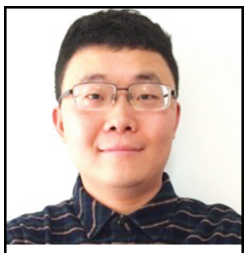
Commentary

The Effects of Psychological Stress on Microglial Cells in the Brain

Ti-Fei Yuan[*,1], Gonglin Hou[*,2], Ying Zhao[2] and Oscar Arias-Carrión[*,3,4]



Ti-Fei Yuan

[1]*School of Psychology, Nanjing Normal University, Nanjing, China*

[2]*Department of Psychology, Zhejiang Sci-Tech University, Hangzhou, China*

[3]*Unidad de Trastornos del Movimiento y Sueño (TMS), Hospital General Dr. Manuel Gea González/IFC-UNAM, Mexico City, Mexico*

[4]*Unidad de Trastornos del Movimiento y Sueño (TMS), Hospital General Ajusco Medio/Secretaria de Salud, Mexico City, Mexico*

Oscar Arias-Carrión

Abstract: Psychological stress leads to activation and proliferation of microglial cells in different brain regions. These effects are mediated by inflammatory cytokines, as well as stress hormones including glucocorticoids and norepinephrine. Eliminating microglia from the nervous system or blocking their activation prevented the stress-induced impairments on brain cognitive functions. We conclude that microglial cells are important meditators underlying anti-depression therapies.

Keywords: Antidepressant, glucocorticoid, microglia, norepinephrine, stress.

INTRODUCTION

Chronic stress leads to psychological adaption and physiological changes [1, 2]. Within the central nervous system, stressful experiences raise neuroinflammation, reflected by activated microglial cells and increased cytokine secretion [3]. This secretion of cytokines can be prevented by minocycline administration [4], an inhibitor of pro-inflammatory M1 type microglia [5]. This indicates that microglia are responsible for stress-induced neuroinflammation signaling. In fact, in animals suffering from stress, brain microglial cells exhibit an "activated' phenotype, with retracted and thickened processes as shown by immunohistochemical staining. In addition, these changes are restricted to stress-responsive regions, especially the prefrontal cortex, hippocampus and hypothalamus.

Moreover, stress-induced microglia activation impairs brain function, such as spatial working memory [6]. In addition, microglial cells regulate synapse formation through trophic factor (e.g. brain-derived neurotrophic factor) signaling pathways [7], or effect long-term synaptic plasticity *via* complement receptor 3 (CR3) activation [8]. Therefore, microglia could be important in mediating synaptic adaptations to stress stimuli in different brain areas [9, 10], and contribute to depression-like behavior.

MORPHOLOGICAL CHANGES OF MICROGLIA FOLLOWING STRESS

Microglial cells can be differentially staged according to their morphological characteristics [11], such as soma size and shape, and number and thickness of processes. Resting microglia exhibit a "ramified" phenotype, with elongated processes in constant movement to detect potential inflammatory events; partially activated microglia often retract these processes, with enlargement of the soma and may proliferate, while fully activated microglia display an "ameboid" shape, with limited or no clear processes, and are phagocytic.

Within days of unpredictable stress (2-4 days) hippocampal microglial cells exhibit certain degrees of activation, such as shorter processes [12]. Interestingly, the initial phase of stress stimulation (e.g. 2 days) leads to microglia proliferation and activation (soma size increase) while prolonged stress (e.g. >4 days) results in microglial cell atrophy (smaller soma size) and even apoptosis [12], but remain "activated" (shortened processes, etc). Consistently, in chronically-stressed animals, microglial somal size in stress-responsive brain regions is smaller [13]. It is proposed that the dynamic effects of stress on microglia depend on these cells' receptor expression.

ACUTE STRESS AND MICROGLIAL FUNCTION

A single session of inescapable foot shock stress leads to increased hypothalamic interleukin(IL)-1β, which is blocked by previous administration of minocycline [4]. This suggests that microglia act as the main source of IL-1β secretion in acute

*Address Correspondence to these authors at (Ti-Fei Yuan, *PhD*) School of Psychology, Nanjing Normal University, Nanjing, China;
E-mail: ytf0707@126.com; (Gonglin Hou, *PhD*) Department of Psychology, Zhejiang Sci-Tech University, Hangzhou, China; E-mail: hougonglin@163.com; (Oscar Arias-Carrión) Unidad de Trastornos del Movimiento y Sueño (TMS), Hospital General Dr. Manuel Gea González/IFC-UNAM. Mexico City, Mexico; E-mail: arias@ciencias.unam.mx

stress. Activation of microglial cells is accompanied by the expression of certain cellular markers, such as CD11b [14, 15].Notably, CD11b expression is correlated to c-fos expression in stress-responsive brain regions, and is restricted to some types of stressors (e.g. cold) [16].

The effect of acute stress on microglial cell proliferation is dependent on IL-1 receptor expression, since pharmacological antagonism of the receptor reduced cell proliferation [12]. Glutamatergic receptors such as the N-methyl-D-aspartate subtype on microglia also play a role in this response [17].

Dissociated microglial cells from brain tissues of animals with acute stress exposure were found to be "primed" by stressor, and able to secrete more cytokines when challenged *in vitro* [18]. The priming effect was mediated by glucocorticoid receptors (GRs) on microglia [19], as well as norepinephrine (NE)-activated beta adrenergic receptor signaling pathways [4, 15]. This leads to transcriptome changes in microglia following acute stress [15], such as increased mRNA levels for IL-1 and CD14, and a decreased level for CD200R mRNA. Therefore, microglia could at least partly contribute to acute stress-induced sensitization to other stimuli, including following stress or immune challenges.

THE EFFECTS OF CHRONIC STRESS ON MICROGLIA FUNCTION

Repeated stress or chronic stress is associated with a protracted increase of glucocorticoids, aberrant neuroinflammation signaling, and adaptive behaviors. Microglia react by proliferating and expressing a full panel of inflammatory biomarkers, such as CD11b. As for acute stress, most of these changes still exhibit region specificity to stress-responsive brain areas, such as prefrontal cortex, nucleus accumbens, and hippocampus.

With repeated restraint stress, chronic social defeat stress, or chronic unpredictable mild stress, microglial cell numbers are increased in hippocampus, prefrontal cortex (especially infralimbic cortex), amygdala, and nucleus accumbens [20-23]. Their proliferation can be blocked by N-methyl-D-aspartate receptor antagonists, and the increase in cell number can be prevented by minocycline administration [13, 17, 24]. In addition, microglia exhibit altered morphology, such as increased number of processes, branching points, process length and therefore the covering area [24].

Under the above conditions, microglial cells which develop an "inflammatory" phenotype after chronic stress respond with a significant increase in cytokine secretion and vulnerability to other inflammatory stimuli, such as lipopolysaccharide (LPS) or injury signals [20, 22, 23, 25-29]. This could impair neurotransmission [30, 31], regulate the cell survival pathway, and contribute to neuronal cell injury in chronic diseases (e.g. neurodgenerative diseases) [32, 33]. Interestingly, minocycline administration into the prefrontal cortex blocks microglia activation and prevents chronic stress-induced deficits in spatial working memory [6], suggesting that microglial cells roles change when mediating stress-related brain diseases. Notably, stress-induced neuronal cell remodeling is highly circuit-specific [34]. In the case of acute stress CD11b-expressing microglia seem to be distributed adjacent to c-Fos-positive neurons [16]. Given that each microglial cell "controls" multiple neurons and with unique spatial distribution [24, 35], it will be important to examine if chronic stress-altered microglia also distribute within certain circuits.

MECHANISTIC INSIGHTS

As stated above, the effects of stress on microglia are mainly mediated by their GRs [19], as well as NE-activated alpha/beta-adrenergic receptor signaling pathways [4, 15]. The respective ligand-receptor complexes enter the nucleus and inhibit transcription control pathways, including nuclear-factor kappa-B, activator-protein 1, Janus kinase-signal transducer and activator of transcription factors, mitogen-activated protein kinases, signal transducer and activator of transcription 3, and other pathways [36-39], leading to decreased pro-inflammatory cytokine production.

Hypothalamic–pituitary–adrenal axis "fatigue" can occur in the chronic phase of stress stimulation, that is, the axis becomes blunted or insensitive to sustained stress [37]. Further, prolonged exposure to stress hormones leads to down-regulation of GRs, while the immune system's sensitivity to cortisol declines [37, 40, 41]. Recent research indicates that multiple mechanisms contribute to this resistance [39], such as repression of GR gene expression by glucocorticoid-induced GR binding to an negative glucocorticoid response element on a GR-NCoR1-histone deacetylase 3-containing repression complex [42], GRβ antagonizes the action of GRα [43] and phosphorylation of GR by p38 mitogen-activated protein kinase [44]. Epinephrine and NE may down-regulate GR expression [45].

In the case of microglia activation by GR signaling, glucocorticoid administration could either enhance or decrease the stress-induced microglia changes. For instance, corticosterone administration or stress exposure leads to increased inflammation in the brain triggered by LPS exposure [19, 20, 46, 47]; yet, in other studies GR signaling decreased cytokine synthesis by microglia [48-50]. These differences could result from differences in the temporal relationship between LPS challenge and stress stimuli [19, 46], or the nature of the stress stimulus and its intensity [51].

As for NE signaling, the findings are also equivocal. Some studies have shown that NE administration enhances and NE receptor antagonists reduce stress-induced microglial cell changes [4, 26, 52]. On the other hand, some reports claim that the NE signaling pathway leads to decreased inflammatory cytokine secretion from microglia [53-57]. Timing differences between drug delivery and stress stimuli could contribute to these variances [51]. Additional studies are needed to differentiate signaling pathway interactions between glucocorticoids and NE on microglial cells *in vivo* (Fig. **1**).

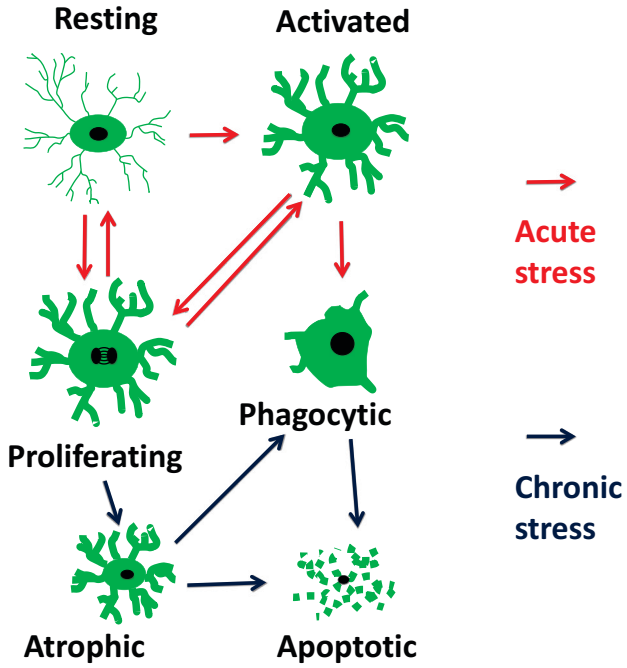


Fig. (1). Acute psychological stress induces immediate microglia activation and cell proliferation, accompanying an “activated" morphology. In chronic psychological stress, some microglial cells undergo apoptosis and atrophy, while others remain “activated”.

CONCLUSION

Stress leads to changes in microglial cell structure/morphology and function. Both glucocorticoid and NE signaling contribute to the upregulation of pro-inflammatory cytokine production by brain microglia. In addition to being activated, the microglial cells proliferate and increase their numbers. Pharmacological prevention of microglial cell alterations could heal the stress-resulted behavioral deficits, at least in certain aspects. Because many antidepressants modulate cytokine production from microglia, it will be interesting to investigate if such a mechanism is responsible for the anti-depressive efficacy of these drugs.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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