Minireview

The Janus face of antipsychotics in glial cells: Focus on glioprotection

Izaviany Schmitz[1]* ⓘD, Amanda da Silva[1]*, Larissa Daniele Bobermin[2], Carlos-Alberto Gonçalves[1,2,3] ⓘD, Johann Steiner[4] and André Quincozes-Santos[1,2,3] ⓘD

[1]Programa de Pós-Graduação em Ciências Biológicas: Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre 90035-003, Brazil; [2]Programa de Pós-Graduação em Neurociências, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre 90035-003, Brazil; [3]Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre 90035-003, Brazil; [4]Department of Psychiatry, University of Magdeburg, Magdeburg 39120, Germany
*These authors contributed equally to this paper.
Corresponding author: André Quincozes-Santos. Email: andrequincozes@ufrgs.br

Impact statement

Glial cells are crucial to maintain brain homeostasis, although they can also participate in the pathogenesis of neuropsychiatric disorders, such as schizophrenia. In addition, these cells are putative targets of antipsychotics. These medications are subdivided in typical and atypical, depending on their receptor interaction. Our group has published several studies investigating the effects of antipsychotics on glial functions, particularly glutamate metabolism, redox homeostasis, trophic factors release, and inflammatory response. In addition, in this review, we described glioprotective agents that could act as adjuvants to attenuate glial dysfunctions associated with neuropsychiatric disorders.

Abstract

Antipsychotics are commonly prescribed to treat several neuropsychiatric disorders, including schizophrenia, mania in bipolar disorder, autism spectrum disorder, delirium, and organic or secondary psychosis, for example, in dementias such as Alzheimer's disease. There is evidence that typical antipsychotics such as haloperidol are more effective in reducing positive symptoms than negative symptoms and/or cognitive deficits. In contrast, atypical antipsychotic agents have gained popularity over typical antipsychotics, due to fewer extrapyramidal side effects and their theoretical efficacy in controlling both positive and negative symptoms. Although these therapies focus on neuron-based therapeutic schemes, glial cells have been recognized as important regulators of the pathophysiology of neuropsychiatric disorders, as well as targets to improve the efficacy of these drugs. Glial cells (astrocytes, oligodendrocytes, and microglia) are critical for the central nervous system in both physiological and pathological conditions. Astrocytes are the most abundant glial cells and play important roles in brain homeostasis, regulating neurotransmitter systems and gliotransmission, since they express a wide variety of functional receptors for different neurotransmitters. In addition, converging lines of evidence indicate that psychiatric disorders are commonly associated with the triad neuroinflammation, oxidative stress, and excitotoxicity, and that glial cells may contribute to the gliotoxicity process. Conversely, glioprotective molecules attenuate glial damage by generating specific responses that can protect glial cells themselves and/or neurons, resulting in improved central nervous system (CNS) functioning. In this regard, resveratrol is well-recognized as a glioprotective molecule, including in clinical studies of schizophrenia and autism. This review will provide a summary of the dual role of antipsychotics on neurochemical parameters associated with glial functions and will highlight the potential activity of glioprotective molecules to improve the action of antipsychotics.

Keywords: Antipsychotics, glial cells, glioprotection, schizophrenia, resveratrol

Introduction

In the 1950s, the discovery of the effects of antipsychotics changed paradigms in the treatment of several neuropsychiatric disorders, such as schizophrenia, mania in bipolar disorder, autism spectrum disorder, delirium, and organic or secondary psychosis, for example, in dementia.[1,2]

Typical antipsychotics were first developed and were used to treat schizophrenia. These drugs act on dopamine receptors (D1, D2, D3) in the brain, particularly blocking D2 receptor in the mesolimbic and mesocortical systems, which are respectively associated with reward/motivation and emotion/cognition.[3] In line with this, blockade of limbic D2 receptors is associated with the attenuation of the
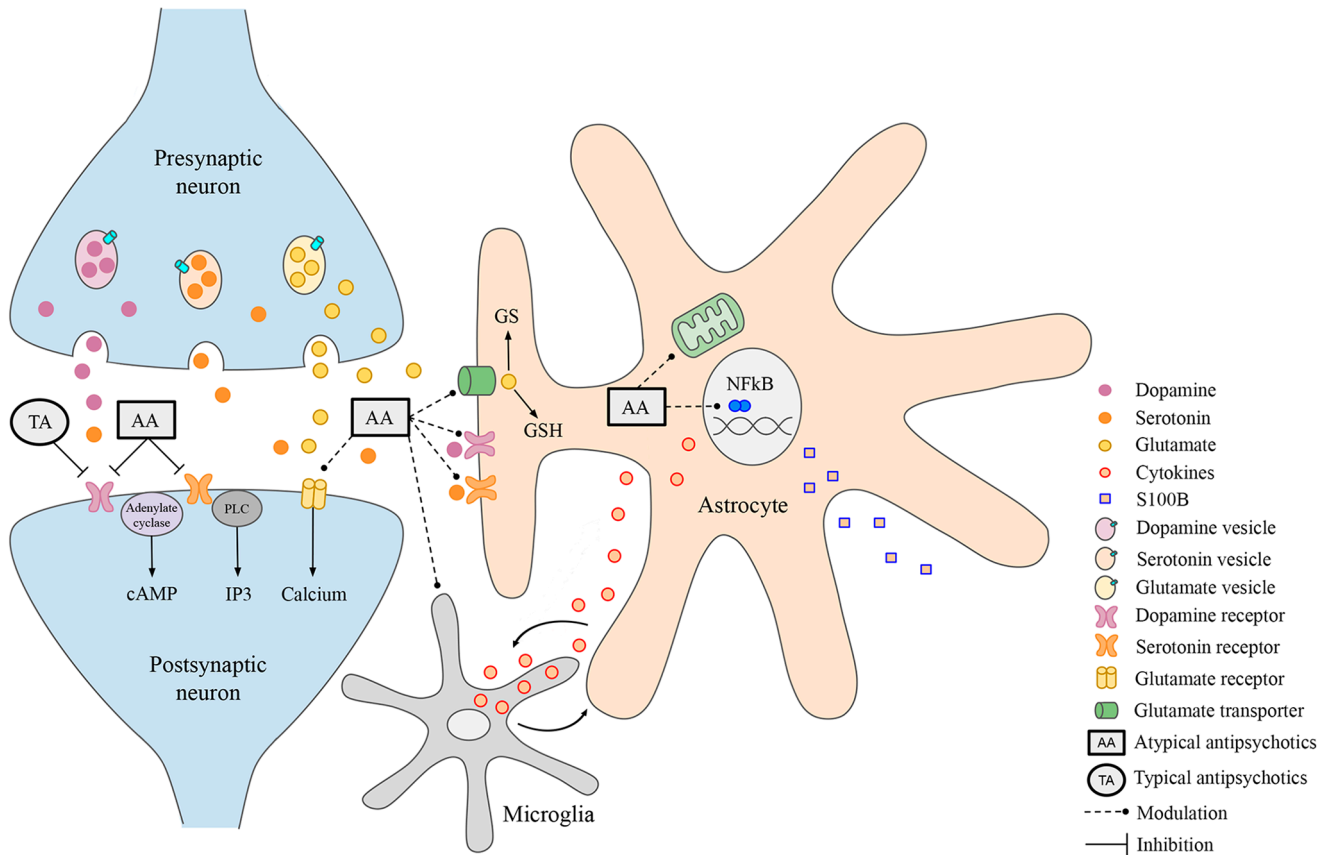
Figure 1. The tripartite synapse as a target of antipsychotics. Presynaptic neurons release neurotransmitters (dopamine, serotonin, glutamate), accordingly to their specialization and brain region, from synaptic vesicles within the synaptic cleft. Neurotransmitters interact with their specific ionotropic and/or metabotropic receptors at postsynaptic neurons. Astrocytes also express dopamine and serotonin receptors, as well as glutamate transporters, therefore modulating synaptic transmission. Typical and atypical antipsychotics, TA and AA, respectively, can act blocking mainly neuronal dopamine and/or serotonin receptors. In addition, AA can modulate glutamate receptors and transporters (dashed lines). Therefore, astrocytes can also be putative targets of antipsychotic medications, as discussed in the text. Astrocytes actively participate in NFκB-coordinated inflammatory, mitochondrial responses, and glutamate metabolism via GS activity and GSH synthesis, all of which are involved in the pathogenesis of neuropsychiatric disorders and may be also modulated by antipsychotics. Finally, there is a close relationship between astrocytes and microglia, particularly related to inflammatory response.

positive symptoms of schizophrenia, such as hallucinations and delusions. Classic examples of typical antipsychotics are chlorpromazine and haloperidol, and this last medication can induce sedative side effects and increased weight.[4] In psychiatric patients, chronic treatment with typical antipsychotics is limited by extrapyramidal side effects induced by dopamine blockade, such as parkinsonism, akathisia, dystonia, and tardive dyskinesia.[5]

The second-generation antipsychotics, also known as atypical antipsychotics, include clozapine, risperidone, quetiapine, and olanzapine. These drugs reduce not only dopamine neurotransmission but also act on serotonin receptors, especially 5HT2A receptors, typically as antagonists.[4,6] In addition, atypical antipsychotics act as adrenergic (α1, α2), cholinergic (M1), and histaminergic (H1) receptor antagonists.[7,8] Therefore, these antipsychotics are more effective for treating negative and cognitive symptoms of schizophrenia, since they also contribute to improve mood and anxiety.[9] It is important to note that although there are some efficacy differences between antipsychotics, the most relevant are associated with differences in side effects.[10] However, this greater range of action brought about new side effects, especially weight gain, hyperglycemia, dyslipidemia, insulin resistance, and even type 2 diabetes mellitus, which affect almost

half of patients. Weight gain effects are more pronounced with clozapine and olanzapine, attributed to their actions on serotonergic 5HT2C and histaminergic H1 receptors. Ziprasidone and aripiprazole act less on 5HT2C receptors and cause less weight gain.[11] Figure 1 depicts some mechanisms of antipsychotics.

Finally, receptor pleiotropism (D2/5HT2) and the rapid D2 receptor dissociation must be considered to differentiate typical from atypical antipsychotics, as well as the better tolerability and improved effectiveness for negative, affective, and cognitive symptoms.[12,13] Moreover, although antipsychotics are available for treating neuropsychiatric disorders, multidisciplinary treatments are needed, such as modern therapy and psychological support, to improve not only the symptoms of these conditions but also behavioral aspects and social interactions.[14,15]

Considering that our research group has studied the effects of typical and atypical antipsychotics on glial cells, this review will provide a summary of the dual role of these drugs on cellular, molecular, and pharmacological mechanisms associated with glial functions. In addition, we will highlight the potential activity of glioprotective molecules to improve the action of antipsychotics on neurochemical parameters, particularly related to glial cells, reducing side

effects of these drugs and consequently improving life quality during the aging process, since these medications are chronically used.

Glial cells as targets of antipsychotics

Although neurons have been assumed to be the major mediators of antipsychotic pharmacological effects, glial cells have emerged as important cellular targets for these drugs. Glial cells (astrocytes, oligodendrocytes, and microglia) are critical for the central nervous system (CNS) in both physiological and pathological conditions. Astrocytes are the most abundant glial cells and play important roles in brain homeostasis, being responsible for trophic support, maintenance of the blood-brain barrier (BBB), energy metabolism, antioxidant defenses, inflammatory responses, gliotransmission, among others.[16,17] These cells express a wide variety of functional receptors for different neurotransmitters, such as glutamate, GABA, as well as adrenergic, purinergic, dopaminergic, and serotonergic receptors.[18,19] However, the effects of antipsychotics in these cells are potentially relevant and appear not to be only directly related to these receptors; thus, typical and atypical antipsychotics can differentially modulate glial-related processes. With regard to the tripartite synapse, in particular, the communication between neurons and astrocytes reinforces the versatility of the glial cells in the regulation of neural functions from development to mature brain.[16] Of note, alterations in neuron–glia communication are critical for understanding the pathomechanisms of psychiatric disorders due to commitment of neurotransmitter systems, excitatory-inhibitory balance, neurotrophic state, and inflammatory response.[20,21] In terms of astrocytes and dopamine-glutamate neurotransmitter systems, D2 receptors are highly expressed in astrocytes[22,23] and, therefore, glial cells may participate in the pathophysiology of neuropsychiatric disorders, and may consequently be involved in the mechanism of action of antipsychotic drugs.[24,25]

Excessive activation of dopamine receptors can lead to a decrease in the activity of the glutamatergic system, which contributes to psychotic symptoms, commonly observed in neuropsychiatric disorders. By blocking dopamine receptors, antipsychotics can increase the activity of the glutamatergic system, helping to reduce psychotic symptoms.[26,27] Glutamate is the main excitatory neurotransmitter in the CNS and plays a key role in regulating synaptic plasticity and memory formation.[28] However, high glutamate levels in the extracellular space are potentially neurotoxic.[29] Most of the synaptically released glutamate is taken up by astrocytes, the main cells that express glutamate transporters.[26] Thus, these cells optimize neuronal functions and prevent glutamate excitotoxicity.[30] Moreover, astrocytes convert glutamate into glutamine via the enzyme glutamine synthetase (GS), and glutamine is then released back to the neurons where glutamate is regenerated by glutaminase.[31]

Schizophrenia is among the most disabling mental health conditions and affects approximately 24 million people worldwide.[6] With the reformulation of the hyperdopaminergic hypothesis and its integration with the glutamatergic hypofunction hypothesis, the role of astrocytes in schizophrenia has been further valued, since glutamate uptake and glutamine synthesis are specific functions of these cells.[27,32] Furthermore, as the relevance of astrocytes has grown in synaptic communication, they have a role in underpinning other neuropsychiatric disorders, including bipolar and autism spectrum disorders, that use atypical antipsychotics as therapeutic strategies.[17,33–36] In addition, atypical antipsychotics have been prescribed for delirium, for example, postsurgery, alcohol withdrawal, and organic or secondary psychosis, for example, dementias including Alzheimer's disease.[13,37–39]

Evidence suggests abnormalities in astroglial glutamate transporter functions and perisynaptic glutamate buffering in schizophrenia,[40] as well as in neurodegenerative conditions.[41] It has been shown that the atypical antipsychotic, clozapine, can reduce glutamate transporter 1 (GLT-1) expression and function in astrocytes, which can be driven by nuclear factor kappa B (NFκB), protein kinase B (Akt), and extracellular signal-regulated kinase (ERK) pathways,[42,43] and is associated with changes in the expression of the synaptic vesicle protein synaptophysin.[43] The release of glutamate by astrocytes can also be enhanced by clozapine, quetiapine, and brexpiprazole through activated hemichannels, which can enhance tripartite synaptic glutamatergic transmission.[44] In addition, clozapine activates glial exocytosis of D-serine, an endogenous N-methyl-D-aspartate (NMDA) receptor partial agonist.[45] Of note, reduced levels of both glutamate and D-serine were found in astrocytes derived from schizophrenia patients and could be rescued by clozapine only in cells from clozapine responders, providing evidence that these mechanisms are associated both with schizophrenia pathophysiology and the action of clozapine.[46]

With particular regard to risperidone and haloperidol, over the last two decades, our group has published several studies that have investigated the effects of these antipsychotics on glial functionality (Table 1). In line with this, in C6 astroglial cells, a comparative study between typical and atypical antipsychotics showed that risperidone, but not haloperidol, is able to increase glutamate uptake and GS activity.[47,48] In addition, the chronic blockade of D2 receptors with haloperidol elevates extracellular glutamate levels in the striatum.[49,50] Taken together, these findings indicate that the modulation of astrocyte functions related to the maintenance of glutamate neurotransmission is relevant for the therapeutic effects of antipsychotics. In this context, while specific antipsychotics, such as clozapine and haloperidol, ameliorate schizophrenia-related glutamate hypofunction, their long-term use can be associated with glutamate imbalance toward excitotoxicity and the emergence or progression of neurodegeneration. On the contrary, other antipsychotics, such as risperidone, may exert neuroprotective effects against brain disorders associated with excitotoxicity, including autism.[51–53]

Glutamate can also be used for the synthesis of the antioxidant molecule, glutathione (GSH), particularly in astrocytes. Notably, oxidative stress may be another common mechanism in the pathogenesis of psychiatric and neurodegenerative disorders.[54,55] In this regard, both glutamate and dopamine neurotransmitters are redox active molecules and can be involved in the generation of reactive oxygen species (ROS) even during normal neurotransmission. Following alterations in glutamatergic and dopaminergic activity,

Table 1. Effect of typical and atypical antipsychotics in glial cells.

Atypical antipsychotics	Main effects	References
Aripiprazole	Inhibition of pro-inflammatory cytokine release	87
Brexpiprazole	Increase of glutamate release	44
Clozapine	Increase of glutamate release	44
	Reduction of glutamate transporter (GLT-1) expression	42,43
	Release of D-serine	45,46
	Attenuation of oxidative stress	47,48
	Modulation of synaptophysin expression	43
	Regulation of microglial activation	92
	Inhibition of NLRP3 inflammasome	89
	Reduction of S100B secretion	103
	Increase of trophic factor release	47,48
Olanzapine	Reduction of oxidative stress induced by microglial overactivation	47,48
Quetiapine	Increase of glutamate release	44
	Induction of proliferation and/or differentiation of oligodendrocyte precursors	73
	Induces oligodendrocyte regeneration and myelin repair	74
	Inhibition of NFκB p65 activation	39
	Modulation of inflammatory processes	93
	Increase of trophic factor release	107,108
Risperidone	Increase of glutamate uptake and GS activity	44
	Attenuation of oxidative stress induced by microglial overactivation	47,48
	Increase of GSH levels	48,58
	Anti-inflammatory activity (decrease of TNF-α, IL-1β, and IL-6 cytokine levels and increase of IL-10)	58
	Decrease of NFκB transcriptional activity	58
	Modulation of S100B release	99,101
Typical antipsychotics		
Chlorpromazine	Anti-inflammatory effect in microglial cells	90,94
Haloperidol	Elevation of glutamate extracellular levels	49
	Pro-oxidant activity (increase of ROS production)	48,58
	Pro-oxidant activity (reduction of antioxidant enzymes)	84,85
	Modulation of the redox homeostasis	59
	Anti-inflammatory effects in microglial cells	93
	Activation of p38 MAPK and NFκB pathways	58
	Reduction of S100B secretion in oligodendroglial cells	103
	Increase in trophic factor release	108,109

GLT-1: glutamate transporter 1; GS: glutamine synthetase; GSH: glutathione; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; NFκB: nuclear factor kappa B; p38 MAPK: p38 mitogen-activated protein kinase; ROS: reactive oxygen species; TNF-α: tumor necrosis factor α.

ROS production may be exacerbated and contribute to an increased brain vulnerability to oxidative damage, such as glutamate transporter oxidation.[56,57] Concomitantly with the increase in glutamate uptake and GS activity, risperidone increases GSH levels in C6 astroglial cells. However, haloperidol did not change this antioxidant defense and increased the production of ROS.[48,58] Accordingly, chronic treatment with haloperidol has been associated with oxidative stress,[59,60] at least in part due to an impairment in GSH levels,[61–64] and therefore with the pathogenesis of extrapyramidal side effects.[59] The cytotoxicity induced by the typical antipsychotics, haloperidol, and chlorpromazine in astrocytes depends on increased intracellular calcium levels,[63,64] which is also a mechanism underlying oxidative stress. Therefore, although typical antipsychotics such as haloperidol can solve neurotransmitter dysfunctions, they can aggravate oxidative stress. In contrast, the ability of risperidone to modulate the endogenous antioxidant, GSH, reinforces its neuroprotective properties rather than neurotoxic ones. Corroborating this idea, it has been suggested that *N*-acetylcysteine, a precursor

of cysteine for GSH synthesis, may be an adjunctive strategy in the treatment of psychiatric disorders.[65,66]

It is important to note that risperidone has been used to treat behavior problems such as aggression, self-injury, and sudden mood changes in children who have autism, a condition that causes difficulty in interacting with others, and problems with communication.[67] In this context, risperidone offers a valuable emerging option for the treatment of social behavior associated with autistic disorder in children and adolescents,[68,69] and our research group contributes to demonstrate the neuroprotective effects of this antipsychotic drug against brain illness, at least partially via modulation of astrocyte functions.

In addition to astrocytes, oligodendrocytes and microglia are crucial to the maintenance of brain homeostasis.[30] Oligodendrocytes form myelin around axons in the CNS to ensure fast and efficient electrical conduction along myelinated axons.[70] Decreased numbers of oligodendrocytes and/or abnormalities involving myelin-related structures may be involved in the pathogenesis of neuropsychiatric disorders,

while protection of oligodendrocytes/myelin may improve symptoms associated with schizophrenia.[71,72] The atypical antipsychotics, quetiapine and olanzapine, promote the proliferation and/or differentiation of precursor oligodendrocyte cells *in vitro*,[73] and quetiapine also enhances oligodendrocyte regeneration and myelin repair in experimental models of cuprizone-induced demyelination[74] and global cerebral ischemia.[75] These neuroprotective effects are also related to the anti-inflammatory properties of atypical antipsychotics,[76–78] which are possibly associated with their H1 receptor antagonism.[77] In contrast, the typical antipsychotic haloperidol was not effective in promoting differentiation and maturation of oligodendrocyte precursor cells exposed to cuprizone, reinforcing the differential effects of antipsychotics in the development of oligodendrocytes.[79]

Microglia are responsible for innate brain immune response. These cells may initiate the formation of intracellular multiprotein complexes called inflammasomes, as well as cytokine release and production, and consequently, neuroinflammation.[80] In this context, they can trigger neurodegenerative processes, which can result in cognitive dysfunction, being a potential aggravating factor of psychiatric disorders.[81] It is important to note that, in neuropsychiatric disorders, such as schizophrenia, microglia can induce astrocyte reactivity, neuroinflammation, and oxidative stress, which can cause neuronal death.[17,82,83] Table 1 also shows that treatment with antipsychotics such as risperidone, clozapine, and olanzapine reduce oxidative stress induced by microglial overactivation by increasing GSH, the main antioxidant of the CNS.[47,48] Interestingly, first-generation antipsychotics can induce oxidative stress by reducing antioxidant enzymes, as observed with haloperidol treatment, which can contribute to the development of side effects.[84,85] In addition, several *in vitro* studies in microglial cells have demonstrated anti-inflammatory effects particularly related to the atypical antipsychotics quetiapine, clozapine, risperidone, olanzapine, and aripiprazole. In general, these molecules are able to inhibit the release of a wide range of pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-2 (IL-2), monocyte chemoattractant protein-1 (MCP-1), and interferon-γ (IFN-γ), in addition to decreasing nitric oxide (NO) generation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity.[86–89] Moreover, atypical antipsychotics can increase the anti-inflammatory cytokine interleukin-10 (IL-10).[89,90] The anti-inflammatory effects of these drugs may occur both at basal conditions and upon inflammatory stimuli and may involve different mechanisms. Of note, clozapine can inhibit the NLR family pyrin domain containing 3 (NLRP3) inflammasome,[89] while quetiapine inhibits the activation of the NFκB p65 pathway,[39] a master regulator of inflammation. Inhibition of microglial proton currents is also involved in the anti-inflammatory effect of clozapine and does not involve serotonin receptors.[91] Moreover, *in vivo* studies showed that clozapine can regulate microglial activation in a model of chronic experimental autoimmune encephalomyelitis,[92] while quetiapine modulates brain inflammatory processes in adult rats prenatally exposed to lipopolysaccharide (LPS), a model of schizophrenia-like disturbances,[93] and in a transgenic mice model of Alzheimer's disease.[39] With regard to typical antipsychotics, chlorpromazine and haloperidol have been demonstrated to exert some anti-inflammatory effects in microglial cells,[90,94] also by decreasing the release of pro-inflammatory cytokines. However, it is important to note that more significant anti-inflammatory activities have been associated with atypical drugs in microglial cells.

Converging lines of evidence indicate that psychiatric disorders are commonly associated with the triad neuroinflammation, oxidative stress, and excitotoxicity.[52,95,96] However, information about the effects of antipsychotics on inflammatory response in astrocytes is still scarce, but typical and atypical drugs seem to have differential roles. While risperidone decreased TNF-α, IL-1β, and IL-6 and increased IL-10 in astroglial cells, haloperidol had the opposite effect. The anti-inflammatory response induced by risperidone also involved a decrease in transcriptional activity of NFκB, in contrast to an activation of the p38 mitogen-activated protein kinase (p38 MAPK)/NFκB pathway by haloperidol.[58]

In addition to pro-inflammatory cytokines, activated astrocytes can release elevated levels of S100B, a glia-derived protein that has been shown to be increased in psychiatric disorders, including schizophrenia.[17,97,98] S100B release is increased by pro-inflammatory cytokines, and both the antipsychotics, haloperidol, and risperidone can decrease S100B release stimulated by IL-6 in astroglial cells,[99,100] while risperidone positively modulates S100B extracellular levels at basal conditions.[101] These drugs also inhibited the decrease in S100B secretion induced by dopamine agonist apomorphine.[102] Furthermore, both haloperidol and clozapine reduce the release of S100B from oligodendroglial cells.[103] Therefore, although differential effects are observed, dopamine receptors seem to regulate S100B release by astrocytes, and this protein may represent a specific astroglial target of antipsychotics. Indeed, S100B can have dual functions, acting either as a pro-inflammatory signal or exerting trophic roles.[104–106] In line with a role in modulating trophic signaling, quetiapine, clozapine, and haloperidol increased the release of trophic factors, including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) from cultured astroglial cells.[107–109]

Ultimately, there is a close relationship between the triad neuroinflammation, oxidative stress, and excitotoxicity with the release of trophic factors, which can be modulated by transcription factors including NFκB and nuclear factor erythroid 2-related factor 2 (Nrf2).[30] Furthermore, the AMP-activated protein kinase (AMPK) signaling pathway regulates energy balance, mitochondrial function, detoxification, and antioxidant defenses, promoting cellular homeostasis.[110] This pathway crosstalks with Nrf2 and is increased by quetiapine in cultured astrocytes from the hypothalamus, a brain region that is crucial for the control of metabolism, indicating a potential link between antipsychotics and metabolic dysfunction and antipsychotic-induced obesity.[30,111] Thus, changes in cellular responses and mechanisms related to glial cells may be associated with the pathogenesis of neuropsychiatric disorders and side effects caused by these medications.

Antipsychotics and gliotherapy

The role of glial cells in the development and progression of CNS diseases, commonly associated with gliotoxicity, as well as specific responses of glial cells by which they can protect themselves or neurons (a process named as glioprotection) is critical for brain homeostasis.[30] In this regard, glial cells may represent putative cellular targets to treat neuropsychiatric disorders, as well as to improve preventive and therapeutic strategies to reduce the side effects associated with these medications. It is important to note that although the pathophysiology behind the psychiatric disorders, such as schizophrenia and mood disorders, is not fully understood, several studies indicate alterations in neuron–glia interaction as potential mechanisms for these conditions.[20]

Table 1 displays specific effects of typical and atypical antipsychotics on glial parameters, particularly related to astrocyte functions. As demonstrated, antipsychotics can induce glial responses, including glial damage. In this sense, glial cells are key players in schizophrenia pathology since a plethora of studies have shown structural and functional abnormalities in all three types of glial cells in schizophrenia patients. In this context, both the progression of schizophrenia as well as the effects of the prolonged use of these medications can be associated with changes in glial cells. Moreover, alterations in glutamate neurotransmission are common in hippocampus of schizophrenia patients,[40] and cognition problems may be less common in people with late onset schizophrenia,[112] while people who receive a diagnosis of very late onset schizophrenia (over 60 years old) have a significant risk of dementia.

Psychosis is a common symptom in schizophrenia, as well as in Alzheimer's disease, and few safe and effective treatments are available for this later condition. In addition, psychotic symptoms are associated with hospitalization or institutionalization, and cognitive and functional impairment may accelerate cognitive decline and mortality in these patients.[113] It is noteworthy that around 40% of people with Alzheimer's disease reported psychosis, and atypical antipsychotics are used to treat psychosis in dementia. These medications can also modulate the inflammatory profile, which is an important contributor the pathogenesis/progression of dementia.[114,115]

Although atypical antipsychotics present relevant efficacy for treating schizophrenia and autism spectrum disorder, they demonstrate modest efficacy for dementia with substantial adverse effect burden and mortality risk. Overall, meta-analytical evidence best supports aripiprazole and risperidone, compared to olanzapine and quetiapine.[113] However, the risk of each medication must be evaluated in the choice of the treatment. Thus, pharmacokinetic–pharmacodynamic studies have explored nuanced dosing approaches to better optimize the balance between efficacy and safety, and astrocytes emerge as potential targets, because they are also responsible for BBB maintenance and integrity. It is important to note that neuropsychiatric disorders, such as Alzheimer's disease, present disrupted BBB;[116,117] thus, astrocytes may be key cells to control the entry of drugs within the CNS, and consequently, the dose of medications needed to ensure a successful treatment. In line

with this, many studies strive to develop specific therapies for neuropsychiatric disorders, but they are not focused on glial cells. With gliotherapy approaches, the development of new drugs or the repurposing of existing drugs could contribute to improve the treatment of neurodegeneration associated with antipsychotic use. The long-term effects of antipsychotics on glial cells in different brain regions should be properly considered, as these may present innovative perspectives for pharmacotherapy.[17]

Could glioprotective molecules attenuate neuropsychiatric disorders? Focus on glioprotection/glial pharmacology

Increased evidence shows glial impairment in *in vitro* and *in vivo* experimental models of autism, a neurodevelopmental disorder. In addition, atypical antipsychotics used to treat this condition can induce glial alterations and the long-term treatment with these medications can contribute to the progression of neurodegenerative diseases; thus, new drugs for autistic patients need to be investigated. Glioprotective strategies may attenuate these abnormalities, particularly because mood disorders are glial disorders resveratrol, a well-tested glioprotective molecule, presents efficacy, tolerability, and safety, as well as anti-inflammatory, antioxidant, and neuroprotective properties, emerging as a promising therapeutic strategy for large-scale studies in autism spectrum disorder, as well as in schizophrenia.[118]

Resveratrol can also protect neurons in brain-implantable electrodes, such as those used in deep brain stimulation.[119] In this regard, glioprotective molecules can result in an overall improvement in CNS functioning, including during glial damage associated with long-term use of antipsychotics in neuropsychiatric disorders. Our group has demonstrated that resveratrol and other molecules can regulate several astrocyte functions, including antioxidant defenses, inflammatory response, trophic factor release, and glutamate homeostasis, both at basal conditions and against harmful stimuli.[30] In addition, resveratrol is able to prevent age-related functional alterations of astrocytes. These effects are associated with different signaling pathways, including Nrf2, heme oxygenase 1 (HO-1), SIRT1, PI3K/Akt, AMPK, and NFκB.[30] In this context, selective overexpression of HO-1 in the astrocytes of mice induced subcortical oxidative stress and mitochondrial damage and resulted in a neurophenotype that bears resemblances to human schizophrenia, suggesting a role of HO-1 in the development of monoaminergic circuitry.[120,121] Interestingly, we recently demonstrated that resveratrol was able to decrease Nrf2 and HO-1, indicating that these pathways may not be the main target of resveratrol in hypothalamic astrocytes.[122] Furthermore, evidence suggests a possible link between hypothalamic gliogenesis and weight gain associated with olanzapine treatment in mice.[123] In addition, olanzapine seems to increase the expression of astrocyte markers (glial fibrillary acidic protein—GFAP and S100B) and hypothalamic activation of the toll-like receptor 4 (TLR4) signaling pathway, which may be associated with olanzapine-induced
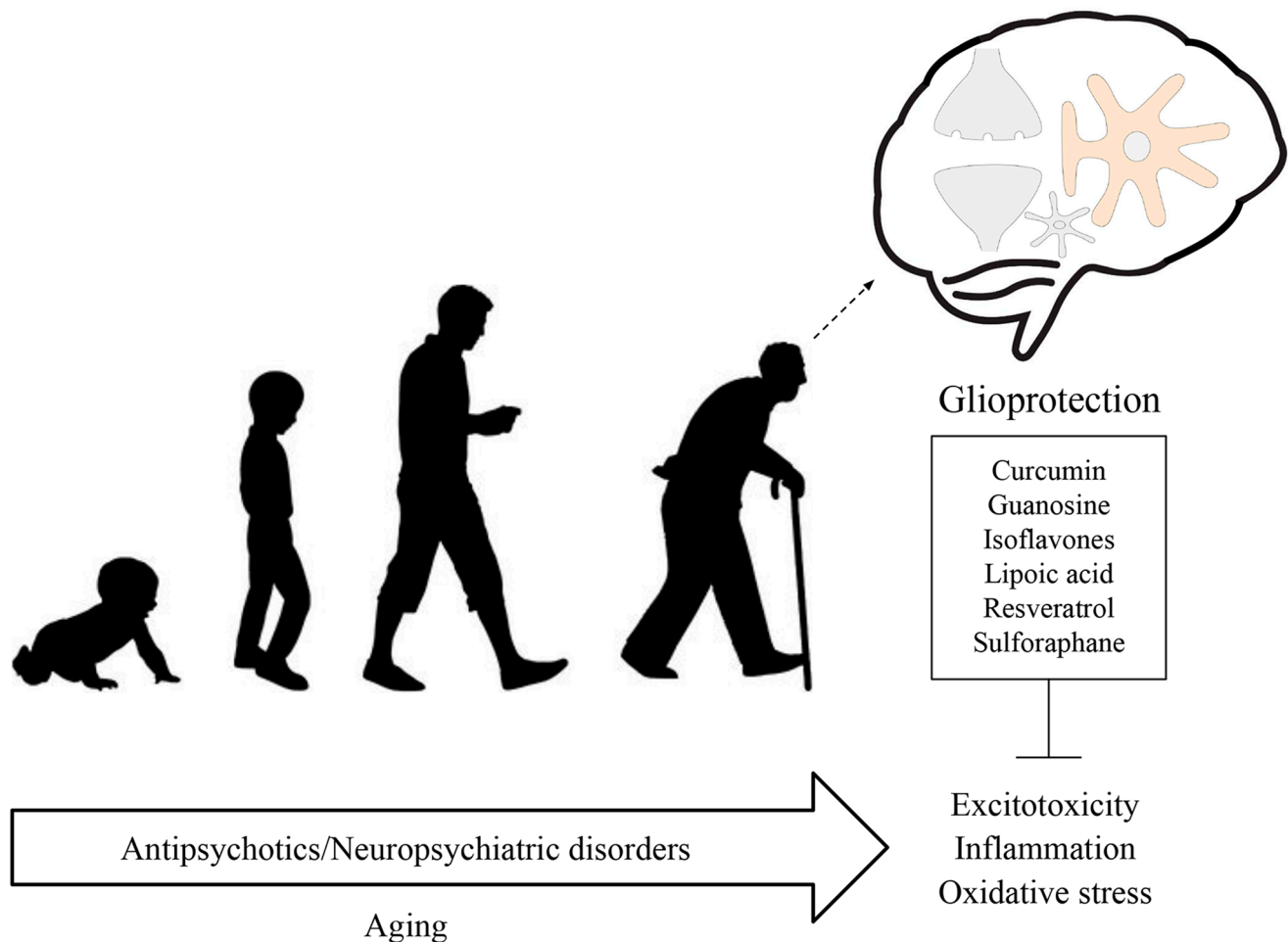
Figure 2. The Janus face of antipsychotics. Glial cells display key roles in the pathogenesis and progression of neuropsychiatric disorders. Accumulating evidence has shown that antipsychotics can affect glial functions. The long-term use of these medications, in association with age, may lead to changes in inflammatory response, oxidative stress, and glutamate homeostasis imbalance/excitotoxicity. Of note, all these processes are also closely related to neuropsychiatric disorders. Therefore, glioprotection (glial-based preventive/therapeutic strategies) might emerge to avoid such detrimental effects.

obesity.[124] Another study from our group showed that resveratrol decreased the expressions of GFAP, S100B, TLR4, and NFκB after long-term treatment in hypothalamic astrocyte cultures from aged rats.[125] These data corroborate the potential multitarget feature of resveratrol and its potential role for avoiding antipsychotic side effects involving the hypothalamus, which is also critically affected in neuropsychiatric disorders.

Moreover, resveratrol exhibits glioprotective effects on microglial and oligodendroglial cells.[30] Haloperidol and olanzapine significantly decreased the number of astrocytes, but not of oligodendrocytes, in the brain of antipsychotic-exposed monkeys.[126] Thus, resveratrol could attenuate this astrocyte damage, presenting a significant glial pharmacological potential.

Finally, specific interleukins, such as IL-10, IL-12, IL-2, interferon-α (INF)-α, TNF-α, and transforming growth factor β (TGF-β), are signaling mediators that normally increase during the early stages of schizophrenia but are normalized by antipsychotic treatment. Resveratrol can modulate cytokine release in several experimental models and could contribute to regulate this early inflammatory response and, consequently, the onset and/or progression of neurodegeneration. Besides resveratrol, other naturally occurring molecules of plant origin can promote glioprotection, such as curcumin, isoflavones, and sulforaphane, as well as endogenous mammalian compounds including lipoic acid and guanosine (a guanine-based purine). Therefore, these potential glioprotective agents could be investigated as adjuvants to attenuate glial disorders, because neuropsychiatric disorders are also indeed glial disorders.

Concluding remarks

In summary, due to the critical role of glial cells in the pathogenesis and progression of neuropsychiatric disorders, as well as their potential role as cellular targets to treat these conditions, we highlight in this review how glioprotective molecules can attenuate the long-term effects associated with typical and atypical antipsychotics (Figure 2). In addition, glial cells, particularly astrocytes, may be relevant in the repurposing of existing antipsychotics, as these cells are the most versatile in the brain. With this in mind, glioprotective molecules can form part of adjuvant treatments, as proposed in clinical studies that indicated resveratrol as adjuvant therapy for negative symptoms in patients with

schizophrenia. By understanding how antipsychotics act in glial cells, glial-based preventive/therapeutic strategies might emerge to delay and to prevent the development of undesirable consequences associated with these medications. Therefore, antipsychotics have two faces (Janus face), because they are critical to treat neuropsychiatric disorders, but they can induce side effects and contribute to glial reactivity; however, glioprotective molecules could attenuate these contrasting aspects.

AUTHORS' CONTRIBUTIONS

IS, AdS, LDB, C-AG, JS, and AQ-S conceptualized the review, written the original draft of the manuscript, revised, edited, and approved the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID IDS

Izaviany Schmitz https://orcid.org/0000-0001-6083-9105

Carlos-Alberto Gonçalves https://orcid.org/0000-0001-8430-5650

André Quincozes-Santos https://orcid.org/0000-0001-8611-4890

REFERENCES

1. Cunningham Owens D, Johnstone EC. The development of antipsychotic drugs. *Brain Neurosci Adv* 2018;**2**:2398212818817498
2. Lieberman JA, First MB. Psychotic disorders. *New Engl J Med* 2018;**379**:270–80
3. Dold M, Samara MT, Li C, Tardy M, Leucht S. Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders. *Cochr Datab Syst Rev* 2015;**1**:CD009831
4. Shen WW. A history of antipsychotic drug development. *Comprehen Psych* 1999;**40**:407–14
5. Ali T, Sisay M, Tariku M, Mekuria AN, Desalew A. Antipsychotic-induced extrapyramidal side effects: a systematic review and meta-analysis of observational studies. *PLoS ONE* 2021;**16**:e0257129
6. Fabrazzo M, Cipolla S, Camerlengo A, Perris F, Catapano F. Second-generation antipsychotics' effectiveness and tolerability: a review of real-world studies in patients with schizophrenia and related disorders. *J Clin Med* 2022;**11**:4530
7. Corena-McLeod M. Comparative pharmacology of risperidone and paliperidone. *Drugs R D* 2015;**15**:163–74
8. Foster DJ, Bryant ZK, Conn PJ. Targeting muscarinic receptors to treat schizophrenia. *Behav Brain Res* 2021;**405**:113201
9. Khokhar JY, Henricks AM, Sullivan EDK, Green AI. Unique effects of clozapine: a pharmacological perspective. *Adv Pharmacol* 2018;**82**:137–62
10. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019;**394**:939–51
11. Singh R, Bansal Y, Medhi B, Kuhad A. Antipsychotics-induced metabolic alterations: recounting the mechanistic insights, therapeutic targets and pharmacological alternatives. *Euro J Pharmacol* 2019;**844**:231–40
12. Li P, Snyder GL, Vanover KE. Dopamine targeting drugs for the treatment of schizophrenia: past, present and future. *Curr Top Med Chem* 2016;**16**:3385–403
13. Dremencov E. Mechanism of action of atypical antipsychotic drugs in mood disorders. *Int J Mol Sci* 2020;**21**:9532
14. Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. *Br Med Bull* 2015;**114**:169–79
15. Weintraub D, Aarsland D, Biundo R, Dobkin R, Goldman J, Lewis S. Management of psychiatric and cognitive complications in Parkinson's disease. *BMJ* 2022;**379**:e068718
16. Stevens B. Neuron-astrocyte signaling in the development and plasticity of neural circuits. *Neurosignals* 2008;**16**:278–88
17. Brisch R, Wojtylak S, Saniotis A, Steiner J, Gos T, Kumaratilake J, Henneberg M, Wolf R. The role of microglia in neuropsychiatric disorders and suicide. *Eur Arch Psychiatry Clin Neurosci* 2022;**272**:929–45
18. Ben Achour S, Pascual O. Glia: the many ways to modulate synaptic plasticity. *Neurochem Int* 2010;**57**:440–5
19. Bernaus A, Blanco S, Sevilla A. Glia crosstalk in neuroinflammatory diseases. *Front Cell Neurosci* 2020;**14**:209
20. Wartchow KM, Scaini G, Quevedo J. Glial-neuronal interaction in synapses: a possible mechanism of the pathophysiology of bipolar disorder. *Adv Exp Med Biol* 2023;**1411**:191–208
21. Reis de Assis D, Szabo A, Requena Osete J, Puppo F, O'Connell KS, Akkouh IA, Hughes T, Frei E, Andreassen OA, Djurovic S. Using iPSC models to understand the role of estrogen in neuron–glia interactions in schizophrenia and bipolar disorder. *Cells* 2021;**10**:209
22. Khan ZU, Koulen P, Rubinstein M, Grandy DK, Goldman-Rakic PS. An astroglia-linked dopamine D2-receptor action in prefrontal cortex. *Proc Natl Acad Sci USA* 2001;**98**:1964–9
23. de Bartolomeis A, Barone A, Vellucci L, Mazza B, Austin MC, Iasevoli F, Ciccarelli M. Linking inflammation, aberrant glutamate-dopamine interaction, and post-synaptic changes: translational relevance for schizophrenia and antipsychotic treatment: a systematic review. *Mol Neurobiol* 2022;**59**:6460–501
24. Molofsky AV, Krencik R, Ullian EM, Tsai H, Deneen B, Richardson WD, Barres BA, Rowitch DH. Astrocytes and disease: a neurodevelopmental perspective. *Genes Dev* 2012;**26**:891–907
25. Heider J, Vogel S, Volkmer H, Breitmeyer R. Human iPSC-derived glia as a tool for neuropsychiatric research and drug development. *Int J Mol Sci* 2021;**22**:10254
26. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol* 2015;**29**:97–115
27. Lander SS, Khan U, Lewandowski N, Chakraborty D, Provenzano FA, Mingote S, Chornyy S, Frigerio F, Maechler P, Kaphzan H, Small SA, Rayport S, Gaisler-Salomon I. Glutamate dehydrogenase–deficient mice display schizophrenia-like behavioral abnormalities and CA1-specific hippocampal dysfunction. *Schizophr Bull* 2019;**45**:127–37
28. Ota Y, Zanetti AT, Hallock RM. The role of astrocytes in the regulation of synaptic plasticity and memory formation. *Neural Plast* 2013;**2013**:185463
29. Mahmoud S, Gharagozloo M, Simard C, Gris D. Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. *Cells* 2019;**8**:184
30. Quincozes-Santos A, Santos CL, de Souza Almeida RR, da Silva A, Thomaz NK, Costa NLF, Weber FB, Schmitz I, Medeiros LS, Medeiros L, Dotto BS, Dias FRP, Sovrani V, Bobermin LD. Gliotoxicity and glioprotection: the dual role of glial cells. *Mol Neurobiol* 2021;**58**:6577–92
31. Rose CR, Ziemens D, Untiet V, Fahlke C. Molecular and cellular physiology of sodium-dependent glutamate transporters. *Brain Res Bull* 2018;**136**:3–16

32. Kondziella D, Brenner E, Eyjolfsson EM, Sonnewald U. How do glial–neuronal interactions fit into current neurotransmitter hypotheses of schizophrenia. *Neurochem Int* 2007;**50**:291–301

33. Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, Cunha AB, Ceresér KM, Santin A, Gottfried C, Salvador M, Kapczinski F, Gonçalves CA. Serum S100B and antioxidant enzymes in bipolar patients. *J Psychiatr Res* 2007;**41**:523–9

34. Kanda Y, Okada M, Ikarashi R, Morioka E, Kondo T, Ikeda M. Bimodal modulation of store-operated Ca2+ channels by clozapine in astrocytes. *Neurosci Lett* 2016;**635**:56–60

35. Lee HG, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. *Nat Rev Drug Discov* 2022;**21**:339–58

36. Okada M, Oka T, Nakamoto M, Fukuyama K, Shiroyama T. Astroglial connexin43 as a potential target for a mood stabiliser. *Int J Mol Sci* 2021;**22**:339

37. Caraci F, Santagati M, Caruso G, Cannavò D, Leggio GM, Salomone S, Drago F. New antipsychotic drugs for the treatment of agitation and psychosis in Alzheimer's disease: focus on brexpiprazole and pimavanserin. *F1000Res* 2020;**9**:F1000 Faculty Rev-686

38. Wang J, Zhu S, Wang H, He J, Zhang Y, Adilijiang A, Zhang H, Hartle K, Guo H, Kong J, Huang Q, Li XM. Astrocyte-dependent protective effect of quetiapine on GABAergic neuron is associated with the prevention of anxiety-like behaviors in aging mice after long-term treatment. *J Neurochem* 2014;**130**:780–9

39. Zhu S, Shi R, Li V, Wang J, Zhang R, Tempier A, He J, Kong J, Wang J-F, Li X-M. Quetiapine attenuates glial activation and proinflammatory cytokines in APP/PS1 transgenic mice via inhibition of nuclear factor-κB pathway. *Int J Neuropsychopharmacol* 2015;**18**:pyu022

40. Shakory S, Watts JJ, Hafizi S, Da Silva T, Khan S, Kiang M, Bagby RM, Chavez S, Mizrahi R. Hippocampal glutamate metabolites and glial activation in clinical high risk and first episode psychosis. *Neuropsychopharmacology* 2018;**43**:2249–55

41. Andersen JV, Markussen KH, Jakobsen E, Schousboe A, Waagepetersen HS, Rosenberg PA, Aldana BI. Glutamate metabolism and recycling at the excitatory synapse in health and neurodegeneration. *Neuropharmacology* 2021;**196**:108719

42. Vallejo-Illarramendi A, Torres-Ramos M, Melone M, Conti F, Matute C. Clozapine reduces GLT-1 expression and glutamate uptake in astrocyte cultures. *Glia* 2005;**50**:276–9

43. Bragina L, Melone M, Fattorini G, Torres-Ramos M, Vallejo-Illarramendi A, Matute C, Conti F. GLT-1 down-regulation induced by clozapine in rat frontal cortex is associated with synaptophysin up-regulation. *J Neurochem* 2006;**99**:134–41

44. Fukuyama K, Okada M. Effects of atypical antipsychotics, clozapine, quetiapine and brexpiprazole on astroglial transmission associated with connexin43. *Int J Mol Sci* 2021;**22**:5623

45. Tanahashi S, Yamamura S, Nakagawa M, Motomura E, Okada M. Clozapine, but not haloperidol, enhances glial D-serine and L-glutamate release in rat frontal cortex and primary cultured astrocytes. *Br J Pharmacol* 2012;**165**:1543–55

46. Akkouh IA, Hribkova H, Grabiec M, Budinska E, Szabo A, Kasparek T, Andreassen OA, Sun Y-M, Djurovic S. Derivation and molecular characterization of a morphological subpopulation of human iPSC astrocytes reveal a potential role in schizophrenia and clozapine response. *Schizophr Bull* 2022;**48**:190–8

47. Quincozes-Santos A, Bobermin LD, Kleinkauf-Rocha J, Souza DO, Riesgo R, Gonçalves C-A, Gottfried C. Atypical neuroleptic risperidone modulates glial functions in C6 astroglial cells. *Progr Neuro-Psychopharm Biol Psych* 2009;**33**:11–5

48. Quincozes-Santos A, Bobermin LD, Tonial RP, Bambini-Junior V, Riesgo R, Gottfried C. Effects of atypical (risperidone) and typical (haloperidol) antipsychotic agents on astroglial functions. *Eur Arch Psychiatry Clin Neurosci* 2010;**260**:475–81

49. De Souza IEJ, McBean GJ, Meredith GE. Chronic haloperidol treatment impairs glutamate transport in the rat striatum. *Euro J Pharmacol* 1999;**382**:139–42

50. Kimura M, Oda Y, Hirose Y, Kimura H, Yoshino K, Niitsu T, Kanahara N, Shirayama Y, Hashimoto K, Iyo M. Upregulation of heat-shock protein HSP-70 and glutamate transporter-1/glutamine synthetase

51. in the striatum and hippocampus in haloperidol-induced dopamine-supersensitivity-state rats. *Pharmacol Biochem Behav* 2021;**211**:173288

51. Essa MM, Braidy N, Vijayan KR, Subash S, Guillemin GJ. Excitotoxicity in the pathogenesis of autism. *Neurotox Res* 2013;**23**:393–400

52. Olloquequi J, Cornejo-Córdova E, Verdaguer E, Soriano FX, Binvignat O, Auladell C, Camins A. Excitotoxicity in the pathogenesis of neurological and psychiatric disorders: therapeutic implications. *J Psychopharmacol* 2018;**32**:265–75

53. Montanari M, Martella G, Bonsi P, Meringolo M. Autism spectrum disorder: focus on glutamatergic neurotransmission. *Int J Mol Sci* 2022;**23**:3861

54. Teleanu DM, Niculescu A-G, Lungu II, Radu CI, Vladâcenco O, Roza E, Costăchescu B, Grumezescu AM, Teleanu RI. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *Int J Mol Sci* 2022;**23**:5938

55. Chen Y, Qin C, Huang J, Tang X, Liu C, Huang K, Xu J, Guo G, Tong A, Zhou L. The role of astrocytes in oxidative stress of central nervous system: a mixed blessing. *Cell Prolif* 2020;**53**:e12781

56. Trotti D, Danbolt NC, Volterra A. Glutamate transporters are oxidant-vulnerable: a molecular link between oxidative and excitotoxic neurodegeneration. *Trends Pharmacol Sci* 1998;**19**:328–34

57. Todd AC, Hardingham GE. The regulation of astrocytic glutamate transporters in health and neurodegenerative diseases. *Int J Mol Sci* 2020;**21**:9607

58. Bobermin LD, da Silva A, Souza DO, Quincozes-Santos A. Differential effects of typical and atypical antipsychotics on astroglial cells in vitro. *Int J Dev Neurosci* 2018;**69**:1–9

59. Pillai A, Parikh V, Terry AV Jr, Mahadik SP. Long-term antipsychotic treatments and crossover studies in rats: Differential effects of typical and atypical agents on the expression of antioxidant enzymes and membrane lipid peroxidation in rat brain. *J Psychiatr Res* 2007;**41**:372–86

60. Ermakov EA, Dmitrieva EM, Parshukova DA, Kazantseva DV, Vasilieva AR, Smirnova LP. Oxidative stress-related mechanisms in schizophrenia pathogenesis and new treatment perspectives. *Oxid Med Cell Longev* 2021;**2021**:8881770

61. Smythies J. Redox mechanisms at the glutamate synapse and their significance: a review. *Eur J Pharmacol* 1999;**370**:1–7

62. Thaakur SR, Jyothi B. Effect of spirulina maxima on the haloperidol induced tardive dyskinesia and oxidative stress in rats. *J Neural Transm (Vienna)* 2007;**114**:1217–25

63. Hsu SS, Liang WZ. Ca2+ signaling as a mechanism of haloperidol-induced cytotoxicity in human astrocytes and assessing the protective role of a Ca2+ chelator. *Naunyn Schmiedebergs Arch Pharmacol* 2020;**393**:2117–27

64. Chu CS, Lin YS, Liang WZ. The impact of the antipsychotic medication chlorpromazine on cytotoxicity through Ca2+ signaling pathway in glial cell models. *Neurotox Res* 2022;**40**:791–802

65. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Judd F, Katz F, Katz P. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biol Psych* 2008;**64**:361–8

66. Aoyama K. Glutathione in the brain. *Int J Mol Sci* 2021;**22**:5010

67. Horrigan JP, Barnhill LJ. Risperidone and explosive aggressive autism. *J Autism Dev Disord* 1997;**27**:313–23

68. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. *Paediatr Drugs* 2007;**9**:343–54

69. Fieiras C, Chen MH, Escobar Liquitay CM, Meza N, Rojas V, Franco JVA, Madrid E. Risperidone and aripiprazole for autism spectrum disorder in children: an overview of systematic reviews. *BMJ Evid Based Med* 2023;**28**:7–14

70. Stadelmann C, Timmler S, Barrantes-Freer A, Simons M. Myelin in the central nervous system: structure, function, and pathology. *Physiol Rev* 2019;**99**:1381–431

71. Takahashi N, Sakurai T. Roles of glial cells in schizophrenia: possible targets for therapeutic approaches. *Neurobiol Dis* 2013;**53**:49–60

72. Schmitt A, Simons M, Cantuti-Castelvetri L, Falkai P. A new role for oligodendrocytes and myelination in schizophrenia and affective disorders. *Eur Arch Psychiatry Clin Neurosci* 2019;**269**:371–2

73. Kimoto S, Okuda A, Toritsuka M, Yamauchi T, Makinodan M, Okuda H, Tatsumi K, Nakamura Y, Wanaka A, Kishimoto T. Olanzapine stimulates proliferation but inhibits differentiation in rat oligodendrocyte precursor cell cultures. *Progr Neuro-Psychopharmacol Biol Psych* 2011;**35**:1950–6

74. Zhang Y, Zhang H, Wang L, Jiang W, Xu H, Xiao L, Bi X, Wang J, Zhu S, Zhang R, He J, Tan Q, Zhang D, Kong J, Li XM. Quetiapine enhances oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination. *Schizophr Res* 2012;**138**:8–17

75. Bi X, Zhang Y, Yan B, Fang S, He J, Zhang D, Zhang Z, Kong J, Tan Q, Li XM. Quetiapine prevents oligodendrocyte and myelin loss and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice. *J Neurochem* 2012;**123**:14–20

76. Mei F, Guo S, He Y, Wang L, Wang H, Niu J, Kong J, Li X, Xiao L. Quetiapine, an atypical antipsychotic, is protective against autoimmune-mediated demyelination by inhibiting effector T cell proliferation. *PLoS ONE* 2012;**7**:e42746

77. Shao Y, Peng H, Huang Q, Kong J, Xu H. Quetiapine mitigates the neuroinflammation and oligodendrocyte loss in the brain of C57BL/6 mouse following cuprizone exposure for one week. *Euro J Pharmacol* 2015;**765**:249–57

78. Gouvêa-Junqueira D, Falvella ACB, Antunes ASLM, Seabra G, Brandão-Teles C, Martins-de-Souza D, Crunfli F. Novel treatment strategies targeting myelin and oligodendrocyte dysfunction in schizophrenia. *Front Psychiatry* 2020;**11**:379

79. Xu H, Yang HJ, Li XM. Differential effects of antipsychotics on the development of rat oligodendrocyte precursor cells exposed to cuprizone. *Eur Arch Psychiatry Clin Neurosci* 2014;**264**:121–9

80. Prinz M, Jung S, Priller J. Microglia biology: one century of evolving concepts. *Cell* 2019;**179**:292–311

81. Fourrier C, Singhal G, Baune BT. Neuroinflammation and cognition across psychiatric conditions. *CNS Spectr* 2019;**24**:4–15

82. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung W-S, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, Barres BA. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 2017;**541**:481–7

83. Tarasov VV, Svistunov AA, Chubarev VN, Sologova SS, Mukhortova P, Levushkin D, Somasundaram SG, Kirkland CE, Bachurin SO, Aliev G. Alterations of astrocytes in the context of schizophrenic dementia. *Front Pharmacol* 2019;**10**:1612

84. Caruso G, Grasso M, Fidilio A, Tascedda F, Drago F, Caraci F. Antioxidant properties of second-generation antipsychotics: focus on microglia. *Pharmaceuticals* 2020;**13**:457

85. Mezzomo NF, da Silva Schmitz I, de Lima VB, Dorneles GP, Schaffer LF, Boeck CR, Romao PRT, Peroza LR. Reversal of haloperidol-induced orofacial dyskinesia and neuroinflammation by isoflavones. *Mol Biol Rep* 2022;**49**:1917–23

86. Bian Q, Kato T, Monji A, Hashioka S, Mizoguchi Y, Horikawa H, Kanba S. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-γ. *Progr Neuro-Psychopharmacol Biol Psych* 2008;**32**:42–8

87. Kato T, Mizoguchi Y, Monji A, Horikawa H, Suzuki SO, Seki Y, Iwaki T, Hashioka S, Kanba S. Inhibitory effects of aripiprazole on interferon-γ-induced microglial activation via intracellular Ca2+ regulation in vitro. *J Neurochem* 2008;**106**:815–25

88. Jiang L, Wu X, Wang S, Chen S-H, Zhou H, Wilson B, Jin C-Y, Lu R-B, Xie K, Wang Q. Clozapine metabolites protect dopaminergic neurons through inhibition of microglial NADPH oxidase. *J Neuroinfl* 2016;**13**:1–14

89. Giridharan VV, Scaini G, Colpo GD, Doifode T, Pinjari OF, Teixeira AL, Petronilho F, Macêdo D, Quevedo J, Barichello T. Clozapine prevents poly (I: C) induced inflammation by modulating NLRP3 pathway in microglial cells. *Cells* 2020;**9**:577

90. Obuchowicz E, Bielecka-Wajdman AM, Paul-Samojedny M, Nowacka M. Different influence of antipsychotics on the balance between pro- and anti-inflammatory cytokines depends on glia activation: an in vitro study. *Cytokine* 2017;**94**:37–44

91. Shin H, Kim J, Song J-H. Clozapine and olanzapine inhibit proton currents in BV2 microglial cells. *Eur J Pharmacol* 2015;**755**:74–9

92. Ceylan U, Haupeltshofer S, Kämper L, Dann J, Ambrosius B, Gold R, Faissner S. Clozapine regulates microglia and is effective in chronic experimental autoimmune encephalomyelitis. *Front Immunol* **12**. https://www.frontiersin.org/articles/10.3389/fimmu.2021.656941 (2021, accessed 21 June 2023)

93. Chamera K, Curzytek K, Kamińska K, Trojan E, Basta-Kaim A. Quetiapine ameliorates MIA-induced impairment of sensorimotor gating: focus on neuron-microglia communication and the inflammatory response in the frontal cortex of adult offspring of Wistar rats. *Cells* 2022;**11**:2788

94. Labuzek K, Kowalski J, Gabryel B, Herman ZS. Chlorpromazine and loxapine reduce interleukin-1β and interleukin-2 release by rat mixed glial and microglial cell cultures. *Euro Neuropsychopharm* 2005;**15**:23–30

95. Bhandari R, Kaur J, Kaur S, Kuhad A. The Nrf2 pathway in psychiatric disorders: pathophysiological role and potential targeting. *Expert Opin Ther Targets* 2021;**25**:115–39

96. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, Kapczinski F, Quevedo J. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience* 2015;**300**:141–54

97. Steiner J, Bielau H, Bernstein H-G, Bogerts B, Wunderlich MT. Increased cerebrospinal fluid and serum levels of S100B in first-onset schizophrenia are not related to a degenerative release of glial fibrillar acidic protein, myelin basic protein and neurone-specific enolase from glia or neurones. *J Neurol Neurosurg Psych* 2006;**77**:1284–7

98. Lara DR, Gama CS, Belmonte-de-Abreu P, Portela LV, Gonçalves CA, Fonseca M, Hauck S, Souza DO. Increased serum S100B protein in schizophrenia: a study in medication-free patients. *J Psychiatr Res* 2001;**35**:11–4

99. de Souza DF, Wartchow K, Hansen F, Lunardi P, Guerra MC, Nardin P, Gonçalves C-A. Interleukin-6-induced S100B secretion is inhibited by haloperidol and risperidone. *Progr Neuro Psychopharm Biol Psych* 2013;**43**:14–22

100. Long Y, Wang Y, Shen Y, Huang J, Li Y, Wu R, Zhao J. Minocycline and antipsychotics inhibit inflammatory responses in BV-2 microglia activated by LPS via regulating the MAPKs/ JAK-STAT signaling pathway. *BMC Psych* 2023;**23**:514

101. Quincozes-Santos A, Abib RT, Leite MC, Bobermin D, Bambini-Junior V, Gonçalves CA, Riesgo R, Gottfried C. Effect of the atypical neuroleptic risperidone on morphology and S100B secretion in C6 astroglial lineage cells. *Mol Cell Biochem* 2008;**314**:59–63

102. Nardin P, Tramontina AC, Quincozes-Santos A, Tortorelli LS, Lunardi P, Klein PR, Wartchow KM, Bobermin LD, Gottfried C, Elisabetsky E, Gonçalves C-A. In vitro S100B secretion is reduced by apomorphine: effects of antipsychotics and antioxidants. *Progr Neuro-Psychopharm Biol Psych* 2011;**35**:1291–6

103. Steiner J, Schroeter ML, Schiltz K, Bernstein HG, Müller UJ, Richter-Landsberg C, Müller WE, Walter M, Gos T, Bogerts B, Keilhoff G. Haloperidol and clozapine decrease S100B release from glial cells. *Neuroscience* 2010;**167**:1025–31

104. Donato R, Sorci G, Riuzzi F, Arcuri C, Bianchi R, Brozzi F, Tubaro C, Giambanco I. S100B's double life: intracellular regulator and extracellular signal. *Biochim Biophys Acta* 2009;**1793**:1008–22

105. Angelopoulou E, Paudel YN, Piperi C. Emerging role of S100B protein implication in Parkinson's disease pathogenesis. *Cell Mol Life Sci* 2021;**78**:1445–53

106. Langeh U, Singh S. Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders. *Curr Neuropharmacol* 2021;**19**:265–77

107. Luo G, Huang Y, Jia B, Zhang X, Mo D, Ma N, Gao F, Song L, Wang B, Miao Z. Quetiapine prevents A25-35-induced cell death in cultured neuron by enhancing brain-derived neurotrophic factor release from astrocyte. *Neuroreport* 2018;**29**:92–98.

108. Dalwadi DA, Kim S, Schetz JA. Activation of the sigma-1 receptor by haloperidol metabolites facilitates brain-derived neurotrophic factor secretion from human astroglia. *Neurochem Int* 2017;**105**:21–31

109. Shao Z, Dyck LE, Wang H, Li XM. Antipsychotic drugs cause glial cell line–derived neurotrophic factor secretion from C6 glioma cells. *J Psychiatry Neurosci* 2006;**31**:32–7

110. Petsouki E, Cabrera SNS, Heiss EH. AMPK and NRF2: interactive players in the same team for cellular homeostasis. *Free Radic Biol Med* 2022;**190**:75–93

111. Okada M, Fukuyama K, Motomura E. Dose-dependent biphasic action of quetiapine on AMPK signalling via 5-HT7 receptor: exploring pathophysiology of clinical and adverse effects of quetiapine. *Int J Mol Sci* 2022;**23**:9103

112. Stafford J, Dykxhoorn J, Sommerlad A, Dalman C, Kirkbride JB, Howard R. Association between risk of dementia and very late-onset schizophrenia-like psychosis: a Swedish population-based cohort study. *Psychol Med* 2023;**53**:750–8

113. Ismail Z, Creese B, Aarsland D, Kales HC, Lyketsos CG, Sweet RA, Ballard C. Psychosis in Alzheimer disease—mechanisms, genetics and therapeutic opportunities. *Nat Rev Neurol* 2022;**18**:131–44

114. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psych* 2005;**162**:2022–3030

115. Xu J. Dopamine D3 receptor in Parkinson disease: a prognosis biomarker and an intervention target. In: Boileau I, Collo G (eds) *Therapeutic applications of dopamine D3 receptor function: new insight after 30 years of research*. Cham: Springer International Publishing, pp.89–107

116. Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV. Brain imaging of neurovascular dysfunction in Alzheimer's disease. *Acta Neuropathol* 2016;**131**:687–707

117. Song K, Li Y, Zhang H, An N, Wei Y, Wang L, Tian C, Yuan M, Sun Y, Xing Y, Gao Y. Oxidative stress-mediated blood-brain barrier (BBB) disruption in neurological diseases. *Oxidat Med Cell Longev* 2020;**2020**:e4356386

118. Marchezan J, Deckmann I, da Fonseca GC, Margis R, Riesgo R, Gottfried C. Resveratrol treatment of autism spectrum disorder —a pilot study. *Clin Neuropharmacol* 2022;**45**:122

119. Constant JP, Fraley GS, Forbes E, Hallas BH, Leheste JR, Torres G. Resveratrol protects neurons from cannulae implantation injury: implications for deep brain stimulation. *Neuroscience* 2012;**222**:333–42

120. Song W, Zukor H, Lin S-H, Hascalovici J, Liberman A, Tavitian A, Mui J, Vali H, Tong X-K, Bhardwaj SK, Srivastava LK, Hamel E, Schipper HM. Schizophrenia-like features in transgenic mice overexpressing human HO-1 in the astrocytic compartment. *J Neurosci* 2012;**32**:10841–53

121. Kim Y, Park J, Choi YK. The role of astrocytes in the central nervous system focused on BK channel and heme oxygenase metabolites: a review. *Antioxidants* 2019;**8**:121

122. Leite Santos C, Vizuete AFK, Becker Weber F, Thomaz NK, Bobermin LD, Gonçalves C-A, Quincozes-Santos A. Age-dependent effects of resveratrol in hypothalamic astrocyte cultures. *Neuroreport* 2023;**34**:419–25

123. Yamauchi T, Tatsumi K, Makinodan M, Kimoto S, Toritsuka M, Okuda H, Kishimoto T, Wanaka A. Olanzapine increases cell mitotic activity and oligodendrocyte-lineage cells in the hypothalamus. *Neurochem Int* 2010;**57**:565–71

124. He M, Qian K, Zhang Y, Huang X-F, Deng C, Zhang B, Gao G, Li J, Xie H, Sun T. Olanzapine-induced activation of hypothalamic astrocytes and toll-like receptor-4 signaling via endoplasmic reticulum stress were related to olanzapine-induced weight gain. Front Neurosci 2021;**14**:589650, https://www.frontiersin.org/articles/10.3389/fnins.2020.589650 (accessed 21 June 2023).

125. Sovrani V, Bobermin LD, Santos CL, Brondani M, Gonçalves CA, Leipnitz G, Quincozes-Santos A. Effects of long-term resveratrol treatment in hypothalamic astrocyte cultures from aged rats. *Mol Cell Biochem* 2023;**478**:1205–16

126. Konopaske GT, Dorph-Petersen K-A, Sweet RA, Pierri JN, Zhang W, Sampson AR, Lewis DA. Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. *Biol Psych* 2008;**63**:759–65