Journal of Ageing and Restorative Medicine
JARM, 2(2): 98-100
www.scitcentral.com

ISSN: 2637-7403

Mini Review: Open Access

Aging, Neuroinflammation and Depression: Models and Mechanisms

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Received February 01, 2019; Accepted February 25, 2019; Published June 14, 2019

ABSTRACT

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant morbidity and mortality. About one in six individuals will succumb to clinical depression during their lifetime. In addition to mortality associated with suicide, depressed patients are more likely to develop dementia, coronary artery disease and type 2 diabetes. However, biological mechanisms underlying depression remains poorly understood due to lack of biomarkers, relatively low rates of heritability, and heterogeneity of precipitating factors, including stress. Despite advances in the treatment of major depression, one-third of depressed patients fail to respond to conventional antidepressant medication. One pathophysiologic mechanism hypothesized to contribute to treatment resistance in depression is neuroinflammation. Recent evidence has shown that MDD is also associated with increased levels of inflammatory markers in the periphery. Recent work also suggest that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation and shifts the CNS into a proinflammatory state ultimately resulting in demyelination and neurodegeneration. Of note, decreased inflammatory markers have also been associated with remitted stages of depression in response to treatment with conventional antidepressant medications.

Keywords: Aging; Neuroinflammation; Depression; Mechanisms

DEPRESSION AND INFLAMMATION

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant morbidity and mortality. About one in six individuals will succumb to clinical depression during their lifetime [1]. In addition to mortality associated with suicide, depressed patients are more likely to develop dementia, coronary artery disease and type 2 diabetes [2]. However, biological mechanisms underlying depression remains poorly understood due to lack of biomarkers, relatively low rates of heritability and heterogeneity of precipitating factors, including stress [3]. Despite advances in the treatment of major depression, one-third of depressed patients fail to respond to conventional antidepressant medication [4].One pathophysiologic mechanism hypothesized to contribute to treatment resistance in depression is neuroinflammation. Recent evidence has shown that MDD is also associated with increased levels of inflammatory markers in the periphery [5]. Of note, decreased inflammatory markers have also been associated with remitted stages of depression in response to treatment with conventional antidepressant medications [6].

AGING, NEUROINFLAMMATION, SYNAPTIC PLASTICITY AND DEPRESSIVE BEHAVIOR

Neuroinflammation has been associated with greater rates of major depression. On a background of systemic inflammation, proinflammatory cytokines can access the central nervous system and interfere with serotonin metabolism, and reduce both synaptic plasticity and hippocampal neurogenesis [7,8]. Evidence is accumulating showing that reduced, enhanced and imbalanced neuroplasticity-synaptic plasticity, neuronal remodeling and neurogenesis — is implicated in the etiology of neuropsychiatric conditions including depression [9]. Recent studies suggest that microglia may play a role in synaptic remodeling and plasticity in the healthy brain [10,11].

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Citation: Popa-Wagner A, Driga MP, Pinosanu LR & Hermann D. (2019) Aging, Neuroinflammation and Depression: Models and Mechanisms. J Ageing Restor Med, 2(2): 98-100.

Furthermore, disrupting microglia-specific CR3/C3 or CX3CR1 signaling resulted in sustained deficits in synaptic connectivity [11]. Taken together these results highly suggest that there is a deep connection between inflammation, microglia and neuroplasticity and mood regulation.

AGING, PERFUSION DEFICITS, INFLAMMATION AND DEPRESSION

Among elderly individuals, depressive symptoms are common and burdensome [12]. In addition, another 15-25% of elders experience depressive symptoms that, while not meeting criteria for major depressive disorder, do cause significant distress and interfere with daily functioning [13]. It is well known that normal aging is characterized by a chronic low-grade, pro-inflammatory state [14], with an overexpression of systemic inflammatory factors, including pro-inflammatory cytokines [15].

Previous studies in rodents indicate that aging and preclinical neurodegenerative disease processes promote proinflammatory states in older individuals and leads to the development of a primed and immune-reactive population of microglia [16-19]. Recent data suggests that the inflammatory process is potentially intricately linked with multiple neurodegenerative pathways for depression and pro-inflammatory cytokines [20] and plays a central role in the pathophysiology of both depression and dementia [21-24]. Further, immune activation can be a characteristic of depression [8,25] and precipitate depressive symptoms [26].

Recent work suggests that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation and shifts the CNS into a proinflammatory state [19,27,28] ultimately resulting in demyelination and neurodegeneration [29]. There is strong evidence that in humans vascular disease vascular Abeta deposition in the brain promotes development of depression and increases the risk of dementia by causing loss of vascular autoregulation associated with rigidity of arterioles, leading to infarction in the territory of their branching vessels in the temporal cortex of patients with cerebral angiopathy (CAA). This is associated with marked vascular/perivascular infiltration of inflammatory cells, a condition mimicked in mice subjected to chronic cerebral hypo perfusion [30,31].

Perfusion deficits do not need to cause ischemia in order to influence brain function. Instead perfusion deficits may thus contribute to the affective and cognitive symptoms observed in LLD. Indeed, vascular dysregulation is common in LLD and CBF reductions can impair regional brain function, contributing to affective and cognitive symptoms [32,33]. The subcortical white matter is particularly susceptible to infarction due to impaired autoregulation of the blood flow in terminal arterioles with limited collateral flow. Depressed elders with white matter hyperintensities (WMH) in the medial and lateral PFC, subcortical and temporal structures exhibit reduced CBF in both white matter and gray matter regions [34].

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