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INFLAMMATORY GENES AND NEURAL ACTIVITY: INVOLVEMENT OF IMMUNE GENES IN SYNAPTIC FUNCTION AND BEHAVIOR

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1. ABSTRACT

The function of pro-inflammatory cytokines and chemokines in brain injury and autoimmune diseases has been long recognized. There is however, a significant lack of information regarding the role of constitutively expressed immune genes in the normal brain. The current evidence points to the involvement of certain cytokines and major histocompatibility complex (MHC) molecules in synaptic function and plasticity. Furthermore, constitutively expressed chemokines in neurons provide an additional indication of a role for these molecules in neural function. In addition, clinical data suggests a dysregulation of immune genes in the cerebrospinal fluid of psychiatric patients who have neither brain injury nor autoimmune diseases. This review will discuss recent data indicating a role for immune genes in synaptic stability and will also discuss the implications for specific brain functions involving mood and cognition.

2. INTRODUCTION

The expression and function of pro-inflammatory cytokines in the brain such as interleukin-1 (IL-1) beta and tumor necrosis factor (TNF) alpha has been well documented in brain injury cases including ischemia, head trauma, infections and stroke (1,2,3,4). In addition, cytokines and chemokines have been shown to play a role in the pathogenesis and progression of autoimmune diseases such as multiple sclerosis and experimental allergic encephalomyelitis (5,6,7). Cytokine signaling to the brain and propagation within the brain parenchyma have also been shown to be important routes of immune to central nervous system feedback regulation (8,9,10,11,12,13,14,15). There is, however, some controversy regarding a role of immune-related genes in normal "healthy" brain function. One argument is that cytokine expression in the normal brain is very low or absent. The specific evidence indicating constitutive expression or absence has been discussed in detail by Vitkovic (16). Although there is not conclusive evidence indicating the source of constitutive cytokine expression in the normal brain, increasing evidence is accumulating in favor of this idea. Alternatively, constitutive expression of other immune genes, including chemokines such as fractalkine and class I major histocompatibility complex molecules (MHC), has been determined in neuronal and non neuronal cells of the brain (17,18,19). While the function of constitutive chemokines in neurons is under investigation, the proposed role of class I MHC molecules has been related to neural plasticity at the synaptic level (20). Together, these data suggest that immune-related genes expressed in the brain may have additional functions beyond mounting a response to injury, tissue trauma or immune challenge.

In parallel with *in vivo* studies, *in vitro* studies using neuronal cell cultures or brain slices have suggested a role for cytokines in synaptic function including long-term potentiation (LTP), long-term depression (LTD) and synaptic vesicle trafficking (21,22,23). These studies indicate that immune-related genes may regulate brain function by acting at the synaptic level affecting neurotransmission in conditions of normal neural activity. At the systems level, these actions would have important outcomes in neural circuits governing sensory systems, cognitive functions and behavior. Therefore, it can be postulated that immune-related genes may have an essential homeostatic role in the brain and are required for normal brain function. The behavioral alterations observed in cytokine knock-out (KO) mice provide further evidence for this idea (24,25). Moreover, several reports indicate that individuals with psychiatric conditions display abnormal levels of immune related molecules in their cerebrospinal fluid (26,27). In these studies, no evidence of an autoimmune disease or chronic infection was observed that might explain the presence of pro-inflammatory molecules. If so, psychiatric diseases such as depression, anxiety and perhaps schizophrenia, currently believed to develop as a result of alterations in specific neurochemical systems, may also involve a previously unconsidered dysregulation of neural-immune interactions at the level of cytokine gene expression within the brain.

3. MAJOR HISTOCOMPATIBILITY COMPLEX MOLECULES AND SYNAPTIC PLASTICITY

Class I MHC molecules are cell surface glycoproteins important for initiating immune responses against antigens. The function of class I MHC in the immune system to bind antigenic peptides for presentation to CD8+ T cells has been reviewed elsewhere (28). Initially, the brain was considered an "immune privileged site" due to the absence of MHC molecule expression and the presence of the blood brain barrier impeding the trafficking of immune cells. However, there is now increasingly convincing evidence that neurons express MHC molecules and associated proteins, including the cosubunit beta 2-microglobulin and the ζ subunit of the CD3 receptor complex (20,29). The expression of these genes has been shown to be specific for a subset of neurons and to be developmentally regulated. These include pyramidal cells of the somatosensory cortex, pyramidal cells of the hippocampal formation, reticular thalamic and geniculate nucleus neurons, nigral dopaminergic neurons, brainstem motoneurons and neurons of the paraventricular hypothalamic nucleus (20,29,30,31).

During development of the visual system, a crucial event in the establishment of functional connections between retinal ganglion cells and cells of the lateral geniculate nucleus is the refinement of connectivity achieved by eliminating inappropriate connections and stabilizing appropriate ones. This process of synaptic plasticity and remodeling is dependent on neural activity (30). The electrical input provided by retinal ganglion cells is the key signal determining the stabilization or elimination of appropriate synapses. In class I MHC KO mice, the pattern of connectivity in this system is altered due to a lack of elimination of synapses (20). After extensive study of the role of MHC in this process, it was concluded that class I MHC molecules are necessary for the proper formation of activity dependent synaptic connections and elimination of silent non-functional synapses (32).

The involvement of class I MHC molecules in activity-dependent synaptic plasticity in the adult brain has also been determined. For example, differences in these molecules affect N-methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation (LTP), a critical process in learning and memory. In the hippocampus of class I MHC KO mice, LTP has been shown to be enhanced with respect to wild type mice. In contrast, no long-term depression (LTD) effect in class I MHC KO mice was observed. This effect was shown to be specific for the NMDA induction of LTP, and no differences in basal synaptic transmission were detected in KO compared to wild type mice (20,32). Such enhancement of LTP and lack of effect on LTD in class I MHC KO mice is indicative of the involvement of MHC molecules in synaptic regression and refinement of synaptic connections. Taken together, these findings indicate that class I MHC molecules are necessary for proper activity-dependent synaptic remodeling in the normal brain in specific neuronal and neurochemical systems.

There are many implications for these findings regarding the interaction of neural and immune genes in the modulation of brain function. Perhaps the most relevant implication is that neural and immune genes interact in the normal brain to modulate specific processes such as learning and memory. Also, this interaction is specific for some neurochemical systems and neuronal groups. Furthermore, cytokines present at the time this process occurs can have important effects by inducing the expression of class I MHC molecules. If these postulates are correct, cytokines should affect synaptic plasticity in specific neurochemical systems. We will next discuss recent evidence supporting this hypothesis.

4. TUMOR NECROSIS FACTOR ALPHA AND GLUTAMATERGIC SYNAPSES

There is increasing evidence suggesting that TNFα is a cytokine that may be expressed in the brain, specifically in glial cells, under normal physiological conditions (16). In addition to its role in brain tissue trauma and repair, TNFα has been also implicated in many other brain functions including neuroendocrine activation, sleep regulation, and circadian rhythms (4,9,13,16). There has been a series of reports analyzing the exogenous administration of cytokines including TNFα in modulating LTP. However, to our knowledge, there has been only one report analyzing more specifically the involvement of TNFα modulating LTP by using TNFα receptors KO (21). In this study, the authors reported very similar functions for TNFα in the modulation of LTP and LTD to that observed in class I MHC studies. Remarkably, the phenotype of the class I MHC and TNFα receptor KO mice vis-a-vis the characteristics of activity-dependent synaptic changes were the same. There was no difference in the basal synaptic transmission with respect to wild type controls, and both groups of KO animals exhibited the same deficit in induction of LTD at low frequency stimulation. Both studies were performed in parallel by independent laboratories. However, studies of the potential role of TNFα induced class I MHC expression as a molecular pathway that might explain these phenomena have not been performed.

In a more recent study using cultured hippocampal neurons, another molecular mechanism of synaptic plasticity at the glutamatergic synapse has also implicated TNFα. This study showed that TNFα released by glial cells enhanced the surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), thus increasing synaptic efficacy (22). It also reported that the continuous presence of TNFα is required to maintain synaptic strength induced by neural activity. This effect observed in cultured neurons was replicated when it was tested in hippocampal slices. In summary, this study indicated that TNFα may contribute to synaptic strength during NMDA receptor-dependent LTP by increasing AMPAR trafficking. The previously discussed studies are in some ways complementary to each other and indicate a very similar molecular mechanism of action for TNFα at the glutamatergic synapse. It is noteworthy that there are a large number of studies showing inhibition of LTP and cytotoxic effects of TNFα associated with

neuronal injury and inflammatory processes. The major difference between these studies is that the above reviewed studies analyze the effects of endogenous and small amounts of TNFα while those showing TNF cytotoxicity use significantly larger concentrations of TNFα. Therefore, it is important to differentiate between the effects of physiological and pathological actions of TNFα in the models analyzed. Nonetheless, both studies support the notion that TNFα acting at the synaptic level may influence brain function and behavior.

Behavioral studies using transgenic mice provide additional evidence that support both models of TNFα in activity-dependent synaptic plasticity. For instance, mice over-expressing TNFα show memory impairments and disrupted learning capabilities (33,34). Alternatively, TNFα KO mice display increased anxiety and have increased serotonin levels in the hippocampus (24). Both functions have been shown to involve the hippocampus and perhaps activity-dependent changes at the synaptic level.

In addition to TNFα, IL-1ß is a cytokine shown to be constitutively expressed in the brain. Its many actions in the brain include regulation of fever, sleep and endocrine activation and have been explored in detail (2,8,35). Regarding its potential involvement in synaptic function, the case is very similar to that of TNFα. IL-1ß has been known for many years to disrupt LTP and to induce neuronal death (2). However, recent studies have determined that endogenous IL-1ß may indeed have important roles in synaptic plasticity. Studies using IL-1 receptor KO mice have reported a complete absence of LTP and impairments in behavioral task associated with learning and memory (36). Moreover, blocking endogenous IL-1ß with IL-1β receptor antagonist in wild type mice prevented LTP formation (37). It was also observed in these studies that at higher doses IL-1β inhibited LTP.

Together, the studies on TNFα and IL-1ß regarding their potential involvement in synaptic function and plasticity indicate a similar pattern of effects. Both molecules may be necessary to promote activity-dependent changes and both molecules seem to interact with the glutamatergic synapse. Both TNFα and IL-1ß receptor KO mice show alteration of behaviors and both molecules at pathophysiological levels disrupt LTP and induce neurodegeneration.

5. CHEMOKINES IN SPECIFIC NEURONAL POPULATIONS

While cytokines are primarily expressed in glial cells, and their presence in neurons is debated (16), certain chemokines and chemokine receptors are well established as constitutively expressed in neurons. Chemokines are pro-inflammatory molecules known for their function mediating migration of leukocytes. The chemokine superfamily is divided into four subfamilies according to their structure determined by the conservation of cysteine residues in their N-terminus (38). Most chemokines exist as small, secreted proteins with chemotactic properties. However one subfamily of chemokines, the δ-chemokines, exist in the soluble secreted form and as a membrane-anchored protein. Fractalkine is the only known member of this family and its expression in the normal brain in specific neuronal cells has been established by several methods (19,39,40,41). Fractalkine has been shown to be constitutively expressed in the normal brain of the rat, mouse and humans. Under normal conditions, transcription of fractalkine and protein expression has been shown in pyramidal neurons and granule dentate cells of the hippocampal formation, layers II and III of the cerebral cortex, amygdala, caudate putamen, nucleus accumbens, olfactory tubercle, anterior olfactory nucleus and olfactory bulb, among other regions (19). The specific pattern of expression of fractalkine in neuronal cells under normal physiological conditions has suggested a role in neuronal function in addition to its inflammatory effects (42, 43).

Furthermore, the receptor for fractalkine (CX_3CR1) has been demonstrated in both neurons and microglia (41,42,43). Activation of the CX_3CR1 by fractalkine induces calcium increase in microglia and astrocytes (41,42). In addition, fractalkine induces protein phosphorylation through activation of the mitogen-activated protein kinase (MAPK) cascade specifically in microglia (42). This process was completely inhibited by the MAPK kinase/extracellular signal-regulated kinases (MEK) inhibitor PD98059. Although this intracellular signaling mechanism in microglia has been related to activation, migration and actin rearrangement in these cells, the same intracellular pathway in neurons has been shown to be necessary for activity-dependent excitatory synaptic rearrangement such as LTP or LTD (44). If neurons have the capability of expressing chemokine receptors, then activation of these receptors may promote synaptic plasticity by this very well documented intracellular mechanism. Indeed, it has been shown that hippocampal neurons, at least in culture, express several chemokine receptors including CX_3CR1 (45). Administration of fractalkine to hippocampal neurons produces transient intracellular calcium increases and inhibition of glutamatergic excitatory postsynaptic currents (45). Fractalkine was able to inhibit the frequency but not the amplitude of the postsynaptic currents. It was suggested that fractalkine (but not other chemokines) can regulate the release of glutamate at the synapses.

In the same study, many other chemokines were also tested with varying results to that observed for fractalkine. For instance, fractalkine and macrophage-derived chemokine (MDC) produced a time-dependent activation of extracellular response kinases (ERK) -1 and 2 (42). As mentioned earlier, ERKs are activated in neurons in response to glutamatergic signaling and are necessary for synaptic plasticity that have important implications for cognitive and emotional brain functions. In contrast to the studies with MHC, TNFα and IL-1ß KO mice, there are no reports on behavioral performance of mice lacking chemokines or their receptors. There are instead, some indirect indications that chemokines affect at least cognitive function. For example, in mice infected with Borna disease virus, impaired performance in the water

maze test that is a measure of both learning and memory was correlated with increased levels of the α-chemokine IP-10 (46). Furthermore, no increases in IL-1ß or TNFα were observed in this model. Moreover, inhibition of LTP by another α-chemokine, interleukin-8 (IL-8), was reported in rat hippocampal slices (47). Although these data are fragmentary regarding the implications on cognitive and emotional functions, they indicate a similar pattern to that predicted by the neuronal cell culture studies.

In summary, inflammatory genes expressed in the brain such as class I MHC, TNFα, IL-1ß and fractalkine have all been shown to be involved in activity-dependent structural synaptic remodeling of the glutamatergic synapsis. This process might involve not only neuronal cells but also resting microglia and astrocytes in close anatomical relationship with the synapse. Finally, this process may be independent of immune activation caused by foreign pathogens or tissue trauma. If these observations are correct, there is the possibility that diseases of the nervous system involving the glutamatergic synapse may be related to dysregulation of the neural-immune interaction at this synapse. We will present next some clinical data indicating the plausibility of this hypothesis.

6. CYTOKINES IN THE CEREBROSPINAL FLUID OF PSYCHIATRIC PATIENTS.

The involvement of glutamatergic neurotransmission in the etiology of psychiatric illness has been very well established (48,49). Alterations in specific glutamatergic circuits and components of the glutamatergic neurotransmission have been revealed in cases of schizophrenia and mood disorders. Pharmacological, imaging, post-mortem and animal model studies supports a role for altered NMDA receptors in several manifestations of these diseases (48,49,50,51). Furthermore it has been proposed that an interaction of the glutamatergic synapse with other neurotransmitter systems, in particular the GABAergic transmission, may be accountable for the effects of antidepressants targeting the glutamatergic system (48). Interestingly, this idea has been based in a very well established finding from post-mortem studies indicating decreased glial cell number and density in depressed individuals. Since glial cells provide the major pathway for both neuronal glutamate and GABA synthesis, decreased glial function has been linked to the altered amino acid neurotransmission observed in depressed individuals (48). As previously mentioned, immune genes play an important role in the interaction of neurons and glial cells, in particular at the glutamatergic synapse. However, studies analyzing the relationship between immune activation and mood disorders have been focused on peripheral activation of immunity, but no studies have been done evaluating the role of immune genes in the neuropathology of psychiatric illnesses. There are, however, some indications that immune genes in the brain may be dysregulated in cases of psychiatric diseases. Increased IL-1ß and decreased IL-6 was reported in the cerebrospinal fluid (CSF) of 13 unmedicated patients with severe depression (26). In another study, elevated IL-6 was reported in the CSF of 23 schizophrenic patients (52). Moreover, increased IL-6 was also reported in another study evaluating patients with schizophrenia (27). There has been a recent report that failed to detect IL-6 alterations in the CSF of depressed patient (53).

Another set of data indicating the potential involvement of inflammatory genes in psychiatric illnesses has been reported on gene expression microarrays of postmortem human tissue. By screening 1200 genes in the frontal cortex of patients suffering from bipolar disorders, several receptors for immune genes were found to be differentially regulated compared to control samples (54). Those included interferon alpha/beta receptor, interleukin-8 receptor and granulocyte-macrophage colony-stimulating factor receptor among others. In a more recent study comparing the gene expression profiles in the frontal cortex of bipolar patients with those that suffered from major depression or schizophrenia, interferon gamma-inducible protein 16 (IFI-16) was found up regulated in bipolar and depressed patients but not in schizophrenics (55). Interestingly, this protein exerts its known immunomodulatory effects through regulation of p53 activity, a key tumor suppressor protein necessary in the signal cascade activated by TNFα (56,57). Although the clinical data presented here is not sufficient to draw any conclusions and in some cases is contradictory, it suggests that there may in fact be some neural-immune dysregulation underlying at least some aspects of mental illness (58). Indeed, the clinical association between depression and rheumatoid arthritis (59) and the inverse correlation between schizophrenia rheumatoid arthritis (60) have been long noted but poorly understood.

In summary, there is substantial evidence to support a role for pro-inflammatory genes in synaptic plasticity and activity-dependent arrangements of neural circuits in addition to their functions in brain inflammatory processes. There is, however, a need to establish the specific mechanisms by which dysregulation of this interaction might promote altered neural and glial function affecting specific neurochemical systems. This may provide new understanding of the causes of mental disorders and open new therapeutic strategies for the treatment of these diseases.

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