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Cortical gray matter loss in schizophrenia: Could microglia be the culprit?

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ABSTRACT

Cortical gray matter loss in schizophrenia remains a great therapeutic difficulty. Each psychotic episode causes irreversible cortical gray matter loss, that causes the patients to never regain their previous state of functioning. Microglial cells are part of the innate immune system and their functions, among others, include phagocytosis and release of neurotrophic factors. They have a key impact on developmental and plasticity-induced removal of neuronal precursors, live-but-stressed neurons and synapses, while also stimulating synaptic growth and development. We hypothesize that microglia are the culprit for the cortical gray matter loss in schizophrenia through abnormal synaptic pruning, phagocytosis of stressed neurons and lacking neurotrophic factor release. Furthermore, we propose a research that could validate the hypotheses using serum samples of first-episode early-onset patients. By measuring the serum levels of milk fat globule-EGF factor 8 (MFG-E8), subcomponent in the classical pathway of complement activation (C1q), brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6) and interleukin-10 (IL-10), we could gain an insight into the state of microglial activation during various stages of the disease. If this hypothesis is valid, new targeted drugs could be developed in order to reduce the deterioration of cortical gray matter, thereby possibly improving negative symptoms and cognitive deficits.

Introduction

Schizophrenia is a severe chronic mental illness of unknown cause. It is generally characterized by psychotic episodes followed by phases of remission [1]. Each psychotic episode causes irreversible cortical gray matter loss, causing the patients to never regain their previous state of functioning [2]. Cortical gray matter loss is greater in early-onset schizophrenia, which is more severe and difficult to treat [3]. Symptoms of schizophrenia are classified into three categories: positive (hallucinations, delusions, thought and movement disorders), negative (social withdrawal, inability to feel pleasure, difficulty in expressing emotion) and cognitive (poor executive functioning, working memory problems) [1]. Antipsychotics have been a mainstay of schizophrenia therapy since their discovery. Two known groups of antipsychotics are the older, first generation psychotics like haloperidol and the newer, second generation psychotics (risperidone, olanzapine). There is evidence that treatment with second generation antipsychotics like olanzapine lessens the extent of gray matter loss, while contrary to that is the progressive cortical gray matter loss found in treatment with first generation antipsychotics like haloperidol [4]. Negative symptoms have been linked to cortical gray matter loss in prodromal stages of schizophrenia, which could indicate the protective effect of second generation antipsychotics on the cortical gray matter as they are potent in alleviating negative symptoms [5]. This can be explained by an increased amount of neurotrophic factors in the brain [6] and stimulation of neurogenesis [7]. Olanzapine and haloperidol show a difference when they are used to treat lipopolysaccharide stimulated microglia cells in vitro, with only olanzapine suppressing their activation [8]

Microglial cells are the main innate immune cells of the complex cellular structure of the brain. They originate from the yolk sac and migrate into the brain during embryonic development [9]. These cells respond quickly to pathogens and injury and accumulate in regions of neurodegeneration, producing a wide variety of inflammatory mediators. Microglia are often perceived as a sensor in the central nervous system. They react to every disruption in the homeostasis by rapidly changing their form and function. The main physiological function of microglial cells is phagocytosis, enabling them to have a key impact on developmental and plasticity-induced removal of neuronal precursors, live-but-

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stressed neurons and synapses [10]. They are also an important source of neurotrophic factors and are known to potentiate synapse formation and neurogenesis [11]. Microglia can assume multiple phenotypes with unique features depending on their environment. However, M1 and M2 phenotypes are the most researched so far. The M1 phenotype is considered proinflammatory and represents the first line of defense of the innate immune system, with the predominant production of inherent cytokines such asinterleukin (IL)-1α, -1β, -6, -12, -23 and tumor necrosis factor-α (TNF-α). M1 polarized microglia also produce reactive oxygen species and nitric oxide which are essential in the process of phagocytosis. Alternatively, M2 microglia are considered anti-inflammatory by IL-4, -10, -13 and various growth factors including vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) with potential functions in repair and tissue remodeling [12]. Microglial involvement has been implicated in numerous diseases like schizophrenia, Parkinson's disease, Alzheimer's disease, prion diseases and multiple sclerosis [13].

The hypotheses

We hypothesize that the microglia cells are responsible for the cortical gray matter loss in schizophrenia through abnormal synaptic pruning, phagocytosis of stressed neurons and lacking neurotrophic factor release.

Rationale of the hypotheses

Our theory stems from the novel functions that are attributed to the microglia cells and possible links of inflammation and schizophrenia presented further in the paper. Theories about microglial involvement in schizophrenia have been present for a number of years.

One of the most prominent theories is the neurodevelopmental theory This theory that schizophrenia is the outcome of neurodevelopmental processes that began long before the onset of clinical symptoms and is caused by a combination of environmental and genetic factors [14]. Cortical gray matter loss in schizophrenia can be attributed to the loss of dendritic spines and possibly the neurons themselves. The loss of dendritic spines was reported in relation to excessive synaptic pruning in adolescence, which coincided with the common age of onset for the disease. Moreover, human studies show that the excessive pruning occurs much earlier, even during the toddler age [15]. On the other side, one of the novel functions attributed to the microglial cells is synaptic pruning during development. Paolicelli et al. have demonstrated that microglia engulf and eliminate synapses during development, and alterations of such physiological pruning could lead to disorders with altered synapse numbers like schizophrenia [17]. Thus, the timing of synaptic pruning suggests that pruning itself could not be the trigger for schizophrenia, but merely contribute to it [16], even though it is still unclear how synapses are chosen for phagocytosis. Recent evidence points out that the complement system, namely the subcomponent of the C1 system, C1q, complement component 3 (C3) and its receptor 3 (CR3), act as a tagger. Mice deficient in one of those factors show decreased phagocytosis of synapses, which leads to reduced synaptic activity [18]. However, synapse loss and excessive synaptic pruning are unlikely to be the sole reason for the reduced gray matter volume in schizophrenia. According to recent studies, synapses account for only 6% of cortical gray matter [19], while a loss of 11% has been reported in schizophrenia [20].

We believe that a loss of stressed neurons could also be a factor for cortical gray matter loss. There is a growing body of evidence that microglial cells have the capability to phagocyte live-but-stressed neurons. This is achieved through the presence of "eat-me" signals like phosphatidylserine (PS), which can be expressed both reversibly or irreversibly [10]. Thus, PS marks the neuron for phagocytosis driven by microglial cells [21]. In inflammatory conditions, microglia and astrocytes release increased amounts of milk fat globule EGF-factor 8 (MFG-E8), which mediates phagocytosis of viable neurons. MFG-E8 binds to PS via its C1 and C2 receptors domains and to microglial vitronectin receptors (VNR), which activation induces phagocytic activity by remodeling of the microglial actin cytoskeleton [22]. Numerous studies have noted imbalances in cytokine levels during inflammatory conditions that are present in schizophrenia as well, which imply a significant role of the immune system in the disease [23]. Such a milieu could be one of the reasons for the loss of the cortical gray matter through the aforementioned mechanism. Furthermore, there is some evidence about secreted exosomes containing MFG-E8 during the proinflammatory responses [24]. In addition, the presumption that MFG-E8-containing exosomes secreted from activated microglia could act as a bridging secretory molecule with the ability to bind to αvβ3 integrins on the endothelial cells could be a valuable observation in terms of passage through the blood–brain barrier, thus serving as a systemic biomarker.

Lower values of the brain-derived neurotrophic factor (BDNF) values have been documented in patients with schizophrenia [25]. BDNF is a neurotrophin that supports survival and growth of neurons and synapses, which leads to improved long-term memory, learning and higher thinking [26,27]. Microglial BDNF is known to be an important regulator of synaptic plasticity and function [11]. Binding its TrkB receptor, BDNF activates various intracellular signaling pathways, such as mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), phosphoinositide 3-kinase (PI3K) pathways and phospholipase Cγ (PLCγ) [28]. Schizophrenia patients have severe cognitive deficits that impact their long-term quality of life. Cognitive impairment is most profound in learning, memory and executive functions [29]. One of the causes for the impairment could be the lower levels of neurotrophic factors as seen in patients with schizophrenia [25].

Microglia polarization towards M1 and M2 phenotypes could also play a role in schizophrenia. Cytokine irregularities are often reported in schizophrenia [30]. IL-6 is a proinflammatory cytokine that is considered one of the M1 phenotype markers [12]. Elevated IL-6 levels have been reported in acute phases of schizophrenia, with decreases in the state of remission [31]. On the other end is IL-10, a M2 phenotype marker, which is considered anti-inflammatory. Contrary to IL-6, the levels of IL-10 during acute schizophrenia are decreased and inversely correlated with the standardized Positive and Negative Syndrome Scale (PANSS) negative and cognitive subscores in patients [32]. The aforementioned study results point to a M1 polarization in schizophrenia, although the precise role of M1 microglia-phenotype in schizophrenia remains unknown.

Rationale of our study is also based on the effects of antipsychotics on microglia, in both in vitro and in vivo animal models. Most second-generation antipsychotics like risperidone [33], olanzapine [8], ziprasidone [34] and aripiprazole [35] have a suppressive effect on activated microglia in vitro. Haloperidol and other first generation antipsychotics exhibit weaker microglial suppression [8]. There haven't been many studies focused on the anti-inflammatory characteristics of antipsychotics. Possible explanation for the anti-inflammatory effect of aripiprazole could be its effect on the suppression of intracellular Ca^{2+} mobilization. Intracellular Ca^{2+} is one of the endogenous activators of protein kinase C (PKC), which induces the M1 activation of microglia through the MAPK-ERK1/2-p38 cascade [36]. The difference in microglial suppression of first and second generation antipsychotics has been