The Monoaminergic Tripartite Synapse: A Putative Target for Currently Available Antidepressant Drugs

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Abstract: Antidepressant drugs such as the serotonin (5-HT)/norepinephrine (NE) and dopamine (DA) reuptake inhibitors activate monoaminergic neurotransmission in various brain regions, such as the amygdala, the frontal cortex or the hippocampus. Although this property is well established, the post-synaptic mechanisms by which these pharmacological agents exert therapeutic activity in major depressive disorders (MDD) is not fully understood. Recent clinical and preclinical studies have indicated that the density and reactivity of glia and more particularly of astrocytes is reduced in MDD patients. These data along with the fact that astrocytes express monoaminergic transporters and receptors make these cells putative targets for antidepressant treatments. Accordingly, in vitro evidence has demonstrated that the application of various classes of antidepressant drugs on rodent primary astrocyte cultures elicits a wide spectrum of responses, from the rise in cytosolic calcium concentrations, as a marker of cellular activity, to the release of glucose metabolites, gliotransmitters and neurotrophic factors. Remarkably, antidepressant drugs also attenuate the release of inflammatory molecules from reactive astrocytes or microglia, suggesting that part of the beneficial effects in depressed patients or animal models of depression might result from the ability of antidepressants to regulate the synthesis and release of psychoactive substances acting on both pre- and post-synaptic neurons. Among the many long-term targets of antidepressant drugs, brain-derived neurotrophic factor (BDNF) has been well studied because of the positive influence on adult hippocampal neurogenesis, synaptogenesis and the local serotonergic tone. This review will illustrate how the concept of the tripartite synapse, which is classically associated with different forms of plasticity involving glutamate, could be expanded to the monoaminergic systems to regulate antidepressant drug responses. The recent in vivo data supporting that hippocampal astrocytes act in concert with neurons to release BDNF under pharmacological conditions and thereby regulating different facets of anxiolytic-/antidepressant-like activities through neurogenesis-dependent and independent mechanisms will be emphasized.

Keywords: Antidepressants, astrocytes, depression, gliotransmitters, neurotrophic factors, tripartite synapse.

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) block serotonin (5-HT) reuptake, leading to the increase in synaptic 5-HT. This increase in synaptic 5-HT activates a feedback mechanism mediated by 5-HT1A autoreceptors in the dorsal raphe (DR), which reduces 5-HT neuronal activity and limits the release of this monoamine at the nerve terminals in regions such as the amygdala (AMY), frontal cortex (FC) and hippocampus (HP). Long-term treatment with these antidepressant drugs desensitizes the inhibitory 5-HT1A autoreceptors, and 5-HT neurotransmission is enhanced [1]. Similar observations have been made with noradrenergic and dopaminergic reuptake inhibitors, whose therapeutic activities also depend on the ability of these drugs to desensitize inhibitory alpha-2 and D2 autoreceptors located in the locus coeruleus (LC) and ventral tegmental area (VTA), respectively [2]. Despite these well documented properties, the post-synaptic mechanisms by which antidepressant drugs, more particularly SSRIs, exert beneficial effects in depressed patients or relevant animal models remains largely unknown. In particular, the nature of the post-synaptic receptors and cell types targeted by monoamine reuptake inhibitors or monoamine oxidase blockers has yet to be understood.

There is increasing evidence that astrocytes play a significant role in major depressive disorders (MDD). A recent review by Rajkowska and Stockmeier (2013) [3] examined human post-mortem studies that demonstrated that MDD is associated with a decrease in the density of astrocytes in the AMY, FC or HP. Such a decrease has also been reported in rodents subjected to stressful conditions [4-6], whereas the gliotoxin L-alpha amino adipic acid-induced reduction in the number of glial fibrillary acidic protein (GFAP)-positive cells in the preFC, also produces behavioral anomalies indicative of a depressive-like phenotype [7]. Despite these findings, whether the modifications of astrocytic density and activity are the causes or consequences of chronic stress and related symptoms/disorders is still unclear. However, these findings raise the possibility that part of antidepressant drug activity could rely on the ability of these treatments to modulate astrocytes at different levels. Several arguments support this assumption. First, the identification of the monoaminergic-
The Monoaminergic Tripartite Synapse

1. ASTROCYTIC MONOAMINERGIC TRANSPORTERS

1.1. Monoamine Uptake

1.1.1. The Serotonin Transporter (SERT)

Historically, the monoamine uptake site was the first type of monoamine transporter observed in primary astrocyte cultures [8, 29]. This reuptake mechanism is a high-affinity Na⁺-dependent system that allows astrocytes to participate in the clearance of 5-HT, NE and DA in the synaptic cleft [29].

1.1.2. The Norepinephrine Transporter (NET)

The expression of the norepinephrine (NE) transporters was initially observed in primary cultures of rat astrocytes [40] and was further confirmed by RT-PCR and western-blots analyses [41]. Although the Na⁺-dependent or independent uptake of NE by astrocytes has led to heterogeneous results [32, 40, 42, 43], it is now well accepted that selective and non-selective NE reuptake inhibitors, such as nisoxetine, milnacipran or desipramine, inhibit the in vitro Na⁺-dependent NE uptake from cultured rat astrocytes [41]. Remarkably, a heterologous uptake of DA from glial NET was also initially observed in primary cultures of rat astrocytes [9].

1.1.3. The Dopamine Transporter (DAT)

In a marked contrast to the SERT and NET, the expression of the DAT on astrocytes is poorly documented. Recent
RT-PCR analyses in primary cultures of astrocytes suggest the presence of the DAT on this cell type but its expression would depend on the brain region from which the cell cultures derive [45, 46]. Moreover, although evidence suggests that astrocytes can uptake DA through a high-affinity Na⁺-dependent process [29, 40], other studies in rat primary cultures of astrocytes failed to unveil such a mechanism [42, 47, 48]. More recently, a study in cultured rat cortical astrocytes showed that the high-affinity DAT inhibitor GBR12935 had no effect on DA uptake [45], whereas nisoxetine or higher concentrations of GBR12935, which blocks both the DAT and NET, inhibit DA uptakeactivity [44, 45]. These results point out the putative ability of astrocytic NET to uptake DA. Finally, it has been proposed that bFGF and EGF increase the DA uptake in rat astrocyte cultures, probably through the regulation of DAT expression [49]. This interesting finding warrants further investigation.

1.2. Monoamine Uptake 2

The uptake 2 transporters, such as the extraneuronal monoaminergic transporters (EMTs), display distinct pharmacological profiles compared to the monoamine uptake 1 transporters and were identified several years after the monoamine uptake 1 [50, 51]. Also named organic cation transporters (OCTs), these transporters act through a Na⁺-independent, corticosterone-sensitive process [52] with transporters that have a low affinity but a high-capacity for monoamines in the brain [53, 54]. In vitro, functional studies have demonstrated the presence of OCT3 in rodent and human primary astrocyte cultures [41, 45, 49], as these transporter-mediated-uptake 2 processes appear to be insensitive to antidepressant drugs, such as amitryptiline or fluoxetine [43]. However this notion has been recently challenged by studies suggesting that these transporters would be secondary targets of antidepressant drugs [54, 55]. A particular characteristic of OCT3 relies on the ability to uptake all three monoamines from non-neuronal cells [56, 57], not only in the FC or HP, but also in the main monoaminergic brain nuclei, including the DR or LC [58-60]. These observations open the way for new investigations aimed at determining the influence of OCT3 on the homeostasis of the monoaminergic systems and the regulation of OCT3 neuronal activities.

2. ASTROCYTIC MONOAMINERGIC CATABOLIC ENZYMES

Glia cells do not express tryptophan hydroxylase. However, the catabolic isoenzymes responsible for the degradation of monoamines (i.e. monoamine oxidase A and B) were clearly identified in this cell type. Several studies report the presence of both isoforms in cultures of astrocytes [47, 61, 62], suggesting that monoamine oxidase inhibitors could exert some therapeutic activity by acting on these cells. Catechol-O-methyltransferase (COMT) mRNA and protein, another metabolic enzyme regulating monoamine concentration, was also detected in astrocytes using microscopic, biochemical and pharmacological approaches [63-66]. These observations emphasize the fact that astrocytes can regulate the extracellular monoamine levels by modulating the expression and function of MAO-A, MAO-B and COMT.

3. ASTROCYTIC MONOAMINERGIC RECEPTORS, RELATED SIGNALING PATHWAYS AND ENERGETIC METABOLISM

Astrocytes express several monoaminergic receptor subtypes at the surface that make these cells sensitive to increases in the extracellular 5-HT, NE and DA levels in response to the pharmacological inactivation of the glial or neuronal monoaminergic transporters and catabolic enzymes.

3.1. Astrocytic 5-HT Receptors

3.1.1. The 5-HT 1 Receptor Subtypes

The 5-HT 1A receptor subtype has been detected in both cultured astrocytes and in situ in the HP or entorhinal cortex [67] (Table 1). Despite the controversial coupling of the 5-HT 1A receptor to adenylyl cyclase in astrocytes [12, 34], several studies have shown that the 5-HT 1A receptor agonist 8-OHDPAT stimulates the synthesis and release of the Ca²⁺-binding protein s100beta from astrocytes [68-70] (Fig. 1). This protein regulates cell shape, energy metabolism, cell to cell communication and cell growth [71]. Remarkably, at low concentrations, s100beta positively regulates neuronal and astrocytic differentiation while reducing neuronal death and astroglisis in response to brain injury [69, 70, 72, 73]. However, high concentrations of s100beta induce apoptosis, suggesting that the regulation of this neurotrophic factor by the 5-HT 1A receptor could play a significant role in both the physiopathology of MDD and the antidepressant activity of SSRIs [74].

3.1.2. The 5-HT 2 Receptor Subtypes

The presence of the 5-HT 2A, 5-HT 2B and 5-HT 2C receptor subtypes in primary astrocyte cultures from various brain regions, including the HP [12, 75, 76], and also from in situ analyses [77] has been repeatedly documented. The 5-HT 2 receptors are Gq/11 protein-coupled receptors (Table 1), and the activation of these receptors leads to the activation of the phospholipase C (PLC) production of diacylglycerol (DAG) and inositol triphosphate (IP3). The ultimate step of this intracellular cascade is an increase in cytosolic calcium concentrations ([Ca²⁺])]. This signaling pathway is of particular importance because astrocyte excitability depends on this rise of [Ca²⁺], and such an increase is the starting point to other events, such as the release of neuroactive substances. As expected, the stimulation of the 5-HT 2 receptors by 5-HT and the SSRIs fluoxetine or citalopram in rodent primary cultures of cortical astrocytes increases [Ca²⁺], and protein kinase C (PKC) activity, which is responsible for the extracellular signal-regulated kinase 1/2 (ERK 1/2) activation [78, 79] (Fig. 1). In the dentate gyrus of the HP, ERK 1/2 has been implicated in the regulation of mood as supported by the blunted activation and expression of ERK 1/2 in a mouse model of depression [80]. Similarly, western-blots analyses showed decreased levels of ERK in the postmortem FC of individuals with MDD [81]. Because a downregulation of ERK 1/2 has been associated with an impairment of the adult hippocampal neurogenesis during brain development [82], it is possible that such an effect in the adulthood could also dampen this process in the adult HP. Conversely, these results suggest that antidepressant drugs exert therapeutic activity by reversing these alterations. Consistent with this
Table 1. Serotonergic Receptor Subtypes Identified on Primary Cultures of Astrocytes.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>G Protein</th>
<th>Brain region</th>
<th>Experimental conditions</th>
<th>References</th>
</tr>
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<td>5-HT₁A</td>
<td>-</td>
<td>Hippocampus</td>
<td>In vitro</td>
<td>[12, 263]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entorhinal cortex</td>
<td>In situ</td>
<td>[67]</td>
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<td>G₉</td>
<td>Cortex</td>
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<td>[75]</td>
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<td></td>
<td></td>
<td>Striatum</td>
<td></td>
<td>[263]</td>
</tr>
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<td>G₉</td>
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<td>[12, 263]</td>
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<td>Hippocampus</td>
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<td>[34]</td>
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<tr>
<td>5-HT₂C</td>
<td>G₉</td>
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<td></td>
<td>[264]</td>
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<td>G₈</td>
<td>Mesencephalon</td>
<td>In vitro</td>
<td>[86]</td>
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<td>[265]</td>
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<tr>
<td>5-HT₅A</td>
<td>Gᵢ</td>
<td>-</td>
<td>In vitro</td>
<td>[87]</td>
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<td>G₈</td>
<td>Frontal cortex</td>
<td>In vitro</td>
<td>[89]</td>
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<td>Hypothalamus</td>
<td>In situ</td>
<td>[88]</td>
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<td></td>
<td></td>
<td></td>
<td>In situ</td>
<td>[12]</td>
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Fig. (1). Regulation of brain astrocytic activity by 5-HT and related receptor subtypes identified on this cell type.

assumption, the SSRI fluoxetine stimulates the astrocytic 5-HT₂A and 5-HT₂B receptors to promote the synthesis of fibroblast growth factor (FGF) and epidermal growth factor (EGF), two molecules known to favor ERK₁/₂ pathway in primary cultures of mouse astrocytes [79, 83]. In addition to these effects, the activation of the 5-HT₂ receptor types has been proposed to stimulate the synthesis glial-derived neurotrophic factor (GDNF) in C6 glioma cells, a model of astrocytes, and this effect could result from ERK phosphorylation/activation [84, 85]. As detailed in the next chapter of this review, all of these factors play a role in adult hippocampal neurogenesis, making these 5-HT₂ receptor subtypes molecular elements potentially involved in the therapeutic action of serotonergic antidepressant drugs.

3.1.3. Other 5-HT Receptor Subtypes

Recent immunohistochemical studies using double immunostaining with antibodies directed against the GFAP demonstrate that astrocytes from mesencephalic rat cultures express the 5-HT₄ receptors [86] (Table 1). The 5-HT₅A mRNA and proteins have also been detected in primary astrocyte cultures [87], but the precise role of 5-HT₅A in these cells remains undetermined. Finally, growing evidence emphasizes the presence of 5-HT₇ receptors in rat cultured as-
trocytes from the FC, thalamus (TH) and hypothalamus (HYP) [12, 88-90] (Table 1). The 5-HT7 receptors are positively coupled to AC through Gs proteins [12] (Table 1). Long-term treatment with tricyclics elicits a time- and concentration-dependent increase in the production of cAMP in rat cultured astrocytes, which is attenuated by a pretreatment with 5-HT7 receptors antisense oligonucleotides [89]. Although the functional consequences of the activation of astrocyl 5-HT7 receptors have been poorly documented, in vitro studies suggest that the 5-HT7-induced release of the proinflammatory interleukin-6 (IL-6) in a human astrocytoma cell line is mediated by this receptor subtype [91] (Fig. 1).

3.2. Astrocytic Adrenoceptors

3.2.1. The Alpha Adrenoceptor Subtypes

In vitro and in situ experiments have demonstrated that both the α1- and α2-adrenoceptors are expressed on astrocytes from various brain regions [92-96]. In particular, α1-adrenoceptors have been detected on astrocytes in the LC and DR and also at the monoaminergic nerve terminal in regions such as the FC and nucleus accumbens (NAcc) [97]. The stimulation of these receptors, through coupling with Gs proteins, activates PLC and the production of DAG and IP3, which in turn increases the activity of PKC and the [Ca2+]i concentration, respectively [16] (Table 1, Fig. 2). In the FC, the local release of NE induced by the electrical stimulation of the LC neurons increases astrocyl [Ca2+]i [98]. The activation of the PKC favors the synthesis of some neurotrophic factors, including BDNF in rat neonatal cortical primary cultures of astrocytes [99, 100]. This synthesis might involve specific neurotransmitter systems because the cellular content of BDNF is upregulated by the catecholamines but not by the kainic acid. In a marked contrast, the stimulation of NGF synthesis is mediated by histamine [100]. These data are of particular interest because these differences also exist between the levels of NGF and BDNF in vivo, with BDNF being the most abundant in the adult rat central nervous system [101, 102]. Evidence also demonstrates that the α1-adrenoceptors regulate the energetic metabolism of astrocytes because the stimulation of these receptors promotes astrocytic glycolysis, resulting in the synthesis of energetic substrates, such as ATP or lactate, which are necessary for the neuronal activity [103, 104]. The α2-adrenoceptors are Gs/o protein-coupled receptors that are negatively coupled to the AC [16]. The activation of these receptors decreases cAMP levels, leading to glucose incorporation into glycogen, whereas α2-adrenergic receptor antagonists increase glycogenolysis [96]. The α2-adrenoceptors are also coupled to the PKC through the βγ subunit, inducing transient [Ca2+]i in response to the glycogenolysis [105]. Given that astrocytes are the main cerebral source of glycogen and that the glycogenogenesis and glycogenolysis are key processes for the rapid production of energetic substrates [106-109], it is likely that the stimulation of the astrocytic α1- and α2-adrenoceptors plays a major role in the metabolism necessary for the neuronal activity.

3.2.2. The Beta Adrenoceptor Subtypes

In vitro and in situ studies have shown the presence of the β1-, β2- and β3-adrenoceptors mRNA in astrocytes [92, 96, 110-113]. These receptors were primarily described as being positively coupled to AC through Gs proteins [114] (Table 2). In the FC, the local release of NE induced by the electrical stimulation of the LC neurons increases astrocyl [Ca2+]i [98]. The activation of the PKC favors the synthesis of some neurotrophic factors, including BDNF in rat neonatal cortical primary cultures of astrocytes [99, 100]. This synthesis might involve specific neurotransmitter systems because the cellular content of BDNF is upregulated by the catecholamines but not by the kainic acid. In a marked contrast, the stimulation of NGF synthesis is mediated by histamine [100]. These data are of particular interest because these differences also exist between the levels of NGF and BDNF in vivo, with BDNF being the most abundant in the adult rat central nervous system [101, 102]. Evidence also demonstrates that the α1-adrenoceptors regulate the energetic metabolism of astrocytes because the stimulation of these receptors promotes astrocytic glycolysis, resulting in the synthesis of energetic substrates, such as ATP or lactate, which are necessary for the neuronal activity [103, 104]. The α2-adrenoceptors are Gs/o protein-coupled receptors that are negatively coupled to the AC [16]. The activation of these receptors decreases cAMP levels, leading to glucose incorporation into glycogen, whereas α2-adrenergic receptor antagonists increase glycogenolysis [96]. The α2-adrenoceptors are also coupled to the PKC through the βγ subunit, inducing transient [Ca2+]i in response to the glycogenolysis [105]. Given that astrocytes are the main cerebral source of glycogen and that the glycogenogenesis and glycogenolysis are key processes for the rapid production of energetic substrates [106-109], it is likely that the stimulation of the astrocytic α1- and α2-adrenoceptors plays a major role in the metabolism necessary for the neuronal activity.

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<th>G Protein</th>
<th>Brain region</th>
<th>Experimental conditions</th>
<th>References</th>
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<td>α1</td>
<td>Gs</td>
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<tr>
<td>β1</td>
<td>Gs</td>
<td>Cortex</td>
<td>In vitro</td>
<td>[92], [110], [111]</td>
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<td>β2</td>
<td>Gs</td>
<td>Hippocampus</td>
<td>In situ</td>
<td>[112], [96], [113]</td>
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<tr>
<td>β3</td>
<td>Gs</td>
<td>Hypothalamus</td>
<td>In situ</td>
<td>[113]</td>
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stimulate protein kinase A (PKA) through the stimulation of AC activity, leading to the stimulation of the glycogen phosphorylase that is required for glycogenolysis [114, 118, 119] (Fig. 2). In addition to the modulation of astrocytic metabolic activities, β-adrenergic receptors have been implicated in the neurotrophic support of neurons. Studies have shown that the application of NE in cultured neonatal rat astrocytes increases the synthesis of BDNF, an effect partially inhibited by specific β1- and β2-adrenoceptors antagonists [99, 120]. Through positive coupling with AC, the β1- and β2-adrenoceptors increase cAMP, leading to the activation of cAMP responsive element binding protein (CREB) and the regulation of BDNF synthesis [121] (Fig. 2). As an example of the physiological relevance of these mechanisms, BDNF has been proposed to have a neuroprotective effect on NE neurons in the LC [99, 122-124]. Finally, it has been well documented that astrocytes play a crucial role in the control and maintenance of ionic extracellular homeostasis, including K+ [125]. Other studies have demonstrated that the β-adrenoceptor agonist isoproterenol stimulates the astrocytic Na+/K+-ATPase activity, thereby facilitating the extracellular clearance of K+ [96, 126, 127]. Due to the importance of the extracellular K+ concentrations on neuronal firing, these findings suggest that NE could optimize astrocytic Na+/K+-ATPase activity during high neuronal activity.

3.3. Astrocytic Dopaminergic Receptors

3.3.1. The D1- and D2-Like Receptors

Historically, the DA receptors were divided in two types: the D1 receptor superfamily, positively coupled to AC through the Gs proteins, and the D2 receptor superfamily, negatively coupled to AC through the Gi proteins (Table 3). Thereafter, other subtypes of dopaminergic receptors were discovered: the D3 and D4 subtypes joined the D2 receptor superfamily, and D5 now belongs to the D1 receptor superfamily. Several studies have reported the presence of all of the DA receptor subtype mRNAs in primary astrocyte cultures from the mouse striatum, and these observations were confirmed by western-blot and in situ analyses [15, 128, 129]. Interestingly, the application of DA in primary astrocyte cultures induces cAMP accumulation and p-CREB expression. This effect is inhibited by a D4 receptor antagonist. Due to the implication of p-CREB in the transcriptional activation of some neurotrophic factors, this observation is consistent with previous reports demonstrating that DA upregulates BDNF and NGF in the mouse astrocyte cultures [130, 131]. Similarly, the application of D2 and D3 receptor agonists, such as apomorphine and ropinirol, increases the synthesis and secretion of NGF and GDNF, but not of BDNF, in cultured mouse astrocytes [132, 133]. Moreover, apomorphine stimulates the synthesis and release of FGF-2 through the cAMP/PKA and PKC/MAPK signaling cascades in striatal primary cultures of astrocytes [134, 135] (Fig. 3). Such a release promotes the survival of dopaminergic neurons, thus demonstrating the potential therapeutic role of the astrocytes in neurodegenerative diseases, such as Parkinson disease [134], or in psychiatric disorders, such as MDD, which are characterized by specific symptoms involving this system. In situ and in vitro experiments also demonstrated the presence of the D2 receptor in cortical astrocytes cultures [136], and these results must be considered in the
Table 3. Dopaminergic Receptor Subtypes Identified on Primary Cultures of Astrocytes.

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<tr>
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<th>G Protein</th>
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<td>Gₛ</td>
<td>Striatum</td>
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<td>[141]</td>
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Fig. (3). Regulation of brain astrocytic activity by DA and related receptor subtypes identified on this cell type.

devlopment of a new class of antidepressant drugs that simultaneously increase all the three monoamines [137]. The triple reuptake inhibitor DOV216303 has been recently shown to stimulate the synthesis of BDNF from hippocampal and cortical primary cultures of astrocytes [138], emphasizing a possible role of DA on glial cells to promote neurotrophic effects.

3.3.2. The Phosphatidylinositol-Linked D₁-Like Receptor

Finally, studies have revealed the existence of a new dopamine D₁ receptor that is not coupled to AC. This receptor, named non-cyclase-coupled D₁ receptor or phosphatidylinositol-linked D₁-like receptor (PI-linked D₁-like), is coupled to G₄-proteins and induces phosphatidyl-inositol (PI) hydrolysis by PLCβ [139, 140]. In vitro, the selective agonist to this receptor, SKF83959 ([3-methyl-6-chloro-7,8-hydroxy-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine]), activates the synthesis and release of FGF-2 in rat astrocyte cultures through IP3 and Ca²⁺CaMK (Fig. 3). The activation of this receptor is believed to favor the survival of the dopaminergic neurons in the striatum [141, 142].
4. NEUROACTIVE SUBSTANCES RELEASED BY ASTROCYTES IN RESPONSE TO ANTIDEPRESSANT DRUGS

The above section sheds some light on the ability of antidepressant drugs to modulate astrocytic activity in response to increased extracellular monoamines levels. Indeed, 5-HT, NE and DA promote the synthesis of various neuroactive substances and favor the production of metabolic substrates that derive from glycogen and that are essential for neuronal activity. Martin and collaborators examined the regulation of energy metabolism by astrocytes in response to antidepressant drugs [143], and we will detail in this section the most recent findings that support a role for the gliotransmitters, neurotrophic factors or inflammatory molecules that are released by astrocytes in the mechanism of action of these pharmacological treatments.

4.1. Gliotransmitters

Astrocytes release gliotransmitters, such as the adenosine triphosphate (ATP), adenosine, D-serine and glutamate. The in vivo relevance of this process on the improvement of antidepressant responses.

4.1.1. ATP

It is well established that various classes of antidepressant drugs increase the levels of ATP in cultured astrocytes [147]. A recent study demonstrated that the astrocytic release of ATP is involved in the mood regulation and antidepressant response [148]. Indeed, mice susceptible to chronic social defeat or subjected to the forced swimming test exhibit low ATP brain levels. Moreover, mice with deficiencies in astrocytic ATP release induced by the inactivation of the glitoxin L-alpha-aminoadipic acid in rats is sufficient to induce anxiodepressive-like behaviors, such as anhedonia and anxiety [7], while the enhancement of glial cells activity, particularly through the release of gliotransmitters, promotes antidepressant responses.

4.1.2. D-serine and Glutamate NMDA Receptors

The role of D-serine, a potent agonist at the glycine site of the NR1 subunit of glutamatergic NMDA receptors [161] in MDD and antidepressant response, has been recently addressed. The systemic administration of D-serine produces antidepressant-like effects in various paradigms in rats as indicated by the ability of D-serine to reduce the immobility time in the forced swimming test and to rescue the 5-HT depletion-induced learned helplessness behaviors [162]. Although the mechanisms underpinning the antidepressant-like effects of D-serine are unknown, it is possible that the facilitatory action at the NMDA receptors plays a significant role. However, growing evidence suggests that the expression of the major glutamate transporter EAAT2 is impaired in rat models of depression [163, 164]. Similar observations were made post-mortem in the cortical regions [165] and in the LC [166] of MDD patients in which microarray analyses showed a down-regulation of members of the glial glutamate/neural amino acid transporter protein family. Such an astroglial distribution of glutamate transporters suggests a link between key components of glial cells and the pathophysiology of depression. It is hypothesized that these changes could elevate the levels of extracellular glutamate considerably, which is potentially neurotoxic [165]. Long-term treatment with fluoxetine significantly increases the expression of the glutamate transporter GLT1 in the rat HP and cortex [163]. In summary, it is difficult to reconcile the fact that an increase in synaptic extracellular glutamate levels would be associated with mood disorders, whereas D-serine, which stimulates glutamatergic NMDA receptor transmission, can produce antidepressant-like effects. Further preclinical studies are therefore warranted to help understand the putative link between the regulation of synaptic glutamate transmission and D-serine release by astrocytes.
4.2. Inflammatory Molecules

Pro-inflammatory agents such as lipopolysaccharide (LPS) are known to promote depressive-like behaviors in rodents [167], likely through the recruitment of various events, including the activation of microglia, the synthesis of reactive oxygen species (ROS) and pro-inflammatory molecules in the brain [i.e. interleukin 1 (IL-1), interleukin 2 (IL-2) and tumor necrosis factor-α (TNF-α), chemokines] [168]. These processes are also believed to decrease hippocampal neurogenesis [169], which could account for the negative impact on mood. The initial evidence demonstrating that activated microglia impairs hippocampal neurogenesis was reported ten years ago [170]. In this study, the authors demonstrated that the intraperitoneal injection of LPS significantly decreased new cell survival and the differentiation of new cells into neurons as evidenced by a reduction in the expression of the early neuron marker doublecortin in LPS-treated rats [170]. In this study, the survival of new neurons was negatively correlated with the number of activated microglia. Remarkably, the acute administration of tricyclics and of paroxetine, fluoxetine or desipramine prevented the release of inflammatory mediators in the rat cortex, in primary cultured forebrain microglia and in astrocytes from newborn mice [171, 172] suggesting that antidepressant drug activity could rely on action on microglia. This is confirmed by the observation that fluoxetine prevents LPS-induced inhibition of adult hippocampal neurogenesis in rats [173] by attenuating microglia activation [174]. Additionally, antidepressant drugs also inhibit the synthesis and release of pro-inflammatory cytokines in the peripheral immune cells in patients suffering from MDD [175, 176] and in inflammatory models of depression [177, 178], leading to the theory that psychiatric disorders might have peripheral causes and consequences. In addition to the ability to inhibit the synthesis and release of pro-inflammatory molecules by peripheral immune cells, reactive astrocytes or microglia, antidepressant drugs elicit the astrocytic expression of neurotrophic factors. This is of particular interest because BDNF has anti-inflammatory properties [179] as demonstrated, for example, by the ability to reduce in vitro TNF-α mRNA from activated microglia in an animal model of sclerosis [180]. It is therefore possible that in the HP, astrocytic or neuronal BDNF maintains microglia in a resting state, which is an essential step for enhancing adult neurogenesis by removing the apoptotic cells through phagocytosis [181]. Notably, all of these pro-inflammatory processes could also have deleterious effects on synaptogenesis, which is associated with MDD. In a recent review, Di Benedetto et al. (2013) described how antidepressant drugs might influence the dynamic of neuronal circuits through the impact on microglial cells and, consequently, on neuronal synapses [182, 183]. However, these considerations do not preclude the possibility of a positive effect of inflammation on brain plasticity. A recent study conducted in the adult zebrafish brain suggested that inflammation is required and sufficient for enhancing the proliferation of neuronal progenitors and subsequent neurogenesis [184]. This notion should also be integrated to better understand the impact of antidepressant drugs on the functions of the monoaminergic tripartite synapse.

4.3. Neurotrophic and Growth Factors

As described in the previous chapter, antidepressant drugs may modify the release of various neurotrophic and growth factors from cultured astrocytes. We will describe in this section the putative role of these factors in the mechanism of action of these agents.

4.3.1. S100beta

Among these factors, it has been shown that the SSRI fluoxetine stimulates s100beta synthesis in hippocampal astrocyte cultures [185] and in vivo in the HP of rats and mice subjected to the chronic mild stress [185-187]. These beneficial effects have been attributed to a facilitatory effect and the paracrine neurotrophic activity of s100b on neuroplasticity [74] and more specifically on hippocampal neurogenesis [188]. Moreover, higher serum levels of s100beta have been found to efficiently predict the response to antidepressant drugs in MDD patients after 4 or 6 weeks of treatment [189, 190]. Nevertheless, the impact of central administration of s100beta on the behavioral paradigms relevant to antidepressant-like activity has never been studied and requires further attention. Interestingly, SERT is a target of microRNA-16 (miR-16), which is expressed at higher levels in noradrenergic cells than in serotonergic cells. S100b has been reported to trigger miR-16 in noradrenergic neurons of the LC to stimulate the expression of SERT by this neuronal population [191]. The role of miR-16 could be to limit the accumulation of 5-HT in the synaptic cleft in the LC, a process potentially favorable to the activation of the NE neurons [192, 193].

4.3.2. GDNF

GDNF is another neurotrophic factor that modulates neuronal survival in the central and peripheral nervous systems. Additionally, GDNF affects the proliferation, migration, differentiation and survival of neuroblasts [194-196]. Human studies supporting a role for GDNF in MDD are scarce. However, preclinical studies have reported that the expression of GDNF is significantly decreased in the ventral striatum by chronic ultra-mild stress in mice but is increased after a prolonged treatment with imipramine [197]. In another study, animals exposed to the chronic unpredictable stress display a decreased GDNF expression in the HP, while chronic treatment with clomipramine reverses these behavioral deficits [198]. These results strongly suggest that epigenetic changes in GDNF gene expression contribute to behavioral stress responses. Consistent with the latter study, in vitro data showed that different classes of antidepressant drugs, including TCAs and SSRIs, modulate GDNF expression in cultured cortical rat astrocytes and in C6 glioma cells [199-201]. The role of 5-HT in the synthesis of GDNF has been recently proposed from in vitro studies showing that this monoamine induced GDNF mRNA expression in rat C6 glioma cells via 5-HT2 receptor-mediated FGFR2 transactivation [84, 85].

4.3.3. VEGF

VEGF, a pleiotropic factor that possesses multiple activities in blood vessels and neurons, has been shown to increase the proliferation of neuronal progenitors [202], to stimulate
the neurogenesis [203, 204] and to modulate the neuronal plasticity in the adult HP [205]. The chronic administration of antidepressant drugs increases the expression of VEGF in the HP [206, 207], and the intracerebroventricular infusion of VEGF stimulates adult hippocampal neurogenesis. This process likely explains why VEGF elicits antidepressant-like activities in different paradigms, predicting the antidepressant-like activity of pharmacological agents in rodents and in another animal model of depression [206, 207]. There is also evidence that VEGF signaling is required for the effects of fluoxetine in different behavioral paradigms and that the chronic administration of this SSRI increases the expression of VEGF in neurons and endothelial cells of the HP [208]. In addition to neurons and endothelial cells, fluoxetine, paroxetine and TCA amitriptyline upregulate VEGF in cortical primary cultures of astrocytes [17, 199]. Given that VEGF increases astroglial proliferation [209], it is suspected that the upregulation of VEGF by antidepressant drugs contributes to the reversal of structural abnormalities detected in the preFC of depressed patients.

4.3.4. FGF2, FGFR1

FGF2 is a growth factor that is essential for the proper formation of the synaptic connections in the cerebral cortex, the maturation and survival of catecholamine neurons, and the enhancement of neurogenesis. It has been suggested that FGF-2 is involved in the regulation of mood because the expression of FGF-2 is decreased in the HP of patients suffering from MDD [210]. Moreover, treatment with antidepressants reduces this decreased expression of FGF-2 in MDD patients [211]. Animal studies have also shown that the expression of FGF-2 is reduced notably in the HP of rats subjected to the social defeat model of depression [212], whereas antidepressant drugs produced the opposite effects in the HP and in the FC [213, 214]. These observations are consistent with the fact that the intracerebroventricular administration of FGF-2 induces antidepressant-like effects in various animal models of depression [212]. FGF2 proteins predominantly increase in neurons of layer V throughout cortical areas and in some neurofilament-positive cells of the HP. FGFR1 mRNA also increases in the dentate gyrus of the HP 24 h post-FGF2 injection, confirming the role of this factor in neuronal modeling as well as in antidepressant drug responses. Indeed, cortical FGF-2/FGFR signaling is necessary for mediating the antidepressant-like effects of imipramine and fluoxetine in the chronic unpredictable stress model of depression in rats [215].

5. EXAMPLE OF BDNF AT THE TRIPARTITE SYNAPSE – LINK WITH 5-HT NEUROTRANSMISSION

A large body of evidence has emphasized the role of BDNF in the pathophysiology and treatment of MDD [216]. The role of serotonergic antidepressant drugs in the regulation of this neurotrophic factor is complicated because the outcome is largely dependent on the length of treatment. Although the acute administration of various SSRIs or the monoamine oxidase inhibitor tranylcypromine decreases the expression of BDNF in the HP [217-220], notably exon VI and V mRNA [219, 221, 222], the repeated administration (2-3 weeks) of these drugs produces the opposite effect [123, 219, 220, 222, 223] and reverses stress-induced BDNF downregulation in the adult rat brain [223, 224]. It is therefore suspected that a prolonged increase in extracellular 5-HT levels results in the long-term activation of second messenger signal transduction systems, such as cAMP/PKA and DAG/PKC, leading to increased expression of the CREB gene [225, 226]. This transcription factor would then enhance BDNF expression [227, 228]. Because BDNF expression, identified in rat cultured embryonic cortical neurons, can be stimulated by the activation of the cAMP system and voltage sensitive Ca2+ channels [229], it is now accepted that mature hippocampal neurons represent the major source of BDNF. Accordingly, in situ hybridization studies in the HP of the adult rat brains reported that cells expressing the BDNF gene are found in pyramidal and granule neurons and in target cells receiving projections from BDNF-synthesizing neurons [101]. There is, however, a paucity of direct in vivo evidence supporting the specific involvement of neurons in BDNF synthesis, while growing arguments suggest that astrocytes might participate in the production of this factor. For example, the BDNF transcription factor CREB has been identified in cortical or hippocampal cultured astrocytes [230], and antidepressant drugs, such as imipramine, stimulate CREB activity [231].

Despite the fact that the precise source of BDNF remains somewhat equivocal, preclinical studies have clearly indicated that the intracerebroventricular and intra-hippocampal infusion of BDNF produces antidepressant-like activity in naive and stressed rodents [232-235], thereby demonstrating that the therapeutic activity of antidepressant drugs depends, at least in part, on BDNF synthesis and TrkB signaling in neurons. Accordingly, as the high affinity receptor of BDNF, TrkB is autophosphorylated in response to the chronic administration of various classes of antidepressant drugs in the mouse HP and cingulate cortex [236, 237], whereas transgenic mice with the non-functional truncated TrkB are less sensitive to these treatments [238]. Conversely, the ability of acute administration of SSRIs to produce antidepressant-like effects [239] and to increase hippocampal extracellular 5-HT levels is blunted in mice lacking 50% of BDNF [137]. Although the link between BDNF and 5-HT neurotransmission has not been completely elucidated, evidence suggests that BDNF favors the expression and activity of SERT, thereby increasing 5-HT clearance in the synaptic cleft [137]. The role of BDNF and the related TrkB receptor in adult hippocampal neurogenesis has stimulated number of studies showing that this factor promotes the in vivo proliferation and differentiation of neuronal progenitor cells [240-243], accelerates the maturation of new neurons and facilitates neuronal survival [242-244]. In human post-mortem studies, the expression of BDNF is increased in the HP of depressed patients treated with antidepressant drugs compared to untreated individuals [245].

Together, these data strongly suggest that BDNF is predominantly synthesized by neurons [246], but reactive astrocytes could also produce this factor under particular conditions, such as in neurodegenerative diseases or after the exposure of cultured astrocytes to kainic acid [247, 248]. Although the extremely low levels of BDNF in neurons have greatly complicated attempts to reliably localize this factor [249], the presence of SERT and 5-HT receptor subtypes on astrocytes, along with the recent observations that fluoxetine,
BDNF in primary cultures of astrocytes [17, 138, 231], suggest that glial cells represent a permissive microenvironment for the production of new neurons and neuronal integration into existing functional networks in the dentate gyrus of the HP. To address the question of the in vivo contribution of astrocytic BDNF to antidepressant drug actions, we applied a new lentiviral strategy [250] aimed at overexpressing this neurotrophic factor in the hippocampal astrocytes of adult mice. Our results show that such a manipulation produces anxiolytic-antidepressant-like activity in mice subjected to novelty suppressed feeding (NSF), a behavioral paradigm in relation to the stimulation of adult hippocampal neurogenesis [251]. However, BDNF overexpression did not potentiate the effect of chronic fluoxetine, suggesting that SSRIs and astrocytic BDNF could act through a similar downstream mechanism. Interestingly, neurochemical data showed that the overexpression of BDNF within astrocytes did not modify hippocampal extracellular 5-HT levels, suggesting that the behavioral and neurogenic effects of astrocytic BDNF were not dependent on the modulation of serotonergic presynaptic activity. In a marked contrast, although BDNF overexpression or chronic fluoxetine alone are devoid of behavioral activity, the combination of both viral and pharmacological interventions elicited anxiolysis in behavioral paradigms used to unveil anxiolytic-like activity such as the elevated plus maze (EPM). At the neurochemical level, such a combination attenuated the ability of fluoxetine to enhance extracellular hippocampal 5-HT levels, a mechanism that could be favorable to anxiolysis. These results illustrate the concept of the tripartite synapse in which the increase in the 5-HT neurotransmission induced by the SSRI fluoxetine could promote the synthesis and release of BDNF from astrocytes. In turn, once released in the synaptic cleft, BDNF would exert a negative feedback upon extracellular hippocampal 5-HT release to limit the 5-HT neurotransmission and favor anxiolysis. Several explanations could be advanced to explain how BDNF released from astrocytes attenuates the extracellular 5-HT levels in HP. It is possible that BDNF promotes the sprouting of the serotonergic terminals, as previously described in adult animals [252]. Alternatively, hippocampal BDNF could be transported retrogradely to the DR, which could result in the remodeling and growth of 5-HT dendrites at somatodendritic levels, thereby increasing the density of the inhibitory 5-HT_{1A} autoreceptors in response to chronic fluoxetine treatment. In addition to these paracrine effects on the neuronal cell population in the HP, BDNF might also produce autocrine effects on astrocytes. This possibility should be further explored because TrkB [253, 254] and pan-neurotrophin receptor p75 on hippocampal astrocytes [255-257] are both required for BDNF-mediated effects. Interestingly, in cultured astrocytes, the p75 receptor has been shown to participate in pro-BDNF internalization, and this recycling suggests the existence of a specialized form of bidirectional communication between neurons and glia [258].

Although interesting, the above-mentioned results suggest some sufficiency but do not investigate the necessity of astrocytic BDNF in antidepressant drugs activity. The appropriate tool to decipher such a role would be to knockdown this factor through the intra-hippocampal injection of a specific shRNA within the astrocytes in adult mice, a strategy that should prevent the positive effects of chronic fluoxetine treatment. It thus appears possible that under particular conditions, such as following the overexpression of astrocytic BDNF in adult mice [251], astrocytes could be a source of BDNF or can re-uptake BDNF as peripheral platelets do for 5-HT. To our knowledge, this “astrocytic BDNF synthesis” hypothesis has not been demonstrated in vivo, and we do not know whether these results can be observed under physiological conditions or in an animal model of depression.

CONCLUSION

This review illustrates the fact that astrocytes could respond to antidepressant drugs in vivo by sensing and regulating extracellular monoamine levels. In turn, these cells might provide instructive signals to neurons regulating the formation and development of synapses, cell fate in neurogenic niches and neurotransmission in glial-neuronal synaptic units. Given the emerging hypothesis of depression stipulating the existence of an impairment of glial network in this psychiatric disorder [27], antidepressant drugs could act on these cells to restore a normal dialogue between astrocytes and neurons. The Cxs proteins play a major role in this communication, and the observations that the expression and function of these proteins are decreased under stressful conditions [28] and are enhanced in response to antidepressant drugs [28] suggest that gap junctions are promising new targets for the treatment of MDD. This hypothesis is strengthened by the fact that astrocytic Cxs proteins are involved in the direct intercellular exchange of ions and small molecules (e.g., IP3, ATP, glutamate, and energy metabolites) between neighboring cells [259] and in the exchange of neuroactive substances between the cell cytoplasm and the extracellular medium [260]. A current limitation in evaluating the role of the monoaminergic tripartite synapse in the mechanism of action of acute or sub-acute antidepressant drugs lies in the fact that most studies are based on in vitro experiments that do not necessarily mimic the complex events occurring in living animals or humans and do not allow for the extrapolation of behavioral consequences on the antidepressant-like activity. For this prospect, adapted tools, such as genetic and viral knock-down approaches, are required to identify the molecular partners recruited in response to these medications. Finally, one would also expect that the development of optogenetics in transgenic mice overexpressing excitatory channelrhodopsins in astrocytes [261] or the engraftment by glial progenitor cells [262] would be useful to elucidate the precise role of this cell type in higher brain function and the regulation of mood.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

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<tr>
<th>Acronym</th>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>AC</td>
<td>Adenylate Cyclase</td>
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