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Invited review

mGlu3 receptor and astrocytes: Partners in neuroprotection

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ABSTRACT

Astrocytes are currently studied intensively because of their now highlighted relevance as key players with neurons that modulate a wide range of central functions, from synaptic plasticity and synaptogenesis to regulation of metabolic and neuroinflammatory processes.

Since the discovery of mGlu3 receptors on astrocytes, accumulating evidence supports a role of these receptors not only in maintaining synaptic homeostasis and treating psychiatric disorders but also in promoting astrocyte survival in several pathologic conditions.

This review focuses on providing up-to-date knowledge regarding effects of activating astroglial mGlu3 receptors on psychiatric disorders, astrocyte and neuronal survival, and neurodegenerative diseases.

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1. Introduction

Current concepts in neuroscience research stress the physiological role of glia in the central nervous system (CNS) and the functional interdependence between neuroglia and neurons. It is now known that astrocyte-neuron partnership is not static but shows dynamic transformations that might be essential for synaptic plasticity (García-Marín et al., 2007). Also, neuropathology, to a very large extent, is shaped by glial performance.

The discovery of the presence of metabotropic glutamate (mGlu) receptors on astrocytes and the study of actions derived from astrocytic mGlu receptor activation has not only enabled us to understand several astrocyte functions but also created novel potentialities for this cell type. This review summarizes exciting findings on actions that subtype 3 mGlu (mGlu3) receptors display in astrocytes and their impact on CNS physiopathology.

2. Astrocytes

Glial cells are currently classified into two major groups: microglia and macroglia, the latter including ependymal cells, Schwann cells, oligodendroglia and astroglia. In turn, the term astroglia includes astrocytes, marginal glia, radial glia, cerebellar Bergmann cells, retinal Müller cells, neurohypophyseal pituicytes and hypothalamic tanycytes (García-Segura and McCarthy, 2004). Ontogenically, all glial cells differentiate from a unique neuroectodermal bipotential cell shared with neural lineage, except for mesenchyme-derived microglia (Carlson, 2004). Macroglial and microglial cells express group II mGlu receptors, although each cell type may exhibit a different receptor subtype profile, as detailed below.

Astroglia form the first line of brain defence by controlling the volume and composition of extracellular space (Rodríguez et al., 2009). Astrocytes maintain normal brain function including survival and migration of neurons during development. They have perivascular feet which connect with brain blood vessels, an interaction that helps to maintain and regulate blood brain barrier permeability (Abbott, 2000; Hayashi et al., 1997; Sobue et al., 1999). Astrocytic end-feet release signals that support the formation and maintenance of tight junctions between endothelial cells as well as the expression of transport molecules in endothelial cells including glucose transporter GLUT1 (Abbott, 2002; Janzer and Raff, 1987; Magistretti et al., 1999). Moreover, in response to synaptic glutamate, astrocytes generate vasoactive metabolites, which regulate blood flow in order to cover neuronal metabolic demand (Blanco et al., 2008). Morphological studies reveal that astrocytes are in close contact with neuronal synapses (Grosche et al., 2002, 1999; Ventura and Harris, 1999) and can send signals directly to neurons (Chaudhry et al., 1995; Lehre et al., 1995; Takano et al., 2006), thus modulating synaptic plasticity and neuronal homeostasis (Fig. 1). Some authors describe this as a "tripartite synapse" formed by the presynaptic neuron, the post-synaptic neuron and surrounding astrocytes (Araque et al., 1999). Astrocytes can sense

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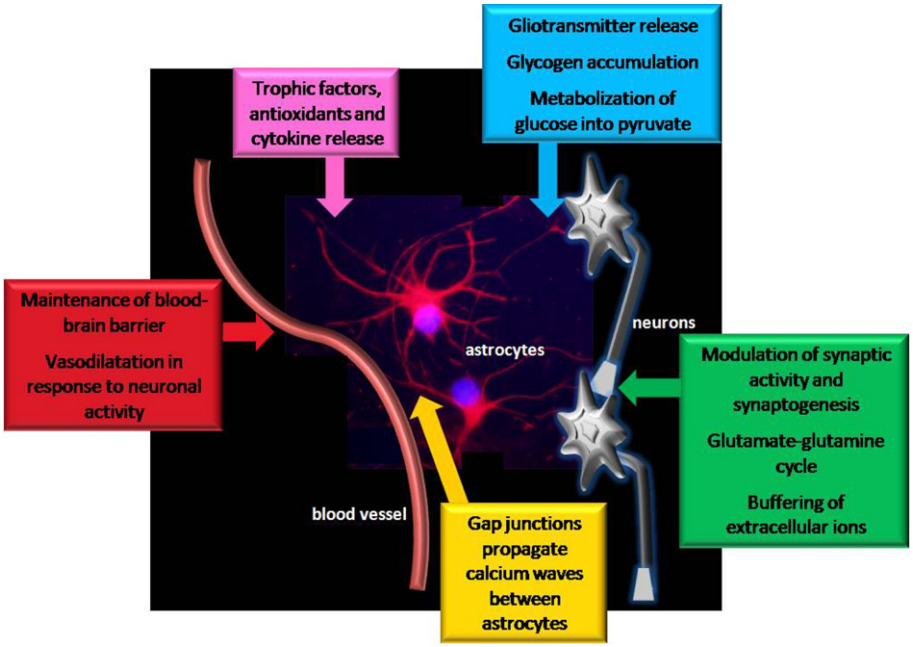


Fig. 1. Astrocyte functions.

the activity of neighboring synapses and respond to neurotransmitters released by synaptic terminals. Their response may induce an increase in the intracellular Ca^{2+} concentration in adjacent glial cells forming an astrocyte network interconnected via gap junctions (Cornell-Bell et al., 1990), and this increase may in turn lead to the release of various glial transmitters, such as glutamate, serine, ATP or taurine (Micevych et al., 2009; Parpura and Haydon, 2000; Pascual et al., 2005; Santello and Volterra, 2009; Theodosis et al., 2008). Astrocytes are also thought to regulate synaptogenesis, since neuron-astrocyte co-cultures developed seven times more synapses than pure neuronal cultures (Pfrieger and Barres, 1997; Ullian et al., 2001).

Astrocytes can transform glucose into lactate, which is taken by neurons and metabolized into pyruvate, a more direct energy source for neurons (Danbolt, 2001). They can also accumulate glycogen as an energy reservoir (Dringen et al., 1993). Glycogen turnover in astrocytes increases with enhanced neuronal activity to provide extra energy supply to neurons, whereas both glutamate and insulin have been shown to increase glycogen synthesis in astrocytes (Benarroch, 2005).

Glial cells also have a role in the regulation of ion concentrations. Since K^+ is osmotically active, $[K^+]_o$ buffering leads to astrocyte swelling (Benarroch, 2005), whereas transportation of H^+ out of the cell results in an "alkaline shift" in astrocytes, which is mirrored by acidification of extracellular space that may serve as a negative feedback mechanism that reduces synaptic activity (Benarroch, 2005).

Astrocytes express aquaporins, water-selective transport proteins that increase water permeability (Amiry-Moghaddam and Ottersen, 2003; Gunnarson et al., 2004) and have a crucial role in brain water homeostasis and cerebrospinal fluid production (Benarroch, 2005).

On another front, in response to injury, astrocytes become "reactive" and develop hypertrophy and a higher number of cellular processes, produce higher levels of glial fibrillary acidic protein, proliferate, release cytokines and participate in the glial scar (Liberto et al., 2004). However, when injury is milder or in astrocytes more distal from damage, reactive changes do not distort the architecture of CNS tissue. Instead, astrocytes increase the activity of antioxidant enzymes and the production of neurotrophic and growth factors such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Albrecht et al., 2002; Marz et al., 1999; Muller et al., 1995; Rudge et al., 1995; Schwartz and Nishiyama, 1994; Swartz et al., 2001), vitamin E and C and glutathione (Wilson, 1997). This type of response is associated with improved tissue recovery, isolation of the damaged area, reconstruction of the blood-brain-barrier and facilitation of remodeling of brain circuits in areas surrounding the lesion region (Rodríguez et al., 2009).

Possibly the most important function of astrocytes is removal of glutamate from the synaptic space through specific transporters (Anderson and Swanson, 2000), thereby avoiding excitotoxicity resulting from glutamate excess. High-affinity glutamate transporters expressed in astrocytes are glutamate/aspartate transporter (GLAST) and glutamate transporter 1 (GLT1). Once within the astrocyte, glutamate is transformed into glutamine by glutamine synthetase or catabolized via tricarboxylic acid cycle. Astrocytes then pass glutamine to neurons for conversion back into glutamate, since neurons are unable to achieve a net synthesis of glutamate through intermediary metabolism (Albrecht et al., 2007). Since the brain lacks an effective urea cycle, astrocyte synthesis of glutamine is the major mechanism for ammonia detoxification in the nervous system (Suarez et al., 2002).

Because of their emerging role as key pieces in the maintenance of normal functioning of the CNS, we now understand that any impairment of astroglial function may ultimately lead to generalized disturbance in the brain. Thus, pharmacological targets associated with protection of neurons as well as prevention of astrocyte death are actually promising.

3. mGlu receptors

mGlu receptors form a complex system regulating neuronal function at several levels: from neuronal development and synaptic transmission/plasticity to neuronal death, since mGlu receptor activation not only modulates excitotoxicity but also induces the release of trophic factors from glial cells. In fact, mGlu receptors are believed to have evolved as part of a modulating mechanism for controlling CNS excitability (Schoepp, 2001). Consequently, mGlu

receptor activation is strongly associated with neuroprotection in several models of neurodegenerative diseases.

mGlu receptors belong to the superfamily of class III G-protein-coupled receptors and, unlike fast responses triggered by ionotropic receptors, mGlu receptors mediate slower responses by coupling to second messenger-mediated reactions. mGlu receptors have been classified into three groups based on molecular structure, sequence homology, pharmacological profile and associated second messengers. Group I includes mGlu1 and mGlu5 receptor subtypes whose activation leads to phospholipase C (PLC) activity, inositol-1,4,5-triphosphate and diacylglycerol production, calcium mobilization and protein kinase C (PKC) activation (Cartmell and Schoepp, 2000). Group II (mGlu2 receptor and mGlu3 receptor subtypes) and group III (mGlu4/6/7/8 receptor subtypes) mGlu receptors are coupled to Gi/G_0 proteins which inhibit adenylate cyclase and reduce cyclic AMP (cAMP) levels (Cartmell and Schoepp, 2000). In group II, the mGlu2 receptor subtype is mainly located in the presynaptic terminals of glutamatergic neurons where it inhibits glutamate release, maintaining glutamatergic transmission within physiological range (Schoepp, 2001) whereas the mGlu3 receptor subtype is preferentially present postsynaptically and in glial cells (Riedel et al., 2003; Schoepp, 2001).

As modulators of synaptic function, group II mGlu receptors reduce glutamate excitatory post-synaptic potentials (EPSP) via a presynaptic mechanism, whereas they presynaptically suppress the release of GABA from neurons enhancing cell excitability (Anwyl, 1999). Thus, the actions of mGlu2/3 agonists may depend on the relative roles of mGlu receptors to modulate presynaptic suppression of glutamate versus GABA release (Schoepp, 2001). Recently, the use of two distinct rat strains expressing different levels of mGlu2 and mGlu3 receptors revealed the ability of mGlu3 receptors to fully regulate synaptic transmission (Ceolin et al., 2011). Presynaptic mGlu2 receptors appear to be essential for inducing long-term depression (LTD) at the hippocampus (Schoepp, 2001), although blockade of mGlu3 receptor with β- N-acetylaspartylglutamate (β-NAAG) prevents hippocampal LTD via a post-synaptic mechanism, suggesting that this receptor would also be critically required for LTD (Pöschel et al., 2005), whereas mGlu3 receptor activation with NAAG impaired the expression of long-term potentiation (LTP) (Lea et al., 2001; Pöschel et al., 2005).

Traditionally, mGlu1/5 receptor antagonists have been extensively studied as neuroprotective agents, possibly because of the generally accepted function of mGlu1/5 receptors as enhancers of cellular excitability. Group III mGlu receptor agonists display some therapeutic actions in models of Parkinson's disease, addiction and anxiety; however, their actions in astrocytes have yet to be studied in detail.

On the other hand, group II mGlu receptors have drawn more attention from neuroresearchers who associated these receptors in most cases with cytoprotective effects in neurons and astroglia. Group II mGlu receptors have became attractive pharmacological targets because of: (i) their presynaptic and glial location which contributes to modulate glutamate excess at the synaptic cleft, which is associated with excitotoxicity and psychiatric and neurodegenerative diseases; (ii) their capability to induce release of trophic factors; and (iii) their high expression in strategic areas of the CNS that are relevant to neuropsychiatric disorders, such as neocortex, thalamus, striatum, hippocampus and amygdala (Ohishi et al., 1998, 1993a,b).

3.1. Group II mGlu receptor ligands

In the late eighties, (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) was launched as the first agonist discriminating between ionotropic and metabotropic glutamate receptors (Palmer et al., 1989), and was followed by the development of several non-selective ligands such as (2S,1′S,2′S)-2-(Carboxycyclopropyl)glycine (L-CCG-I). It was not until the late nineties that group II mGlu receptor-selective ligands such as (1S,2S,5R,6S)-2-Aminobicyclo[3.1.0] hexane-2,6-dicarboxylic acid (LY354740) and (1R,4R,5S,6R)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268) appeared, showing nanomolar affinities for these receptors (Monn et al., 1999, 1997). The highly conserved sequences of mGlu2 and mGlu3 receptors have made it difficult to find agonists able to discriminate between these subtypes. In this sense, positive (PAM) and negative (NAM) allosteric modulators developed recently are yielding new and interesting data on differential functions of mGlu2 and mGlu3 receptors. Even though the development of an mGlu3 receptor selective agonist or PAM is delayed, the use of the endogenous neurotransmitter NAAG as a selective mGlu3 receptor agonist remains a controversial issue. Chopra et al. (2009) and Fricker et al. (2009) postulated that effects reported for NAAG were actually associated with traces of glutamate remaining in unpurified preparations. However, this was rebutted by Neale (2011) after compiling all available papers on this topic. Wroblewska et al. (2011) also vindicated themselves by showing that highly purified preparations of NAAG conserve mGlu3 receptor agonism.

A detail of some currently available mGlu3 receptor ligands is summarized in Tables 1.

3.2. Applications of mGlu2/3 receptor agonists in psychiatry and neurology

In vivo assays have been developed to study group II mGlu receptors in several animal models of neurological diseases and numerous clinical trials have even been run or are being successfully developed.

Group II agonists are used for treatment of panic attack and anxiety disorders (Levine et al., 2002). Dunayevich et al. (2008) showed improved scores in patients with generalized anxiety disorder being treated with the LY354740 prodrug LY544344, although the risk of convulsions demonstrated in preclinical trials led to discontinuation of this study. Although the mechanism of anxiolytic action of mGlu receptor ligands has not been completely elucidated, it could correlate with suppression of enhanced glutamatergic excitation at brain synapses involved in fear/anxiety in animals and humans (Schoepp et al., 2003). This anxiolytic effect has been specifically associated with mGlu2 receptor activation, provided that rats lacking mGlu2 receptors show an anxiety-like profile (Ceolin et al., 2011).

LY379268, LY2140023 (the LY404039 prodrug) and LY404039 suppress the behavioral and physiological effects of psychotomimetic drugs and serotonergic hallucinogenic drugs, both enhancers of glutamate release, and show their efficacy in the treatment of schizophrenia (Chaki et al., 2010; Marek, 2004; Moreno et al., 2009). In clinical trials, LY404039 improved both positive and negative symptoms of schizophrenia compared to placebo (Patil et al., 2007). Some authors have associated schizophrenic phenotype with mutations within mGlu receptor genes GRM2 and GRM3 (Chen et al., 2005; Fujii et al., 2003; Moreno et al., 2009; Sartorius et al., 2008). In particular, an intronic variation in GRM3 was associated with behavioral, physiological and molecular (altered levels of glutamate transporters) phenotypes related to schizophrenia (Egan et al., 2004). Both mGlu2 and mGlu3 receptor levels were reported to be decreased in schizophrenic subjects (Corti et al., 2007; Ghose et al., 2009; González-Maeso et al., 2008). Studies using $mGlu2^{-/-}$ and $mGlu3^{-/-}$ animals suggest that the antipsychotic activity of dual mGlu2/3 receptor agonists is largely mediated by the activation of mGlu2 receptors and is mimicked by

Table 1
Pharmacological agents for mGlu3 receptors.

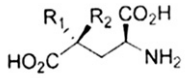
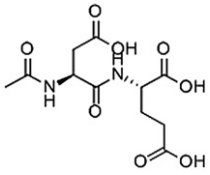
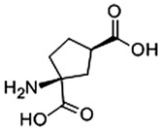
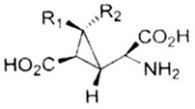
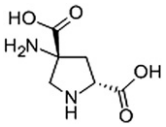
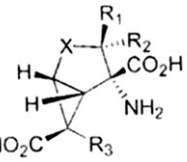
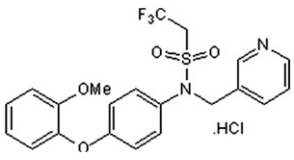
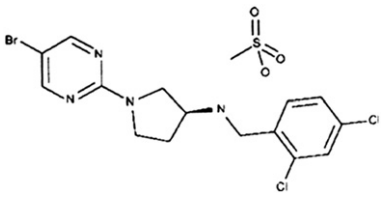
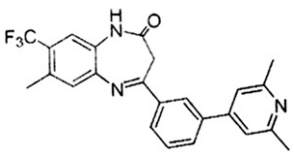
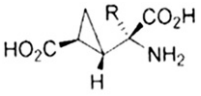
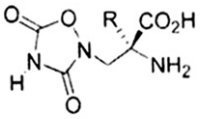
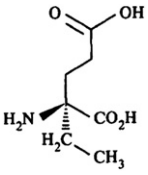
Ligand	Action	Structure	EC_{50} or IC_{50} values (μM)[a]				
			mGlu1/5	mGlu2	mGlu3	mGlu4/6/8	mGlu7
Glutamate	Endogenous, non-selective agonist	 R1,R2=H (glutamate) R1=H; R2= CH2CH(Ph)2 (ADED)	1–13	03–12	2–9	3–38	2300
ADED	Group II antagonist		>300	18	6.1	>300	
NAAG	Endogenous mGlu3 agonist		>300	134–1000	10–65	>300	–
ACPD	Group I/II agonist		15–40	5	–	60 (mGlu6)	–
L-CCG-I	Non-selective agonist	 R1,R2=H (LCCGI) R1=H; R2=CO2H (DCGIV)	2–3	0.5	0.4	3–9	230
DCG-IV	Group II agonist		Antag. >300	0.1–0.4	0.1–0.2	Antag. > 20	
APDC	Group II agonist		>100	0.4		>100	
LY379268	Group II agonist	 X=CH(α-CH3);R1,R2,R3 = H (LY541850).	>100	0.003	0.005	0.4–21	>100
LY354740	Group II agonist		>100	0.01	0.04	3–12 (mGlu6/8)	>100
LY404039[b]	Group II agonist		>10	0.023	0.048	>10	>10
LY541850	mGlu2 agonist, mGlu3 antagonist		–	0.16	Antag.	–	–
LY487379	mGlu2 PAM		–	1.7	>10	–	–
LY2389575[c]	mGlu3 NAM		>12.5	>12.5	0.2	>12.5	
Ro4491533	mGlu2 NAM		–	0.002	–	–	–

Table 1 (*continued*)

Ligand	Action	Structure	EC_{50} or IC_{50} values (μM)[a]				
			mGlu1/5	mGlu2	mGlu3	mGlu4/6/8	mGlu7
LY341495	Group II antagonist	 R=9′xanthylmethyl	6.8–9.7	0.021	0.014	0.17–22	
S-BnQuis	Group II antagonist	 R=benzyl	300	7.1	–	–	–
EGLU[d]	Group II antagonist		–	$K_D = 66$		–	–

[a] Data from Pin and Acher (2002).
[b] Rorick-Kehn et al. (2007).
[c] Caraci et al. (2011a).
[d] Jane et al. (1996).

selective PAMs of mGlu2 receptor (Fell et al., 2008; Fraley, 2009; Galici et al., 2005). However, possible involvement of mGlu3 receptor in antipsychotic actions has also been suggested since NAAG exhibits antipsychotic effects in animal models (Olszewski et al., 2008). Further, increased levels of glial glutamate transporters (Aronica et al., 2003) and transforming growth factor beta (TGF-β) (Bruno et al., 1998) after mGlu3 receptor activation could also contribute to enhancing dendritic growth and spine formation, both of which are reduced in schizophrenia (Chaki, 2010).

The efficacy of mGlu2/3 receptor agonists has been proven in depression (Marek, 2002), chronic pain (Chiechio et al., 2002; Simmons et al., 2002), epilepsy (Klodzinska et al., 2000; Moldrich et al., 2001), hypoxia-ischemia (Bond et al., 1999; Cai et al., 1999; Ciccarelli et al., 2007; Poli et al., 2003), Parkinson's disease (Battaglia et al., 2003; Murray et al., 2002), and drug addiction (Bäckström and Hyytiä, 2005; Baptista et al., 2004; Bossert et al., 2005; Peters and Kalivas, 2006).

Clinical trials with group II mGlu receptor agonists have not been associated with major liabilities such as sedation, amnesic symptoms, withdrawal upon discontinuation of the drug, prolactin elevation, extrapyramidal symptoms, or weight gain (Conn and Jones, 2009). Nevertheless, because of the ubiquity of mGlu receptors in peripheral tissues, unacceptable side effects on other target organs might be associated with long-term mGlu receptor agonist administration and should be more intensively analyzed. Effects such as endocrine alterations, impairment of fertility and defects of embryogenesis, immune deficits, sense function impairment, tumor development and osteoporosis are issues in need of further study (Durand et al., 2011a).

3.3. Targeting astrocytic mGlu3 receptor for neuroprotective therapies

Most reported findings in the mGlu receptor field focus on neuronal mGlu receptors or on the neural impact of activating mGlu receptors. However, only a few research groups have turned their attention to the study of autocrine effects of mGlu receptor ligands on glial cells. In fact, since the pathology of CNS trauma and neurodegeneration is multifactorial, therapies aimed at modulating multiple physiopathological pathways (including neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, and circulating immune cells) may be more effective than those directed at a single target (Byrnes et al., 2009).

3.3.1. mGlu receptor expression in glia

Numerous studies have shown mGlu receptor expression in glial cells. mGlu3 receptor mRNA and protein expression was found in oligodendroglial progenitor cells and in differentiated oligodendrocytes (Luyt et al., 2006). In normal cerebral cortex, septum and caudate-putamen, oligodendrocytes show a homogeneous distribution of mGlu3 receptor mRNA expression, which was increased in injured brain (Mudo et al., 2007). In control human brain, no detectable mGlu2/3 receptor was observed in resting microglia, but was present in a population of microglial cells with ameboid (macrophage-like) morphology on chronic active multiple sclerosis lesions (Geurts et al., 2003). Accordingly, mGlu3 receptor was not found expressed in the microglia of normal rat brain (Mudo et al., 2007). However, primary cultured microglia express mGlu3 receptor (Taylor et al., 2002) and its expression was increased by bacterial lipopolysaccharide (LPS) and enhanced in an amyotrophic lateral sclerosis model (Berger et al., 2012). Schwann cells were also reported to respond to the mGlu3 receptor agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylic acid (APDC) (Berent-Spillson and Russell, 2007).

Astrocytes in particular have been shown to express mainly mGlu3 and mGlu5 receptors (Balázs et al., 1997; Condorelli et al., 1997; Ferraguti et al., 2001; Miller et al., 1995; Nakahara et al., 1997; Schools and Kimelberg, 1999) whereas neither mRNA nor protein for mGlu2 receptor has been found in this cell type. In *in vivo* studies mGlu3 receptor, but not mGlu2 receptor, expression was found in astrocytes (Liu et al., 1998; Mineff and Valtschanoff, 1999; Mudo et al., 2007; Ohishi et al., 1998, 1993a,b; Petralia

et al., 1996; Shigemoto et al., 1997; Tamaru et al., 2001). We have also identified protein expression of this receptor in rat cultured astrocytes by immunocytochemistry and Western blot, also showing that it is functionally active, since LY379268 inhibited forskolin-induced intracellular cAMP accumulation (Durand et al., 2011b, 2010). A recent study revealed that mGlu3 and mGlu5 receptors are compartmentalized within the peripheral astrocyte process associated with the synapse and that these receptors mediate glutamate-induced motility of filopodia, thereby stimulating peripheral astrocyte process plasticity (Lavialle et al., 2011).

Mudo et al. (2007) demonstrated that mGlu3 receptor expression increases in reactive astrocytes after cerebral injury, as did other authors in animal models of epilepsy (Aronica et al., 2000), multiple sclerosis (Geurts et al., 2003) and persistent inflammation (Dolan et al., 2003). In cultured astrocytes, mGlu3 and mGlu5 receptors levels were induced by growth factors such as epidermal growth factor, basic fibroblast growth factor and transforming growth factor alpha (Minoshima and Nakanishi, 1999). We also showed that astrocyte mGlu3 receptor protein levels are raised by the combined inflammatory stimuli LPS and interferon-γ (LPS+IFN-γ) whereas they are diminished by prolonged (24 h) exposure to LY379268, suggesting an auto-regulatory mechanism of mGlu receptor activation possibly involving homologous desensitization that might protect against receptor over-stimulation (Durand et al., 2010).

3.3.2. Neuroprotective actions of astrocytic group II mGlu receptors

Since altered glutamatergic transmission has been postulated as the pathologic base of several degenerative disorders (Nguyen et al., 2011), prevention of excitotoxicity by mGlu2/3 receptor activation is considered one of the most promising findings in psychiatry. LY379268 protects neurons from *N*-Methyl-D-aspartate (NMDA) toxicity through activation of presynaptic mGlu2/3 receptors which reduce glutamate release, while this neuroprotective effect is potentiated by the presence of glial cells (Kingston et al., 1999). Group II mGlu receptor activity induces GLT1 and GLAST expression (Aronica et al., 2003), increasing glutamate reuptake by astrocytes (Yao et al., 2005) and group II mGlu receptor activation was shown to inhibit apoptosis of cultured dopaminergic and mesencephalic neurons induced by conditioned medium of astrocytes challenged by LPS, since glutamate uptake and production of glutathione by astrocytes were recovered (Zhou et al., 2006).

However, glutamate transport modulation is not the only neuroprotective mechanism exerted by these receptors. mGlu2/3 receptor activity can also trigger the synthesis and release of several protective proteins. Bruno et al. (1998) and D'Onofrio et al. (2001) demonstrated that mGlu2/3 receptor activation in astrocytes prevents NMDA-induced neuronal death and induces TGF-β release via activation of Mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K), whereas this neuroprotective action was blocked by application of an antibody against TGF-β. Concordantly, the high expression of mGlu3 receptor in epilepsy models correlates with increased TGF-β production (Aronica et al., 2000). TGF-β regulation of cell proliferation, differentiation, migration, apoptosis and excitotoxicity (Katsuno et al., 2011) has raised the potential therapeutic value of this cytokine for several CNS disorders such as amyotrophic lateral sclerosis, Alzheimer's disease or epilepsy. Also, it is becoming increasingly clear that actions of members of the TGF-β family in the CNS go beyond their roles as neurotrophic and neuroprotective factors, also modulating both excitatory and inhibitory synaptic transmission in the adult mammalian brain (Krieglstein et al., 2011).

On the other hand, Moldrich et al. (2002) showed that LY379268 reduces forskolin-stimulated cAMP formation in astrocytes in the absence of extracellular calcium but enhances cAMP formation in the presence of calcium, which was associated with adenosine release. Adenosine has been shown to be neuroprotective in glial cells because of its regulatory role on Ca^{2+} - and cAMP-dependent intracellular signaling (Schubert et al., 1996) which may lead, for example, to increased expression of glial glutamate transporters (Eng et al., 1997; Schlag et al., 1998).

LY379268 exerts a neuroprotective effect against NMDA neurotoxicity in mixed astrocyte-neuron cultures from wild-type, mGlu2$^{-/-}$ and mGlu3$^{-/-}$ mice, whereas this neuroprotection was suppressed in mixed cultures containing wild-type neurons and mGlu3$^{-/-}$ mice-derived astrocytes, thereby suggesting that the protective actions of this mGlu3 receptor agonist requires activation of their glial receptors (Corti et al., 2007). mGlu3 receptor agonists APDC and NAAG revert oxidative damage and cell death induced by a high dose of glucose in neurons co-cultured with Schwann cells in a cell culture model of diabetic neuropathy (Berent-Spillson et al., 2004). This neuroprotective effect is related to reduction in the accumulation of reactive oxygen species and to increased glutathione content, and is completely dependent on the presence of glial cells (Berent-Spillson and Russell, 2007). The NAAG peptidase inhibition is also a novel potential strategy to reduce both neuronal and astrocyte damage associated with glutamate excitotoxicity after traumatic brain injury (Zhong et al., 2005).

3.3.3. Autocrine functions of astrocytic mGlu2/3 receptor activation

In spite of the emphasis of current studies on the active and crucial participation of glia in neuroprotective actions exerted by the mGlu receptors system, the autocrine effects of astrocytic mGlu receptor activation have been largely neglected.

Increased levels of NAAG after NAAG peptidase inhibition reduces astrocyte loss induced by excitotoxicity after posttraumatic brain injury (Zhong et al., 2005), potentiates interleukin-1β-induced interleukin-6 release (Aronica et al., 2005) and induces the release of NGF and S-100 calcium-binding protein beta subunit (S-100β) from cultured astrocytes (Ciccarelli et al., 1999).

Glial cells are known to utilize the plasma membrane Na+-independent cystine-glutamate exchanger for cystine uptake (Pow, 2001), a substrate for glutathione production that protects cells against oxidative stress. Some studies performed on *in vivo* models or on brain slices have suggested that group II mGlu receptor activation promotes cystine uptake from glial cells (Baker et al., 2002), although the only study to actually explore the role of these receptors in astrocytes shows that APDC 1 and 10 μM (but not 1 mM) increase cystine-glutamate exchange (Tang and Kalivas, 2003).

Ciccarelli et al. (2007) demonstrated that mGlu3 receptor activation by LY379268 protects cultured astrocytes against apoptosis induced by oxygen/glucose deprivation (OGD) by a mechanism involving extracellular-signal-regulated kinases (ERK1/2/MAPK) and PI3K activities. LY379268 promotes Bad phosphorylation (inactivation), increases the cytosolic content of antiapoptotic protein Bcl-xL, reduces the OGD-mediated stimulation of p38 MAPK and c-Jun N-terminal kinases (JNK) pathways and decreases caspase 3 activity induced by OGD (Ciccarelli et al., 2007).

We have shown that mGlu3 receptor activation by LY379268 exerts an autocrine, protective role on cultured rat astrocytes, not only by reducing inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) production (both induced by LPS + IFN-γ) but also by preventing astroglial death induced by the NO donor diethylenetriamine nitric oxide adduct (DETA/NO) (Durand et al., 2010). We demonstrated that the cytoprotective effect of the agonist correlates with decreased p53 expression and phosphorylation, decreased Bax activation, increased Bcl-2 expression and prevention of mitochondrial membrane permeabilization and cytochrome-c and apoptosis inducing factor release into the cytosol, all events altered by NO (Durand et al., 2010). Congruently,

Table 2
Protective actions of astroglial mGlu3 receptor activation on neurons and astrocytes.

Model	Ligand	Effect	References
Neuroprotection			
NMDA toxicity in mixed neuro-glial cultures	LY379268, LY354740 DCG-IV, 4C3HPG, LY379268	Prevention of neuron death	Kingston et al., 1999 Bruno et al., 1998; D'Onofrio et al., 2001
Conditioned media from LPS-challenged astrocytes	DCG-IV	Inhibition of neuron apoptosis	Zhou et al., 2006
NMDA toxicity in mixed neuro-glial cultures from mGlu2$^{-/-}$ and mGlu3$^{-/-}$ mice	LY379268	Prevention of neuron death	Corti et al., 2007
Diabetic neuropathy, neuron-Schwann cells co-cultures	NAAG, APDC	Reversion of oxidative damage and prevention of neuron death	Berent-Spillson and Russell, 2007
Traumatic brain injury	NAAG peptidase inhibitor	Reduction of neuron damage	Zhong et al., 2005
Conditioned media from MPP^{+}-challenged astrocytes	DCG-IV	Inhibition of MPP + neurotoxicity by increasing glutamate reuptake	Yao et al., 2005
Aβ neurotoxicity in mixed neuro-glial cultures from mGlu3^{-}/- mice	LY379268	Prevention of neuron death	Caraci et al., 2011a
Autocrine actions			
Cultured astrocytes and *in vivo* assays	DCG-IV, 4C3HPG, LY379268	Increase in TGF-β levels	Bruno et al., 1998; D'Onofrio et al., 2001
Cultured astrocytes	DCG-IV, APDC	Increase in NGF and S100β levels	Ciccarelli et al., 1999
Cultured astrocytes and glioma cell lines	DCG-IV	Induction of GLT1 and GLAST protein	Aronica et al., 2003
OGD deprivation in cultured astrocytes	LY379268	Reduction of astrocyte apoptosis	Ciccarelli et al., 2007
Traumatic brain injury	NAAG peptidase inhibitor	Reduction of astrocyte damage	Zhong et al., 2005
Nitric oxide toxicity (sodium nitroprusside) in cultured astrocytes	NAAG, FN6, LY354740	Reduction of astrocyte apoptosis	Wroblewska et al., 2006
LPS/IFN-γ and nitric oxide toxicity in cultured astrocytes	LY379268, LY404039, L-CCG-I	Reduction of astrocyte apoptosis and inhibition of NO synthesis	Durand et al., 2010, 2011b

mGlu3 receptor agonism also prevents LPS+IFN-γ-induced astrocyte death, which is mediated by NO synthesis (Durand et al., 2010).

Although our results show no changes in DETA/NO-induced cyclic GMP (cGMP) levels by group II mGlu receptor activation in cultured astrocytes, Wroblewska et al. (2006) showed that NAAG, 4,4′-phosphinicobis-(butane-1,3 dicarboxilic acid), and LY354740 (all group II mGlu receptor agonists) were able to decrease sodium nitroprusside-stimulated cGMP levels in cerebellar granule cells and cerebellar astrocytes and to limit programmed cell death induced by the NO donor.

We also postulated recently that reduction in cAMP content, activation of PI3K/Akt pathway and increased interaction between p65 and c-Rel, members of the NF-κB family, are mechanisms responsible for cytoprotective actions of astroglial mGlu3 receptor against NO challenge (Durand et al., 2011b). These results suggest that astroglial mGlu3 receptor might exert a protective effect against neuroinflammatory processes involving dysregulated production of NO and astrocyte loss, which could lead to the development of neurodegenerative disorders. Table 2 summarizes protective actions of astroglial mGlu3 receptors.

Since ischemic and inflammatory insults induce astrocyte apoptotic death, which contributes to the physiopathology of short- and long-term neurodegenerative disorders (Takuma et al., 2004), it is fundamental to support and promote astrocyte function and survival. In fact, apoptotic astrocytes were found in Alzheimer's disease (Kobayashi et al., 2002), ischemic demyelinating lesions in vascular dementia (Tomimoto et al., 1997), and in the grey matter of frontotemporal dementia (Martin et al., 2000). Also, both astroglial death and reactive astrogliosis may develop in parallel during neurodegenerative processes resulting in dementia (Rodríguez et al., 2009).

3.4. Astrocytic mGlu3 receptor in Alzheimer's disease: an incipient field of research

Accumulation of β-amyloid (Aβ) in the brain is one of the hallmarks of Alzheimer's disease (AD) that might play a key role in initiating and propagating disease pathology (Nicoll and Weller, 2003). Aβ accumulation might result from decreased elimination from the brain as well as from increased production from the amyloid precursor protein (APP) (Nicoll and Weller, 2003). Sequential cleavage of APP by β-secretase and γ-secretase produces soluble APPβ (sAPPβ) and Aβ peptide, the major component of amyloid plaques found in AD (Thinakaran and Koo, 2008). Non-amyloidogenic cleavage by α-secretase and γ-secretase releases the carboxyl-truncated secreted sAPPα and non-amyloidogenic 3 kDa peptide (p3) instead of intact 4 kDa Aβ (Thinakaran and Koo, 2008).

Some studies suggested that astrocytes have a role not only in Aβ clearance (Nagele et al., 2003; Wyss-Coray et al., 2003), but also in Aβ degradation, as was evidenced by the presence of N-terminally truncated Aβ peptides in astrocytes of human AD brains (Funato et al., 1998; Thal et al., 1999) and by the clearance of the majority of ^{35}S-Met-labeled Aβ from culture media of postnatal rat astrocytes (Shaffer et al., 1995).

Given that alterations in the cycling of glutamate-glutamine have been observed in AD (Walton and Dodd, 2007), it is possible that glutamate and its receptors might be involved in AD progression. In fact, stimulation of group I and II mGlu receptors with ACPD in cortical and hippocampal slices rapidly increases sAPP release into the medium, an effect which was prevented by a PKC inhibitor, whereas agonists of ionotropic glutamate receptors had no effect on sAPP production (Ulus and Wurtman, 1997). Unlike neurons, astrocytes do not increase sAPP secretion in response to direct activation of PKC (Gabzuda et al., 1993); instead, astrocytes secrete abundant levels of Aβ (Busciglio et al., 1993). However, Lee and Wurtman (1997) demonstrated that exposure of astrocyte cultures to group I/II mGlu receptor agonist ACPD does promote non-amyloidogenic APP processing and increases sAPP secretion. Since then, no further studies have complemented these results using the newest, subtype-selective mGlu receptor ligands in order to establish which mGlu receptor subtype could be responsible for this neuroprotective effect, although the fact that both cAMP and forskolin inhibited ACPD-induced sAPP secretion (Lee and Wurtman, 1997) would indicate the involvement of group II mGlu receptors (which are negatively coupled to adenylate cyclase) in the

effect of ACPD. Also, an mGlu receptor antagonist L-2-amino-3-phosphonopropionic acid (L-AP3) was able to inhibit sAPP secretion induced by the agonist, but did not inhibit PI hydrolysis, indicating that these two events are not necessarily coupled in astrocytes (Lee and Wurtman, 1997) and discarding the participation of PI-coupled mGlu receptors in this effect. Other findings are in line with the hypothesis that cAMP signaling is involved in APP processing: an increased number of β_2-adrenergic receptors coupled to cAMP formation has been detected in the *post mortem* AD brain (Kalaria et al., 1989); a significant increase of cAMP levels in cerebrospinal fluid from patients of AD (Martinez et al., 1999); elevations in intracellular cAMP levels inhibit sAPP secretion from C6 glial cell lines (Efthimiopoulos et al., 1996). Recently, Caraci et al. (2011a) demonstrated that the selective mGlu2 receptor enhancer LY566332 potentiated toxicity of Aβ peptides both in mixed and in pure neuronal cultures; however, in mixed cultures the mGlu2/3 receptor selective agonist LY379268 reduced Aβ-induced neurodegeneration, an effect abolished by an mGlu3 receptor NAM, whereas LY379268 lost its neuroprotective activity in pure neuronal cultures. These data indicate that activation of glial mGlu3 receptors results in neuroprotection against Aβ. Consistent with this, LY379268 lost its protective activity in murine mixed cortical cultures using astrocytes obtained from mGlu3 receptor knockout mice (Caraci et al., 2011a). In addition, astroglial mGlu3 receptor activation induces TGF-β, which protects neurons against Aβ-toxicity; whereas type 2 TGF-β receptors are defective in the AD brain (Caraci et al., 2011b; Tesseur et al., 2006).

All together, these findings are a powerful driving force for further advances in this research area, which has just opened.

4. Concluding remarks

In recent years the traditional neuro-centric view of CNS physiopathology has been replaced by a neuronal-glial paradigm in which glial mGlu receptor activity gathers strength as a potential therapeutic target for neurologic diseases. Here, we have discussed the relevance of preserving astrocytes as major neuroprotective players in the CNS, highlighting the role of mGlu3 receptor activation in astrocyte survival as wells as in the prevention of several psychiatric and neurodegenerative diseases. Evidence compiled here about the spreading neuroprotective mechanisms triggered by astroglial mGlu3 receptor activation (such as modulation of excitotoxicity and glutamate transport, neurotrophin production, glutathione production and reduction of oxidative damage, or the amelioration of inflammatory processes) illustrates the potential of these receptors for the treatment of yet unstudied neurological and degenerative diseases. As an example, involvement of astroglial mGlu3 receptor in Alzheimer's disease deserves to be further studied based on Lee and Wurtman's old findings (1997) and given the novel and interesting evidence brought to this field by Caraci et al. (2011a).

Another issue that remains to be confirmed is the absence of mGlu2 receptor protein in astrocytes, considering the recent development of an mGlu2 subtype-selective antibody. In the same line, the lack of mGlu3 receptor-selective agonists has delayed further advances in this field. This issue originates in the number of studies reporting opposite effects of mGlu2 and mGlu3 receptors, such as those by Higgins et al. (2004) on memory consolidation and Caraci et al. (2011a) on Aβ toxicity. These studies reveal the importance of using subtype-selective ligands in order to define specific actions of mGlu3 receptor in the CNS. Moreover, the use of mGlu3$^{-/-}$ mice has provided interesting data on mGlu3 receptor functioning *in vivo*, although this model can also be questioned, given the evidence on compensatory changes in protein expression in animals lacking one mGlu receptor subtype with up-regulation of the remaining subtype (Lyon et al., 2008). Taken all together, this evidence points to the need to develop new animal models for the study of mGlu3 receptors, including models of cell-specific ablation of mGlu3 receptor in astrocytes, which may yield more reliable information concerning the role of these receptors in astrocytes, a cell type intimately involved in both normal and pathologic brain.

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