

Aging, Neuroinflammation and Depression: Models and Mechanisms

Aurel Popa-Wagner^{1,2*}, Mircea Popescu Driga¹, Leonard Radu Pinosanu¹ and Dirk Hermann²

¹Center of Clinical and Experimental Medicine, University of Medicine and Pharmacy, Craiova, Romania

²Department of Neurology, Chair of Vascular Neurology and Dementia, University of Medicine Essen, Germany.

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].

Corresponding author: Aurel Popa-Wagner, Center of Clinical and Experimental Medicine, University of Medicine and Pharmacy, Craiova, Romania, E-mail: aurel.popa-wagner@geriatrics-healthyageing.com

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.

Copyright: ©2019 Popa-Wagner A, Driga MP, Pinosanu LR & Hermann D. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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].

REFERENCES

1. de Jonge P, Rosmalen JGM (2006) Comment on: Knol MJ, Twisk JWR, Beekman ATF, Heine RJ, Snoek FJ, Pouwer F. (2006) depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia*; 49: 837-845. *Diabetologia* 49: 2797-2798.
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, et al. (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62: 593-602.
3. Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. *Nature* 455: 894-902.
4. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, et al. (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 163: 1905-1917.
5. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, et al. (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70: 31-41.
6. Baune BT, Smith E, Reppermund S, Air T, Samaras K, et al. (2012) Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology* 37: 1521-1530.
7. Caraci F, Copani A, Nicoletti F, Drago F (2010) Depression and Alzheimer's disease: Neurobiological links and common pharmacological targets. *Eur J Pharmacol* 626: 64-71.
8. Maes M, Yirmiya R, Norberg J, Brene S, Hibbeln J, et al. (2009) The inflammatory and neurodegenerative (I&ND) hypothesis of depression: Leads for future research and new drug developments in depression. *Metab Brain Dis* 24: 27-53.
9. Pittenger C (2013) Disorders of memory and plasticity in psychiatric disease. *Dialog Clin Neurosci* 15: 455-463.
10. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, et al. (2011) Synaptic pruning by microglia is necessary for normal brain development. *Science* 333: 1456-1458.
11. Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, et al. (2012) Microglia sculpt postnatal

- neural circuits in an activity and complement-dependent manner. *Neuron* 74: 691-705.
12. Lippa M, Luck T, Ritschel F, Angermeyer MC, Villringer A, et al. (2013) Depression and incident dementia. An 8 year population-based prospective study. *PLoS One* 8: e59246.
 13. Brevik EJ, Eikeland RA, Lundervold AJ (2013) Subthreshold depressive symptoms have a negative impact on cognitive functioning in middle-aged and older males. *Front Psychol* 4: 309.
 14. Bruunsgaard H, Pedersen M, Pedersen BK (2001) Aging and proinflammatory cytokines. *Curr Opin Hematol* 8: 131-136.
 15. Capuron L, Miller AH (2011) Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacol Ther* 130: 226-238.
 16. Henry CJ, Huang Y, Wynne A M, Godbout JP (2008) Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1beta and anti-inflammatory IL-10 cytokines. *Brain Behav Immunity* 23: 309-317.
 17. Bilbo SD, Schwarz JM (2009) Early-life programming of later-life brain and behavior: A critical role for the immune system. *Front Behav Neurosci* 3: 14.
 18. Murray C, Sanderson DJ, Barkus C, Deacon RMJ, Rawlins JNP, et al. (2012) Systemic inflammation induces acute working memory deficits in the primed brain: Relevance for delirium. *Neurobiol Aging* 33: 603-616.
 19. Dilger RN, Johnson RW (2008) Aging, microglial cell priming and the discordant central inflammatory response to signals from the peripheral immune system. *J Leukocyte Biol* 84: 932-939.
 20. Walker AK, Kavelaars A, Heijnen CJ, Dantzer R (2013) Neuroinflammation and comorbidity of pain and depression. *Pharmacol Rev* 66: 80-101.
 21. Maes M (2011) Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Progr Neuropsychopharmacol Biol Psychiatry* 35: 664-675.
 22. Leonard BE (2007) Inflammation, depression and dementia: Are they connected? *Neurochem Res* 32: 1749-1756.
 23. Rojo LE, Fernández JA, Maccioni AA, Jimenez JM, Maccioni RB (2008) Neuroinflammation: Implications for the pathogenesis and molecular diagnosis of Alzheimer's disease. *Arch Med Res* 39: 1-16.
 24. Byers AL, Yaffe K (2011) Depression and risk of developing dementia. *Nat Rev Neurol* 7: 323-331.
 25. Surtees PG, Wainwright NWJ, Boekholdt SM, Luben RN, Wareham NJ, et al. (2008) Major depression, C-reactive protein and incident ischemic heart disease in healthy men and women. *Psychosom Med* 70: 850-855.
 26. Taylor WD, Aizenstein HJ, Alexopoulos GS (2013) The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry* 18: 963-974.
 27. Downes CE, Crack PJ (2010) Neural injury following stroke: Are toll-like receptors the link between the immune system and the CNS? *Br J Pharmacol* 160: 1872-1888.
 28. Ransohoff RM, Cardona AE (2010) The myeloid cells of the central nervous system parenchyma. *Nature* 468: 253-262.
 29. Becker KG, Holmes KA, Zhang Y (2011) Aging-kb: A knowledge base for the study of the aging process. *Mechanisms of Ageing and Development* 132: 592-594.
 30. Reimer MM, McQueen J, Searcy L, Scullion G, Zonta B, et al. (2011) Rapid disruption of axon-glia integrity in response to mild cerebral hypoperfusion. *J Neurosci* 31: 18185-18194.
 31. Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, et al. (2012) Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathologica* 123: 381-394.
 32. Paranthaman R, Greenstein AS, Burns AS, Cruickshank JK, Heagerty AM, et al. (2010) Vascular function in older adults with depressive disorder. *Biol Psychiatry* 68: 133-139.
 33. Greenstein AS, Paranthaman R, Burns A, Jackson A, Malik RA, et al. (2010) Cerebrovascular damage in late-life depression is associated with structural and functional abnormalities of subcutaneous small arteries. *Hypertension* 56: 734-740.
 34. Brickman AM, Zahra A, Muraskin J, Steffener J, Holland CM, et al. (2009) Reduction in cerebral blood flow in areas appearing as white matter hyperintensities on magnetic resonance imaging. *Psychiatry Res* 172: 117-120.