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REVIEW

Antidepressants act directly on astrocytes: Evidences and functional consequences

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Abstract
Post-mortem histopathological studies report on reduced glial cell numbers in various frontolimbic areas of depressed patients implying that glial loss together with abnormal functioning could contribute to the pathophysiology of mood disorders. Astrocytes are regarded as the most abundant cell type in the brain and known for their housekeeping functions, but as recent developments suggest, they are also dynamic regulators of synaptogenesis, synaptic strength and stability and they control adult hippocampal neurogenesis. The primary aim of this review was to summarize the abundant experimental evidences demonstrating that antidepressant therapies have profound effect on astrocytes. Antidepressants modify astroglial physiology, morphology and by affecting gliogenesis they probably even regulate glial cell numbers. Antidepressants affect intracellular signaling pathways and gene expression of astrocytes, as well as the expression of receptors and the release of various trophic factors. We also assess the potential functional consequences of these changes on glutamate and glucose homeostasis and on synaptic communication between the neurons. We propose here a hypothesis that antidepressant treatment not only affects neurons, but also activates astrocytes, triggering them to carry out specific functions that result in the reactivation of cortical plasticity and can lead to the readjustment of abnormal neuronal networks. We argue here that these astrocyte specific changes are likely to contribute to the therapeutic effectiveness of the currently available antidepressant treatments and the better understanding of these cellular and molecular processes could help us to identify novel targets for the development of antidepressant drugs.

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1. Introduction

Despite the existing effective treatment strategies, the prevalence of depressive spectrum disorders is increasing worldwide. This growing burden calls for a better understanding of the pathophysiology of mood disorders and of the real therapeutic action of antidepressants. Already a decade ago, a theory has been put forward that suggested that abnormal functioning of glial cells could contribute to the pathophysiology of mood disorders (Coyle and Schwarcz, 2000; Cotter et al., 2001; Rajkowska and Miguel-Hidalgo, 2007). This theory was based on the numerous observations originating from post-mortem histopathological studies that reported on reduced glial cell numbers in various fronto-limbic areas of depressed patients, including the prefrontal and medial prefrontal cortex, the dorsolateral and orbito-frontal cortex, the amygdala and the hippocampus as well (for reviews see: Cotter et al., 2001; Harrison, 2002; Rajkowska and Miguel-Hidalgo, 2007; Drevets et al., 2008; Hercher et al., 2009).

During the last decade, our understanding on the various forms of astrocytic functions increased at a faster rate than for any other cell type in the nervous system, still astrocytes have often been neglected in the field of psychopharmacology. Our aim with this review was to gather the scattered, but abundant experimental evidences on the fact that antidepressant therapies do act on astrocytes, modify their function and morphology. We argue here, that the understanding of astrocytic involvement in antidepressant actions could help us to identify novel targets for the development of antidepressant drugs. We will focus mainly on astrocytes, but we will occasionally mention relevant data on other glial cell types, i.e. on oligodendrocytes, NG2-positive cells and microglia.

1.1. A brief introduction on astrocyte identity, structure and function

Historically, astrocytes have been viewed as a homogeneous population of cells, providing passive support for the neurons and carrying out numerous housekeeping functions, including energy supply and removal of toxic metabolites. This view has dramatically changed after numerous unexpected findings. However, our knowledge on astrocytic functions is still incomplete.

Astrocytes are considered the most numerous cell type in the mammalian brain (Sofroniew and Vinters, 2010). According to the general assumption, the human brain consists of 10–100 billion neurons and because glial cells are believed to outnumber neurons by 10–50 times, thus, astrocytes should be the most abundant cell type in the brain, probably making up almost one half of the entire cell population in the adult brain (Kandel, 2000; Rajkowska and Miguel-Hidalgo, 2007; Kimelberg and Nedergaard, 2010). Recent experimental data based on stereological cell counting – the gold standard for cell quantification – however report on much lower astrocyte (and glial cell) numbers. A study by Pelvig et al. (2008) quantified the number of neurons and various types of glial cells in the neocortex of adult humans, and reported the following numbers: the total number of glial cells were 27.9 billion in females and 38.9 billion in males, whereas the total number of neocortical neurons were 21.4 billion in females and 26.3 billion in males, providing a glia/neuron ratio of 1.3 for females and 1.5 for males. Furthermore, they documented the following distribution of the three main types of glial cells in the human neocortex: 75% oligodendrocytes, 20% astrocytes and 5% of microglial cells (Pelvig et al., 2008). Based on these data one can conclude that the total number of astrocytes in the four lobes of the adult human neocortex is ranging between 4.8 billion (in females) and 7.8 billion (in males). This also indicates that astrocytes make up only about 10% of the total cell number (neuron+glia) in the adult human neocortex.

The exact identification and classification of astrocytes is also a controversial issue since these cells might be as heterogeneous in physiology and form as neurons (Kimelberg, 2004, 2010; Barres, 2008; Cahoy et al., 2008; Hewett, 2009; Matyash and Kettenmann, 2010). The traditional classification was based on the morphology and location of these cells and grouped them into two main categories, the protoplasmic and the fibrillary (or fibrous) astrocytes (Miller and Raff, 1984). Protoplasmic astrocytes are found in the gray matter and their processes ensheath synapses as well as blood vessels while the fibrillary astrocytes are located to the white matter where they contact nodes of Ranvier and blood vessels (Hewett, 2009; Sofroniew and Vinters, 2010). There are other, more specialized astrocytes, like the Müller glia of the retina and Bergmann glia in the cerebellum and some suggests that certain types of astrocytes might be unique and specific to the human and primate neocortex (Oberheim et al., 2009).

Another classification approach is based on the antigenic phenotype of these cells and relies largely on the most commonly used astrocytic markers like GFAP, S100B, Aquaporin 4, GLAST or GLT-1 (Hewett, 2009). This classification has its own limits as many of these commonly used astrocytic markers are either not uniformly expressed in all astrocytes, or do not label completely the cell body and all the processes. For example, GFAP, the best known astrocytic marker is preferentially expressed in white matter over gray matter astrocytes and does not label all the processes (Bushong et al., 2002). Aquaporin 4 is a highly astrocyte specific marker, but it is localized only to the endfeet of the cells. Another problem with these astrocytic markers is their specificity: for example, GFAP is also expressed by stem cells in the adult brain, but these cell types are normally not considered as astrocytes (Hewett, 2009; Robel et al., 2011). The other most widely used marker S100B labels both the gray and white matter astrocytes, but it also labels oligodendrocyte progenitor cells and premyelinating, postmitotic oligodendrocytes.

Recent methodical advances greatly increased our knowledge about the identity, structure and organization of astrocytes. Microinjection of fluorescent dyes into single hippocampal astrocytes revealed a highly ordered arrangement of these cells, with each astrocyte covering its own specific territory that interfaces with the microvasculature and enveloping possibly thousands of synapses (Bushong et al., 2002). Genetic engineering enables us to generate transgenic mice in which astrocytes are labeled by fluorescent proteins that are expressed under the control of various astrocyte specific promoters (e.g. Zhuo et al., 1997;