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Dysregulated microglia and the neurotoxic process in schizophrenia [time frame]

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Abstract

Recent research suggests that schizophrenia may be an autoimmune condition. Schizophrenic patients exhibit irregularities in their neuroimmune systems. Many of the characteristic dysregulations involve microglia, which are the primary immune cells in the brain and are responsible for eliminating neuron connections. Microglia and its signaling molecules are overactive in both high-risk and diagnosed populations. It is probable that a neurotoxic process effected by microglia is a driving factor in the development of schizophrenia. Preventions and treatments targeting microglia are promising.

Introduction

Schizophrenia is a biologically and behaviorally invasive condition with no known preventions or cures, but biological clues indicate that it may be treatable. Scientists are examining the cellular mechanisms recruited for the disease's development in order to identify targets for treatment.

Schizophrenia in society

Schizophrenia entails two or more qualifying positive symptoms (e.g. psychosis, delusions, paranoia, and hallucinations) alongside negative symptoms (e.g. catatonia and emotional detachment). Symptoms often cause emotional, social or occupational burden[1,17]. The condition afflicts an estimated 1 out of every 100 people[14] and is disproportionately prevalent among unemployed, homeless, and incarcerated populations[9]. In spite of decades of research, the mechanisms of the disease's development are not fully known. Medical approaches for patients have been limited to cognitive behavioral therapy and poorly understood medications[9,10]. Examining the characteristic dysfunctions of schizophrenia on a cellular level is necessary to elute effective treatment strategies.

Symptoms of schizophrenia

Schizophrenia has distinct observable effects on the central nervous system (CNS)[3,6,9-14,17,20]. Patients with schizophrenia have many neurological abnormalities, both structurally and functionally[14]. The abnormalities have behavioral consequences, including difficulty with organized thought and negative affect[1,13,14,17]. Schizophrenia is highly comorbid with chronic affective disorders including depression and anxiety[13]. Many patients frequently report a state of cognitive dissonance that exacerbates chronically poor moods[17]. Recent research focusing on neuron connectivity and mood has found that the immune system has a significant role in regulating these[2-16,19,20].

Clues point to the immune system

Immune dysfunction in psychiatric disorders is a predictable phenomenon. The remainder of this review will focus on evidence that microglia, the primary immune effectors in the brain, are active in an exaggerated neurotoxic process that occurs in schizophrenia. This review will also present evidence of the causality of this process to the disease and options for treatment and prevention.

The immune system in disease

The immune system is responsible for monitoring the health of all cells, so we can conclude that immune cells must be relevant in the development of disease in general. Microglia are the immune cells that are dispersed throughout all brain regions and provide structural support to the neurons around them. Their position between the neurons enables microglia to facilitate neuron maintenance by sending and receiving communicator molecules. These cells exist to ensure the most efficient connections possible.

Microglia are main players in brain immune system

Microglia are macrophages, a class of cells that respond to pathogens in the CNS[3,8,10,12,13,20]. Their default resting state can be disturbed under immune threat, when they transform to an active, ameboid state[11] and locally proliferate[7]. Active microglia facilitate biochemical processes to confront pathogens, evacuate the system of toxins, and heal damaged tissue[6,13,20]. These cells, having receptors for most known CNS neurotransmitters, can mediate intercellular communication[10,13]. Microglia are biochemically receptive to even slight changes in the environment. They can suppress or activate the release of pro-inflammatory agents, like cytokines, nitric oxide (NO), and neurotrophic factors[11-13], in response to contact with immunogens and neurotransmitters[10,12]. It has been recently discovered that microglia facilitate elimination, or 'pruning,' of synapses[6,8]. Microglia can use communicating molecules including neurotransmitters and pro-inflammatory agents to initiate changes that can be neuroprotective or neurotoxic[13].

Synapses are the areas where neurons interact with one another. The brain processes information by connecting neurons (each representing a different, very specific sensation or perception) to one another with synapses. A single comprehensive thought occurs only after many neurons connected by synapses have communicated in a chain reaction. Microglia, as facilitators of synaptic pruning, are therefore extremely important to cell connectivity and cognition. Disease and other immune burdens cause microglia to transform from resting state to active state. Activated microglia exhibit inflamed cell bodies (figure 1).

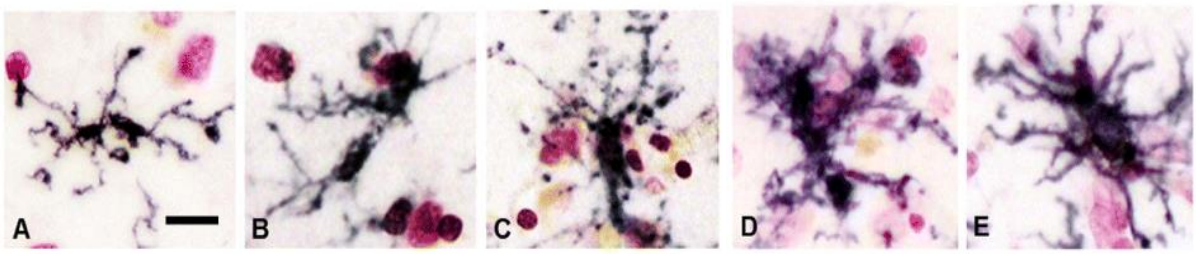

Figure 1. Various morphologies of microglia in human brain sections. Progressive changes in morphology of HLA-DR-expressing microglia in a pathology-rich section from an AD case. HLA-DR-expressing microglia can be found with various activation morphologies ranging from **A** highly ramified to **C** moderately hypertrophic to **E** highly activated with enlarged cell body and processes. **B**, **D** Intermediate changes in morphology. Sections were stained using antibody LN3 (1:1,000 dilution; Abcam, Cambridge, MA, USA) using nickel-enhanced diaminobenzidine peroxidase immunohistochemistry and counterstained with neutral red[18]

Microglia are active in an inflammatory neurotoxic process

Microglia have a critical role in an inflammatory neurotoxic process to rid the brain of undesirable matter including pathogens, debris, and dysfunctional or unnecessary cells[6,13,20]. Under persistent and severe inflammation, microglia will release signals that induce degeneration of synapse or potentially entire neurons [6,13]. A neurotoxic process has been described in other conditions involving chronic brain inflammation, including autoimmune diseases (e.g. Multiple Sclerosis, post-streptococcal disorders, lupus erythematodes, and scleroderma)[13], age-related neurodegenerative conditions (e.g. Alzheimer's disease, Parkinson's disease, dementia, and stroke)[4,8,10,13,20], and infection (e.g. HIV and other viral, bacterial, and protozoan infections)[3,13]. In acute infections (during which microglia are highly active), brain inflammation is potentially life-threatening[13]. Neurotoxic inflammation can result in significant structural and functional changes over the entire brain.

The inflammatory response of microglia is an adaptive process which exists to eradicate pathogens, poorly functioning cells, and unnecessary connections between cells. It may become maladaptive when genetic defects, trauma, or toxins are involved[4,13]. Considering that schizophrenia is associated with certain single nucleotide polymorphisms (SNPs) [3], childhood abuse[9,17], and drug use[2,9,14], it is logical that something maladaptive is occurring with this process.

Microglia activation and neurotoxic process are occurring in schizophrenia

Behavioral symptoms of schizophrenia reflect a chronic overactivation of microglia[7,12,13,14]. Psychosis is associated with excessive neuroinflammation[3,13]. Poor mood is related to a high ratio of active microglia both short-term (sickness behavior[16,19)] and long-term (depression-like changes in behavior, cognition, and mood[20]) in people with and without schizophrenia. The alarming majority of schizophrenia cases co-occur with chronic affective disorders[17], which suggests that the neurotoxic process is an underlying mechanism rather than a phenomenon.

Morphological features of schizophrenia support a hypothesis that a maladaptive neurotoxic process has occurred[2,6,13,14]. MRI and post-mortem studies reveal dysfunctional white matter connectivity in schizophrenia and lower overall CNS volume[2]. Since schizophrenia entails behavioral and emotional changes at its onset (caused by neuroinflammation) and fewer neurons and synapses in its development (caused by synaptic pruning), we can deduce that the neurotoxic process is heavily implicated in the progress of the disease.

Evidence of immune dysregulation in schizophrenia

Abnormal inflammatory conditions[3,5] and elevated pro-inflammatory biomarkers[13] are observed in fully-developed schizophrenia. Several fields provide supporting evidence that dysfunctioning microglia are responsible for causing the disease.

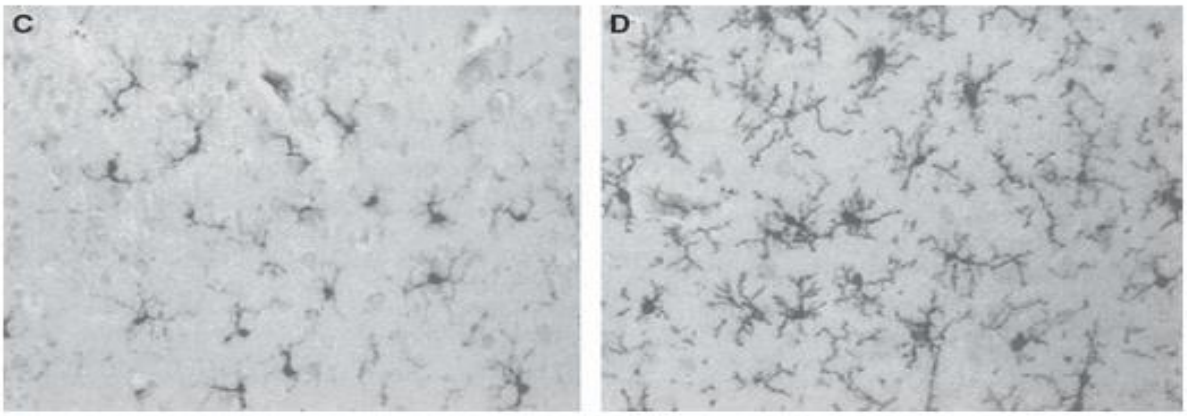

Figure 2. 11 LN3 staining for microglia in layer III of the temporal cortex of control (C) and schizophrenic (D) subjects. Scale bar = 40 lm. There is no obvious astrogliosis in schizophrenia, but there is microgliosis. From Radewicz et al. (2000)[7]

Microglia are overactive in schizophrenia

A high proportion of microglia are seen in their activated form in both *in vivo*[3] and post-mortem[3,7] imaging experiments of schizophrenia. Several experiments have also found greater microglial density in schizophrenic brains[14]. As illustrated in figure 2, when schizophrenic brains (D) are compared to control brains (C), microglia are numerous and more robust (a state known as microgliosis) in the frontal and temporal cortices[7]; these regions are responsible for many cognitive and sensory faculties that are disrupted in schizophrenia. Microglia in schizophrenia have greater sensitivity to activating compounds than in control subjects[14]. It is evident that microglia are chronically stimulated in schizophrenia, and that the microgliosis is more concentrated in the white matter in areas related to higher processing[14].

Chronic activation of microglia causes excess neuroinflammation

More pro-inflammatory compounds (especially interleukin 1β) can be detected in schizophrenic subjects than in control subjects in a wide variety of experiments[3-14]. The genes encoding these compounds are expressed by microglia[3]. We can conclude from the patterns of gene expression that microglia are responsible for stimulating inflammation in schizophrenia. Upregulated expression of normal genes suggests that the immune abnormalities do not originate externally, but are rather systematic dysfunctions.

Structure is related to symptoms

Since we know that schizophrenic brains have more active microglia and fewer synapses, we may assume that persistent inflammation has resulted in a neurotoxic process. Ultrastructural analysis experiments have found phagocytic activated microglia with neuronal elements inside in schizophrenic brains[14]. The neuronal degeneration caused by microglia explains the classically poor cellular connectivity associated with schizophrenia. Improper discretion of synaptic pruning by microglia could contribute to the irrational thoughts and behaviors common in the disease.

Evidence for causality

It is unquestionable that the neuroimmune system is dysregulated in schizophrenia, but analysis of prominent risk factors supports that this dysregulation is actually causal to development of the condition. Many events that are stressors on the immune system are risk factors for schizophrenia[3,12,13,16]. Risk genes are often related to normal immune functioning and have a direct effect on microglia[3,12,15].

Experiential risk factors

A number of events increase one's lifetime risk for schizophrenia[3,5-15]. Schizophrenia has been correlated with gestational events. Animal models of maternal stress have illustrated that microglia that become overactivated in early development produce abnormal white matter connectivity[3]. Rodent studies have demonstrated that inducing immune trauma during the late stages of gestation or early in life leads to neurotransmitter imbalances later in life[13] and may pose a risk for long-term hypersensitivity of the immune system in general[3]. In humans, the children of mothers who had respiratory, reproductive tract, and/or viral infections while pregnant were more likely receive a diagnosis of schizophrenia[6,13,14]. Prenatal infections are known to elevate the inflammatory process[12], and this could significantly disrupt the development of adaptive neural networks.

Postnatal events that burden the immune system, including infections and autoimmune diseases, also increase the risk of being diagnosed with schizophrenia[3]. Correlation studies have found that schizophrenic people were more likely to have been hospitalized for infections before disease onset than non-schizophrenic people[3,13]. Physical and emotional trauma are also known risk factors for schizophrenia[12,13]. Trauma has a profound impact on the immune system in both the presence and absence of schizophrenia[8,12,13,16,20]. Injury can have direct effects on microglia and lead to neuroinflammation[12]. Emotional trauma may dysregulate pro-inflammatory neurotransmitters[10,20] and subsequently perpetuate

the chronic activation of microglia. Chronic stress is known to sensitize microglia[13]. These events are substantial to mechanisms that activate the immune system and launch neurotoxicity.

The lifetime risk factors for schizophrenia are cumulative in damaging the neuroimmune system's ability to regulate[13]. As we have established that microglia maintain neurons and delegate synaptic pruning, it is not unlikely that their chronic overactivation is detrimental to healthy neuron connections. Dysfunctional microglia are apt to inappropriately eliminate cells and synapses.

Genetic risk factors

Schizophrenia can be heritable and many individuals with the disease have common genetic qualities, indicated by SNPs. Many of these genes encode proteins relevant to immune function[3].

Recently, a team of nearly 20 scientists collaborated on a groundbreaking study which determined the molecular mechanism of the highest-risk gene locus[15]. They found that these genes (*C4*) coded for a protein, Human *C4* protein, which is used between neurons to signal synaptic pruning. Additionally, they found that most of the receptors that can recognize Human *C4* protein are located on microglia. The allele combinations associated with schizophrenia cause *C4* to be produced in excess, subsequently causing microglia to be overactive. These experiments are the first to provide direct evidence associating a gene with molecular dysfunction in the disease. The discoveries about the *C4* genes strongly indicate the causal role of a neurotoxic process.

Proposed model of causation

Schizophrenia appears to result from a combination of three factors implicating the immune system: genetic vulnerability, environmental stressors, and inflammation[3,13]. Individuals with high risk genes may be more prone to immune dysregulation when faced with events that burden the immune system. Without the conditions for optimal regulation, these individuals lack the biological tools to overcome emotional trauma, infection, chronic conditions, or even puberty. Stressors cause an activation of microglia that is adaptive, but a genetic vulnerability may cause microglia to be overactivated to the point that it is maladaptive.

People exposed to many risk factors will be more sensitive to stressors and are more likely to have a persistent inflammatory response[14]. Over years, the neurodegenerative effects of perpetually active microglia may accumulate into significant structural and functional deficits in the brain with behavioral consequences[3]. The onset of schizophrenia is consistent with this model. Schizophrenic people are more likely to have experienced abuse or prior health issues. It is common for patients to experience their first psychotic episode during a hormonal change or traumatic event[17].

Microglia may be good targets for treatment

Many fields of research support that blocking the impacts of overactivated microglia may alleviate some symptoms of schizophrenia[11-14,19,20]. Many antipsychotics and antidepressants have had anti-inflammatory effects ascribed to them[11,13]. The antipsychotics risperidone and haloperidol inhibited microglia from releasing excess pro-inflammatory cytokines and NO[11]. The antibiotic and microglia inhibitor minocycline improved cognition and reduced symptoms across animal model experiments, patient trials, and clinical studies[6,13]. Anti-inflammatory cyclooxygenase-2 inhibitors have also been successful in reducing symptoms[13].

Interrupting the neurotoxic process of microglia could also be promising for disease prevention[11-14]. If excess inflammation can be blocked, symptom development may be slowed or prevented in at-risk individuals. Medications such as ariprazole that downregulate levels of intracellular Ca^{2+}, which is used by microglia to induce the release of pro-inflammatory agents, could reduce inflammation and slow the neurotoxic process[11].

Conclusion

A brain's ability to process information is contingent on its ability to organize it. Organization of neurons in the CNS occurs through synaptic pruning when activated microglia selectively invoke

inflammation and ultimately neurodegeneration. Dysregulation of the immune system is devastating to the organizing process.

Synaptic pruning can occur excessively when overactive microglia cause chronic inflammation. Elevated indicators of inflammation are expected in many psychiatric conditions. The presence of overactive microglia, poor organization of neurons, and behavioral symptoms of schizophrenia indicate that the immune system has been dysregulated.

A combination of biological risk factors informs an individual's natural ability to regulate their neuroimmune system and optimize the synaptic pruning process. Environmental stressors necessitate an optimal balance of immune regulation. Genetic vulnerabilities may prevent a person not be able to downregulate inflammation. This paper proposes that at least some forms of schizophrenia develop when genetic vulnerabilities are acted upon by stressors. Immune dysregulation creates a maladaptive neurotoxic process which, over time, will damage the efficiency of neuronal organization.

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