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A Role for Microglia in Repeated Stress-Induced Functional Changes in the Medial Prefrontal Cortex in Rodents

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Abstract

In rodents, repeated stress alters the function of the medial prefrontal cortex (mPFC), associated with dendritic atrophy and synaptic loss, leading to emotional and cognitive changes. Roles for monoamines, namely dopamine and noradrenaline, have been implicated in this process. Thus, dopaminergic activity in the mPFC confers stress resilience, and repeated social defeat stress attenuates this dopaminergic activity, leading to social avoidance. In contrast, the activation of adrenergic receptors promotes emotional and cognitive changes induced by repeated stress. Especially, adrenergic signaling in the mPFC during stress exposure is critical for a decline in an mPFC-dependent behavioral performance after repeated stress. Repeated stress activates microglia in multiple brain areas, and recent studies have suggested a link between microglial activation and monoaminergic functions in repeated stress. For example, blockade of β-adrenergic receptors impairs microglial activation by repeated stress. It has also been suggested that stress-activated microglia release prostaglandin (PG) E_2, an inflammation-related molecule that attenuates mPFC dopaminergic activity and causes behavioral depression. Recent studies in non-stressed mice have shown that microglial processes can directly contact with neuronal structures in an activity-dependent manner, leading to structural remodeling of neurons. Since repeated stress activates microglia in multiple brain areas including the mPFC, we hypothesize that microglia may play direct and indirect roles in stress-induced alteration in mPFC functions.

Keywords: Stress; Medial prefrontal cortex; Dopamine; Prostaglandin E_2; Microglia

Abbreviations: mPFC: Medial Prefrontal Cortex; RGC: Retinal Ganglion Cell

Introduction

Excessive or prolonged exposure to stress leads to emotional and cognitive changes, and is a common risk factor for psychiatric disorders, such as major depression. To understand the mechanism underlying neural changes associated with repeated stress, many studies using rodent models of repeated stress have been performed and found structural alterations induced by repeated stress in various brain areas, especially dendritic atrophy, a decrease in the volume of dendritic spines and synaptic loss in pyramidal neurons in the medial prefrontal cortex (mPFC) [1-4]. Previous findings have shown the functional importance of such structural remodeling of mPFC neurons. For example, dendritic atrophy in mPFC neurons correlates to stress-induced decline in mPFC function as measured by attentional set shifting [2], and rapid antidepressant actions of NMDA receptor antagonists in chronic mild stress are associated with the recovery from deficits in spine density and synaptic functions in the mPFC [5]. Further, GATA1, a transcription factor that induces the loss of spines and dendrites in primary neurons, functions in mPFC neurons to cause repeated stress-induced anhedonia, as measured by a reduction in sucrose consumption [6]. Stress-induced structural remodeling in the mPFC also appears to be clinically relevant. Thus, brain imaging and post-mortem brain studies have shown a reduction in the mPFC volume in depressive patients [7], and the deep brain stimulation targeting the white matter adjacent to this region ameliorates depressive symptoms in half of treatment-resistant patients [8]. However, the mechanism underlying structural and functional alterations in the mPFC in stress and depression remains elusive.

Several groups including ours have shown a role for dopamine and noradrenaline in the mPFC [9-12] and inflammation-related molecules, such as IL-1β [11,13,14] and prostaglandin (PG) E_2 [9], in behavioral changes induced by repeated stress. It has been suggested that repeated stress activates microglia as a cellular source of inflammation-related molecules [9,11]. Since PGE_2 mediates the effect of repeated stress in attenuating mPFC dopaminergic activity [9], it is suggested that microglia regulate mPFC functions indirectly through PGE_2 and dopamine signaling. On the other hand, recent studies using in vivo brain imaging and electron microscopy, combined with mice deficient in microglial functions, have suggested a direct action of microglia on neurons for their functional and structural remodeling [15-19]. Since several groups including ours have reported that repeated stress induces microglial activation in various brain areas including the mPFC [9,11,20-22], it is speculated that stress-activated microglia can directly affect functions of mPFC neurons. In this review, we will summarize these recent findings, and will hypothesize direct and indirect actions of microglia on mPFC neurons for emotional and cognitive changes induced by repeated stress.

A Role for Monoaminergic Signaling in the mPFC in Repeated Stress

Dopaminergic neurons in the midbrain project to multiple brain areas including the dorsal and ventral striatum and the prefrontal cortex, and each of these dopaminergic projections exerts a distinct function. It has been suggested that acute exposure to mild stressors, such as electric foot shock and social defeat, preferentially augments dopamine release in the mPFC, as measured by dopamine turnover,

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a biochemical index for local dopamine release [23]. Recent studies showed that repeated social defeat stress in mice reduces dopaminergic response to stress in the mPFC [9] and the firing rate of dopamine neurons projecting to the mPFC [10]. Further, it was reported that pharmacological depletion and optogenetic inactivation of the dopaminergic pathway projecting to the mPFC facilitate the induction of social avoidance by repeated stress [9,10]. These results demonstrate that dopaminergic activity in the mPFC confers resilience to stress, and that repeated stress attenuates this dopaminergic activity, leading to social avoidance. Since it was reported that mice lacking either dopamine D1 or D2 receptor show the reduced number of basal dendrites in mPFC pyramidal neurons [24], it is plausible that the dopaminergic attenuation associated with repeated stress underlies structural remodeling of mPFC neurons, such as dendritic atrophy and synaptic loss.

Besides a role for dopamine, recent studies have also shown a role for noradrenaline in behavioral changes induced by repeated stress [11,12]. Thus, systemic administration with propranolol, a blocker for β-adrenergic receptors, reduces elevated anxiety induced by repeated social defeat stress, as measured by the light-dark box test [11]. Furthermore, local injection of a cocktail of α1, β1 and β2 adrenergic antagonists to the rat mPFC blocked chronic stress-induced decline in the performance of attentional set shifting, an mPFC-dependent cognitive task [12]. Therefore, noradrenaline and dopamine in the mPFC appear to play opposite roles in regulating stress susceptibility, though it is important to analyze and compare roles for these monoamines in the same behavioral platform in the future.

A Role for Inflammation-related Molecules in the Brain in Repeated Stress

Clinical studies frequently reported an elevation in inflammation-related molecules, such as cytokines and prostaglandin (PG) E_2, in blood samples taken from depressive patients [25,26]. Recently, several groups have reported that add-on treatment with non-steroidal anti-inflammatory drugs that inhibit PG synthesis augments a therapeutic effect of conventional antidepressants [27-29], suggesting a role for inflammation-related molecules in the pathogenesis of depression. In rodents, it has been shown that exposure to stress increases the level of inflammation-related molecules, such as IL-1β and prostaglandin E_2 (PGE_2), in the brain [30-32]. Later studies using genetically engineered mice have shown a critical role for these molecules in behavioral changes induced by repeated stress [9,11,13,14]. Thus, mice deficient in IL-1 receptor type I and EP1, a PGE receptor subtype, fail to show depression-like and anxiety-like behaviors after repeated stress. These inflammation-related molecules are thought to act inside the brain, since transgenic mice overexpressing IL-1 receptor antagonist selectively in the brain fail to show a reduction in sucrose consumption by chronic mild stress [13]. It was reported that IL-1 signaling can directly suppress the proliferation of neural stem cells *in vitro*, and is critical for stress-induced reduction in adult neurogenesis in the hippocampus *in vivo* [13,14]. On the other hand, mice deficient in EP1 lack the attenuation of dopaminergic activity in the mPFC with repetition of stress [9], suggesting a role for PGE_2-EP1 signaling in stress-induced attenuation of mPFC dopaminergic activity. Consistently, EP1 stimulation augments inhibitory synaptic inputs to dopamine neurons in acute midbrain slices [33]. Since blockade of dopamine receptor antagonists restores stress-induced social avoidance in these mice [9], PGE_2-mediated attenuation of mPFC dopaminergic activity appears to be critical for induction of social avoidance by repeated stress. Combined with a role for IL-1 signaling in suppressing adult neurogenesis, inflammation-related molecules in the brain play multiple roles in behavioral changes induced by repeated stress.

A Role for Microglia as a Source of Inflammation-Related Molecules in Repeated Stress

As described above, inflammation-related molecules, such as PGE_2 and IL-1β, are critical for behavioral changes induced by repeated stress in mice. Accumulating evidence indicates a role for microglia as a primary source of these molecules in repeated stress. For example, IL-1β mRNA was detected in CD11b-positive cells containing microglia, but not in other cells, isolated from the adult rat hippocampus [34]. It was reported that repeated social defeat stress in mice increases IL-1β mRNA in microglia [11]. PGE_2 derived from microglia has also been implicated in behavioral changes induced by repeated stress, since genetic deletion or pharmacological inhibition of cyclooxygenase-1, an enzyme responsible for PGE_2 synthesis enriched in microglia, abolishes social avoidance induced by repeated social defeat stress [9]. Therefore, it is suggested that microglia regulates mPFC functions indirectly through PGE_2-EP1 signaling, which in turn attenuates mPFC dopaminergic activity.

Consistent with a role for microglia in repeated stress, repeated stress appears to activate microglia in multiple brain areas, as observed by an increase in Iba-1 immunoreactivity in microglia and its enhanced ramification after repeated stress [9,11,20-22]. Interestingly, systemic administration with propranolol, an antagonist for β-adrenergic receptors, blocks microglial activation in several brain areas including the mPFC [11], suggesting a role for noradrenergic signaling in microglial activation upon stress. IL-1 receptor signaling is also critical for microglial activation by repeated stress, since genetic deletion of IL-1 receptor type I abolish an increase in Iba-1 signals in microglia as well as behavioral changes induced by repeated stress [11]. Since IL-1β is produced in microglia and its mRNA level is increased after repeated stress, it is plausible that IL-1 signaling constitutes a positive feedback loop for microglial activation by repeated stress.

Do Stress-activated Microglia Directly Act on mPFC Neurons for their Functional Plasticity?

Several groups including ours have reported that repeated stress activates microglia in various brain areas including mPFC [9,11,20-22]. These findings have led us to speculate that stress-activated microglia might have a direct action on mPFC neurons for their functional plasticity. Indeed, recent studies using two-photon confocal imaging and electron microscopy suggest that microglia directly contact with synaptic structures and contribute to activity-dependent synaptic remodeling during and after development [15,19]. For example, in the visual cortex of juvenile mice, light deprivation increases the number and the area of microglial contacts with synaptic apparatuses, especially synaptic clefts [15]. About a half of dendritic spines shrink during microglial contacts, whereas most dendritic spines grow without microglial contacts. It was also reported that microglial processes contact synaptic apparatuses in adult visual cortices in an activity-dependent manner [19]. Interestingly, when cerebral ischemia was transiently induced by the occlusion of middle cerebral artery in the adult brain, some synapses in ischemic cortical areas disappeared after prolonged microglial contact [19]. These studies suggest a role for microglia in eliminating synaptic structures in both physiological and pathological conditions.

Several studies have implicated a role for the phagocytosis of neuronal components by microglia in structural remodeling of neurons. For example, light deprivation increases the inclusion of synaptic apparatuses in microglia in the juvenile visual cortex [15]. Microglia in the hippocampus contains presynaptic and postsynaptic structures during postnatal development [16]. A functional role for the phagocytosis of neuronal components by microglia has been most clearly shown in the dorsal lateral geniculate nucleus during postnatal development [17]. In this study, fragments of axons of retinal ganglion cells (RGC) were observed in lysosomes of microglia, suggesting that microglial cells engulf RGC axons to be eliminated. Notably, genetic deletion of complement protein C3 and its receptor CR3 abolishes the engulfment of RGC axons by microglia as well as the elimination of RGC axons during development.

As described in the Introduction, studies using rodent stress models have shown that repeated stress induces dendritic atrophy and synaptic loss of pyramidal neurons in the mPFC [1-4]. Since the removal of cells or cell components should be coupled to their clearance by phagocytosis for the tissue homeostasis in theory, microglia activated by repeated stress could contribute to the removal of dendrites and synapses in mPFC neurons. It was reported that chronic mild stress induces the expression of β1-integrin (CD29) in microglia [22]. Given a previous report that β1-integrin is involved in the phagocytosis of fibrillar β-amyloid by primary microglial cells [35], the phagocytic activity of microglial cells could be enhanced by repeated stress. However, whether stress-activated microglia engulf dendrites and synapses remains to be examined. As an alternative mechanism, activated microglia secrete many proteases, and some of these proteases, such as tissue plasminogen activator and matrix metalloproteases, have been implicated in synaptic and behavioral plasticity [36]. Interestingly, it was reported that mice lacking either tissue plasminogen activator or its substrate, plasminogen, do not show repeated restraint stress-induced decline in spatial learning, nor stress-induced loss of dendritic spines in the hippocampus [37]. These studies provide multiple testable hypotheses for future investigations about direct and indirect actions of microglia on mPFC functions in repeated stress.

Conclusions

In this review, we have summarized a role for dopamine and noradrenaline in the mPFC and inflammation-related molecules, especially IL-1β and PGE_2, derived from microglia. As described, our previous findings suggest that stress-activated microglia regulate mPFC function indirectly through PGE_2-mediated attenuation of dopaminergic activity. On the other hand, since repeated stress activates microglia in multiple brain areas including the mPFC, we speculate that stress-activated microglia may also directly act on mPFC neurons in their vicinity, leading to structural and functional alterations in the mPFC. To dissect these possibilities, it is crucial to manipulate specific molecular and cellular events in microglia and to observe the effect of such manipulations in structural and functional changes in the mPFC induced by repeated stress.

Whereas a reduced volume of the mPFC in depressive patients suggests some structural remodeling of this brain structure, microglial activation has rarely been reported in the brains of depressive patients. Since IL-1β, a molecule primarily derived from microglia, is increased in the cerebrospinal fluid during acute depressive episodes [38], microglial activation might be associated with exacerbation of depressive symptoms. On the other hand, studies using brain imaging and post-mortem brains reported microglial activation in other types of psychiatric disorders, such as schizophrenia [39] and autism [40]. A question about whether such microglial activation underlies the pathogenesis of psychiatric disorders remains for future studies.

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