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The formative role of microglia in stress-induced synaptic deficits and associated behavioral consequences

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ABSTRACT

Psychological stress can precipitate depression, and emerging preclinical data suggest a link between stress-induced alterations in microglia function and development of depressive-like behaviors. Microglia are highly dynamic, and play an integral role in maintaining neuronal homeostasis and synaptic plasticity. In this capacity, microglial dysfunction represents a compelling avenue through which stress might disrupt neuronal integrity and induce psychopathology. This review examines preclinical and clinical postmortem findings that indicate microglia-neuron interactions contribute to stress-induced synaptic deficits and associated behavioral and cognitive consequences. We focus on pathways that are implicated in microglia-mediated neuronal remodeling, including CSF1-CSF1R, CX3CL1-CX3CR1, and CD11b (CR3)-C3, as well as purinergic signaling via P2RX7 and P2RY12. We also highlight sex differences in stress effects on microglia, and the potential for microglia in the development of sex-specific treatments for depressive disorders.

1. Introduction

Depression is a heterogeneous mood disorder marked by negative affect, anhedonia, somatic distress, and cognitive impairment [1,2]. It is often chronic and pernicious, and carries a significant global burden – approximately one in four women and one in six men will suffer from depression during their lifetime [3]. Dysfunction of corticolimbic brain regions critical in emotion and cognition are implicated in depression. For instance, post-mortem findings indicate reduced neuronal complexity [4], synaptic loss [5], and – more recently – microglial perturbations [6,7] in prefrontal cortex (PFC) of depressed individuals.

Psychological stress can precipitate depression [8], and preclinical models demonstrate a significant link between stress, microglia, and depressive-like behaviors [9–11]. Microglia are highly dynamic, and play an integral role in maintaining neuronal homeostasis and synaptic plasticity [12]. As such, microglial dysfunction represents a compelling, novel pathway through which stress might disrupt neuronal integrity and induce psychopathology. In this review, we will discuss stress effects on microglia, microglial signaling, and microglia-neuron interactions in corticolimbic brain regions, with a specific focus on medial PFC (mPFC). Moreover, we will summarize important sex differences in microglia function, microglia-mediated neuronal remodeling, and their potential implications in depression.

2. Microglia modulate neuronal function: and vice versa

Microglia are the tissue-resident macrophages of the central nervous system [13]. These innate immune cells are distributed throughout the brain, and function as a critical line of defense against injury and pathogenic insult [14]. Ongoing research has outlined the physiological role of microglia, and their contributions to brain homeostasis and behavior [15]. Microglia are diverse in shape and function, and can vary dramatically across development, brain region [16,17], and sex [18–21]. Moreover, these cells are exquisitely sensitive to perturbations in their microenvironment. Using highly ramified, constantly surveying processes, microglia respond to hormones, cytokines, chemokines, neurotransmitters, and purines, among other homeostasis-relevant signals [22–24].

On sensing a perturbation, microglia shift their morphology, reorienting and extending their processes toward the disturbance. In respect to neurons, this often involves contact with neuronal elements, including pre- and post-synaptic structures. At the level of the synapse, microglia can modulate neurotransmission and regulate synaptic plasticity [25]. In fact, microglial processes are able to envelop and prune dendritic spines [26,27] and sculpt dendritic architecture [28]. While this is a normal function, aberrations in microglial surveillance and phagocytosis (e.g. under- or over- pruning of synaptic elements)

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contribute to neuronal dysfunction and disease; indeed, you can have too little or too much of a good thing [29].

3. The neuroimmune milieu in health, stress, and depression

Several lines of evidence indicate a link between peripheral immune signals and depression, including altered cytokine and acute phase protein levels in subsets of depressed individuals [30] and depressive-like symptoms that are observed following immune stimulation [31,32]. In addition, administration of cytokine inhibitors is effective in reducing depressive symptoms in patients with cancer, autoimmune disorders, and treatment-resistant depression [33,34]. In line with these findings, stress perturbs peripheral immune factors, increases circulating granulocytes and monocytes, and shifts immune cell distribution throughout the body [35,36]. Further, chronic stress promotes activation of the inflammasome, NLRP3 [37], upregulation of transcription factors associated with immune activation, including NF-κB [38], and expression of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-10, amongst other cytokines [37,39].

Cytokines released in the periphery are able to cross the blood-brain-barrier through saturable transport systems, conduits of peripheral immune system-to-brain communication. Moreover, cytokines are synthesized *de novo* by brain endothelial cells, microglia, astrocytes, and even neurons [40]. Although typically associated with inflammation, cytokines have physiological roles in neurotransmission, synaptic maintenance, and trophic factor release [41,42]. Therefore, dysregulated (either decreased or increased) cytokine signaling may contribute to neurobiological and behavioral dysfunction. For instance, TNF-α and IL-1β increase levels of neuronal and astrocytic glutamate transporter (GLT)-1 under homeostatic conditions [43], and basal, glia-derived TNF-α is important in synaptic scaling [44]. Moreover, TNF-α is required for normal, cognitive-behavioral development [45]. Whereas homeostatic levels of TNF-α maintain the neuronal milieu, heightened TNF-α stimulates excessive glutamate release, neuronal dystrophy, and reduced neurogenesis [46], which may underlie inflammatory-related behavioral and cognitive consequences.

Consistent with this idea, chronic restraint stress-induced inflammatory signaling (TNF-α, IL-1β IL-6) was associated with increases in glutamate and reductions in GABA levels in mPFC and hippocampus [47]. Notably, inhibition of TNF-α signaling with infliximab, (TNF-α antibody), attenuates stress effects on anxiety- and depressive-like behaviors [48]. Together, these studies suggest that inflammatory signaling may contribute to stress-linked psychopathology by modulating glutamate. Although this pathway is compelling, alterations in cytokine expression vary significantly between studies, and appear to be stressor- and brain region-dependent. For instance, chronic unpredictable stress – but not restraint – *reduces* TNF-α, IL-1β, and IL-6 transcript in mPFC [49]. Indeed our recent work showed that chronic unpredictable stress did not alter IL-1β and TNF-α transcript in mPFC, however, microglia isolated from mPFC showed robust *reductions* in IL-1β and TNF-α expression [11]. Together, these data suggest a different pattern of stress-induced cytokine alterations in microglia versus other neuronal, glial, or vascular cells. Further studies are needed to determine the role of cytokines in the neurobiology of stress and how vasculature-glia-neuron signaling mediates these responses.

4. Phenotypic changes in microglia following chronic stress

Stress alters microglial morphology, functional profile, and microglia-neuron interaction in corticolimbic circuitry (see Fig. 1). For instance, various chronic restraint paradigms (30 min – 6 h/day, 14–21 days) increase microglial area, as measured using Iba-1 immunoreactivity, in mPFC [50,51], basolateral amygdala, and hippocampus [52]. Likewise, chronic unpredictable stressors [10,37,53] and social defeat [11,54,55] increase the surface area of Iba-1 + microglia in these same regions. More refined studies of microglial morphology indicate stress-induced increases in ramification and branch length in mPFC [56] are associated with deficits in working memory [51] and depressive-like behaviors [11]. Notably, treatment with minocycline, a tetracycline antibiotic that dampens microglial activity, blocks working memory deficits in chronic restraint stress [51].

Microglia can shape behavior by remodeling dendritic architecture and synaptic connectivity [57]. Stress leads to profound dendritic atrophy [58] and dendritic spine loss [59] in pyramidal neurons in mPFC, amongst other stress-susceptible brain regions. Several mechanisms contribute to these neurobiological responses (e.g. glucocorticoids, NMDA receptors); however, recent findings indicate that neuron-derived signals direct microglia function and subsequent structural remodeling of neurons. In fact, chronic unpredictable stress increases microglia-neuron contact and engulfment of neuronal elements (e.g., pre- and post-synaptic structures) by microglia in mPFC [11] and hippocampus [60]. These microglial actions reduce markers of synaptic plasticity in these regions, inducing depressive-like behaviors [11,60].

Stress-linked alterations in microglial morphology are paralleled by increased expression of CX3CL1-CX3CR1 alongside CSF1-CSF1R, both pathways critical in microglia-neuron communication and chemoattraction [11]. Whereas CX3CL1-CX3CR1 signaling is associated with microglial inhibition, CSF1 promotes microglial proliferation and survival. Viral-mediated knockdown of CSF1 in mPFC attenuates stress effects on microglial morphology, reduces microglia-neuron interactions, and prevents depressive-like behaviors [11]. In contrast, studies using mice lacking CX3CR1 show that microglia display dampened phagocytic capacity, which limited stress-induced synaptic plasticity deficits in hippocampus [60,61]. Together, these findings indicate that CX3CL1-CX3CR1 and CSF1-CSF1R have an integral role in stress-induced microglia-neuron interaction, neuronal remodeling, and behavioral consequences.

Additional signals may facilitate microglia-mediated neuronal remodeling and associated behavioral or cognitive consequences. Notably, the complement cascade (e.g. complement component 3; C3) is critical in microglia-mediated synaptic pruning during development [27]. Chronic stress upregulates C3 and microglial complement receptor C3 (CR3 or CD11b) expression in mPFC [37,62]. Further studies showed that mice lacking C3 have attenuated stress-induced social withdrawal, whereas viral-mediated upregulation of C3 in the PFC – independent of stress – reduced social interaction [62]. These data, in accord with a known role for complement in synaptic tagging [63], suggest that CD11b-C3 may be important in microglia-mediated neuronal remodeling and synaptic deficits following chronic stress. However, further studies will need to address this hypothesis.

Alongside chemokine and complement pathways, alterations in neuronal activity and purinergic signaling may drive stress effects on microglial function. Microglia are responsive to neuronal activity, and stress-induced neuronal activity may provoke increased surveillance of synaptic structures [25]. In fact, recent data from our lab suggests that chronic stress-induced neuronal activity contributes to microglia-mediated neuronal remodeling in mPFC, and behavioral dysfunction (unpublished data). Heightened neuronal activity is associated with an increase in extracellular purines. In particular, activity-dependent release of synaptic adenosine triphosphate (ATP) plays a pivotal role in microglial attraction and process convergence [64,65]. In this context, purinergic signaling may reorient microglia toward neurons with heightened excitatory neurotransmission, and promote microglia-neuron interactions, synaptic pruning, and – in turn – behavioral or cognitive consequences. Chronic stress increases extrasynaptic ATP, and increases expression of the purinergic receptor P2RX7 on microglia in numerous stress-susceptible brain regions [66]. Interestingly, P2RX7 antagonism prevents stress-induced behavioral deficits and chronic administration of ATP promotes development of depressive-like behaviors [66–69]. This may have translational relevance as a recent meta-analysis indicates that a polymorphism in the P2RX7 allele is associated

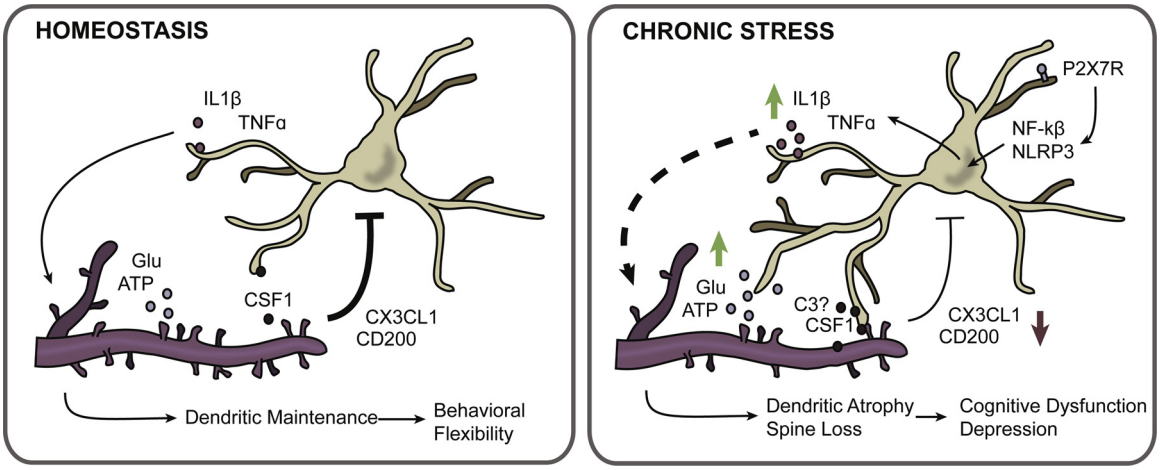

Fig. 1. Microglia-neuron interactions in homeostasis and chronic stress. Left: Microglia interact heavily with neurons to regulate neurotransmission, dendritic structure, and neural homeostasis. These interactions are mediated by various signals, including cytokines, neurotransmitters, and neuron-microglia inhibitory factors, such as CX3CL1 and CD200. Tonic levels of CSF1 maintain microglial survival and process surveillance. Right: Chronic stress induces neuronal activation, heightened glutamatergic signaling, and extracellular ATP release in mPFC. Engagement of NF-κB (transcription factor) and NLRP3 (inflammasome) increase cytokine expression. These cytokines can signal neurons and astrocytes, and may promote monocyte trafficking to the brain. Neuronal glutamate-microglial NMDA and neuronal ATP-microglial P2RY12/P2RX7 signaling attract microglia processes. Correspondingly, reductions in inhibitory CX3CL1-CX3CR1 and CD200-CD200R pathways encourage increased microglial scanning. Chronic stress increases neuronal CSF1, which provokes microglia-mediated neuronal remodeling. Synaptic engulfment may be mediated by the CD11b(CR3)-C3 pathway. Altered microglia functions contribute to neuronal dystrophy and synaptic deficits in the PFC and hippocampus, leading to cognitive dysfunction and depressive-like behavior.

with depression [70]. It should be noted that other purinergic receptors expressed by microglia, including P2RY12 and P2RY6, are implicated in synaptic plasticity [71] and microglial phagocytosis [24,72] following ATP stimulation. Given the significant role of purinergic signaling in microglial process convergence, studies addressing stress effects on other purine receptors, including P2RY12 [73], as well as purine-mediated microglia-neuron contact are warranted.

5. Sex-dependent stress effects on microglia and microglia-neuron interactions

Numerous stress-linked psychological disorders, including most anxiety disorders and depression, occur more frequently in women. For instance, women are three times as likely to suffer from depression following a stressful life event [74]. Moreover, women report greater depressive symptom severity, including fatigue, sympathetic arousal, and somatization, as compared to men [75,76]. These differences in men and women may have a neurobiological basis. Recent studies revealed sex-specific molecular changes in the dorsolateral PFC of depressed individuals [7,77]. In particular, pathway analyses show increased expression of microglia markers that correspond with reduced synaptic markers in depressed males, while females show decreased expression of microglia markers and increased markers associated with neuronal and synaptic function [7]. Together, these findings suggest divergent pathways toward psychopathology in males and females, and need for sex-specific interventions in depression [78].

Emerging preclinical data indicate that microglia play a critical role in shaping sex-specific neuronal functions and behavior [20,57]. In addition, recent work shows that microglia in males and females have divergent transcriptional and translational profiles, which contribute to varied functional responses following insults [19,79]. Thus, it isn't surprising that chronic stress elicits sex-specific alterations in microglial phenotypes that contribute to divergent neurobiological and behavioral responses. Indeed chronic stress increases microglial activation in mPFC in males [52,56], but it produces either no change- or microglial atrophy- in females [11,80]. Moreover, chronic stress induces synapse loss and dendritic atrophy in mPFC in males [58,59], yet either no change- or dendritic growth- in females [81,82]. In this context, chronic stress in mice increases microglia-neuron interaction and synapse phagocytosis in the mPFC of males, leading to more pronounced depressive-like behaviors as compared to females [11]. Despite these results, there are limited studies that have explored mechanisms underlying sex-dependent differences in microglia function. It is likely that gonadal hormones have a pivotal role in shaping microglia responses to stress. Indeed, recent findings indicate a necessary role for estradiol in stress-induced microglial atrophy in females [83]. In addition to gonadal hormones, chromosomal sex and varied neurodevelopment likely set the stage for sex differences in microglia-neuron interactions and microglial responsivity. In all, these studies provide compelling evidence that sex-specific microglial phenotypes are critical mediators of chronic stress-induced neurobiological deficits and associated behavioral consequences.

In addition to mPFC, there are pronounced sex differences in chronic stress effects on microglia and expression of immunoregulatory factors in orbitofrontal cortex, basolateral amygdala, and hippocampus [morphological atrophy in all regions in males but not females; [84]]. These alterations lead to coupling of microglial morphology across corticolimbic circuitry in males (i.e. increased homogeneity) yet uncoupling in females (i.e. decreased homogeneity), suggesting that stress-linked changes in microglia may contribute to sex differences in neuronal responses in a brain region-specific manner. In line with these data, Fonken et al. [85] report sex differences in acute stress-induced neuroimmune priming and microglial function in hippocampus. Male and female rats exhibit comparable pro-inflammatory cytokine responses in the hippocampus following immune stimulation and tail shock stress. Notably, they observed that hippocampal microglia primarily drove cytokine responses in males, while cytokine responses in hippocampal microglia were attenuated in females. These findings suggest that different neuroimmune pathways contribute to exaggerated neuroinflammation in the hippocampus of males and females following stress exposure, and provide impetus to examine sex differences in stress effects on other neuroimmune cells (e.g. astrocytes, vascular endothelial cells).

These neurobiological differences in rodents align with sex-specific patterns in frontal cortex in depression [7,77]. However, a contradictory behavioral pattern exists: whereas there are greater rates of depression in women, female rodents rarely show stress-induced deficits in behavior. This is likely due to a number of broader issues,

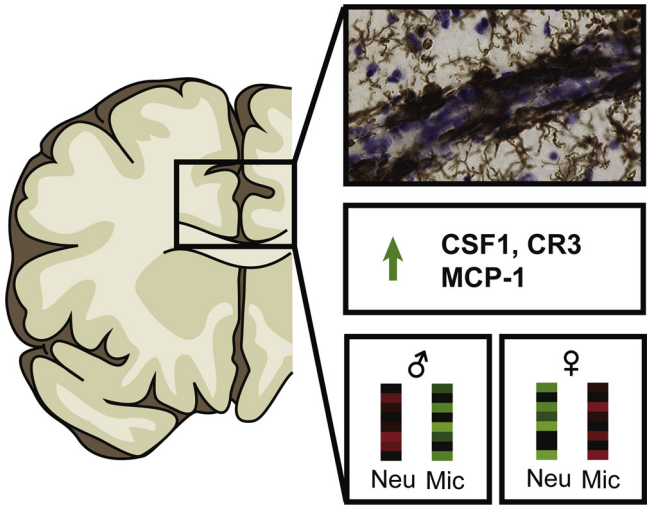

Fig. 2. Evidence of altered microglia phenotype and function in PFC of depressed individuals: Post-mortem findings. Top panel: histological studies indicate heightened morphological priming of microglia, and increased perivascular microglia in depressed suicides in ACC [6] and PFC [95]. Microglial image adapted- and reproduced- from Torres-Platas, Cruceanu [6]. Middle panel: gene expression analyses reveal increased transcription of microglia proliferation-associated factors in depression, including monocyte chemoattractant protein (MCP)-1 in ACC [6] and CSF1 in PFC [11], and signals implicated in synaptic tagging and microglia-mediated synaptic pruning in PFC in depressed suicides [i.e. C3; 62]. Bottom panel: RNA-sequencing data suggest heightened microglia-associated gene expression and reduced neuron-associated transcript in PFC in depressed males, yet the opposite in depressed females: decreased microglia-associated gene expression and heightened neuron-associated transcript in PFC [7].

including a lack of experiments addressing the enduring consequences of stress, limited studies assessing females in biomedical research, and the development of relatively few behavioral assays appropriate for female rodents [86]. Despite contrasting behavioral phenotypes, findings point toward a role for microglia in the sex-specific neurobiological effects of stress, and suggest that microglia may contribute to stress-linked psychopathology.

6. The imprint of chronic stress on microglia: implications for aging and neurodegenerative disease

Chronic stress is a putative risk factor for numerous aging-associated disorders, including cognitive decline and neurodegenerative disease [87]. Many of these conditions are marked by neuronal dysfunction and aberrant microglial activation [88]. In line with this, recent findings suggest that there may be long lasting- or compounding-effects of stress on microglia, including heightened responsivity to subsequent psychological stressors or inflammatory signals [89,90]. For instance, repeated social defeat and chronic unpredictable stress increase microglial activation in various corticolimbic brain regions, and induce anxiety- or depressive-like behaviors, and cognitive impairment [53,89,91]. In these models, stress-induced alterations in microglia morphology and gene expression are generally resolved following a recovery period (2–4 weeks after stress). However, prior exposure to chronic stress increases stress responsivity, with subsequent acute stress exposure leading to significant microglial activation and rapid re-instatement of behavioral deficits. Interestingly, recent work indicates that microglial ablation (CSF1R antagonist-induced reduction of ~95% of population) during chronic stress does not prevent subsequent stressor-induced anxiety-like behavior, whereas ablation just prior to a secondary stressor does [92]. As microglia repopulate from the ~5% of cells remaining post-ablation, these data suggest that surviving microglia maintain the imprint of stress exposure and that increased stress responsivity is perpetuated throughout microglial repopulation. Together, these reports indicate numerous, long-term effects of stress on microglial responsivity, alongside a critical role for microglia in re-establishment of behavioral deficits following subsequent stressors.

Given the link between glia and brain homeostasis, it is interesting to speculate that microglia may be involved in stress recovery, and that stress-sensitized microglia may contribute to deleterious effects on neuronal function over time. As noted, chronic stress induces dendritic atrophy and spine loss in mPFC [58,59]. During stress recovery, neurons undergo significant remodeling, which includes dendritic outgrowth at 7 days post-stress, with a return to unstressed dendritic branch length by 10 days [82]. Microglia can engulf and prune dendritic elements, as well as stimulate dendritic outgrowth through direct contact [29,93] and the release of neurotrophic factors [94]. Therefore, microglia act as a cellular intermediate to promote neuronal remodeling during- and after- stress. In this regard, microglial sensitization could contribute to rapid, aberrant neuronal modulation, and may represent a susceptibility factor for stress-linked cognitive and behavioral dysfunction later in life. Additional studies exploring neuronal and microglial dynamics during stress recovery, as well as in the context of compounding stressors throughout life will provide important insights.

7. Microglia-neuron interactions: pathways toward translation

This review highlighted recent work that indicates microglia-neuron interactions contribute to stress-induced synaptic deficits, and subsequent behavioral and cognitive consequences. This is not only clear in preclinical data, but also in clinical and postmortem reports. Indeed, morphological changes in microglia [6], and increased expression of CSF1 [11] and C3 [62] are observed in postmortem PFC of depressed individuals (see Fig. 2). Moreover, preclinical studies with chronic stress demonstrate sex-specific microglia responses in corticolimbic brain regions that align – quite remarkably – with histological and molecular findings in postmortem tissue from depressed individuals. In particular, chronic stress induces microglial hypertrophy, microglia-mediated neuronal remodeling, and dendritic atrophy in mPFC of male rodents, whereas the opposite occurs in females [11,80,81]. Likewise, microglia-associated genes are upregulated and synapse-associated genes are downregulated in PFC in males with depression, whereas females with depression show a near opposite molecular signature [7].

Together, preclinical and clinical data implicate microglia-neuron interactions in stress and depression. As the majority of pharmaceutical approaches are aimed at neurotransmitter systems, microglia represent an innovative therapeutic target in stress-linked psychopathology. Furthermore, given sex differences in expression of microglia- and synapse-related genes in depression, alongside greater rates of depression in women, approaches targeting microglia may open novel avenues toward sex-specific treatments for depressive disorders – bringing the field one step closer to the goal of individualized medicine.

Declaration of Competing Interest

The authors have declared no conflict of interest exists.

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