PERSPECTIVE IN CURRENT NEUROPHARMACOLOGY

The Forgotten Cells: Role of Astrocytes in Mood Disorders During the Aging

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Mood disorders are frequent during old age and their prevalence increases as people age. Owing to their severe consequences, late-life mood disorders may be regarded as an important public health problem given their association with medical and cognitive deficits, as well as the increased risk of dementia and suicide mortality [1]. In spite of this evidence, the occurrence of mood disorders during aging, especially anxiety and depression, is underestimated because these psychopathologies are qualitatively different from those experienced by younger persons, and the symptoms experienced by elders are commonly similar to frequent disabilities generated by senescence, *i.e*. apathy, cognitive impairments and sleep disorders [2]. Fortunately, not all elderly people develop mental disorders and some of them can even have an adaptive response in the face of stress and adversity, which is known as resilient ability [3]. As it is deeply described in the manuscripts included in our CN Editorial [4], evidence suggests that a healthy lifestyle (good eating habits, moderate exercise, challenging mental activities, social support…) has a crucial role in promoting a resilient brain during aging.

Depression is a chronic, recurring, and serious mood disorder that affects up to 20% of the global population. Several studies about depression have reported structural changes such as decreased frontal lobe volumes (prefrontal, orbitofrontal and anterior cingulate cortices), as well as decreased volumes of subcortical and limbic structures (hippocampus, amygdala, caudate nucleus and putamen) that are critical components of the emotional and cognitive circuitry [5]. On the other hand, regarding neuronal mechanisms, the monoamine hypothesis of depression has dominated our knowledge about underlying pathophysiologic basis of depression for more than half a century. This classic theory considers that a depletion in the levels of monoamines, such as serotonin, norepinephrine, and/or dopamine is the main neurobiological basis of this disorder. Besides, this hypothesis seemed to be supported by the mechanism of action of antidepressants. Nevertheless, more cellular mechanisms must be considered and, recently, glia cells and in particular, astrocytes have shown to play a central role in brain homeostasis due to their involvement in the supply of energy metabolites to the neurons, as well as neurotransmitter recycling and synaptic connectivity functions [6, 7]. In view of these findings, these cells are considered as important contributors to neuronal dysfunction and they have shown to take part not only in neurodegenerative diseases, but also in mood disorders [8].

Regarding depression, since astrocytes participate in the uptake, metabolism and recycling of glutamate, it is possible that an astrocytic deficit may account for the alterations in glutamate/GABA neurotransmission in depression. For instance, a recent study of Fullana *et al*. (2019) [9] showed that the regionally selective knockdown of glutamate uptake by astrocytes in the infralimbic cortex evokes a depressive-like phenotype in mice along with a serotonergic hypoactivity. Apart from this alteration, impairments in another glial functions such as deficiency in neurotrophic and angiogenic factors, as well as reduction of number and morphological changes might be also involved in the pathogenesis of depression [8]. As we mentioned before, depression is usually associated with volume reductions in several key frontal-subcortical regions, but when these brain regions were analyzed histologically in aged people, no evident reduction of glial cells was found in the grey matter compared to younger individuals [10]. Hence, gliosis has been postulated to account for this finding suggesting that subtle vascular or inflammatory changes may be important in late-life depression.

As Czéh and Benedetto (2013) [11] proposed in their outstanding review on this topic, antidepressant treatment could not only affect neurons, but also activate astrocytes, triggering them to participate in specific functions that result in the reactivation of cortical plasticity and can lead to the readjustment of abnormal neuronal networks. Thereby, one possibility would be to promote specific astrocyte changes which could contribute to their therapeutic effectiveness in depression during the aging. Regarding this, antidepressant treatments, such as fluoxetine and paroxetine, have shown to induce a stimulatory effect on the expression levels of various trophic factors in astrocytes (brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and VGF mRNA expression [12]. On the other hand, astrocytes are also an important target for antidepressants which act on monoamine oxidase B (MAO-B), localized almost exclusively in astrocytes. Consequently, and taking this into account, a healthy lifestyle during aging could also promote these astrocytic changes constituting a non-pharmacological therapeutic approach for depression. For instance, several findings demonstrated a positive effect of physical

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activity on depressive-related symptoms by increasing BDNF levels in key brain regions which promote neuronal repair [13]. In addition, a promising avenue to improve mood disorders focuses on the effects of nutrients and dietary supplementation. Specifically, docosahexaenoic acid, the most abundant component of the n-3 PUFAs family, induced an astrocytosis reduction occurring with age showing that astrocytes are optimal targets of n-3 PUFA action in the brain. Interestingly, n-3 PUFA deficiency worsens age-induced hippocampal astrocytosis and promotes neuroinflammation [14]. Finally, the environmental enrichment paradigm, in which social, sensorial, physical and cognitive stimulation is provided to the rodents, has shown to be useful for studying a range of psychiatric conditions, including protective phenotypes in depression models. In line, with this downregulation of neurotrophic factor and decreased astrocytes was restored by this housing condition [15].

To sum up, there is promising evidence about the therapeutic potential of astrocytes questioning the classical neurocentric point of view of heath and disease. Moreover, modulation of astrocytic structure and function could result in an effective approach to modify and repair impaired neuronal function. With regard to the latter, we propose that a healthy lifestyle during our lifetime, and even throughout aging, could constitute a good approach to induce astroglial changes involved in an antidepressant effect.

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