

How Stress Shapes Neuroimmune Function: Implications for the Neurobiology of Psychiatric Disorders

Ja Wook Koo and Eric S. Wohleb

ABSTRACT

Chronic stress causes physiological and hormonal adaptations that lead to neurobiological consequences and behavioral and cognitive impairments. In particular, chronic stress has been shown to drive reduced neurogenesis and altered synaptic plasticity in brain regions that regulate mood and motivation. The neurobiological and behavioral effects of stress resemble the pathophysiology and symptoms observed in psychiatric disorders, suggesting that there are similar underlying mechanisms. Accumulating evidence indicates that neuroimmune systems, particularly microglia, have a critical role in regulating the neurobiology of stress. Preclinical models indicate that chronic stress provokes changes in microglia phenotype and increases inflammatory cytokine signaling, which affects neuronal function and leads to synaptic plasticity deficits and impaired neurogenesis. More recent work has shown that microglia can also phagocytose neuronal elements and contribute to structural remodeling of neurons in response to chronic stress. In this review we highlight work by the Duman research group (as well as others) that has revealed how chronic stress shapes neuroimmune function and, in turn, how inflammatory mediators and microglia contribute to the neurobiological effects of chronic stress. We also provide considerations to engage the therapeutic potential of neuroimmune systems, with the goal of improving treatment for psychiatric disorders.

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CLINICAL AND PRECLINICAL EVIDENCE LINKING CHRONIC STRESS, NEUROIMMUNE DYSREGULATION, AND PSYCHIATRIC DISORDERS

Psychiatric disorders are a major source of disability and cause considerable economic and health burdens globally (1,2). Despite significant efforts to define genetic and biological mechanisms that underlie psychiatric disorders, the etiology and pathophysiology of these disorders have not yet been fully characterized (3–5). Clinical studies suggest that symptoms of psychiatric disorders are caused by structural and neurochemical alterations in corticolimbic and mesolimbic circuits, which include the hippocampus (HPC), prefrontal cortex (PFC), nucleus accumbens, and amygdala (4–7). Although there is some genetic risk to developing psychiatric disorders, substantial evidence indicates that severe and/or prolonged exposure to psychosocial or environmental stress increases the risk of onset and recurrence of affective disorders (4,5,8–11). In particular, stress exposure increases the risk for developing major depressive disorder (MDD) and post-traumatic stress disorder (PTSD); thus, these will be referred to as stress-related psychiatric disorders (10,11).

Stress is experienced when stimuli cause a perceived or actual threat to an organism, and if these “stressors” persist it can overwhelm the organism’s adaptive capacities (12,13). Stress exposure is accompanied by activation of the

hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to release of glucocorticoids and norepinephrine, respectively. These canonical stress pathways have been shown to drive the neurobiological effects of chronic stress (14). In support of the clinical findings, rodent models have demonstrated that chronic stress exposure causes cellular and/or synaptic plasticity deficits (e.g., dendritic or synaptic atrophy, impaired neurogenesis) and causes neurochemical dysregulation (e.g., neurotransmitter dysregulation, neuroinflammation) in corticolimbic and mesolimbic brain regions (4,15–18). These preclinical studies indicate that stress-induced neurobiological effects contribute to behavioral and cognitive impairments (e.g., anhedonia, behavioral despair, working memory deficit, social withdrawal) that are relevant to stress-related psychiatric disorders (7,19–22). Indeed, several preclinical models of stress—which include chronic social defeat stress, chronic unpredictable mild stress, or stress-enhanced fear learning—reiterate cardinal neurobiological mechanisms that contribute to the onset of and susceptibility to anxiety- and depressive-like behaviors (15,22–24).

Importantly, a wealth of clinical studies indicates that markers of low-grade inflammation (i.e., elevated cytokines and other mediators) are also observed in patients with mood (e.g., MDD) and anxiety-related (e.g., PTSD) disorders. Meta-analyses of the literature have reported that peripheral interleukin (IL) 1 β , IL-6, tumor necrosis factor (TNF) α , and

C-reactive protein are the most reliable biomarkers of inflammation in depression (25,26) and in PTSD patients (27–29). This is relevant because clinical studies have shown that levels of the inflammatory cytokines IL-1 β and TNF- α are associated with more severe depressive symptoms (30). Other reports have shown that inflammatory factors are elevated in the cerebrospinal fluid of patients with MDD (31,32). Some post-mortem data have suggested that suicide is associated with microglia activation in the PFC (33), which may contribute to changes in inflammatory cytokine expression in the PFC of MDD subjects (34).

Other studies have sought to examine markers of microglia or neuroimmune activation in clinical populations using positron emission tomography for the translocator protein (TSPO). This research has yielded compelling results, with depressed individuals showing broad increases in TSPO levels across corticolimbic brain regions (35). Other studies have suggested that the highest levels of TSPO are detected in unmedicated MDD patients (36). Interestingly, a recent report showed that PTSD patients have lower prefrontal-limbic TSPO levels compared with control subjects and that TSPO levels were negatively correlated with symptom severity (37). These contrasting findings highlight the heterogeneity of these disorders and suggest that TSPO binding may not be a definitive marker of neuroimmune activation (38).

There are likely several factors that promote immune dysregulation in psychiatric conditions (including genetic polymorphisms), but there is clear evidence that severe and prolonged stress exposure is associated with elevated levels of IL-6, IL-1 β , TNF- α , and/or C-reactive protein and an increased risk for developing depression, anxiety, and other psychiatric conditions (8,39). Further studies have indicated that stressful life experiences promote transcriptional pathways that increase immune reactivity, and these molecular changes likely precipitate neuroimmune dysregulation (40–42). Interestingly, there is evidence that antidepressant medication can normalize the elevated levels of IL-1 β , IL-6, and TNF- α in depressed patients, and reductions in cytokine levels are associated with improvement in depressive symptoms after antidepressant treatment (31,43,44). With that, it is important to note that elevated inflammatory markers are observed in a subset of depressed individuals (45,46). In addition, other studies have shown that antidepressant treatments have minimal or opposite effects on inflammatory markers (47). These results suggest that neuroimmune systems may be relevant therapeutic targets in a subset of patients. In this context, it may be useful to examine immunophenotypes across psychiatric conditions to optimize treatment strategies (48).

Another critical consideration is sex differences in neuroimmune function and how they may affect the risk of stress-related psychiatric disorders. Emerging evidence has indicated that depressed men and women have divergent transcriptional changes in the PFC (49,50). Regarding neuroinflammation, women who have enhanced responses after immune challenge or stress are at higher risk of depressive symptoms as compared with men (51,52). Unfortunately, these sex differences have been understudied, so additional work is needed to define the sex-specific role of neuroinflammation in psychiatric disease.

Building on these clinical findings, studies using rodent models indicate that dysregulation of microglia in stress-responsive brain

regions as well as peripheral immune signaling contribute to the neurobiological deficits caused by chronic stress (29,53). In particular, rodent models have demonstrated that chronic stress alters microglia function and increases inflammasome activity, which is a protein complex that can detect diverse danger signals and promotes release of inflammatory cytokines (54–56). This is relevant because inflammatory cytokines or their relevant signaling pathways (e.g., nuclear factor- κ B) mediate stress-induced behavioral deficits in animal models (57–62). Other studies have suggested that stress-induced mobilization and recruitment of peripheral immune cells leads to inflammatory cytokine release in the brain as well (63). More recent work has indicated that microglia also contribute to structural remodeling of neurons in response to chronic stress (15,63).

In this review, we will focus on mechanisms that alter neuroimmune systems in response to chronic stress. Subsequently we will examine how microglia disrupt synaptic and cellular functions in different brain regions and promote development of cognitive and behavioral consequences.

SOLUBLE FACTORS REGULATE NEURON-MICROGLIA INTERACTIONS

Microglia are tissue-resident macrophages that migrate to the brain early in neurodevelopment (63), and their primary role is to maintain brain homeostasis and support neuronal function (64). In physiological conditions, microglia display a surveying phenotype that enables them to rapidly respond to the changes in neuronal homeostasis or brain injury. Microglia processes extend and retract, presenting a constant motility of their ramifications (65,66). This microglia surveillance is guided by local neuronal activity as well as activity-dependent release of purines (i.e., uridine triphosphate and adenosine triphosphate [ATP]) from neurons (66,67) (Figure 1A). Notably, microglia processes are attracted to and directly contact hyperactivated neurons, and this interaction reduces neuronal activity (68). Extracellular ATP from neurons is detected by microglia through the purinergic receptor P2RY12, guiding movement of microglial processes (65,66,69). Indeed microglia in mice lacking P2RY12 show impaired mobility toward sites of neuronal damage when nucleotides are released (69) and have impaired neuroplasticity in the visual cortex that influences ocular dominance. These data suggest that activity-dependent neuron–microglia interactions are important for shaping neurocircuitry.

Other factors released by neurons, including CX₃CL1 (CX3C chemokine ligand 1; fractalkine) (70), transforming growth factor β (71), and colony-stimulating factor 1 (CSF1) (72), regulate microglia functions through binding to CX₃CR1, transforming growth factor β receptor, and CSF1 receptor, respectively (Figure 1A). These neuron-derived factors are essential to maintain the molecular phenotype of microglia (73). More recent studies have demonstrated that microglia morphology and surveillance are “restricted” by increased levels of norepinephrine in wakeful states. In particular, microglia show retracted processes and less process motility when mice are in wakeful states, and microglia-specific depletion of the β_2 -adrenergic receptor prevents this effect (74). In all, these findings indicate that microglia are dynamic

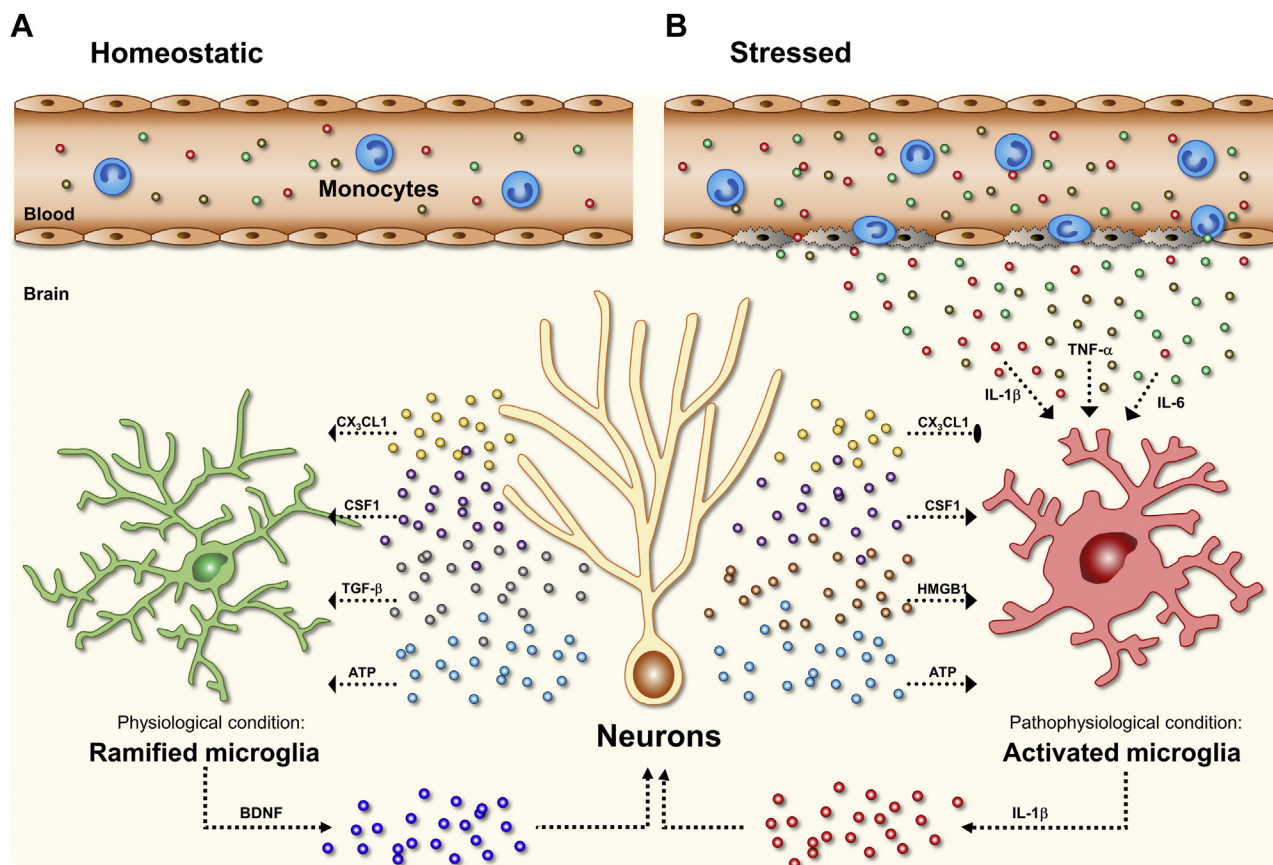


Figure 1. Bidirectional microglia–neuron interactions in the healthy or stressed brain. **(A)** Under physiological or homeostatic conditions, neurons can produce and release soluble factors such as CX₃CL1 (also named fractalkine), CSF1, and TGF-β, which bind to their receptors on microglia to maintain their functional state (e.g., ramified phenotype). In particular, ATP released from neurons guides movement of microglial processes by binding to microglial P2RY12. Further, microglia have been suggested to involve synaptogenesis through microglia-derived BDNF. In these steady-state conditions, there are low levels of circulating monocytes patrolling for infection or tissue damage in the vasculature. **(B)** Under pathological conditions and chronic stress, microglia alter their morphology with increased cell body size and thickened processes. In this state, CX₃CL1 from neurons can regulate microglia activation by binding to its receptor CX₃CR1 on microglia. In contrast, elevated levels of CSF1, HMGB1, and ATP in pathological conditions such as stress exposure have been implicated in neuronal plasticity and psychiatric disorders. Notably, DAMP-associated pathways (e.g., HMGB1-RAGE, ATP-P2X7R signaling) trigger a critical convergent molecular pathway, termed the NLRP3 inflammasome. Finally, the activation of NLRP3 inflammasome in microglia results in the production and release of proinflammatory cytokines, including IL-1β. In response to chronic stress, monocytes can be released to circulate and traffic to the brain. The peripheral monocytes in the brain converge with activated microglia to amplify inflammatory signaling. Increased peripheral cytokines (i.e., IL-1β, TNF-α, IL-6) also can penetrate the brain via passive or active mechanisms and activate microglial stress responses. ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CSF1, colony-stimulating factor 1; CX₃CL1, CX₃C chemokine ligand 1; DAMP, danger-associated molecular pattern; HMGB1, high-mobility group box 1; IL, interleukin; NLRP3, NOD-, LRR-, and pyrin domain-containing 3; P2RY12, purinergic receptor P2Y G-protein coupled, 12; RAGE, receptor for advanced glycation end products; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

macrophages that develop unique phenotypes to respond to and support neuronal function.

Soluble factors, including cytokines, released by microglia have a fundamental role in modulating neuronal function (75). A growing body of studies have elucidated the diverse ways that microglia-derived cytokines and other immune mediators influence neuronal function and neural plasticity. In physiological conditions, basal levels of IL-1β are required for long-term potentiation (76), and TNF-α release is necessary for homeostatic synaptic scaling (77). Other studies have shown that microglia can be a source of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) that support neuroplasticity and learning (78), and it has been reported that

microglia increase BDNF release in response to activating stimuli (79) (Figure 1A). In this context, alterations in microglia function after chronic stress, which may contribute to varied stress-induced BDNF levels in amygdala and nucleus accumbens compared with PFC and HPC (80,81). Recent research has also identified a novel pathway by which microglia can inhibit neuronal activity. This study showed that elevated neuronal activity triggered microglia responses that converted ATP into adenosine, which provided a negative feedback mechanism to suppress neuronal activity (82). Altogether this work indicates that microglia-derived cytokines and other soluble factors contribute to homeostatic neuroplasticity in those brain areas (15) (Figure 1A).

CONTACT-DEPENDENT PATHWAYS SHAPE NEURON–MICROGLIA INTERACTIONS

Recent advances in neuroimmunology have revealed that microglia impact neuronal function through contact-dependent mechanisms. It is now well established that microglia contribute to synaptic pruning through active phagocytosis during neurodevelopment (83,84). Further work has shown that microglia-mediated synaptic remodeling in neurodevelopment occurs in an activity- and complement-dependent manner (85). Complement factor C3 and C1q bind to synapses with reduced activity and initiate microglia-mediated phagocytosis via complement receptor 3 (also known as CD11b) (85).

Other studies have expanded on these findings, showing that microglia processes can contact neuronal structures in the adult brain. In particular, microglia processes interact frequently with active synapses; in a model of ischemia, extended microglial contacts resulted in synapse loss (86). Several other studies have demonstrated that microglial contacts influence the excitability of neural networks (87) and promote the development of new synapses (88) as well as prevent activity-dependent neurotoxicity (89). Furthermore, recent high-resolution microscopy approaches have shown that in physiological conditions microglia can partially engulf (referred to as trophocytosis) presynaptic elements in HPC slice cultures (90). Although it is yet to be elucidated how microglia target specific neuronal compartments in response to altered neuronal activity, these findings demonstrate that reciprocal neuron–microglia interactions are critical mediators of synaptic plasticity and structural remodeling of neurons.

MICROGLIA ACTIVATION: IT'S ALL RELATIVE

Disruptions in brain homeostasis, such as infection, injury, disease, or stress, lead to changes in microglia phenotype and function. In particular, microglia undergo several cellular adaptations: processes often move rapidly toward sites of injury or infection, the soma is enlarged, and the diameter of primary processes is increased while distal processes are shortened. Altogether, these adaptations lead to substantial changes in microglia morphology. In severe pathological conditions, fully activated microglia show complete retraction of processes, which leads to an amoeboid-like phenotype. These cellular changes are often accompanied by altered molecular signaling that promotes cytokine and chemokine signaling, increased proliferative activity, and enhanced levels of phagocytic activity (91,92).

It is important to note that microglia activation exists on a continuum, and the magnitude and duration of these microglial responses are determined by the context (i.e., infection, injury, or stress) (93). Indeed cutting-edge molecular approaches, including single-cell RNA sequencing and mass cytometry, have uncovered varied functional profiles in physiological (i.e., across development) and pathological (i.e., aging or neurodegeneration) states (94). Further studies are likely to provide unique insight into how microglia phenotypes shape neurobiology and behavior.

Microglia activation can be triggered by a variety of peripheral and central molecules. Pathogen-associated molecular patterns (PAMPs; e.g., endotoxin), danger (or damage)-associated molecular patterns (DAMPs; e.g., ATP and HMGB1), inflammatory cytokines, and other mediators can

activate microglia in the brain (15,95). In the absence of blood-brain barrier disruption, these factors can affect the brain function by being transported directly across the blood-brain barrier or by binding specific receptors on the blood-brain barrier and initiating release of secondary messengers (96,97). In response to these inflammatory challenges, brain-derived PAMPs, DAMPs, cytokines, chemokines, inflammatory mediators, and various neurotransmitters, as well as centrally acting peripheral hormones such as glucocorticoids, can affect microglia function by binding to specific receptors (15,95) (Figure 1B). Activated microglia can drive neuropathology through release of proinflammatory cytokines (e.g., IL-1 β and TNF- α) that propagate neuroinflammation, recruit peripheral immune cells, and lead to neuronal injury and/or death (98) (Figure 1B). In this context, it is relevant to note that the magnitude and duration of microglia activation observed with chronic stress is modest as compared to models of neurological disease.

CANONICAL STRESS PATHWAYS DRIVE MICROGLIA ACTIVATION

Early studies demonstrated that repeated stress altered the morphology of microglia in stress-responsive brain regions, suggesting that stress exposure shifted the functional state of microglia (99,100) (Figure 1B). Further studies indicated that stress-induced glucocorticoids as well as noradrenergic signaling drive alterations in microglia phenotype. Indeed, pre-clinical studies using adrenalectomy or treatment with the glucocorticoid receptor antagonist RU486 reduced microglia activation after inescapable stress (101). Other rodent studies showed that blockade of stress-induced noradrenergic signaling reduced proinflammatory cytokine levels in the brain (102).

Further studies supported this work; treatment with the β -adrenergic receptor antagonist propranolol diminished microglia activation and reduced proinflammatory cytokine levels in microglia after repeated social defeat (103). In the repeated social defeat model, microglia activation was accompanied by increased monocyte trafficking to the brain, and these monocytes contributed to elevated inflammatory signaling as well (104–107). While many studies showed that stress caused microglia activation, other work has suggested that chronic unpredictable stress causes microglia dystrophy in the dentate gyrus of the HPC (108). These findings indicate that stress-induced neuroendocrine and sympathetic pathways drive brain region-specific alterations in microglia function that may contribute to the divergent neurobiological effects observed in these models.

STRESS PROMOTES INFLAMMASOME ACTIVATION AND INFLAMMATORY CYTOKINE RELEASE

Several lines of evidence have demonstrated that microglial NLRP3 (nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3) inflammasome, a multi-protein complex that is activated by diverse danger signals, plays a critical role in neuroimmune responses to chronic stress (54). In the brain, the NLRP3 inflammasome is activated after pattern recognition receptor binding of PAMPs and/or DAMPs (e.g., ATP). These pathways may be initiated by stress-related processes (109), and, in turn, NLRP3 signaling leads to caspase-1 activation, which induces cleavage and the eventual release of proinflammatory cytokines such as IL-1 β (110)

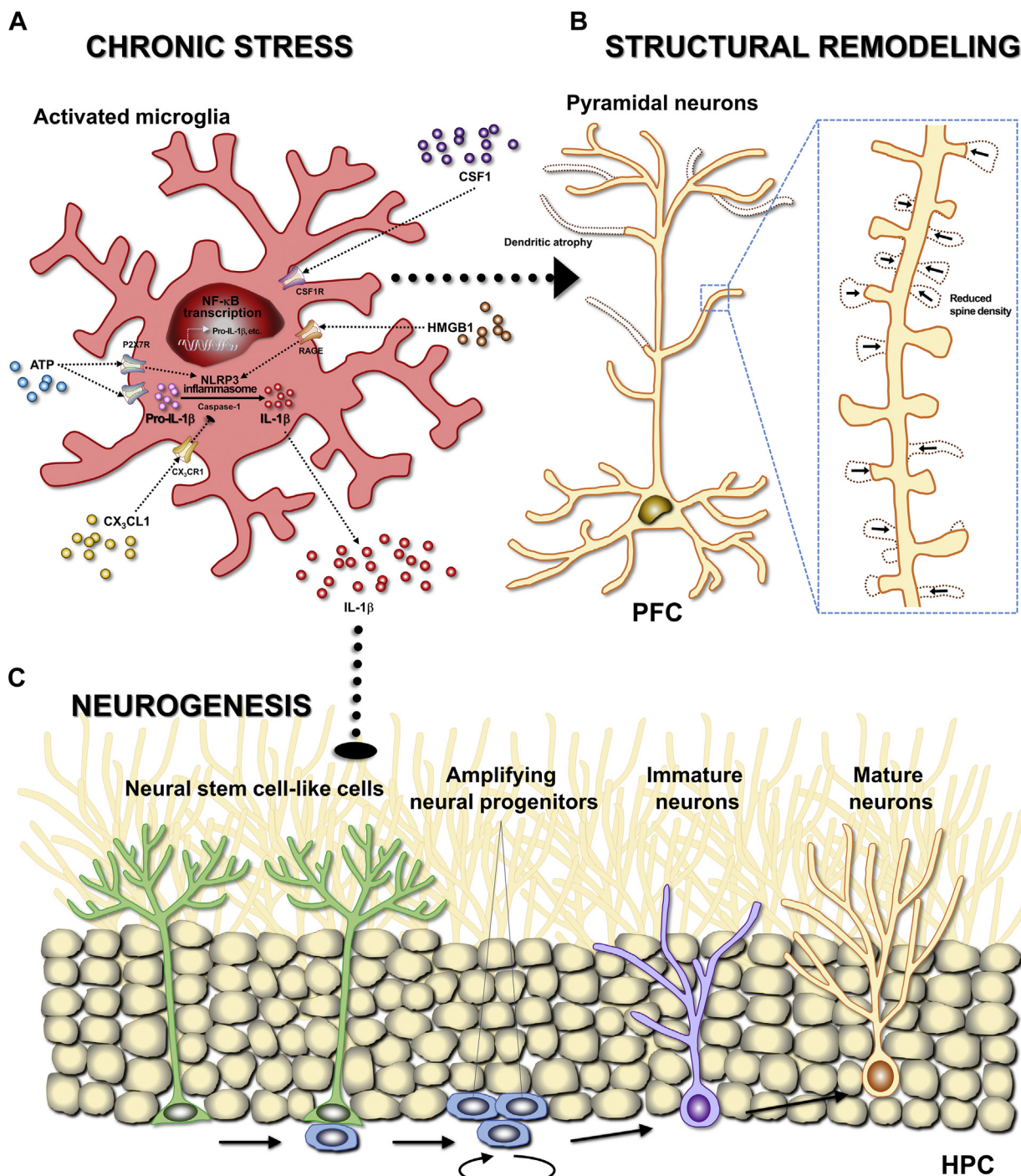


Figure 2. Microglia shape the neurobiology of stress by reducing neurogenesis and remodeling neurons. Chronic stress exposure alters microglial morphology and function in various stress-responsive brain areas, including corticolimbic and mesolimbic circuits. In response to chronic stress, neurons can release ATP and HMGB1 that can signal microglia through P2X7R and RAGE, respectively. The binding of the danger-associated molecular patterns to pattern recognition receptors activates NLRP3 and recruits adaptor proteins and procaspase-1, which thereby makes a large multiprotein complex termed the inflammasome. The NLRP3 inflammasome cleaves procaspase-1 to mature caspase-1, which cleaves prointerleukin 1 β to mature IL-1 β . Released IL-1 β is thought to induce TNF- α release. Collectively, the stress-induced microglial activation produces and releases proinflammatory cytokines, including IL-1 β and TNF- α , through activation of NLRP3 inflammasome. The stress-induced proinflammatory cytokines elicit neuronal dystrophy such as dendritic atrophy and reduction of spine density in glutamatergic pyramidal neurons in the PFC. Microglia, in response to chronic stress, mediate the structural remodeling by increasing microglia–neuron contact and engulfment of synaptic structures. Neuron-derived factors, CSF1, and CX₃CL1 regulate microglial phagocytosis of neuronal elements. In addition, chronic stress impairs proliferation of neural stem-like cells in the HPC through activation of neuroimmune system (e.g., IL-1 β /NF- κ B signaling). Of note, microglia actively phagocytize the apoptotic newborn cells in the neuronal niche. ATP, adenosine triphosphate; CSF1, colony-stimulating factor 1; CX₃CL1, CX₃C chemokine ligand 1; HMGB1, high-mobility group box 1; HPC, hippocampus; IL, interleukin; NF- κ B, nuclear factor- κ B; NLRP3, NOD-, LRR-, and pyrin domain-containing 3; PFC, prefrontal cortex; P2X7R, P2X7 receptor; RAGE, receptor for advanced glycation end products; TNF- α , tumor necrosis factor α .

(Figure 2A). Animal studies have shown that exposure to chronic unpredictable stress leads to activation of microglial NLRP3 inflammasome and increased production of IL-1 β in the PFC, inducing depressive-like behavior in rats. The chronic stress-induced activation of the NLRP3 inflammasome and its relevant inflammatory risk factors in PFC and depressive-like behaviors are reversed by long-term fluoxetine treatment (111). Similarly, chronic stress-induced hippocampal IL-1 β and its consequential depressive-like behaviors are blocked by pharmacological inhibition of NLRP3 inflammasome in mice (112).

In addition, multiple studies have implicated DAMPs in stress effects on microglia. For example, prolonged stress caused release of HMGB1 (high-mobility group box 1), which is a DAMP that binds to pattern recognition receptors such as RAGE (receptor for advanced glycation end products). This HMGB1 signaling promotes NLRP3 activation and proinflammatory cytokine production by microglia in the HPC (113). These effects may be mediated by the NLRP3 inflammasome (Figure 2A), as blockade of the HMGB1-RAGE complex has resulted in reduced microglia activation and dampened IL-1 β levels after stress exposure (111,112). These findings are consistent with another study that showed that stress increased extracellular ATP levels in the HPC, which is proposed to activate microglia and increase neuroinflammation via the purinergic receptor P2RX7 (55) (Figure 2A). In these studies, the stress-induced IL-1 β and TNF- α expression in the HPC were blunted by a P2RX7 antagonist. This work indicates that stress causes dysregulation of neuron-microglia interactions, which leads to functional alterations in microglia and release of inflammatory mediators that, in turn, can influence neuroplasticity.

EFFECTS OF INFLAMMATORY CYTOKINES ON NEUROGENESIS

Ample research has demonstrated that stress-induced microglial activation and inflammatory cytokines regulate behavior and cognition through direct actions on neurons (15,20,21,25). Relevant to this review, hippocampal neurogenesis has been evaluated as a candidate mechanism for the pathophysiology of depression and as a target for antidepressant action (17,114). Microglial activation inhibits hippocampal neurogenesis under inflammatory and stressful conditions (115,116). Consistently, inflammatory challenges such as lipopolysaccharide or irradiation suppress hippocampal neurogenesis (116,117). In parallel, chronic stress-induced hippocampal IL-1 β signaling mediates the antineurogenic and depressive-like behavioral effects of chronic stress (58,59) (Figure 2C). Further studies have revealed that the stress-induced impairment of hippocampal neurogenesis and depression-like behaviors are mediated by nuclear factor- κ B signaling (58,60). In addition to IL-1 β , other inflammatory cytokines, including IL-6 and TNF- α , can reduce adult hippocampal neurogenesis and/or promote depressive-like behaviors (117–119).

In contrast, antidepressants increase the number of adult-born neurons in the HPC (120,121). Adult-born neurons are required for the antidepressant effects on some but not all depressive-like behaviors (122–124) and for the normal

expression of those behaviors after acute stress (125). In parallel, enhanced hippocampal neurogenesis is sufficient for reducing depressive-like behaviors (126). Antidepressants can also normalize markers of neuroinflammation in rodent models (127,128), and treatment-associated reductions in cytokines are linked to improved mood in MDD patients (31,43,44). Despite this, further studies are needed to directly tease apart the effects of antidepressants on neurogenesis and neuroinflammation.

The suppressive effects of activated microglia on neurogenesis are mainly related to the survival of newborn neurons rather than their proliferation or differentiation. Microglia actively eliminate excess apoptotic newborn cells in the neuronal niche through phagocytosis (115). Previous studies have shown that the number of newborn neurons is inversely proportional to the number of activated microglia under various inflammatory conditions (116,117). Above all, in vitro experiments have demonstrated that conditioned media from lipopolysaccharide-challenged microglia induces the death of hippocampal neuroblasts, which is mediated by the secretion of IL-6 (117) or TNF- α (129).

Inflammatory cytokines also regulate neurogenesis by prompting gliogenesis at the expense of neuronal differentiation. For instance, overexpression of IL-6 in mice brains reduces proliferation, survival, and neuronal differentiation (119). Similarly, systemic administration of TNF- α decreases neural stem cell proliferation in the dentate gyrus (130). TNF- α administration to cultured hippocampal cells induces cell death (131) as well as an increase in astrocytic differentiation at the expense of neuronal differentiation (132). Furthermore, IL-1 β treatment over cultured hippocampal neural stem cells reduces cell proliferation and neurosphere formation (133).

Such effects of proinflammatory cytokines on neurogenesis may result from altered integration of newly produced neurons in the adult brain. For example, an in vitro study found that newly born neurons that matured in a chronic inflammatory environment had increased inhibitory synaptic inputs (134). In parallel, disruption in signaling of CX₃CL1, an endogenous neuronal regulator of microglial IL-1 β , TNF- α , and IL-6 in the brain (135,136), has resulted in reduced neurogenesis (137) (Figure 2C), lipopolysaccharide-induced sickness-like behavior (138), and stress-induced depressive-like behavior (139). This work suggests that CX₃CL1 regulates microglial function, inducing stress resilience. Thus, adult hippocampal neurogenesis may reciprocally regulate inflammatory signaling and affective behaviors.

In animal models of PTSD, which is associated with overgeneralized memories of traumatic experiences, hippocampal neurogenesis plays a beneficial role (140). Enhanced adult hippocampal neurogenesis by treatment with memantine facilitates forgetting of remote contextual fear memory after prolonged reexposure to the conditioning context (141,142) and forgetting of social avoidance memory after repeated exposure to social defeat stress, improving PTSD (anxiety)-like behavior (143). By contrast, blocking hippocampal neurogenesis after conditioning stabilizes or strengthens existing HPC-dependent memories (141,144). A recent transcriptome and epigenome analysis using a social defeat stress model revealed that activated inflammatory signaling pathways and inhibited pathways involved in neuronal growth factors

(e.g., neurogenesis) in brain regions were implicated in fear memory and extinction (145). These data support the notion that neuroinflammatory signaling may promote this behavioral phenotype, potentially by inhibiting neurogenesis (145).

EXPOSURE TO CHRONIC STRESS PROVOKES MICROGLIA-MEDIATED NEURONAL REMODELING

With their ability to shape neuronal function through phagocytosis of synaptic components, microglia may contribute to stress-induced alterations in synaptic plasticity and associated behavioral consequences (146). Indeed, recent work has shown that chronic stress alters neuron–microglia interactions, leading to increased microglial engulfment of synaptic elements. In separate studies, chronic unpredictable stress was shown to increase microglia–neuron contact and engulfment of neuronal elements (e.g., presynaptic and postsynaptic structures) by microglia in the PFC (147) and HPC (108). In particular, microglia in the PFC showed increased engulfment of neuronal elements that was linked to synapse loss on apical dendrites of pyramidal neurons and development of depressive-like behaviors (147).

At the molecular level, chronic stress increased neuronal CSF1 and viral-mediated knockdown of neuronal CSF1 in the PFC reduced microglia-mediated neuronal remodeling and associated behavioral consequences. Of note, gene expression analyses in postmortem dorsolateral PFC showed that depressed individuals have increased *Csf1* levels as well (147) (Figure 2B). Follow-up studies have revealed that stress-induced glucocorticoid signaling promotes neuronal CSF1 signaling as well as increased microglia-mediated neuronal remodeling in the PFC (148). More recent studies have indicated that elevated neuronal activity in response to stress leads to alterations in microglia function. Indeed, pretreatment with the GABA (gamma-aminobutyric acid) A receptor modulator diazepam dampened neuronal activity after chronic unpredictable stress, which was associated with decreased CSF1 levels and decreased microglia-mediated neuronal remodeling in the PFC (149).

Ongoing studies are aimed at determining the factors that direct microglia to engulf specific neuronal elements in the PFC. Beyond direct effects on synaptic structures, recent studies have suggested that microglia can also alter neuroplasticity through remodeling of extracellular matrix. In particular, microglia, triggered by the cytokine IL-33, phagocytose the extracellular matrix proteins that stabilize synapses, and this enables growth or reshaping of specific synapses (150). Although these studies were conducted in physiological conditions, it is intriguing to consider how this pathway may contribute to the structural remodeling of neurons after chronic stress. Altogether, this work provides strong evidence that chronic stress increases microglial phagocytosis of synaptic and associated structures, and that neuron–microglia interactions have a formative role in the neurobiological and behavioral effects of stress.

SUMMARY: TRANSLATIONAL IMPLICATIONS AND FUTURE DIRECTIONS

Taken together, there is ample evidence that stress-related psychiatric disorders are associated with excess or

dysregulated neuroimmune function. The neurobiological effects of chronic stress, including reduced neurogenesis in the HPC and synapse loss in the PFC, underlie behavioral and cognitive impairments, including anhedonia, behavioral despair, and/or social withdrawal (4,15,17,19,20,22,44). Clinical and preclinical studies examining other stress-related disorders such as PTSD are at the initial stages toward understanding how immune factors can contribute to their related symptoms (16,21,28,29).

Although preclinical studies have indicated that altered neuroimmune function, particularly changes in microglia, contributes to the neurobiology of stress, it is important to recognize that complex multicellular processes underlie the pathophysiology of associated behavioral and cognitive consequences. However, with the limited efficacy of current treatments for psychiatric disorders, it is worth exploring other therapeutic targets such as neuroimmune systems (9,151). When considering neuroimmune systems as potential therapeutic targets, broad inhibition of cytokine signaling may not be warranted because these pathways support neuroplasticity (98,152). In addition, a recently published study using mass cytometry suggested that microglia from depressed individuals do not display an inflammatory phenotype but instead have increased expression of homeostatic markers (153). In this context, it is relevant to consider the functional profile of microglia and determine what pathways can promote their therapeutic potential.

In particular, novel approaches will be needed to regulate neuron–microglia interactions. Any such interventions will need to be precise—targeting impaired circuits while leaving other circuits unaffected. To accomplish this, clinical and preclinical research will need to refine our diagnostic tools, and researchers will need to consider the heterogeneous functions of microglia across different brain regions. Further, more comprehensive approaches (i.e., single-cell RNA-sequencing) will be needed to fully understand the dynamic neuroimmune processes that contribute to the neurobiology of stress-related psychiatric disorders. With this, we may work toward the goal of more targeted therapeutics for patients with these debilitating disorders.

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ARTICLE INFORMATION

From the Emotion, Cognition and Behavior Research Group (JWK), Korea Brain Research Institute, Daegu, and Department of Brain and Cognitive

Sciences (JWK), Daegu Gyeongbuk Institute of Science and Technology, Daegu, South Korea; and Department of Pharmacology and Systems Physiology (ESW), College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Address correspondence to Eric S. Wohleb, Ph.D., at eric.wohlebe@uc.edu.

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