneration. My impression is that excitotoxicity is the final common pathway responsible for most of the neurodestruction when microglial are activated.\textsuperscript{[13,14]}

It appears that the neurological damage occurs first either during the third trimester of pregnancy or soon after birth and that until the symptoms of psychosis present themselves. There is a progressive interference with neurodevelopment as well as a process of progressive neurodegeneration of the most involved areas of the brain following birth.\textsuperscript{[10,12]}

**NEURODEGENERATION AND SCHIZOPHRENIA**

Another important suggestion of excitotoxic neurodegeneration occurs with the widespread loss of neurons and connectivity as the disorder progresses. One sees progressive loss of grey matter volume beginning early in life which continues chronically.\textsuperscript{[4,23]} The greatest grey matter loss occurs in the superior temporal, medial temporal, superior prefrontal, medial prefrontal, thalamus, basal ganglion, and insular regions.\textsuperscript{[17]} Whole brain degeneration also occurs associated with ventricular enlargement and alterations in white matter.\textsuperscript{[24,29]} NMDA antagonist demonstrate neurotoxic injury and neurodegeneration in specific cells in rats.\textsuperscript{[39]} Yet, there is some evidence that excitotoxicity continues in some brain areas and that mGluR5 is overactive (which is excitotoxic). A more selective suppression of mGluR5 may be beneficial.\textsuperscript{[90]}

Of interest, blocking agonist of metabolic glutamate receptor types 2 and 3 blocks the neurotoxic effects of NMDA antagonists in preclinical models of schizophrenia.\textsuperscript{[24]} These mGluRs negatively modulate glutamate excitotoxicity. These experimental changes are age-dependent just as we see in clinical schizophrenia.\textsuperscript{[40]} As with clinical cases of schizophrenia, experimental models show the greatest neurodegenerative changes beginning with adolescence.\textsuperscript{[7]}

It has been suggested that schizophrenics are generally heavy smokers.\textsuperscript{[71]} It is known that nicotine is a powerful stimulant of the alpha-7 nicotinic acetylcholine receptors, which are suppressors of inflammation and generally responsible for controlling inflammation within the brain—the so-called cholinergic anti-inflammatory system.\textsuperscript{[86]} A loss of nicotinic receptors, which occurs in schizophrenia and ASDs, is thought to enhance brain inflammation.\textsuperscript{[73]} The anti-inflammatory cytokine, TGFB1 is also severely lowered in schizophrenia and ASD.\textsuperscript{[82]} Hence, we see a serious imbalance between pro- and anti-inflammatory mechanisms within the schizophrenic brain, with pro-inflammatory predominance.\textsuperscript{[90]}

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**Figure 3:** Illustration demonstrating the various ways TNF-alpha enhances excitotoxicity. Other pro-inflammatory cytokines also enhance excitotoxicity, such as IL-1, IL-6, and IL-17, but TNF-alpha is the most prominent player. Excitotoxicity appears to be the final and most destructive event triggered by inflammation and/or microglial priming/activation.
SCHIZOPHRENIA AND GUT INFLAMMATION

The big question is: What is causing the chronic, low-level inflammation? It has been shown clearly that prenatal infections in the mother can cause postnatal schizophrenia and more recent studies using non-infectious Poly I: C have shown that the mechanism involves cytokine elevations, principally IL-6 and not actual infection.\cite{5,6,7,9} In animal models, blocking IL-6 (IL-8 and IL-1ß) can prevent the schizophrenia/ASD onset postnatally.\cite{3,12,34,90,99}

Another link that has a lot of validity, certainly in some cases of both ASD and schizophrenia, is gut inflammation. Gliadin and gluten have been shown to trigger chronic microglial activation and are linked clinically to a number of cases of schizophrenia.\cite{38,96} Several reports describe significant improvement of cases on assuming a gluten-free diet, while others found little or no improvement.\cite{38,68} There may be an explanation for the failure of improvement on a gluten free diet in these cases.\cite{100} First, it should be appreciated that these gluten-linked cases are associated with a non-celiac gluten sensitivity, which does not show the usual antibody profile of typical celiac disease cases and there is no villus atrophy on duodenal biopsy. This has been called non-celiac gluten sensitivity.\cite{97}

As for why some cases fail to improve, it has been shown that gluten can trigger increased gut permeability, which can persist in some cases after starting a gluten-free diet, as there are often other contributing factors also linked to gut permeability, such as use of nonsteroidal anti-inflammatory drugs. Translocation of other food proteins and colon/intestinal bacteria can trigger continued microglial activation with resulting persistent immunoexcitotoxicity. In addition, gut inflammation can send afferents through the vagus nerve that activate brain microglia.\cite{97} In addition, once the microglia are primed, other environmental factors can precipitate continued microglial activation, such as heavy metals, aluminum, fluoroauminum, microparticulate fuels, and certain pesticides/herbicides.\cite{101}

CONCLUSION

It is of interest that many of the antipsychotic medications used to treat schizophrenia are known to suppress microglial activation and alter glutamate receptor function.\cite{184} These include risperidone, clozapine, and olanzapine. Some also reduce ROS damage. The studies have shown that drug responses correlate with lowering of S100B levels, a marker for brain inflammation.\cite{90}

As for the neurotransmitters, especially dopamine, it has been shown that treatment resistant forms of schizophrenia (type B patients) were associated with relatively normal levels of dopamine synthesis in the striatum and elevated glutamate levels in the anterior cingulate cortex.\cite{311}

The disruption of several neurotransmitters in schizophrenia is consistent with immunoexcitotoxicity, as a number of neuron types, receptor types and subtypes are affected by high levels of inflammation and excitotoxicity, with associated elevations in reactive oxygen and nitrogen species and lipid peroxidation — that is, these changes are epiphenomenon.

In our opinion, we should be addressing the central mechanism of the problem (immunoexcitotoxicity and microglial activation) rather than attempting to fine tune neurotransmitter disruptions, which can appear in a complex, variable, and often confusing presentation. This also requires attention to gut inflammation and correction of the microbiome.\cite{311} I would refer the reader to my paper in the journal Surgical Neurology International, in which I describe in detail how the mechanism of microglial/macrophage-induced immunoexcitotoxicity plays a central mechanism of neurodegeneration in Parkinson’s disease.\cite{115}

*An AMPA receptor is the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is an ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system (CNS), and it is considered a non-NMDA receptor.

Dr. Russell L. Blaylock is an Associate Editor-in-Chief of the Neuroinflammation and Neuropsychiatry sections and a Consulting Editor in Basic Neuroscience for Surgical Neurology International (SNI).

Dr. Miguel A. Faria is an Associate Editor in Chief in Neuropsychiatry; History of Medicine; and Socioeconomics, Politics, and World Affairs of Surgical Neurology International (SNI).

Declaration of patient consent

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