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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 orbitofrontal 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;

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Nolte et al., 2001; Zuo et al., 2004; Slezak et al., 2007). This approach even allows the non-invasive in situ analysis of astrocytes under physiological and pathological conditions (Zhu et al., 2004; Cordeau et al., 2008). Another significant methodical progress is the production of transcriptome databases for astrocytes, which on one hand revealed surprising molecular diversity among astrocytes and on the other hand brought to light numerous new cell-specific markers e.g. the aldehyde dehydrogenase 1 family, member L1 (Aldh1L1) gene (Bachoo et al., 2004; Lovatt et al., 2007; Cahoy et al., 2008; Roesch et al., 2008). Furthermore, it is expected that the use of optogenetic tools will revolutionize our knowledge on astrocytic functions (Figueiredo et al., 2011).

Traditionally astrocytes have been considered to be passive, non-excitable support cells that provide scaffold to neurons. This view has changed dramatically since the discoveries that these cells express voltage-gated channels and various neurotransmitter receptors. Today, astrocytes are viewed as "excitable" cells that are activated by internal and external signals upon which they – most probably – release "gliotransmitters" affecting synaptic communication (Volterra and Meldolesi, 2005; Hamilton and Attwell, 2010; Kimelberg, 2010). Additionally, astrocytic processes wrap around synaptic connections and by that they not only insulate them, but actively modulate synaptic transmission as a third party member of the so called "tripartite synapse" (Haydon, 2001; Perea et al., 2009). Astrocytes also exert significant control over synapse formation, adult neurogenesis and vascular tone (Horner and Palmer, 2003; Attwell et al., 2010; Eroglu and Barres, 2010; Kimelberg, 2010).

## 2. Experimental evidences that antidepressant therapies act on astrocytes

The first antidepressant drugs were discovered in the late 1950s by serendipity, when two unrelated compounds were found to improve the mood of treated patients. One of them was developed to treat tuberculosis (iproniazid, a monoamine oxidase inhibitor) and the other was imipramine, originally developed to be an antipsychotic compound with anti-histaminic properties. These compounds were later shown to exert their antidepressant effects through enhancement of synaptic serotonin and noradrenaline availability. Based on these findings the monoamine hypothesis of depression has been formulated (Schildkraut, 1965) which dominated the field during the past 40–50 years. This theory explained the biological basis of affective disorders assuming that deficiencies and/or imbalances in the serotonin, the noradrenaline, and presumably the dopamine system underlie the depressive symptoms. Over the years, this hypothesis has been refined, but it has become evident that factors beyond monoamine deficiency or imbalance in the respective neurotransmitter systems must be taken into account (Manji et al., 2001; Nestler et al., 2002; Castrén, 2005; Krishnan and Nestler, 2008, 2010). In the following pages we will list experimental evidence on how the currently available antidepressant therapies affect the morphological and functional characteristics of astrocytes and we argue that these changes are likely to contribute to the therapeutic effectiveness of these treatment strategies.

### 2.1. Antidepressant therapies regulate the expression of GFAP and other astroglia specific proteins

Because of the well known limitations of the currently available antidepressant drugs there is a constant endeavor to discover new treatment strategies. One strategy that was taken by several groups recently was to carry out an unbiased search for common cellular mechanisms underlying the effects of different types of antidepressant treatments. To fulfill this they analyzed antidepressant-induced transcriptional and translational changes in the brains of experimental animals (Conti et al., 2007; Sillaber et al., 2008). One unexpected finding of these studies was a pronounced up- or down-regulation of various glial specific genes like GFAP, vimentin, aquaporin 4 or Ndrg2 (Nichols, 2003; Takahashi et al., 2005; Conti et al., 2007; Sillaber et al., 2008). Others reported on increased expression of Connexin 43 (a major component of astrocytic gap junctions) in the prefrontal cortex following chronic treatment with fluoxetine or clozapine, while it was significantly decreased by haloperidol and lithium (Fatemi et al., 2008). A study using the chronic unpredictable stress model for depression in rats found that the stress-induced reduction of hippocampal GFAP expression was reversed by treatment with the tricyclic antidepressant clomipramine (Liu et al., 2009). In contrast, a recent study that was screening for compounds that could inhibit the increased expression of GFAP after brain injury revealed that clomipramine and amitriptyline caused the strongest reduction in GFAP expression levels in primary astrocytic cultures (Cho et al., 2010).

The most consistent finding on astrocytic activation was observed after electroconvulsive stimulation (ECS). Pronounced up-regulation of GFAP immunoreactivity was described in various brain areas such as the hippocampus, amygdala and piriform cortex of rats after ECS treatment already in the early '90s (Kragh et al., 1993; Steward, 1994). Follow up studies observed alterations in the cellular morphology of astrocytes, NG2-positive glial cells and microglia in response to ECS (Jansson et al., 2009). Furthermore, ECS treatment induced the expression of the antigen-presenting molecule MHC II in microglia and the lysosomal protein ED1 (expressed by phagocytic cells) was also up-regulated in hippocampal microglia (Jansson et al., 2009). A small, but rigorous nonhuman primate study also found a pronounced up-regulation of GFAP immunoreactivity after ECS in the hippocampus and neocortex of monkeys (Dwork et al., 2004). High frequency (25 Hz) transcranial magnetic stimulation (TMS) of rats also resulted in a dramatic increase in the levels of GFAP mRNA in the hippocampal dentate gyrus and modest up-regulation was observed in the cerebral cortex (Fujiki and Steward, 1997).

Antidepressant treatments also have a profound stimulatory effect on the expression levels of various trophic factors. A study using primary cultures of cortical astrocytes showed that treatment of astrocytes with fluoxetine and paroxetine up-regulated brain derived neurotrophic factor

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(BDNF), vascular endothelial growth factor (VEGF), and VGF mRNA expression (Allaman et al., 2011). The same study also reported that the tricyclic antidepressant desipramine and imipramine did not affect the expression of these neurotrophic/growth factors (Allaman et al., 2011).

Finally, it is worth noting here the findings on the ability of certain antidepressants to modulate epigenetic parameters of astrocytes in cell cultures (Perisic et al., 2010). Overall these data clearly indicate that various types of antidepressant treatment strategies activate or at least act directly on astrocytes, as well as on microglia and NG2-positive glial cells.

## 2.2. Antidepressants activate specific intracellular signaling pathways in astrocytes

Several signaling pathways have been implicated in the development of mood disorders and in the response to antidepressant treatment. In vitro studies provide important evidences that astrocytes respond directly to antidepressant treatment. The advantage of the cell culture experiments is that they allow the clear distinction of cell-type specific responses. Several groups have confirmed that the ERK/MAPK pathway is a common target in glial cells for most of the currently used pharmacological treatments for depression (Mercier et al., 2004; Hisaoka et al., 2001, 2007; Li et al., 2009; Di Benedetto et al., 2012). Studies using primary cultures of rat astrocytes treated with fluoxetine pointed out the MAPK signaling pathway as a target, together with further acute induction (already 2 h after the beginning of the treatment) of specific downstream genes like BDNF and GDNF (glial cell line-derived neurotrophic factor) and their respective receptors TrkB and GDNF receptors (Mercier et al., 2004). Hisaoka and colleagues examined the effects of several classes of antidepressants on the MAPK signaling pathway in primary astrocytes and C6 glioma cells (used as an in vitro model for astrocytes) and found this pathway as a common target of all tested antidepressant drugs, with the release of GDNF as a correlated factor (Hisaoka et al., 2007). In the same cell line, we also demonstrated that reboxetine, as well as norquetiapine, the major metabolite of quetiapine (an atypical antipsychotic and recently approved antidepressant), could activate simultaneously both ERK/MAPK isoforms ERK1 and ERK2, with a consequent increased release of GDNF (Di Benedetto et al., 2012).

Because one of the major drawbacks of antidepressant drugs is their slow onset of therapeutic action, it was speculated that a mechanism which could fine-tune the activation of MAPK signaling pathway in astrocytes, may allow a faster response to stimuli and an earlier influence on their cellular microenvironment. This approach might be then used as a mean to induce a faster occurrence of treatment response. We demonstrated, for example, that the specific down-regulation of Erk1 mRNA via RNAi was sufficient to hamper the increased GDNF release observed after norquetiapine and reboxetine treatment in C6 glioma cells (Di Benedetto et al., 2012). This suggests the possibility of a fine modulation of signaling pathways via the controlled regulation of single intermediator molecules.

The NF-kB pathway is another signaling pathway that is cell-autonomously activated in astrocytes upon antidepressant treatment, as it was shown in cultured astrocytes of human origin treated with tianeptine (Hwang et al., 2008; Janda et al., 2011). It should be noted here that the NF-kB pathway has been repeatedly pointed out as a putative molecular target of antidepressant treatment (Post et al., 2000; Koo et al., 2010).

Finally, a study that searched for cell-autonomous mechanisms of action of antidepressants identified the autophagic process as a common downstream mechanism activated specifically in astrocytes by the treatment of two different classes of antidepressants, the tricyclic amytriptyline and the SSRI citalopram (Zschocke et al., 2011). Furthermore, they described the activation of PI3 kinase signaling pathway as a converging point (Zschocke et al., 2011).

## 2.3. Antidepressant treatment alters astrocytic receptor expression and inhibits glial serotonin transporters as well

Astrocytes express receptors and transporters for all the major neurotransmitter systems including the glutamatergic, GABAergic, adrenergic, serotonergic, dopaminergic, acetylcholinergic and purinergic systems (for review see: van Calker and Biber, 2005; Pav et al., 2008). Furthermore, they express receptors for neurotrophic factors, cytokines, neuropeptides and also for mineralocorticoid and glucocorticoid receptors (John et al., 2003; Pav et al., 2008; Sofroniew and Vinters, 2010). However, one should always keep in mind that most of these data are originating from in vitro experiments and cultured cells may express more receptors than cells in situ because of their altered gene expression profile. Verification of the in vitro data in animals has often been difficult (Kimelberg, 2010), but we know for sure that astrocytes in the adult rodent brain express 5-HT1A and 5-HT7 receptors (Whitaker-Azmitia et al., 1993; Shimizu et al., 1996; Hirst et al., 1997) and that SSRIs inhibit glial serotonin transporters as well (Dave and Kimelberg, 1994; Bal et al., 1997). Besides the serotonergic system, the adrenergic neurotransmitter system is the one most commonly suggested to play a key role in the pathophysiology of mood disorders. Non-pharmacological antidepressive interventions such as ECT or sleep deprivation are associated with increased adenosine release and up-regulation of glial adenosine A1-receptors in the brain (van Calker and Biber, 2005). Upon stimulation, these adenosine receptors on astrocytes and microglia release neurotrophic factors that are important for the survival and growth of neurons (van Calker and Biber, 2005). The tricyclic desipramine can decrease the density of beta-adrenoceptors in astroglial cells from rat forebrain without modification of their corresponding affinity (Sapena et al., 1996).

In a series of experiments Kurachi and co-workers found that both fluoxetine and nortriptyline are able to block the astrocytic inwardly rectifying $K^+$ (Kir) channel Kir4.1, which is responsible for astroglial $K^+$ buffering (Ohno et al., 2007; Su et al., 2007; Furutani et al., 2009). This is interesting since potassium channels have been implicated recently in the pathophysiology of mood disorders (Heurteaux et al., 2006) and numerous studies have demonstrated that

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modulation of ion channel activity can reduce depressive behavior both in humans and in animal models and ion channels have been suggested as potential targets for novel antidepressant drugs (Lodge and Li, 2008).

## 2.4. Physiological evidences that antidepressants act directly on astrocytes

Traditionally, astrocytes have been viewed as 'silent', 'non-excitable' cells since they are unable to generate action potentials. Since then we now know that these cells can also be activated by internal or external signals and that they communicate with neighboring neurons and glia and for this reason astrocytes are now days regarded as 'excitable' cells (Volterra and Meldolesi, 2005; Sofroniew and Vinters, 2010). Astrocytic excitation cannot be revealed with electrophysiological recordings, as in neurons, but by assays of $[Ca^{++}]_i$ transients and oscillations. Two types of astrocyte excitation are known. One is triggered by chemical signals from the neuronal circuits (neuron-dependent excitation) and the other one is the intrinsic oscillations resulting from $Ca^{++}$ released from intracellular stores (spontaneous excitation) (Volterra and Meldolesi, 2005; Sofroniew and Vinters, 2010). Many scientists argue that these $Ca^{++}$ signals in turn elicit the release of transmitters such as glutamate into the extracellular space (a phenomena called 'gliotransmission') and thereby trigger receptor mediated currents in neurons, and at the same time can be propagated to neighboring astrocytes as well (Volterra and Meldolesi, 2005; Halassa et al., 2007; Perea et al., 2009; Hamilton and Attwell, 2010).

To the best of our knowledge there is only one study by Schipke et al. (2011) that analyzed the physiological response of astrocytes to antidepressant drugs. They investigated astrocytic calcium signaling in the medial prefrontal cortex of acute mouse brain slices after the application of citalopram and fluoxetine. They found that these two SSRIs could directly elicit calcium signals in about 1/3 of all astrocytes, even when neuronal signal propagation was pharmacologically inhibited. Application of citalopram and fluoxetine triggered calcium transients that were delayed and asynchronous, and very similar to the response they could observe after 5-HT application, but completely different to the glutamate-induced calcium responses in astrocytes. This study is the first that demonstrated that astrocytes in the intact mouse prefrontal cortex exhibit functional 5-HT receptors and are targets for antidepressant drugs. These findings provide evidence that astrocytic function can directly be modulated by SSRIs, but the relevance of these astrocytic calcium signals for the therapeutic effect of SSRIs remains to be elucidated.

Comparable findings have been reported using cultured mouse astrocytes where fluoxetine altered calcium influx and this effect appears to be mediated by interaction and editing of the kainate receptor GluK2 (Li et al., 2011a,b). Intracellular calcium signaling and the downstream consequences of its activation play key roles in the regulation of numerous essential cellular functions. We have just started to learn about the specific roles that calcium signaling plays in astrocytes with the help of advanced genetic tools (Lee et al., 2006; Shigetomi et al., 2010).

## 2.5. Changes in gliogenesis, glial morphology and glial cell numbers after antidepressant treatment

As noted earlier, several post-mortem studies document altered morphology and reduced number of glial cells in various frontolimbic areas of depressed patients (Ongür et al., 1998; Cotter et al., 2001; Bowley et al., 2002; Harrison, 2002; Rajkowska and Miguel-Hidalgo, 2007). These structural changes are likely to reflect functional impairments of the glial cells which may either be the cause or the consequence of the pathophysiology of depression. What is rarely considered is that antidepressant treatment per se could result in such changes. The post-mortem histopathological studies often include patients with a history of various antidepressant and/or antipsychotic treatment. In this respect it is important to know that a well controlled non-human primate study demonstrated that chronic (1.5–2 years) exposure to antipsychotic medications (haloperidol or olanzapine) was associated with a significant reduction in astrocyte number and with a non-significant trend for lower oligodendrocyte number in the parietal cortex of macaque monkeys (Konopaske et al., 2007, 2008).

In a study, using the chronic social defeat stress paradigm as an animal model for depression, we found that stress induced a significant reduction in the number of astrocytes in the hippocampal formation, but this effect of stress was counteracted by chronic concomitant treatment with fluoxetine resulting in hippocampal astrocyte numbers in the control range (Czéh et al., 2006). These data suggest that antidepressant treatment may influence the number of astrocytes. One possible explanation for such findings is that antidepressants may enhance the cellular resilience of glial cells, similarly as it has been suggested for neurons (Manji et al., 2003). In this case, antidepressant treatment could rescue atrocytes from the deleterious effects of stress. Another possible explanation is that antidepressant treatment influences glial cell numbers by affecting glial cell proliferation. This possibility is largely unexplored, but there is some evidence on enhanced gliogenesis in the prefrontal cortex of experimental animals treated with fluoxetine (Kodama et al., 2004; Czéh et al., 2007). Pronounced up-regulation of gliogenesis has been documented by many after ECS treatment both in the hippocampus and in the prefrontal cortex (Madsen et al., 2005; Wennström et al., 2006; Ongür et al., 2007; Jansson et al., 2009). Although in most of these studies the largest population of the newly generated glial cells were NG2-positive cells (in the neocortex), but astrocytes were affected as well (especially in the hippocampal dentate gyrus). NG2-positive cells comprise an abundant glial cell population that is widely and uniformly distributed throughout the mature CNS where they make up the largest population of continuously proliferating cells (Butt et al., 2002, 2005; Robel et al., 2011). The exact classification and functional role of this glial type is not completely understood. Traditionally, NG2 expressing glia were considered to be oligodendrocyte precursor cells that persist in the adult CNS, generating oligodendrocytes throughout life (Butt et al., 2002, 2005). However, these cells have many of the morphological features of astrocytes. They are stellate cells with elaborate multiple branching processes that form multiple contacts with neurons, astrocytes, oligodendrocytes,

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and myelin and for this reason they are also known as "synantocytes", a unique cell type that may be specialized to monitor signals from neurons and glia, and to respond to changes in the integrity of the CNS (Butt et al., 2002, 2005).

It is well documented that antidepressant treatment can stimulate adult neurogenesis in the hippocampal dentate gyrus and this specific effect of antidepressants may contribute to their therapeutic efficacy (Dranovsky and Hen, 2006; Lucassen et al., 2010). Astrocytes are likely to have a significant role in this process since the precursor cells that generate the newborn neurons are in fact radial astrocytes (Seri et al., 2001; Doetsch, 2003; Mori et al., 2005; Robel et al., 2011). Furthermore, neighboring astrocytes within the neurogenic niche also regulate the process of adult neurogenesis by the release of various growth and neurotrophic factors (Song et al., 2002; Horner and Palmer, 2003). Interestingly, a recent in vitro study documented that antidepressant drugs (imipramine, fluoxetine and venlafaxine) could induce human mature astrocytes to differentiate into cells that express various neuron specific markers, i.e. they had a neuronal phenotype (Cabras et al., 2010). Once again, this finding should be interpreted with caution because of the limitations of the in vitro experiments, but it suggests that antidepressant drugs may even guide the differentiation path of precursor cells. One should also emphasize that in this experiment they could not produce functionally intact neurons, i.e. these cells were not electrophysiologicaly active (Cabras et al., 2010).

There is also evidence that antidepressant drugs can affect the cellular morphology of astrocytes both in vitro (Cabras et al., 2010) and in vivo (Czéh et al., 2006), but these findings should be substantiated and extended by further experiments.

### 2.6. Antidepressant treatment affects the expression levels of potential glial specific biomarkers

Identification of objective biomarkers would make a significant advance in our ability to diagnose and assess the treatment response of depressed patients. Sadly, such biomarkers are not yet available. Among the numerous candidates there are a few interesting ones that may serve as glial specific biomarkers reflecting changes not only in disease status, but also indicative of astrocytic function and integrity.

S100B is one such candidate. S100B is a calcium-binding protein predominantly expressed within the cytoplasm of astrocytes, but also known to be secreted to the extracellular space and it can be easily detected in the serum of patients (Zimmer et al., 1995; Sen and Belli, 2007; Steiner et al., 2007). S100B appears to have numerous intra- and extracellular functions. It is an important player of calcium homeostasis, it regulates enzyme activity and inhibits protein phosphorylation, and seems to play a role in the assembly of important components of cell cytoarchitecture (Sen and Belli, 2007). When secreted in the extracellular space it can exert both trophic or toxic effects depending on its concentration. At lower (nanomolar) concentrations S100B can stimulate astrocyte proliferation and neurite outgrowth and enhances both the survival and regeneration of neurons, but in higher (micromolar) concentrations it is neurotoxic (Sen and Belli, 2007). Both in vitro and in vivo studies suggest that S100B is released in a neural- and synaptic-activity-dependent manner and can function as a neuromodulator gliotransmitter (Sakatani et al., 2008).

S100B is also one of the oldest known "brain specific protein" and has long been regarded as a potential biomarker for brain damage. S100B is elevated and released into the blood circulation in a variety of CNS disorders including ones with developmental origin like Down's syndrome, cerebral palsy and Gilles de la Tourette syndrome as well as in acute brain damage, epilepsy and Alzheimer's disease (Sen and Belli, 2007). Importantly, there is consistent experimental evidence for increased S100B serum levels in schizophrenia and in mood disorders (Rothermundt et al., 2009; Schroeter et al., 2010). It has been suggested, that S100B may therefore be a key player in the pathogenesis of these psychiatric disorders, but it cannot differentiate between them (Schroeter and Steiner, 2009). Though some of the above mentioned findings are originating from drug naïve or medication-free patients, it has been suggested that medication may actually contribute to the elevated S100B levels observed in the patients. Cell culture experiments however demonstrate that the typical antipsychotic drug haloperidol and the atypical prototype drug clozapine reduce the synthesis and release of S100B by astrocytic cells (Steiner et al., 2010). In contrast, fluoxetine appears to increase S100B content in the rat hippocampus (Manev et al., 2001; Tramontina et al., 2008), but this finding is not supported by the clinical data. In depressed patients, antidepressant treatment can either normalize or not affect the elevated serum levels of S100B (Hetzel et al., 2005; Schroeter et al., 2002, 2008, 2010). On the other hand, electroconvulsive therapy (ECT) was associated with small, but significant increase in S100B levels shortly (1–3 h) after ECT (Arts et al., 2006) and similar stimulating effects have been reported in animals after ECS treatment (Busnello et al., 2006). It has been also suggested that S100B serum concentrations may be of predictive validity for the response to antidepressant treatment (Arolt et al., 2003).

Clearly, more studies are needed to clarify the effect of antidepressant therapy on S100B expression levels. Furthermore, the crucial question of this field is still open: is it the damaged, decomposing astrocytes that release S100B to the circulation, or is this a result of an active release from intact astrocytes as an attempt to repair neuronal damage? Experts on the field tend to favor the protective role of S100B which is induced by a yet unknown degenerative mechanism involved in the pathogenesis of depression (Hetzel et al., 2005; Kleindienst and Ross Bullock, 2006; Steiner et al., 2006).

The use of in vivo localized proton magnetic resonance spectroscopy (MRS) is another promising approach to identify potential biomarkers for neuropsychiatric disorders and it might be the right tool to identify glial specific biomarker(s) in the brain. Proton MRS can measure cerebral metabolites and because of its noninvasive character (follow-up) proton MRS has the potential and sensitivity to identify treatment effects (Lyoo and Renshaw, 2002). One of the major brain metabolites is *myo*-inositol (Ins) which is regarded as a specific marker for astrocytes (Brand et al., 1993). Our earlier experiments suggest that the tricyclic antidepressant clomipramine can increase CNS *myo*-inositol

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levels in an animal model for depression (van der Hart et al., 2002), and similar positive effects were shown after escitalopram treatment in the hippocampus of maternally separated rats (Hui et al., 2010). There are clinical data corroborating these findings. For example a recent study demonstrated significant reduction of *myo*-inositol concentrations in the left prefrontal cortex of patients with treatment-resistant unipolar depression and this was normalized after high frequency repetitive transcranial magnetic stimulation (rTMS) treatment (Zheng et al., 2010). In the same study, a positive correlation was observed between the clinical improvement and the increment in *myo*-inositol levels (Zheng et al., 2010). In another study, increased *myo*-inositol levels were reported after lithium treatment of older adults with bipolar disorder (Forester et al., 2008). There are also negative findings in the literature and further studies are necessary to clarify the usefulness of *myo*-inositol concentration measurements as a biomarker in patients with mood disorders.

## 3. The functional consequences of antidepressant action on astrocytes

In the second part of this review we will summarize astrocytic functions that were on one hand implicated in the pathophysiology of depression and on the other hand are likely to be modulated by the currently available antidepressant interventions. We will also propose some theories to explain the potential role of astrocytes in antidepressant action.

### 3.1. Does antidepressant treatment activate astrocytes?

As summarized in the first part of the review antidepressant therapies often result in a cellular phenotype that resembles best to activated (reactive) astrocytes. The increased expression of GFAP and vimentin, the increased release of trophic factors and cytokines, the increased proliferation rate all suggest this possibility (Czéh et al., 2006, 2007; Wennström et al., 2006; Ongür et al., 2007; Conti et al., 2007; Sillaber et al., 2008; Jansson et al., 2009; Allaman et al., 2011; Warner-Schmidt et al., 2011). One should however point out that many of the studies reporting on such findings are in fact originating from studies where naive (healthy) animals were treated with antidepressant drugs which do not mimic the clinical practice. It is important because others reported on clear anti-inflammatory effects of antidepressant treatment on glial cells especially in conditions that aimed to model neurological disorders (Hwang et al., 2008; Vollmar et al., 2008; Jin et al., 2009; Zhu et al., 2009). It is possible that antidepressant treatments have differential effect on astrocytes depending on the pre-existing condition.

As a working hypothesis, we propose here that antidepressant treatment causes a mild form of reactive astrocytosis. Reactive astrocytosis is typically associated with CNS injury or disease and with negative consequences such as neural toxicity and inhibition of axon regeneration (Sofroniew, 2005). But this comprehension is too simplistic. We now know that reactive astrogliosis represents a finely gradated continuum of molecular, morphological, and functional changes that range from subtle alterations in gene expression to scar formation (Hamby and Sofroniew, 2010). Furthermore, reactive astrocytes have protective roles as well, as it was shown after ischemic or traumatic brain injury (Myer et al., 2006; Li et al., 2008). Reactive astrocytes can exert both beneficial and detrimental effects in a context-dependent manner and these cells are now identified as potential therapeutic targets for CNS disorders (Hamby and Sofroniew, 2010). We suggest here that the antidepressive interventions activate astrocytes to a certain extent which then results in altered regulation of various astrocytic functions that are listed below.

### 3.2. Control of glutamate and GABA transmission

Astrocytes regulate the extracellular levels of amino acid neurotransmitters glutamate and GABA (Kimelberg, 2010) and by that they are likely to affect virtually all the vital CNS functions as it has been demonstrated for example to corticostriatal information processing (Goubard et al., 2011). Both the glutamatergic and GABAergic neurotransmitter systems have been implicated in the pathopysiology of mood disorders (Krystal et al., 2002; Brambilla et al., 2003; Kalueff and Nutt, 2007; Hashimoto, 2009; Mitchell and Baker, 2010; Luscher et al., 2011; Sanacora et al., 2012). We will focus here on the altered astrocytic regulation of glutamate homeostasis since this is the one most convincingly documented in the literature. However, we will provide only a brief summary since this issue has been extensively discussed by several recent excellent review papers (e.g. Sanacora et al., 2008; Valentine and Sanacora, 2009; Machado-Vieira et al., 2009; Popoli et al., 2011).

It is well demonstrated that the expression or activity of astrocytic glutamate transporters are regulated to a large extent both transcriptionally and post-transcriptionally (Hamby and Sofroniew, 2010). Human studies using post-mortem microarray analysis of the locus coeruleus and specific cortical areas from depressed individuals demonstrated significant changes in the expression levels of several proteins involved in glutamate homeostasis and some of these proteins are specific to astrocytes (Choudary et al., 2005; Bernard et al., 2011). An experimental study demonstrated that depressive-like phenotype was induced by blocking astrocytic glutamate uptake with the astrocytic glutamate transporter (GLT-1) inhibitor, dihydrokainic acid (DHK) (Bechtholt-Gompf et al., 2010). After such treatment anhedonia and cognitive impairment were observed in the animals, both of which are common symptoms of depression (Bechtholt-Gompf et al., 2010). Similar finding was reported by another group which injected DHK into the amygdala of rats and observed reduced social interaction (Lee et al., 2007). The same group also demonstrated that chronic blockade of glutamate uptake by a glial/neuronal transporter antagonist L-trans-pyrrolidine-2,4-dicarboxylic acid (PDC) within the amygdala results in dose-dependent reduction in social exploratory behavior and disrupts circadian activity patterns consistent with symptoms of mood disorders (Lee et al., 2007). Another study observed dysfunctional astrocytic glutamate regulation including down-regulation of the glia glutamate transporter GLAST in an

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animal model for depression (Gómez-Galán et al., 2012). Using another kind of animal model for depression, the chronic stress paradigm, Banasr et al. (2010) demonstrated that chronic stress impairs cortical glial function. Chronic stress resulted in depressive like behavioral phenotype and impaired glial cell metabolism in the prefrontal cortex. Interestingly, the stress-induced cellular, metabolic and behavioral alterations were normalized by treatment with the glutamate-modulating drug riluzole (Banasr et al., 2010). Riluzole is an approved drug marketed for the treatment of amyotrophic lateral sclerosis, but thought to be neuroprotective through its modulation of glutamatergic neurotransmission. It has multiple molecular actions in vitro, and one of them that has been documented to occur at physiologically relevant drug concentrations is the enhanced astrocytic uptake of extracellular glutamate (Pittenger et al., 2008). Glutamatergic agents like riluzole has been proposed as a new class of antidepressant drugs (Zarate et al., 2010).

In summary, there is compelling evidence that in depressed patients the glutamatergic and GABAergic neurotransmitter systems are altered and that traditional antidepressant pharmacotherapies act on the glutamatergic system (Hashimoto, 2009; Mitchell and Baker, 2010). Since astrocytes have a key role in glutamate homeostasis and because there is experimental evidence demonstrating that antidepressant drugs can affect the expression levels of various glial specific glutamate transporters (Reagan et al., 2004; Perisic et al., 2010; Song et al., 2010) thus, it is very likely that this route of action could contribute to their therapeutic efficacy. Furthermore, drugs targeting glutamate neurotransmission are hot candidates for novel antidepressant drugs (e.g. Pittenger et al., 2007; Skolnick et al., 2009; Wieronska and Pilc, 2009; Zarate et al., 2010).

### 3.3. The release of trophic factors

Astrocytes release a variety of trophic factors and cytokines under normal conditions and when activated the number of these secreted factors can further increase (Ridet et al., 1997). Trophic factors are hot candidates in the pathogenesis of mood disorders and antidepressant action as proposed by the ''neurotrophic hypothesis'' of depression (Castrén, 2005; Duman and Monteggia, 2006; Castrén et al., 2007). As discussed in Section 2.2. astrocytes can respond to antidepressant treatment with an increased expression of growth factors like BDNF or GDNF and GDNF appears to be a common downstream factor released upon antidepressant treatment of astrocytes (Hisaoka et al., 2001, 2007; Allaman et al., 2011; Kim et al., 2011; Di Benedetto et al., 2012). GDNF has been described for the first time in 1993 as a protective agent for dopaminergic neurons (Lin et al., 1993). More recently GDNF has been indicated as an important ligand for the establishment of synaptic contacts through a precise alignment of pre- and postsynaptic terminals (Ledda et al., 2007). This could be an underlying molecular mechanism contributing to the putative role of antidepressant to restore ''aberrant'' neuronal networks (Manji et al., 2003; Berton and Nestler, 2006; Pittenger and Duman, 2008; Krishnan and Nestler, 2010).

Interestingly, a recent report documented how the differential epigenetic status of the GDNF gene modulates susceptibility and adaptation to chronic stress in two genetically distinct mouse strains that exhibit different behavioral responses to chronic stress (Uchida et al., 2011). This study described how the differential methylation pattern of the GDNF promoter is sufficient to imprint innate ''high anxiety'' or ''low anxiety'' behavioral responses to BALB/cJ and C57BL/6J strains, respectively. Moreover, they described how they could reverse the maladaptive phenotype of BALB/cJ mice via imipramine administration, a known tryciclic antidepressant (Uchida et al., 2011). This study provides the first evidence for a putative molecular mechanism linking antidepressant treatment to the regulation of GDNF expression often described as a downstream effector released by astrocytes after antidepressant treatment by the in vitro studies.

In addition to these factors, recent reports identified the fibroblast growth factor 2 (FGF2) as a mediator of antidepressant activity in astrocytes (Bachis et al., 2008; Hisaoka et al., 2011). These studies demonstrated how amitriptyline, desipramine and fluoxetine could induce the activation of the FGF receptor signaling cascade and expression of FGF2 in cerebral cortex and hippocampus, respectively. FGF2 is an important growth factor, essential for proper formation and maturation of synaptic connections.

Finally, it is worth mentioning that a recent study demonstrated significant up-regulation in the expression levels of various cytokines like TNF-$\alpha$, IFN-$\gamma$, IL-1b, IL-3, IL-6, IL-10, IL-12(p70) and IL-12(p40) after citalopram treatment in the brain (Warner-Schmidt et al., 2011). Although in this study it was not specified which type of cells was responsible for the up-regulated release of these cytokines, but most probably astrocytes also contributed to these changes.

### 3.4. Affecting synaptic communication and synaptogenesis

Mature protoplasmic astrocytes exhibit a tremendously dense ramification of fine processes, which enables them to maintain intimate relationships with many elements of the brain parenchyma and a single astrocyte may interact with as many as 10,000 synapses (Bushong et al., 2003, 2004). Astrocytic processes wrap around the synaptic contacts and actively modulate synaptic transmission as a third party member of the so called ''tripartite synapse'' (Haydon, 2001; Perea et al., 2009). Furthermore, these astrocytic processes dynamically reshape their apposition to synapses in response to environmental cues similarly to dendritic spines that respond to changes in activity by altering their structure (Allen and Barres, 2005). Via these tight structural relationship astrocytes can induce synaptogenesis and influence synaptic stability, structure and elimination (Allen and Barres, 2005; Freeman, 2006; Chung and Barres, 2011). Experimental studies have started to unravel the exact molecular mechanisms underlying these cellular processes, for example it has been shown that during development immature astrocytes express thrombospondins (TSPs)-1 and -2 and that these TSPs

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promote CNS synaptogenesis in vitro and in vivo (Christopherson et al., 2005). TSPs induce ultrastructurally normal synapses that are presynaptically active, but postsynaptically silent and work in concert with other, as yet unidentified, astrocyte-derived signals to produce functional synapses (Christopherson et al., 2005). It is known that TSP1 and TSP2 levels are normally low in the adult brain, but reactive astrocytes express these proteins (Lin et al., 2003). To the best of our knowledge the effect of antidepressant treatment has not been yet investigated upon TSP expression, but as it has been suggested, drugs that interact with TSPs may help to promote synaptic plasticity. Antidepressant therapies may activate astrocytes and turn them into a status where they have augmented impact on synaptic formation and elimination. It could also happen that upon antidepressant treatment reactive astrocytes simply carry out excessive synaptic stripping either randomly or at specific locations and by that they ''erase'' abnormally formed neuronal networks that have been generated during the pathogenesis of the disorder. Such astrocyte regulated synaptic stripping could allow the development of new networks and healthy synapses and such rewiring could contribute to the recovery from the disease. This theory may sound too speculative, but we know that astrocytes are capable of controlling such events during development and in the adult brain both in physiological and pathological conditions (Allen and Barres, 2005; Eroglu and Barres, 2010; Chung and Barres, 2011).

### 3.5. Metabolic functions of astrocytes: The energy suppliers

The metabolic significance of astrocytes has been long recognized as they were traditionally thought to be the sole energy suppliers of neurons (Pellerin and Magistretti, 2003, 2004). This energy supply is guaranteed by a network connecting astrocyte endfeets and blood vessels for the active transportation of glucose from blood to neurons (Tsacopoulos and Magistretti, 1996; Kacem et al., 1998; Attwell et al., 2010). This astrocyte-neuronal lactate shuttle is vital for neurons and it has been proven to play critical roles in neuronal network functions such as long-term memory formation (Suzuki et al., 2011).

Interestingly, a recent hypothesis proposed that impaired cerebral glucose metabolism in the frontal lobe by astroglia might be the cause of depressive disorder (Hundal, 2007). This hypothesis is based on two observations: first, epidemiologic studies demonstrate that patients with diabetes mellitus have increased incidence of depression, and vice versa (Hundal, 2007). Furthermore, even the non-diabetic depressed patients often have disturbed insulin- and glucose-metabolism, probably as a compensatory reaction, since these disturbances are normalized in remission (Hundal, 2007). The second supporting information is originating from PET-scan studies demonstrating that patients with depressive disorder have reduced glucose metabolism in frontal part of the brain (Drevets, 2000). These findings are completed with the well documented post-mortem data showing reduced glial numbers in the same brain regions (Cotter et al., 2001; Rajkowska and Miguel-Hidalgo, 2007). Thus, according to Hundal's (2007) theory, depressive disorder is a disease with impaired astroglial glucometabolism and the fundamental pathophysiology is the astrocytic dysfunction, with the neuronal pathology being only secondary.

Although this hypothesis has not yet been tested experimentally, there is some evidence that antidepressant treatment modulates the astrocytic glucose homeostasis and the astrocyte–neuronal lactate shuttle. For example glucose metabolism in cultured astrocytes is influenced by fluoxetine administration (Li et al., 2009; Allaman et al., 2011). Another in vivo experiment showed that chronic treatment with riluzole (an agent believed to modulate glutamatergic neurotransmission, see Section 3.1.) induced increased glucose metabolism in the prefrontal cortex and hippocampus of rats (Chowdhury et al., 2008).

Although these ideas are yet in a very preliminary stage, they hold the promise to develop new strategies to readjust energy supply to neurons and to counteract hypofrontality in depression via the modulation of glucose metabolism in astrocytes.

### 3.6. Other less explored functional consequences affecting the blood-brain barrier, ion and water homeostasis

Besides the above discussed functions, astrocytes carry out numerous other vital tasks in the adult CNS such as maintaining the integrity of the blood–brain barrier, control of blood flow and the regulation of fluid, ions (especially potassium) and pH homeaostasis (Attwell et al., 2010; Kimelberg, 2010; Sofroniew and Vinters, 2010). All these functions might be affected by antidepressant treatments. These possibilities are less explored, but there are some interesting examples.

Astrocytes, as part of the blood–brain barrier (BBB), surround blood vessels with their endfeets and form close connections with capillaries and thus are the primary target of any molecule entering the brain. When antidepressant drugs cross the BBB and enter the brain they must come in direct contact with astrocytes. Among the proteins responsible for transport of substances in and out of the BBB, the ATP-dependent *m*ulti-*d*rug *t*ransporter protein MDR, also known as P-gp protein, is one of the very well characterized transport proteins especially in relation to antidepressants (Uhr and Grauer, 2003; Lee et al., 2011). Uhr and colleagues demonstrated that specific polymorphisms in the gene encoding for P-gp could be predictive of a positive clinical response of patients to antidepressants that were found to be a substrate of this protein. They confirmed these clinical findings using a knockout mouse model where the mouse mutants lacking the counterparts of the human allele of P-pg responded with a favorable pharmacological profile, i.e. the penetration of P-gp-sensitive antidepressants into the brain was 2–4 times higher in these animal compared to their wild-type siblings (Uhr et al., 2008). More recently, another study confirmed the results of Uhr and colleagues and showed specifically that polymorphisms in the gene coding for P-gp correlated with positive response to escitalopram treatment (Lin et al., 2011).

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Another interesting example is aquaporin-4, a water channel protein that is responsible for bidirectionally transporting water to and from the blood and brain. A recent study reported on the surprising finding that ablation of the gene coding for aquaporin-4 in knockout mice could disrupt the fluoxetine-induced stimulation of adult hippocampal neurogenesis as well as the behavioral improvement of the depressive-like phenotype in a chronic stress model for depression (Kong et al., 2009). Furthermore, it has been shown that knockout of aquaporin-4 results in cognitive deficits and altered neurotrophin-dependent plasticity, both of which have been implicated in mood disorders (Skucas et al., 2011). Future studies should validate the importance of aquaporins in response to antidepressant treatment.

## 4. Summary

The primary aim of the present review was to put together all the currently available and relevant experimental findings on the evidence that antidepressant therapies act directly on astrocytes. Antidepressants, as any drug that is able to pass the blood–brain barrier, when doing so they come in direct contact with astrocytes. As we demonstrated, there is a large amount of convincing evidence indicating that antidepressant treatments affect diverse astrocytic functions such as the regulation of the availability of various neurotransmitters, like serotonin, glutamate or GABA, the regulation of energy homeostasis and the control of blood–brain barrier integrity. Furthermore, we argued here that antidepressant treatment results in a mild or moderate form of reactive astrocytosis. Such an activation of astrocytes however does not necessarily bound to harmful consequences because reactive astrocytes do not only have their dark side, but instead as recent findings suggest they can also exert a range of neuroprotective and repair-related functions in response to CNS insults (Sofroniew, 2009; Hamby and Sofroniew, 2010). We propose here 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 neuronal networks helping the depressed individual to recover from the disease.

It is very likely that the underlying neurobiology of mood disorders is incorporated in abnormal neuronal networks. These networks have been shaped by stress or adverse environmental experiences during critical periods of early life making the individual susceptible to further stress later in life. Additional stress and developmental changes during adolescence may reactivate and strengthen this unfavorable reorganization of cortical networks leading gradually to full blown clinical symptoms. Reactivation of cortical plasticity by antidepressant therapies in combination with psychotherapy, or behavioral readjustments could allow the reshaping of the miswired neural networks that in the end allows the individual to respond to the environment with a healthy and appropriate behavior. It is very likely that astrocytes are not only providing passive support for this process, instead they are actively guiding this development. Further experiments should present proofs for this concept.

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## Contributors

Both authors contributed to the literature searches and analyses. Both authors contributed to the writing of the paper and both have approved the final version of the manuscript.

## Conflict of interest

No conflict of interest or financial support is present for the authors.

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