Astrocytic Calcium and cAMP in Neurodegenerative Diseases

Marta Sobolczyk and Tomasz Boczek*

Department of Molecular Neurochemistry, Faculty of Health Sciences, Medical University, Lodz, Poland

It is commonly accepted that the role of astrocytes exceeds far beyond neuronal scaffold and energy supply. Their unique morphological and functional features have recently brough much attention as it became evident that they play a fundamental role in neurotransmission and interact with synapses. Synaptic transmission is a highly orchestrated process, which triggers local and transient elevations in intracellular Ca^{2+}, a phenomenon with specific temporal and spatial properties. Presynaptic activation of Ca^{2+}-dependent adenylyl cyclases represents an important mechanism of synaptic transmission modulation. This involves activation of the cAMP-PKA pathway to regulate neurotransmitter synthesis, release and storage, and to increase neuroprotection. This aspect is of paramount importance for the preservation of neuronal survival and functionality in several pathological states occurring with progressive neuronal loss. Hence, the aim of this review is to discuss mutual relationships between cAMP and Ca^{2+} signaling and emphasize those alterations at the Ca^{2+}/cAMP crosstalk that have been identified in neurodegenerative disorders, such as Alzheimer's and Parkinson's disease.

Keywords: astrocyte, calcium, cyclic AMP (cAMP), neurodegeneration, Parkinson's disease, PKA, adenylyl cyclases, Alzheimer's disease

INTRODUCTION

The discoveries made three decades ago that cytosolic Ca^{2+} rise occurs in astrocytes in response to environmental cues have provided new insights into the essential role of these star-shaped glial cells in the CNS. Nowadays, it is commonly known that astrocytes are highly specialized types of glial cells responsible for synapse formation and regulation of ongoing neuronal transmission. They also interact with other glial cells or blood vessels depending on the brain region (Verkhratsky and Nedergaard, 2018). For instance, the astrocytic support is maintained by the release of neurotrophic factors and diverse transmitters called gliotransmitters, including adenosine triphosphate (ATP)/adenosine, D-serine, glutamate, tumor necrosis factor α (TNFα), and γ-aminobutyric acid (GABA) at various timescales to sustain complex information processing and metabolic homeostasis in the brain (Steeland et al., 2018; Durkee and Araque, 2019; Pöyhönen et al., 2019). It is estimated that the ratio of glial cells to neurons is roughly 1:1 and astrocytes constitute ∼19–40% of all glial cells in the CNS (Verkhratsky and Nedergaard, 2018), nevertheless the total number of neurons and glia has long been controversial (von Bartheld et al., 2016).

The morphological and functional heterogeneity of astrocytes determines various protein expression profiles what may explain the sensitivity of certain areas of the brain to the progress of a specific disease entity (Xin and Bonci, 2018; Matias et al., 2019). Moreover, opposed to the neuro-centric view of brain function, astroglia dysfunction is increasingly considered a fundamental cause in the pathogenesis of neurological diseases (Liu et al., 2017; Robertson, 2018).

In contrast to neurons, astrocytes do not fire an action potential. However, in response to the local changes in intracellular Ca^{2+}, often referred to as "Ca^{2+} excitability," they can strongly influence physiological and pathophysiological events in the nervous system. Indeed, astrocytes express the diversity of G protein-coupled receptors (GPCRs) that allow detection and reaction to neuronal signals (Durkee and Araque, 2019). Among the second messengers activated by GPCRs, Ca^{2+}, and cyclic adenosine monophosphate (cAMP) are capable of eliciting diverse pleiotropic responses, thus regulating basic cellular functions, such as growth and differentiation, gene transcription and protein expression as well as astrocyte-mediated synaptic plasticity, gliotransmission, energy supply and maintenance of the extracellular environment (Bazargani and Attwell, 2016; Horvat and Vardjan, 2019; Zhou et al., 2021). It is supposed that dysregulation of Ca^{2+} and cAMP exacerbates structural and functional abnormalities in this cell type, hence restoration of imbalanced Ca^{2+} and/or cAMP signaling may constitute an effective astrocyte-based therapeutic approach Growing body of evidence links deficits in astrocytic Ca^{2+} and cAMP-controlled mechanisms to various brain pathologies (Ujita et al., 2017; Reuschlein et al., 2019; Kofuji and Araque, 2021; Zhou et al., 2021). Recent technological progress in two-photon imaging and development of genetically encoded Ca^{2+} indicators (GECIs) as well as genetically encoded sensors for cAMP and protein kinase A (PKA), allowed for high-resolution detection of astrocytic Ca^{2+}/cAMP fluxes in different physiological and pathological conditions (Reeves et al., 2011; Gee et al., 2015; Semyanov et al., 2020; Massengill et al., 2021).

Despite this progress, the cause-effect relationship between temporal and spatial disturbances in intracellular Ca^{2+}/cAMP signaling machinery and the development of neuropathological disorders are still being sought. Therefore, this review summarizes the latest findings on the crosstalk between cAMP and Ca^{2+} signaling pathways and their contribution to the neurodegenerative process.

Ca^{2+}/cAMP in Astrocyte Homeostasis: A Brief Review

Overall, neuronal information is transferred to astrocytes primarily through spillover of neurotransmitters or other types of neuroligands, which diffuse into the extracellular space and next bind to various astroglial targets, such as membrane ionic channels, transporters or receptors triggering their conformational change (**Figure 1**). As a result, activated GPCR catalyzes dissociation of a heterotrimeric G protein complex (composed of G_α, G_β/G_γ subunits) into G_α subunit and $\beta\gamma$ dimer by the exchange of GDP for GTP. Based on the sequence homology and functionality of α-subunits, G proteins are divided into four main families: $G_{\alpha s}$, $G_{\alpha i}$/$G_{\alpha o}$, $G_{\alpha q}$/$G_{\alpha 11}$, and $G_{\alpha 12}$/$G_{\alpha 13}$ that regulate distinct downstream signaling events (Jastrzebska, 2013). The activation of the G_q subunit stimulates phospholipase C (PLC) that leads to hydrolysis of phosphoinositol diphosphate (PIP2) into diacylglycerol (DAG), known as a membrane-bound regulator of cAMP concentration, and inositol 1,4,5-triphosphate (IP3), known as a soluble messenger triggering the release of Ca^{2+} ions from the endoplasmic reticulum (ER) (Hua et al., 2004) or secretory vesicles (Hur et al., 2010). In astrocytes,
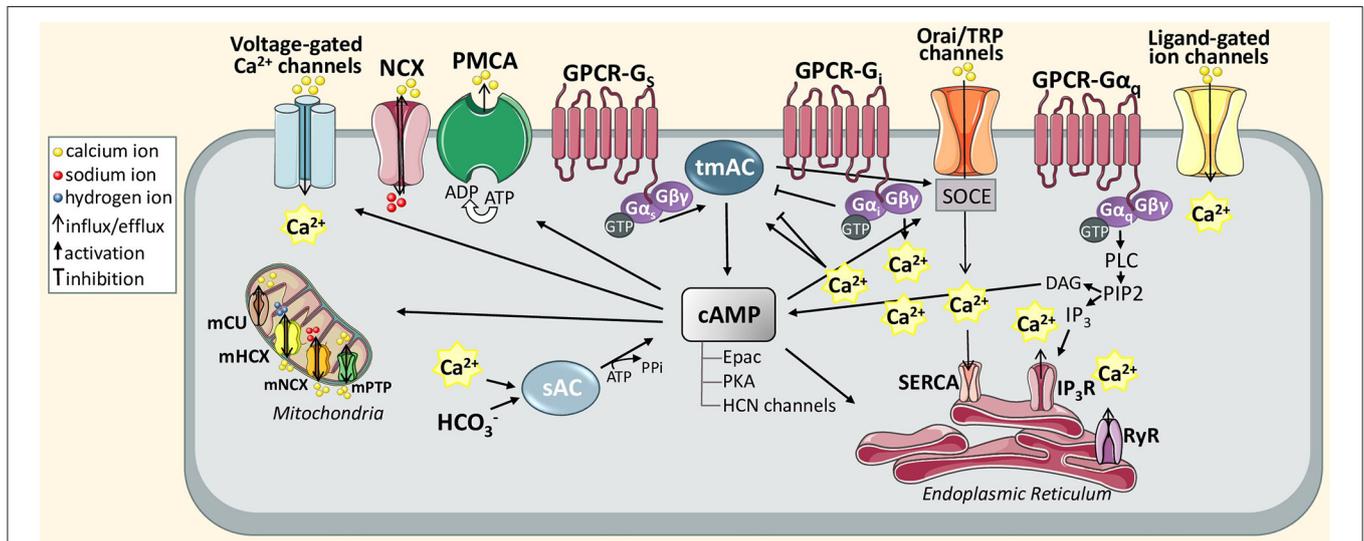
FIGURE 1 | Schematic diagram of astrocytic Ca^{2+} and cAMP signaling pathways discussed in this review. The action of active GTP-bound $G_{\alpha i}$ and GTP-bound $G_{\alpha o}$ stimulates or inhibits transmembrane adenylyl cyclase (tmAC) that produces cAMP. The tmAC may also be controlled indirectly *via* store-operated Ca^{2+} entry (SOCE). To maintain Ca^{2+} homeostasis in the ER, SOCE is orchestrated through the interaction between store-operated plasma membrane calcium channels, called Orai or transient receptor potential (TRP) channel, and can stimulate SERCA pump activity once Ca^{2+} levels fall below the threshold levels. In particular, this mechanism is generated when Ca^{2+} stores in the ER are depleted upon activation of inositol 1,4,5-trisphosphate (IP3) receptor via $G_{\alpha q}$-phospholipase C (PLC)-IP3 signal transduction pathway. In turn, the DAG produced from PIP2 hydrolysis can also catalyze cAMP synthesis. Another activator of cAMP is Ca^{2+} sensitive soluble adenylyl cyclase (sAC). cAMP itself and cAMP-dependent proteins (Epac PKA, and HCN channels) can differently transmit Ca^{2+} signals supporting various astrocytic functions including gliotransmission, glycogen metabolism or synaptic homeostasis.

TABLE 1 | Astrocytic Ca^{2+}/cAMP modulation by GPCR receptors and their physiological role in diverse brain areas.

GPCR(s)	G protein(s)	Effect on 2nd messenger	Brain region	Gliotransmission	Psychological role	References
A_1R	$G_{i/o}$	↓cAMP	Cortex	Glutamate	Modulation of synaptic transmission	Cristóvão-Ferreira et al., 2013
$A_{2A}R$	G_s	↑cAMP	Cortex	-	Enhancement of GABA uptake	Cristóvão-Ferreira et al., 2013
α_1AR	G_q	↑Ca^{2+}	Cortex	ATP/D-serine	Control of synaptic plasticity	Pankratov and Lalo, 2015
α_2AR	$G_{i/o}$	↓cAMP	Cortex	-	-	Kitano et al., 2021
βAR	G_s	↑cAMP	Cortex	-	-	Horvat et al., 2016; Kitano et al., 2021
βAR	G_s	↑cAMP	-	-	Glucose uptake	Catus et al., 2011
D1R	G_q	↑Ca^{2+}	Nucleus Accumbens	ATP/adenosine	Depress excitatory synaptic transmission	Corkrum et al., 2020
D1/5R	G_S	↑cAMP	Cortex	-	Mediation of intracellular NADH increase	Requardt et al., 2010
$GABA_BR$	$G_{i/o}$	↑Ca^{2+}	Cortex	Glutamate	Increase neuronal excitability	Mariotti et al., 2016
$GABA_BR$	$G_{i/o}$	↑Ca^{2+}	Striatum	Thrombospondin-1	Increase synaptic excitability and transmission	Nagai et al., 2019
H_1R	G_q	↑Ca^{2+}	Cortex	Glutamate	-	Kárpáti et al., 2018
H_2R	G_s	↑cAMP	-	-	-	Kárpáti et al., 2018
mGluR2	$G_{i/o}$	↑Ca^{2+}	Thalamus	Glutamate	Synaptic inhibition	Copeland et al., 2017
mGluR3	$G_{i/o}$	↓cAMP	Cortex	-	Protection against hypoxic/ischemic damage	Ciccarelli et al., 2007; Sun et al., 2013
mGluR5	G_q	↑Ca^{2+}	Hippocampus	ATP	Enhance basal synaptic transmission	Panatier et al., 2011
P2Y1R	G_q	↑Ca^{2+}	Hippocampus	Glutamate	Increase synaptic potentiation	Santello et al., 2011; Álvarez-Ferradas et al., 2015
P2Y1R	G_q	↑Ca^{2+}	Cortex	ATP	Modulation of synaptic plasticity	Lalo et al., 2019
PAC1R	G_s	↑cAMP	Cortex	Endozepine	Activate neuronal metabotropic receptor	Masmoudi-Kouki et al., 2007
$5-HT_2$	G_q	↑Ca^{2+}	-	Glutamate	Increase neuronal excitation	Chen et al., 2016
$5-HT_4R$	G_s	↑cAMP	-	-	Regulation of immune responsiveness	Zeinstra et al., 2006
$5-HT_{5A}R$	$G_{i/o}$	↓cAMP	-	-	-	Carson et al., 1996
MOP	$G_{i/o}$	↓cAMP	Hippocampus	-	Decrease neuronal excitability	Machelska and Celik, 2020

↑Means increased.
↓Means decreased.
-Means not detected or not defined.

G_q-coupled receptors, mainly α1-adrenoreceptor (α$_1$-AR; Ding et al., 2013), D1 dopamine receptor (D1R; Corkrum et al., 2020), histamine receptor (H$_1$; Kárpáti et al., 2018), metabotropic glutamate receptor (mGluR; Sun et al., 2013), serotonin 5-HT$_2$ receptor (Peng and Huang, 2012), and P2Y purinoreceptor (Ding et al., 2009), and also G$_i$-coupled receptors, such as GABA$_B$ receptor (Durkee et al., 2019), generate a wide range of inositol 1,4,5-trisphosphate receptor (IP3R)-dependent Ca^{2+} oscillations to differently regulate gliotransmission and neuronal modulation (**Table 1**). For example, synaptically released acetylcholine (ACh) or noradrenaline (NE) can induce an astrocytic Ca^{2+} increase thereby enhancing synaptic plasticity the in the cortex (Takata et al., 2011; Chen et al., 2012) and hippocampus (Navarrete et al., 2012; Papouin et al., 2017). The IP3R-dependent Ca^{2+} release may also occur spontaneously (King et al., 2020). The canonical function of G$_i$-GPCR is to suppress adenylate cyclase-dependent signaling cascade and thus, inhibit cAMP activity, which has been also observed in astrocytes (Gould et al., 2014). The G$_{\beta\gamma}$ released from different G$_i$ subunits targets ion channels such as inwardly rectifying potassium channels and voltage-gated Ca^{2+} channels (Jeremic et al., 2021). Interestingly, the GPCR-G$_{i/o}$ protein signaling in neurons is commonly known to inhibit intracellular Ca^{2+} events and electrical excitability, whereas a recent study has demonstrated that astrocyte G$_{i/o}$ GPCR activation may

stimulate Ca^{2+} elevation involved in the release of inhibitory neurotransmitters into the synapse (Huang and Thathiah, 2015; Durkee et al., 2019). Therefore, such functional diversity of GPCRs enables integrated astrocyte-neuron communication.

Several interesting results regarding global Ca^{2+} elevations in astrocytes have been derived from IP3R type 2 knockout mice (Guerra-Gomes et al., 2021). It has been demonstrated that loss of this receptor may contribute to various types of cognitive dysfunctions (Perez-Alvarez et al., 2014; Padmashri et al., 2015) as well as depressive-like behaviors (Cao et al., 2013), but it seems unlikely that its role in shaping astrocytic Ca^{2+} is predominant (Petravicz et al., 2008, 2014). Although astrocytic IP3R2 expression is required for certain mechanisms of LTD formation, the genetic defects in IP3R2 are not sufficient to fully prevent LTP generation what probably reflects astrocyte diversity in different brain regions (Oberheim et al., 2012). Recently, it has been suggested that IP3R1 and IP3R3 subtypes co-exist in astroglia and retain their functionality by generating local Ca^{2+} events (Sherwood et al., 2017, 2021). The second key type of Ca^{2+}-permeable receptor channel in the ER is the ryanodine receptor (RyR) but the mechanism of its activation and inhibition by Ca^{2+} remains largely unexplored and controversial (Rodríguez-Prados et al., 2020; Skowrońska et al., 2020). The latest report has suggested that RyR-mediated Ca^{2+}-induced Ca^{2+} release (CICR) in astrocytes may be negatively modulated by neuron-derived factors which may alter the Ca^{2+} response triggered by ionotropic receptors (Skowrońska et al., 2020). Other types of stores controlling intracellular Ca^{2+} concentration are mitochondria that buffer cytosolic Ca^{2+} *via* the mitochondrial NCX, mitochondrial H^+/Ca^{2+} exchanger (mHCX), mitochondrial Ca^{2+} uniporter (mCU), and mitochondrial permeability transition pore (mPTP; Agarwal et al., 2017). Interestingly, the expression of some mitochondrial transporters may be controlled by cyclic AMP response element-binding protein (CREB; Shanmughapriya et al., 2015). Primarily, a rise in mitochondrial Ca^{2+} concentration drives energy production needed to modulate glutamate release and prevents excitotoxic neuronal death. On the other hand, Ca^{2+} overload may lead to astrocytic apoptosis (Stephen et al., 2014). It is worth mentioning that Ca^{2+} signaling dynamics diffuse between mitochondria and ER (Okubo et al., 2019), and ER stress triggers mitochondrial dysfunction (Britti et al., 2018).

The resting cytosolic Ca^{2+} concentration independent from IP3-activity is also controlled by transmembrane Ca^{2+} influx through the transient receptor potential A1 (TRPA1) channel. Activation of this receptor can induce constitutive D-serine release from astrocytes for NMDA receptor-dependent LTP maintenance (Shigetomi et al., 2013). Blocking of TRPA1 decreases spontaneous Ca^{2+} events leading to lower extracellular GABA uptake by the astrocyte-specific transporter (GAT3; Shigetomi et al., 2011). In view of that, astrocytic TRPA channels are considered as integral players coordinating Ca^{2+} dynamics involved in the inhibitory efficacy of the hippocampal synapses. Likewise, intracellular Ca^{2+} is also tightly regulated by ionotropic receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and N-methyl-D-aspartate (NMDA) receptors, both gated by glutamate,

and ATP-gated purinergic P2X receptors (Palygin et al., 2010, 2011; Ceprian and Fulton, 2019). The plasma membrane Na^+/Ca^{2+} exchanger (NCX) and plasma membrane Ca^{2+} ATPase (PMCA) are the main regulators of Ca^{2+} extrusion to the extracellular space while the control of Ca^{2+} concentration in the ER is ensured by the sarco/endoplasmic reticulum calcium ATPase (SERCA) (Brini and Carafoli, 2011). Compared to NCX, PMCA has a lower capacity for ionic transport but its basal affinity for Ca^{2+} is higher. This property allows PMCA to respond to even subtle changes in Ca^{2+} concentration within a range of its resting cytosolic level. By contrast, NCX can eliminate significant rises in intracellular Ca^{2+}, although, in the case of increased intracellular Na^+ concentration, due to e.g., glutamate or GABA uptake, the NCX may operate in reverse mode increasing Ca^{2+} influx (Brini and Carafoli, 2011; Rose et al., 2020).

Unlike Ca^{2+} activity, which can be regulated by multiple distinct pathways, the predominant mechanism of cAMP modulation is mediated by GPCRs coupled to either G_s or G_i leading to activation or inhibition of transmembrane adenylate cyclases (tmACs), respectively. In astrocytes, cAMP is regulated mainly by the activation of adenosine receptors (A_1 and A_{2A}), adrenergic receptors (α_2 and β_{1-3}), dopamine receptor (D1/5), glutamatergic receptor (mGlu3), histamine receptor (H_2), PACAP/VIP receptors, serotonin receptors (5-HT$_4$ and 5-HT$_{5A}$) and also opioid receptors, all summarized in **Table 1**. ACs are believed to be pivotal points of integration between Ca^{2+} and cAMP signaling. It is assumed that all of the nine tmAC isoforms, which have also been identified in mice astrocytes (Lee et al., 2018), can be modulated (activated or inhibited) by Ca^{2+}, either directly or indirectly *via* Ca^{2+} binding proteins such as calmodulin (CaM), CaM kinase (CaMK), calcineurin (CaN), protein kinase C (PKC), or G_q-coupled receptor activation. For instance, AC8 activated in a Ca^{2+}/CaM-dependent manner binds the Orai1 channel, which is a major functional component responsible for store-operated calcium entry (SOCE; Willoughby et al., 2012a,b). Accordingly, the AC8 seems to be highly sensitive to modest local Ca^{2+} changes. In primary astrocytic cultures, AC inhibitor 2',5'-dideoxyadenosine prevented cAMP synthesis and significantly decreased SOCE-triggered glycogenolysis. Based on this evidence, the authors proposed a new model for astrocytic coupling of Ca^{2+} homeostasis, AC8-dependent cAMP production and glycogen metabolism which could also impact on learning and memory processes (Müller et al., 2014). However, the physiological interplay between the molecular players of cAMP signaling and depletion of ER Ca^{2+} stores still remains to be determined in this subtype of glial cells.

Recent *in vitro* and *in vivo* studies provided considerable insight into the differences between Ca^{2+} and cAMP dynamics in astrocytes in terms of precise spatiotemporal regulation of complex cellular processes (Horvat et al., 2016; Oe et al., 2020). While stimulation of α_1AR generated rapid and transient Ca^{2+} increase enhancing synaptic plasticity, stimulation of βAR triggered slower and long-lasting cAMP elevations and promoted consolidation of cortical memory. It is supposed that threshold levels for activation of respective second messenger are different due to diverse affinities of NE for AR subtypes. According to

this, moderate NE release may be sufficient to activate the α_1AR coupled to the G_q while activation of βAR coupled to the G_s needs relatively high extracellular NE to elevate cAMP within the cell (Ramos and Arnsten, 2007; Oe et al., 2020). Another type of AC, called soluble AC (sAC), is directly activated by HCO_3^- entry *via* the electrogenic $NaHCO_3$ cotransporter in response to extracellular K^+ rises or aglycemia (Choi et al., 2012; Schmid et al., 2014). sAC is also highly expressed in astrocytes to stimulate the production of intracellular cAMP. Elevated cAMP can provide energy supply and metabolic support for the proper functioning of neurons contributing to glycolysis and delivery of lactate from astrocytes (Choi et al., 2012; MacVicar and Choi, 2017). It is worth noting that sAC is found in distinct subcellular microdomains with local cAMP signals (Tresguerres et al., 2011) and even slight changes in the intracellular Ca^{2+} dynamics may impact the activation of this AC isoform (Gancedo, 2013; Schmid et al., 2014). The fatty acids (Lee et al., 2018), lactate, aspirin (Modi et al., 2013), or some antidepressants (e.g., ketamine or fluoxetin) have been reported to cause the astrocytic cAMP-elevation but their mechanism of action toward second messengers still remains unclear (Kinoshita et al., 2018; Lasič et al., 2019; Stenovec et al., 2020; Stenovec, 2021).

It is commonly known that Ca^{2+} has multiple downstream targets (Scemes and Giaume, 2006; Bagur and Hajnóczky, 2017). cAMP can transmit Ca^{2+} signals through isoforms of exchange protein activated by cAMP (Epac), Epac1 and Epac2, or PKA or cAMP-gated ion channels called hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Halls and Cooper, 2011). cAMP itself or cAMP-dependent proteins may evoke both Ca^{2+} influx *via* cation channels (Catterall, 2011) and Ca^{2+} extrusion by ATP-dependent pumps (Vandecaetsbeek et al., 2011). Phosphorylation of IP3R subtypes seems to be stimulated by PKA or EPAC as well as directly activated by cAMP. This activation requires much higher concentrations of second messengers and is quickly attenuated after removing the AC stimulus (Taylor, 2017). Analysis of acute hippocampal slices has shown that astrocytic cAMP/PKA signaling may modulate oscillatory activity of intracellular Ca^{2+} (Ujita et al., 2017). In cortical astrocytes, cAMP/PKA-dependent Ca^{2+} changes may be mediated by voltage-gated Ca^{2+} channels (VGCCs) to maintain the exocytotic secretion of gliotransmitters (Burgos et al., 2007). The cytosolic Ca^{2+} elevations are necessary for gliotransmission of ATP, serine, and also glutamate to support neuronal plasticity (Harada et al., 2015). In pathological states, the abnormal release of gliosignalling molecules may trigger excitotoxicity and synaptic damage leading to neuroinflammatory and neurodegenerative progress (Agulhon et al., 2012; Kawamata et al., 2014).

Both cAMP and cGMP degradation may be driven by a large group of phosphodiesterases (PDEs) classified into 11 families, some of which are regulated by Ca^{2+} or Ca^{2+}/CaM (Bender and Beavo, 2006; Tenner et al., 2020; Turunen and Koskelainen, 2021). Given that most of tmAC isoforms, PKA and cyclic nucleotide phosphodiesterases (PDEs), may be located at the scaffold protein complexes called A-kinase anchoring proteins (AKAPs), it is plausible that the spatial and temporal organization of AKAPs orchestrates synthesis and degradation of the second

messenger at the specific subcellular sites. Although RNA-sequencing of astrocytes purified from mouse brain suggests the presence of genes encoding various AKAP subtypes (e.g., AKAP15/18, AKAP79, gravin, Yotiao; Reuschlein et al., 2019), their functional role in astrocytic cAMP signaling remains to be uncovered. These multi-functional scaffold proteins have been widely characterized in neurons, both in physiological and pathological states (Wild and Dell'Acqua, 2018). The AKAPs associated with cAMP are regulated by local Ca^{2+} oscillations (Scott and Santana, 2010; Boczek et al., 2021). Global analysis of astroglial transcripts released in 2015 demonstrated that cAMP-dependent signaling regulated 6,221 of 16,594 annotated genes, including 42.1% of them were significantly upregulated whereas the remaining were downregulated by cAMP analogs. As suggested by Gene Ontology enrichment analysis, the upregulated genes were mainly involved in cellular metabolism (e.g., uptake/degradation of catecholamines, glutamate, and glycine) and transport (e.g., Ca^{2+} or K^+ -ion, glucose, or water transport) as well as antioxidant activities, especially glutathione-related defenses. Among genes downregulated by cAMP stimulation, the overwhelming number of encoded modulators of the physiological process as cell cycle, proliferation, or death (e.g., some cyclins and cyclin-dependent kinases, mitogenic agents, BCL2 family proteins), as well as cytoskeletal proteins and mediators of the immune system. Therefore, cAMP is involved in the regulation of a plethora of cellular functions from the antioxidant systems through the control of the normal state of differentiated astrocytic cells (Paco et al., 2016).

It is apparently becoming clear that the existence of an interplay between cAMP and Ca^{2+} messenger systems in astrocytes is non-linear and of great complexity. Undoubtedly, spatial and temporal resolution should be taken under consideration to understand their synergistic and antagonistic relationship.

Ca^{2+} AND cAMP SIGNALING PATHWAYS IN THE NEURODEGENERATIVE DISEASES

The pathological protein accumulation, such as amyloid beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated protein tau are commonly detected hallmarks of Alzheimer's disease (AD). Neurodegeneration manifested by neuronal integrity loss and white matter lesions or gliosis, is widely recognized in postmortem brain of AD patients (Raskin et al., 2015). During progression of AD, the pathological extra-neuronal Aβ deposits interrupt astrocyte's functions leading to disruption of gliotransmission, neurotransmitter uptake, and Ca^{2+} handling. The Aβ-induced astrocytic metabolic failure, including the production of reactive oxygen/nitrogen species, Ca^{2+}-dependent glutathione depletion, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and mitochondrial Ca^{2+} dyshomeostasis, is ultimately linked to synaptic dysfunction and neuronal death (Abramov et al., 2004; Abeti et al., 2011). Indeed, Aβ exposure impaired Ca^{2+} homeostasis *via* activation of Ca^{2+} sensitive channels or Ca^{2+} permeable ionotropic receptors leading to abnormal Ca^{2+}

permeability, and subsequent cytosolic Ca^{2+} overload (Demuro et al., 2010). The application of Aβ oligomers was found to promote Ca^{2+} rise associated with ER stress response initiating reactive astrogliosis, which has been characterized both *in vitro* and *in vivo* (Alberdi et al., 2013). The development of astrocyte reactivity promotes molecular and morphological remodeling of astrocytes that may have neuroprotective or neurotoxic effects depending on the occurrence of pathological condition in the specific brain region. This phenomenon is observed mainly at the early stages of disease. Remodeled astrocytes usually exhibit changes in gene expression profile, increased level of cytoskeletal structural proteins (GFAP and vimentin), and cellular hypertrophy (Pekny et al., 2016). In animal models of AD, astroglial phenotype transformation emerged around Aβ deposits in the hippocampus, but the reactivity has not been reported in the entorhinal and prefrontal cortex (Verkhratsky et al., 2016). The pro-inflammatory bradykinin which is often elevated in the plasma of AD patients with greater cognitive disruption (Singh et al., 2020), may induce Ca^{2+} hyperactivity *via* nicotinic acetylcholine receptors (AChRs) and PI3K-Akt signaling pathway in cortical astrocytes cultures (Makitani et al., 2017). It is also worth mentioning that bradykinin is associated with increased NO production and induction of vascular permeability leading to disruption of the BBB barrier integrity (Erickson and Banks, 2013; Makitani et al., 2017).

Loss of dopaminergic neurons, the presence of α-synuclein and inclusion bodies in brain tissue are the hallmarks of Parkinson's disease (PD), the second most recognized neurodegenerative disorder. The α-synuclein proteins secreted from neurons are easily taken up by astrocytes through endocytosis causing inflammatory response such as release of cytokines (IL1, IL6, and TNFα), oxidative stress and mitochondrial impairment (Gu et al., 2010; Lee et al., 2010). Particularly, dopaminergic neurons in the substantia nigra pars compacta (SNpc) affect movement control as well as reward response and their progressive degeneration caused by chronic inflammation and reactive astrogliosis, is one of the main factors determining characteristic motor disturbance (e.g., bradykinesia, rigidity, tremor at rest) in PD patients (Michel et al., 2013). Generally, dopamine receptors are classified into two subfamilies, D1-like receptor family coupled to $G_{s/olf}$ (consists of D1 and D5), and D2-like receptor family coupled to $G_{i/o}$ (consists of D2, D3, and D4 receptors) to stimulate or inhibit AC/cAMP/PKA transduction pathway, respectively. All five subtypes of dopamine receptors are also expressed in astrocytes. In cultured cortical astrocytes, the application of SKF83959 led to discovery of non-cyclase-coupled D1-like receptor called phosphatidyl-inositol-linked D1 receptor which induces Ca^{2+} mobilization *via* the G_q/PLC/IP3 signaling (Liu et al., 2009).

To date, there is no conclusive evidence on the crosstalk between cAMP and Ca^{2+} in PD pathology, but several reports suggest that mutual modulation of the second messengers in dysfunctional astrocytes likely contributes to neurodegeneration observed in this disorder. So, the following sections highlight this evidence pointing out potential mechanisms that could trigger abnormal Ca^{2+}/cAMP signaling and thus promote loss of supporting astrocyte function.

Effect on Glutamate Excitotoxicity and Neurotrophic Support

Astrocytic excitatory amino acid transporters (EAATs) defects have been repeatedly demonstrated in numerous neurodegenerative diseases, especially AD, PD but also Huntington's disease (Su et al., 2003; Sharma et al., 2019; Hindeya Gebreyesus and Gebrehiwot Gebremichael, 2020). Increased level of Aβ suppresses the expression of two important astroglial transporters: GLAST (glutamate-aspartate transporter, also named EAAT1) and GLT1 (glutamate transporter 1, also named EAAT2) *via* G_s-coupled A_{2A} receptors decreasing glutamate uptake by astroglia (Matos et al., 2012; Zumkehr et al., 2015). Secondarily, adenosine A_{2A} receptor/PKA signaling pathway regulates intracellular Ca^{2+} mobilizations and triggers glutamate release. Remarkably, this pathway can stimulate the rise in cytosolic Ca^{2+} concentration *via* Ca^{2+} efflux from intracellular Ca^{2+} stores independent of IP3 and ryanodine receptor activity (Kanno and Nishizaki, 2012). In AD patients, the overexpression of adenosine A2A receptor gene (ADORA2A) is aggravated (Horgusluoglu-Moloch et al., 2017) which can lead to decreased ability of astrocytes to clear the extracellular glutamate (Matos et al., 2012). In addition to its central function as an energy source, glycogen is also essential to provide energy for glutamate and glutamine synthesis in response to elevated K^+ concentrations or neurotransmitters, such as NE, serotonin or ATP (Gibbs et al., 2006; Gibbs, 2016). It is speculated that glycolytic metabolism can be also regulated by coordinated GPCR-coupled cAMP and Ca^{2+} signals or non-GPCR-coupled Ca^{2+} and cAMP signals (Bak et al., 2018). Pathologically, disturbance in glycogen homeostasis may decrease glycogenesis and increase glycogenolysis in AD. The glycogen synthesis may be diminished by overactivation of synthase kinase 3 (GSK3) which also promotes abnormal hyperphosphorylation of tau and neuroinflammation process (Beurel et al., 2015; Di et al., 2016; Rodríguez-Matellán et al., 2020). Besides, GSK3 activity may be diminished by cAMP-dependent PKA (Llorens-Marítin et al., 2014). On the other hand, exposure to β-amyloid augments the energy consumption of neurons. In such conditions, increased excitability seems to generate a temporary compensation mechanism in response to synaptic loss. Bass and colleagues argue that neuronal metabolic changes drive the depletion of glycogen reserves in the brain *via* elevated levels of Aβ and astrocytic A_{2A} receptors, ultimately resulting in neuronal hypoactivity as the disease progresses (Bass et al., 2015). Considering that the overactive A_{2A} receptor is sufficient to cause hippocampal-dependent cognitive impairments *via* PKA/cAMP/CREB signaling (Li et al., 2015) as well as able to affect transcription of genes related to neuroinflammation, angiogenesis and astrocytic reactivity (Paiva et al., 2019), the development of novel therapeutic target against astrocytic A_{2A} receptor-dependent mechanism seems to be rational in the treatment of the AD. *In vitro* study has demonstrated that A_{2A} receptor antagonism prevented Aβ-induced synaptic degeneration in hippocampus (Gomes et al., 2011). Additionally, the latest results from live-cell imaging of primary cortical astrocytes revealed that application of $Aβ_{25-35}$ peptide can

induce PMCA-mediated Ca^{2+} extrusion *via* cAMP signaling. Thus, ATP-dependent Ca^{2+} extrusion system seems to constitute a protective mechanism aimed to counterbalance the early effects of Ca^{2+} overload in the presence of neurotoxic Aβ oligomers. On the other hand, their increasing chronic aggregation may impair PMCA activity in astrocytes (Pham et al., 2021).

Additionally, astrocytic Ca^{2+} signal may generate a rapid astroglial response to the nearby autoreactive immune cells involved in immune-mediated demyelinating disease, called multiple sclerosis (MS). It is believed that this mechanism of intercellular communication may be linked to astrocytic purinergic activation and participation of ATP release to autoinflammation in the CNS (Bijelić et al., 2020). On the other hand, β2-adrenergic-dependent cAMP signaling in reactive astrocytes appears to be downregulated putatively as a result of complete loss of β2-adrenergic receptor immunoreactivity in the MS, what may contribute to disease pathology (De Keyser et al., 1999, 2004). Recently, amyotrophic lateral sclerosis (ALS)- and frontotemporal dementia (FTD)-linked TAR DNA-binding protein 43 (TDP-43) inclusions have been shown to affect cAMP and Ca^{2+} signaling in astrocytes, most likely due to the downregulation of β2-adrenergic receptors leading to dysregulated astroglial metabolism and disease progression (Velebit et al., 2020).

Similar to AD pathology, reduced glutamate transporters expression has been detected in neurotoxin-induced PD animal models (Holmer et al., 2005; Chung et al., 2008). It is worth noting that the ventral midbrain-derived astrocytes are highly susceptible to D2 receptor-induced Ca^{2+} signaling. They seem to be relatively insensitive to NE and exhibit significantly different Ca^{2+}-related gene expression profile compared to telencephalic astrocytes (Ibáñez et al., 2019; Xin et al., 2019). In mice SNpc, AAV-mediated GLT1 knockdown elicited reactive astrogliosis, dysfunctional Ca^{2+} homeostasis (by altered expression of Ca^{2+} channels and Ca^{2+}/calmodulin-dependent protein kinases) and DA neuronal death generating parkinsonian phenotypes (Zhang et al., 2020). Recent evidence has shown that GLT1 expression is regulated by cAMP and CREB and its internalization depends on Ca^{2+} mobilization driven mainly by the Na^+/Ca^{2+} exchanger (Liu et al., 2016; Ibáñez et al., 2019). Together, oscillations in Ca^{2+} and cAMP may be involved at multiple levels in the regulation of glutamate uptake by astrocytes. Hence, accumulation of pathological changes may determine severity of the excitotoxicity in individual brain areas.

Prior post-mortem studies indicated abnormally lowered brain-derived neurotrophic factor (BDNF) level in brain tissue of patients with PD (Mogi et al., 1999). Several other evidence showed that BDNF genetic polymorphisms increase the risk of PD-related cognitive impairments (Karamohamed et al., 2005; Altmann et al., 2016). In animal PD models, neurotrophic factors supported the function of dopaminergic system, including prevention from degeneration of dopaminergic neurons and improvement of dopaminergic neurotransmission (Migliore et al., 2014; Palasz et al., 2020). Moreover, the comparable level of BDNF expression between astrocytes and neurons of human brain cortex suggests an equally significant role of astrocytic BDNF in maintaining their neuroprotective and neuroregenerative potential (Koppel et al., 2018). On the other hand, increasing evidence shows that dopaminergic protection depends on changes in astrocytic Ca^{2+} and cAMP levels (Jennings and Rusakov, 2016). For example, Koppel et al. reported that dopamine-induced BDNF upregulation is dependent on cAMP/CREB stimulation through β-adrenergic receptors in primary astroglia. Likewise, the activation of PI3K/Akt/CREB pathway *via* FLZ treatment increased GDNF production by astroglia and improved the function of dopaminergic neurons in mouse models of PD (Bao et al., 2020).
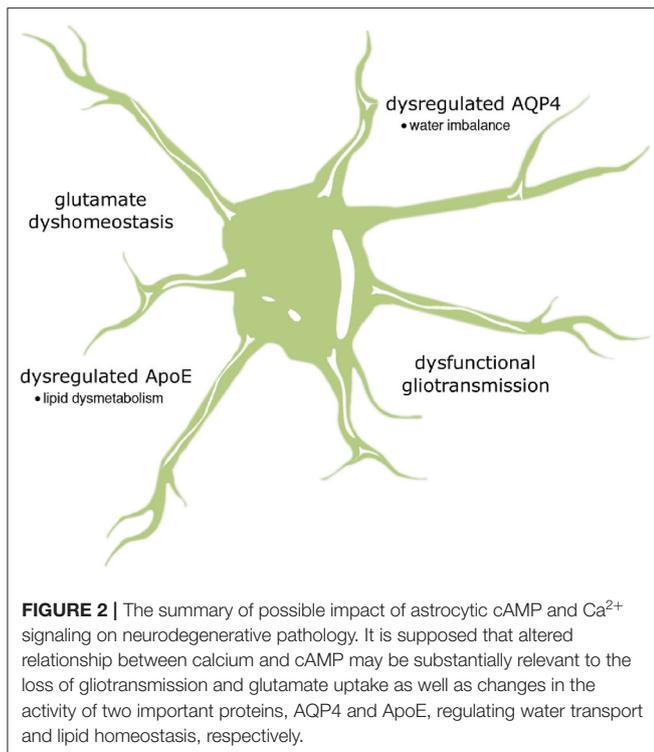
Effect on Water Homeostasis

One of the main proteins responsible for maintaining cerebral water balance are aquaporins (AQPs), especially type 4 (AQP4). It is highly concentrated in glial endfoot membranes and forms a molecular complex with a transient receptor potential cation channel subfamily V member 4 (TRPV4; Benfenati et al., 2011; Lunde et al., 2015). Loss of these channels or their defective membrane assembly, for example during aging, leads to significant impairments in astrocyte polarity, which may exacerbate neurodegenerative progress (Valenza et al., 2020). For example, deletion of AQP4 exacerbated Aβ accumulation and atrophy of astrocytes in APP/PS mouse model of AD (Xu et al., 2015). AQP4 KO mice demonstrated increased 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity toward dopamine neurons in the striatum. This included alterations in astroglial function and reduced GDNF synthesis (Fan et al., 2008). Another study reported the MPTP treatment led to upregulation of AQP4 expression in mouse substantia nigra. The MRI brain scanning revealed increased water accumulation in the substantia nigra of PD patients (Ofori et al., 2015) suggesting an implication of AQP4 in water imbalance in the PD brain. It has also been reported that the modulation of AQP4 may control inflammatory process and AQP4 dysfunction increased the production of IL1β and TNFα triggering microglial reactivity in the midbrain (Sun et al., 2016).

Song and Gunnarson pointed to the relationship between cAMP signaling in astrocyte water permeability and the extracellular potassium concentration. Uptake of K^+ activated AQP4 *via* PKA-dependent pathway and led to water permeability in astrocytes. Prolonged increase in intracellular K^+ due to K_{ir} channel prevented water permeability *via* Ca^{2+}/calmodulin-dependent regulation (Song and Gunnarson, 2012). The relationship between PKA and calmodulin in the regulation of subcellular localization of AQP4 has also been documented (Kitchen et al., 2020). This supports the idea that disrupted Ca^{2+}/cAMP signaling may be involved in altered astrocyte water permeability. The functional coupling between these signaling pathways seems to be involved in neuronal hyperactivity associated with cognitive deficits observed in AD models.

Effect on Apolipoprotein E

Second messengers, such as Ca^{2+} and cAMP, orchestrate the release of signaling molecules, including a peptide, called

FIGURE 2 | The summary of possible impact of astrocytic cAMP and Ca^{2+} signaling on neurodegenerative pathology. It is supposed that altered relationship between calcium and cAMP may be substantially relevant to the loss of gliotransmission and glutamate uptake as well as changes in the activity of two important proteins, AQP4 and ApoE, regulating water transport and lipid homeostasis, respectively.

apolipoprotein (ApoE; Kockx et al., 2007), which is primarily synthesized by astrocytes. This peptide is crucial for synthesis, degradation and removal of Aβ from the brain. *In vitro*, Aβ-upregulated cAMP levels *via* the classical pathway, G$_s$-AC, leading to increased ApoE secretion and altered lipid trafficking in astrocytes (Igbavboa et al., 2006; Rossello et al., 2012). Changes in the lipid composition as a result of ApoE4 dysregulation led to pathological Ca^{2+} influx and Ca^{2+} hyperactivity in astrocytes (Larramona-Arcas et al., 2020). Compelling evidence suggests that polymorphic variants of APOE gene may correlate with the development of sporadic AD. The presence of the APOE4 allele greatly exacerbates the risk of the disease, while the presence of the APOE2 allele decreases the susceptibility to the disease (Yu et al., 2014; Fernandez et al., 2019). Similarly, current data also indicate various influences of APOE genotypes on αSyn aggregation and APOE4 may exacerbate a series of abnormalities characteristic of PD, such as behavioral disturbances, loss of neural connections and astrogliosis (Zhao et al., 2020).

Taken together, isoform-specific effect of ApoE and alterations in second messenger system may have profound consequences on cholesterol transport and neurotoxicity-induced synaptopathy (Veinbergs et al., 2002; Igbavboa et al., 2006; de Chaves and Narayanaswami, 2008).

CONCLUDING REMARKS

It is commonly known that astrocytes can interact with multiple synapses to receive a vast amount of information. This information is next processed by a system of second messengers acting at different levels. Nonetheless, understanding their intricate interactions remains a challenge for the research environment. This review highlights the importance between cAMP and Ca^{2+} signaling in astrocytes, which modulates the surrounding microenvironment and synaptic plasticity. However, how these mutual relationships contribute to the mechanisms driving neurodegeneration is not fully understood. A growing body of evidence indicates that cAMP and Ca^{2+} interdependence can effect glutamate clearance from the synaptic cleft, gliotransmitter release and ion and water homeostasis. Even slight abnormalities in these mechanisms may have severe neuropathological consequences (**Figure 2**). The detailed mechanisms by which Ca^{2+}/cAMP crosstalk in astrocytes affects pathological events leading to neurodegeneration are only beginning to emerge. In conclusion, further studies are essential for a precise understanding of Ca^{2+} and cAMP dynamics in astrocytes, taking into account the astrocyte region-specific phenotype and the regional susceptibility to synaptic damage and neuronal loss.

AUTHOR CONTRIBUTIONS

MS and TB conceived, designed the topic, and wrote the manuscript. Both authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

REFERENCES

Abeti, R., Abramov, A. Y., and Duchen, M. R. (2011). β-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. *Brain* 134, 1658–1672. doi: 10.1093/brain/awr104

Abramov, A. Y., Canevari, L., and Duchen, M. R. (2004). Beta-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase. *J. Neurosci.* 24, 565–575. doi: 10.1523/JNEUROSCI.4042-03.2004

Agarwal, A., Wu, P.-H., Hughes, E. G., Fukaya, M., Tischfield, M. A., Langseth, A. J., et al. (2017). Transient opening of the mitochondrial permeability transition pore induces microdomain calcium transients in astrocyte processes. *Neuron* 93, 587–605.e7. doi: 10.1016/j.neuron.2016.12.034

Agulhon, C., Sun, M.-Y., Murphy, T., Myers, T., Lauderdale, K., and Fiacco, T. A. (2012). Calcium signaling and gliotransmission in normal vs. reactive astrocytes. *Front. Pharmacol.* 3, 139. doi: 10.3389/fphar.2012.00139

Alberdi, E., Wyssenbach, A., Alberdi, M., Sánchez-Gómez, M. V., Cavaliere, F., Rodríguez, J. J., et al. (2013). Ca^{2+}-dependent endoplasmic reticulum stress

correlates with astrogliosis in oligomeric amyloid β-treated astrocytes and in a model of Alzheimer's disease. *Aging Cell* 12, 292–302. doi: 10.1111/acel.12054

Altmann, V., Schumacher-Schuh, A. F., Rieck, M., Callegari-Jacques, S. M., Rieder, C. R. M., and Hutz, M. H. (2016). Val66Met BDNF polymorphism is associated with Parkinson's disease cognitive impairment. *Neurosci. Lett.* 615, 88–91. doi: 10.1016/j.neulet.2016.01.030

Álvarez-Ferradas, C., Morales, J. C., Wellmann, M., Nualart, F., Roncagliolo, M., Fuenzalida, M., et al. (2015). Enhanced astroglial Ca^{2+} signaling increases excitatory synaptic strength in the epileptic brain. *Glia* 63, 1507–1521. doi: 10.1002/glia.22817

Bagur, R., and Hajnóczky, G. (2017). Intracellular Ca^{2+} sensing: role in calcium homeostasis and signaling. *Mol. Cell* 66, 780–788. doi: 10.1016/j.molcel.2017.05.028

Bak, L. K., Walls, A. B., Schousboe, A., and Waagepetersen, H. S. (2018). Astrocytic glycogen metabolism in the healthy and diseased brain. *J. Biol. Chem.* 293, 7108–7116. doi: 10.1074/jbc.R117.803239

Bao, X.-Q., Wang, L., Yang, H.-Y., Hou, L.-Y., Wang, Q.-S., and Zhang, D. (2020). Induction of glial cell line-derived neurotrophic factor by the squamosamide derivative FLZ in astroglia has neuroprotective effects on dopaminergic neurons. *Brain Res. Bullet.* 154, 32–42. doi: 10.1016/j.brainresbull.2019.10.008

Bass, B., Upson, S., Roy, K., Montgomery, E. L., Jalonen, T. O., and Murray, I. V. J. (2015). Glycogen and amyloid-beta: key players in the shift from neuronal hyperactivity to hypoactivity observed in Alzheimer's disease? *Neural Regen. Res.* 10, 1023–1025. doi: 10.4103/1673-5374.160059

Bazargani, N., and Attwell, D. (2016). Astrocyte calcium signaling: the third wave. *Nat. Neurosci.* 19, 182–189. doi: 10.1038/nn.4201

Bender, A. T., and Beavo, J. A. (2006). Cyclic nucleotide phosphodiesterases: molecular regulation to clinical use. *Pharmacol. Rev.* 58, 488–520. doi: 10.1124/pr.58.3.5

Benfenati, V., Caprini, M., Dovizio, M., Mylonakou, M. N., Ferroni, S., Ottersen, O. P., et al. (2011). An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. *Proc. Natl. Acad. Sci. U. S. A.* 108, 2563–2568. doi: 10.1073/pnas.1012867108

Beurel, E., Grieco, S. F., and Jope, R. S. (2015). Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol. Ther.* 16, 114–131. doi: 10.1016/j.pharmthera.2014.11.016

Bijelić, D. D., Milićević, K. D., Lazarević, M. N., Miljković, D. M., Bogdanović Pristov, J. J., Savić, D. Z., et al. (2020). Central nervous system-infiltrated immune cells induce calcium increase in astrocytes *via* astroglial purinergic signaling. *J. Neurosci. Res.* 98, 2317–2332. doi: 10.1002/jnr.24699

Boczek, T., Yu, Q., Zhu, Y., Dodge-Kafka, K. L., Goldberg, J. L., and Kapiloff, M. S. (2021). cAMP at perinuclear mAKAPα signalosomes is regulated by local Ca^{2+} signaling in primary hippocampal neurons. *eNeuro* 8, 2021. doi: 10.1523/ENEURO.0298-20.2021

Brini, M., and Carafoli, E. (2011). The plasma membrane Ca^{2+} ATPase and the plasma membrane sodium calcium exchanger cooperate in the regulation of cell calcium. *Cold Spring Harb. Perspect. Biol.* 3:a004168. doi: 10.1101/cshperspect.a004168

Britti, E., Delaspre, F., Tamarit, J., and Ros, J. (2018). Mitochondrial calcium signalling and neurodegenerative diseases. *Neuronal. Signal* 2:NS20180061. doi: 10.1042/NS20180061

Burgos, M., Pastor, M. D., González, J. C., Martinez-Galan, J. R., Vaquero, C. F., Fradejas, N., et al. (2007). PKCepsilon upregulates voltage-dependent calcium channels in cultured astrocytes. *Glia* 55, 1437–1448. doi: 10.1002/glia.20555

Cao, X., Li, L.-P., Wang, Q., Wu, Q., Hu, H.-H., Zhang, M., et al. (2013). Astrocyte-derived ATP modulates depressive-like behaviors. *Nat. Med.* 19, 773–777. doi: 10.1038/nm.3162

Carson, M. J., Thomas, E. A., Danielson, P. E., and Sutcliffe, J. G. (1996). The 5HT5A serotonin receptor is expressed predominantly by astrocytes in which it inhibits cAMP accumulation: a mechanism for neuronal suppression of reactive astrocytes. *Glia* 17, 317–326. doi: 10.1002/(SICI)1098-1136(199608)17:4<317::AID-GLIA6>3.0.CO;2-W

Catterall, W. A. (2011). Voltage-gated calcium channels. *Cold Spring Harb. Perspect. Biol.* 3:a003947. doi: 10.1101/cshperspect.a003947

Catus, S. L., Gibbs, M. E., Sato, M., Summers, R. J., and Hutchinson, D. S. (2011). Role of β-adrenoceptors in glucose uptake in astrocytes using β-adrenoceptor knockout mice. *Br. J. Pharmacol.* 162, 1700–1715. doi: 10.1111/j.1476-5381.2010.01153.x

Ceprian, M., and Fulton, D. (2019). Glial cell AMPA receptors in nervous system health, injury and disease. *Int. J. Mol. Sci.* 20, 2450. doi: 10.3390/ijms20102450

Chen, N., Sugihara, H., Sharma, J., Perea, G., Petravicz, J., Le, C., et al. (2012). Nucleus basalis-enabled stimulus-specific plasticity in the visual cortex is mediated by astrocytes. *Proc. Natl. Acad. Sci. U. S. A.* 109, E2832–2841. doi: 10.1073/pnas.1206557109

Chen, Y., Du, T., Peng, L., Gibbs, M. E., and Hertz, L. (2016). Sequential astrocytic 5-HT2B receptor stimulation, [Ca^{2+}]i regulation, glycogenolysis, glutamate synthesis, and K+ homeostasis are similar but not identical in learning and mood regulation. *Front. Integr. Neurosci.* 9, 67. doi: 10.3389/fnint.2015.00067

Choi, H. B., Gordon, G. R. J., Zhou, N., Tai, C., Rungta, R. L., Martinez, J., et al. (2012). Metabolic communication between astrocytes and neurons *via* bicarbonate-responsive soluble adenylyl cyclase. *Neuron* 75, 1094–1104. doi: 10.1016/j.neuron.2012.08.032

Chung, E. K. Y., Chen, L. W., Chan, Y. S., and Yung, K. K. L. (2008). Downregulation of glial glutamate transporters after dopamine denervation in the striatum of 6-hydroxydopamine-lesioned rats. *J. Comp. Neurol.* 511, 421–437. doi: 10.1002/cne.21852

Ciccarelli, R., D'Alimonte, I., Ballerini, P., D'Auro, M., Nargi, E., Buccella, S., et al. (2007). Molecular signalling mediating the protective effect of A1 adenosine and mGlu3 metabotropic glutamate receptor activation against apoptosis by oxygen/glucose deprivation in cultured astrocytes. *Mol. Pharmacol.* 71, 1369–1380. doi: 10.1124/mol.106.031617

Copeland, C. S., Wall, T. M., Sims, R. E., Neale, S. A., Nisenbaum, E., Parri, H. R., et al. (2017). Astrocytes modulate thalamic sensory processing *via* mGlu2 receptor activation. *Neuropharmacology* 121, 100–110. doi: 10.1016/j.neuropharm.2017.04.019

Corkrum, M., Covelo, A., Lines, J., Bellocchio, L., Pisansky, M., Loke, K., et al. (2020). Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. *Neuron* 105, 1036–1047.e5. doi: 10.1016/j.neuron.2019.12.026

Cristóvão-Ferreira, S., Navarro, G., Brugarolas, M., Pérez-Capote, K., Vaz, S. H., Fattorini, G., et al. (2013). A1R–A2AR heteromers coupled to Gs and Gi/0 proteins modulate GABA transport into astrocytes. *Purinergic Signal* 9, 433–449. doi: 10.1007/s11302-013-9364-5

de Chaves, E. P., and Narayanaswami, V. (2008). Apolipoprotein E and cholesterol in aging and disease in the brain. *Fut. Lipidol.* 3, 505–530. doi: 10.2217/17460875.3.5.505

De Keyser, J., Wilczak, N., Leta, R., and Streetland, C. (1999). Astrocytes in multiple sclerosis lack beta-2 adrenergic receptors. *Neurology* 53, 1628–1633. doi: 10.1212/WNL.53.8.1628

De Keyser, J., Zeinstra, E., and Wilczak, N. (2004). Astrocytic beta2-adrenergic receptors and multiple sclerosis. *Neurobiol. Dis.* 15, 331–339. doi: 10.1016/j.nbd.2003.10.012

Demuro, A., Parker, I., and Stutzmann, G. E. (2010). Calcium signaling and amyloid toxicity in Alzheimer disease. *J. Biol. Chem.* 285, 12463–12468. doi: 10.1074/jbc.R109.080895

Di, J., Cohen, L. S., Corbo, C. P., Phillips, G. R., El Idrissi, A., and Alonso, A. D. (2016). Abnormal tau induces cognitive impairment through two different mechanisms: synaptic dysfunction and neuronal loss. *Sci. Rep.* 6:20833. doi: 10.1038/srep20833

Ding, F., O'Donnell, J., Thrane, A. S., Zeppenfeld, D., Kang, H., Xie, L., et al. (2013). α1-adrenergic receptors mediate coordinated Ca^{2+} signaling of cortical astrocytes in awake, behaving mice. *Cell Calcium* 54, 387–394. doi: 10.1016/j.ceca.2013.09.001

Ding, S., Wang, T., Cui, W., and Haydon, P. G. (2009). Photothrombosis ischemia stimulates a sustained astrocytic Ca^{2+} signaling *in vivo*. *Glia* 57, 767–776. doi: 10.1002/glia.20804

Durkee, C. A., and Araque, A. (2019). Diversity and specificity of astrocyte-neuron communication. *Neuroscience* 396, 73–78. doi: 10.1016/j.neuroscience.2018.11.010

Durkee, C. A., Covelo, A., Lines, J., Kofuji, P., Aguilar, J., and Araque, A. (2019). Gi/o protein-coupled receptors inhibit neurons but activate astrocytes and stimulate gliotransmission. *Glia* 67, 1076–1093. doi: 10.1002/glia.23589

Erickson, M. A., and Banks, W. A. (2013). Blood–brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *J. Cereb. Blood Flow Metab.* 33, 1500–1513. doi: 10.1038/jcbfm.2013.135

Fan, Y., Kong, H., Shi, X., Sun, X., Ding, J., Wu, J., et al. (2008). Hypersensitivity of aquaporin 4-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and astrocytic modulation. *Neurobiol. Aging* 29, 1226–1236. doi: 10.1016/j.neurobiolaging.2007.02.015

Fernandez, C. G., Hamby, M. E., McReynolds, M. L., and Ray, W. J. (2019). The role of APOE4 in disrupting the homeostatic functions of astrocytes and microglia in aging and alzheimer's disease. *Front. Aging Neurosci.* 11, 14. doi: 10.3389/fnagi.2019.00014

Gancedo, J. M. (2013). Biological roles of cAMP: variations on a theme in the different kingdoms of life. *Biol. Rev. Camb. Philos. Soc.* 88, 645–668. doi: 10.1111/brv.12020

Gee, J. M., Gibbons, M. B., Taheri, M., Palumbos, S., Morris, S. C., Smeal, R. M., et al. (2015). Imaging activity in astrocytes and neurons with genetically encoded calcium indicators following in utero electroporation. *Front. Mol. Neurosci.* 8, 10. doi: 10.3389/fnmol.2015.00010

Gibbs, M. E. (2016). Role of glycogenolysis in memory and learning: regulation by noradrenaline, serotonin and ATP. *Front. Integr. Neurosci.* 9:70. doi: 10.3389/fnint.2015.00070

Gibbs, M. E., Anderson, D. G., and Hertz, L. (2006). Inhibition of glycogenolysis in astrocytes interrupts memory consolidation in young chickens. *Glia* 54, 214–222. doi: 10.1002/glia.20377

Gomes, C. V., Kaster, M. P., Tomé, A. R., Agostinho, P. M., and Cunha, R. A. (2011). Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. *Biochim. Biophys. Acta* 1808, 1380–1399. doi: 10.1016/j.bbamem.2010.12.001

Gould, T., Chen, L., Emri, Z., Pirttimaki, T., Errington, A. C., Crunelli, V., et al. (2014). GABAB receptor-mediated activation of astrocytes by gamma-hydroxybutyric acid. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 369:20130607. doi: 10.1098/rstb.2013.0607

Gu, X.-L., Long, C.-X., Sun, L., Xie, C., Lin, X., and Cai, H. (2010). Astrocytic expression of Parkinson's disease-related A53T α-synuclein causes neurodegeneration in mice. *Mol. Brain* 3, 12. doi: 10.1186/1756-6606-3-12

Guerra-Gomes, S., Cunha-Garcia, D., Marques Nascimento, D. S., Duarte-Silva, S., Loureiro-Campos, E., Morais Sardinha, V., et al. (2021). IP3 R2 null mice display a normal acquisition of somatic and neurological development milestones. *Eur. J. Neurosci.* 54, 5673–5686. doi: 10.1111/ejn.14724

Halls, M. L., and Cooper, D. M. F. (2011). Regulation by Ca^{2+}-signaling pathways of adenylyl cyclases. *Cold Spring Harb. Perspect. Biol.* 3:a004143. doi: 10.1101/cshperspect.a004143

Harada, K., Kamiya, T., and Tsuboi, T. (2015). Gliotransmitter release from astrocytes: functional, developmental, and pathological implications in the brain. *Front. Neurosci.* 9:499. doi: 10.3389/fnins.2015.00499

Hindeya Gebreyesus, H., and Gebrehiwot Gebremichael, T. (2020). The potential role of astrocytes in Parkinson's disease (PD). *Med. Sci.* 8, 7. doi: 10.3390/medsci8010007

Holmer, H. K., Keyghobadi, M., Moore, C., and Meshul, C. K. (2005). l-dopa-induced reversal in striatal glutamate following partial depletion of nigrostriatal dopamine with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 136, 333–341. doi: 10.1016/j.neuroscience.2005.08.003

Horgusluoglu-Moloch, E., Nho, K., Risacher, S. L., Kim, S., Foroud, T., Shaw, L. M., et al. (2017). Targeted neurogenesis pathway-based gene analysis identifies ADORA2A associated with hippocampal volume in mild cognitive impairment and Alzheimer's disease. *Neurobiol. Aging* 60, 92–103. doi: 10.1016/j.neurobiolaging.2017.08.010

Horvat, A., and Vardjan, N. (2019). Astroglial cAMP signalling in space and time. *Neurosci. Lett.* 689, 5–10. doi: 10.1016/j.neulet.2018.06.025

Horvat, A., Zorec, R., and Vardjan, N. (2016). Adrenergic stimulation of single rat astrocytes results in distinct temporal changes in intracellular $Ca^{(2+)}$ and cAMP-dependent PKA responses. *Cell Calcium* 59, 156–163. doi: 10.1016/j.ceca.2016.01.002

Hua, X., Malarkey, E. B., Sunjara, V., Rosenwald, S. E., Li, W.-H., and Parpura, V. (2004). $Ca^{(2+)}$-dependent glutamate release involves two classes of endoplasmic reticulum $Ca^{(2+)}$ stores in astrocytes. *J. Neurosci. Res.* 76, 86–97. doi: 10.1002/jnr.20061

Huang, Y., and Thathiah, A. (2015). Regulation of neuronal communication by G protein-coupled receptors. *FEBS Lett.* 589, 1607–1619. doi: 10.1016/j.febslet.2015.05.007

Hur, Y. S., Kim, K. D., Paek, S. H., and Yoo, S. H. (2010). Evidence for the existence of secretory granule (dense-core vesicle)-based inositol 1,4,5-trisphosphate-dependent Ca^{2+} signaling system in astrocytes. *PLoS ONE* 5:e11973. doi: 10.1371/journal.pone.0011973

Ibáñez, I., Bartolomé-Martín, D., Piniella, D., Giménez, C., and Zafra, F. (2019). Activity dependent internalization of the glutamate transporter GLT-1 requires calcium entry through the NCX sodium/calcium exchanger. *Neurochem. Int.* 123, 125–132. doi: 10.1016/j.neuint.2018.03.012

Igbavboa, U., Johnson-Anuna, L. N., Rossello, X., Butterick, T. A., Sun, G. Y., and Wood, W. G. (2006). Amyloid beta-protein1-42 increases cAMP and apolipoprotein E levels which are inhibited by β1 and β2-adrenergic receptor antagonists in mouse primary astrocytes. *Neuroscience* 142, 655–660. doi: 10.1016/j.neuroscience.2006.06.056

Jastrzebska, B. (2013). GPCR – G protein complexes – the fundamental signaling assembly. *Amino Acids* 45, 1303–1314. doi: 10.1007/s00726-013-1593-y

Jennings, A., and Rusakov, D. A. (2016). Do astrocytes respond to dopamine? *Opera Medica et Physiol.* 2, 34–43. doi: 10.20388/OMP2016.001.0017

Jeremic, D., Sanchez-Rodriguez, I., Jimenez-Diaz, L., and Navarro-Lopez, J. D. (2021). Therapeutic potential of targeting G protein-gated inwardly rectifying potassium (GIRK) channels in the central nervous system. *Pharmacol. Ther.* 223, 107808. doi: 10.1016/j.pharmthera.2021.107808

Kanno, T., and Nishizaki, T. (2012). A(2a) adenosine receptor mediates PKA-dependent glutamate release from synaptic-like vesicles and $Ca^{(2+)}$ efflux from an IP(3)- and ryanodine-insensitive intracellular calcium store in astrocytes. *Cell Physiol. Biochem.* 30, 1398–1412. doi: 10.1159/000343328

Karamohamed, S., Latourelle, J. C., Racette, B. A., Perlmutter, J. S., Wooten, G. F., Lew, M., et al. (2005). BDNF genetic variants are associated with onset age of familial Parkinson disease: GenePD Study. *Neurology* 65, 1823–1825. doi: 10.1212/01.wnl.0000187075.81589.fd

Kárpáti, A., Yoshikawa, T., Nakamura, T., Iida, T., Matsuzawa, T., Kitano, H., et al. (2018). Histamine elicits glutamate release from cultured astrocytes. *J. Pharmacol. Sci.* 137, 122–128. doi: 10.1016/j.jphs.2018.05.002

Kawamata, H., Ng, S. K., Diaz, N., Burstein, S., Morel, L., Osgood, A., et al. (2014). Abnormal intracellular calcium signaling and SNARE-dependent exocytosis contributes to SOD1G93A astrocyte-mediated toxicity in amyotrophic lateral sclerosis. *J. Neurosci.* 34, 2331–2348. doi: 10.1523/JNEUROSCI.2689-13.2014

King, C. M., Bohmbach, K., Minge, D., Delekate, A., Zheng, K., Reynolds, J., et al. (2020). Local resting Ca^{2+} controls the scale of astroglial Ca^{2+} signals. *Cell Rep.* 30, 3466–3477.e4. doi: 10.1016/j.celrep.2020.02.043

Kinoshita, M., Hirayama, Y., Fujishita, K., Shibata, K., Shinozaki, Y., Shigetomi, E., et al. (2018). Anti-depressant fluoxetine reveals its therapeutic effect *via* astrocytes. *EBioMedicine* 32, 72–83. doi: 10.1016/j.ebiom.2018.05.036

Kitano, T., Eguchi, R., Okamatsu-Ogura, Y., Yamaguchi, S., and Otsuguro, K. (2021). Opposing functions of α- and β-adrenoceptors in the formation of processes by cultured astrocytes. *J. Pharmacol. Sci.* 145, 228–240. doi: 10.1016/j.jphs.2020.12.005

Kitchen, P., Salman, M. M., Halsey, A. M., Clarke-Bland, C., MacDonald, J. A., Ishida, H., et al. (2020). Targeting aquaporin-4 subcellular localization to treat central nervous system edema. *Cell* 181:784. doi: 10.1016/j.cell.2020.03.037

Kockx, M., Guo, D. L., Huby, T., Lesnik, P., Kay, J., Sabaretnam, T., et al. (2007). Secretion of apolipoprotein E from macrophages occurs *via* a protein kinase A and calcium-dependent pathway along the microtubule network. *Circ. Res.* 101, 607–616. doi: 10.1161/CIRCRESAHA.107.157198

Kofuji, P., and Araque, A. (2021). GPCRs and astrocyte behavior. *Annu. Rev. Neurosci.* 44, 49–67. doi: 10.1146/annurev-neuro-101920-112225

Koppel, I., Jaanson, K., Klasche, A., Tuvikene, J., Tiirik, T., Pärn, A., et al. (2018). Dopamine cross-reacts with adrenoreceptors in cortical astrocytes to induce BDNF expression, CREB signaling and morphological transformation. *Glia* 66, 206–216. doi: 10.1002/glia.23238

Lalo, U., Bogdanov, A., and Pankratov, Y. (2019). Age- and experience-related plasticity of ATP-mediated signaling in the neocortex. *Front. Cell Neurosci.* 13, 242. doi: 10.3389/fncel.2019.00242

Larramona-Arcas, R., González-Arias, C., Perea, G., Gutiérrez, A., Vitorica, J., García-Barrera, T., et al. (2020). Sex-dependent calcium hyperactivity due to lysosomal-related dysfunction in astrocytes from APOE4 vs. APOE3 gene targeted replacement mice. *Mol. Neurodegener.* 15, 35. doi: 10.1186/s13024-020-00382-8

Lasič, E., Lisjak, M., Horvat, A., BoŽić, M., and Šakanović, A., Anderluh, G., et al. (2019). Astrocyte specific remodeling of plasmalemmal cholesterol composition by ketamine indicates a new mechanism of antidepressant action. *Sci. Rep.* 9:10957. doi: 10.1038/s41598-019-47459-z

Lee, H.-J., Suk, J.-E., Patrick, C., Bae, E.-J., Cho, J.-H., Rho, S., et al. (2010). Direct transfer of α-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. *J. Biol. Chem.* 285, 9262–9272. doi: 10.1074/jbc.M109.081125

Lee, N., Sa, M., Hong, Y. R., Lee, C. J., and Koo, J. (2018). Fatty acid increases cAMP-dependent lactate and MAO-B-dependent GABA production in mouse astrocytes by activating a gαs protein-coupled receptor. *Exp. Neurobiol.* 27, 365–376. doi: 10.5607/en.2018.27.5.365

Li, P., Rial, D., Canas, P. M., Yoo, J.-H., Li, W., Zhou, X., et al. (2015). Optogenetic activation of intracellular adenosine A2A receptor signaling in the hippocampus is sufficient to trigger CREB phosphorylation and impair memory. *Mol. Psychiatry* 20, 1339–1349. doi: 10.1038/mp.2014.182

Liu, B., Teschemacher, A. G., and Kasparov, S. (2017). Astroglia as a cellular target for neuroprotection and treatment of neuro-psychiatric disorders. *Glia* 65, 1205–1226. doi: 10.1002/glia.23136

Liu, J., Wang, F., Huang, C., Long, L.-H., Wu, W.-N., Cai, F., et al. (2009). Activation of phosphatidylinositol-linked novel D1 dopamine receptor contributes to the calcium mobilization in cultured rat prefrontal cortical astrocytes. *Cell Mol. Neurobiol.* 29, 317–328. doi: 10.1007/s10571-008-9323-9

Liu, X., Guo, H., Sayed, M. D. S., Lu, Y., Yang, T., Zhou, D., et al. (2016). cAMP/PKA/CREB/GLT1 signaling involved in the antidepressant-like effects of phosphodiesterase 4D inhibitor (GEBR-7b) in rats. *Neuropsychiatr. Dis. Treat* 12, 219–227. doi: 10.2147/NDT.S90960

Llorens-Marítin, M., Jurado, J., Hernández, F., and Ávila, J. (2014). GSK-3β, a pivotal kinase in Alzheimer disease. *Front. Mol. Neurosci.* 7:46. doi: 10.3389/fnmol.2014.00046

Lunde, L. K., Camassa, L. M. A., Hoddevik, E. H., Khan, F. H., Ottersen, O. P., Boldt, H. B., et al. (2015). Postnatal development of the molecular complex underlying astrocyte polarization. *Brain Struct. Funct.* 220, 2087–2101. doi: 10.1007/s00429-014-0775-z

Machelska, H., and Celik, M. Ö. (2020). Opioid receptors in immune and glial cells-implications for pain control. *Front. Immunol.* 11, 300. doi: 10.3389/fimmu.2020.00300

MacVicar, B. A., and Choi, H. B. (2017). Astrocytes provide metabolic support for neuronal synaptic function in response to extracellular K. *Neurochem. Res.* 42, 2588–2594. doi: 10.1007/s11064-017-2315-8

Makitani, K., Nakagawa, S., Izumi, Y., Akaike, A., and Kume, T. (2017). Inhibitory effect of donepezil on bradykinin-induced increase in the intracellular calcium concentration in cultured cortical astrocytes. *J. Pharmacol. Sci.* 134, 37–44. doi: 10.1016/j.jphs.2017.03.008

Mariotti, L., Losi, G., Sessolo, M., Marcon, I., and Carmignoto, G. (2016). The inhibitory neurotransmitter GABA evokes long-lasting Ca²⁺ oscillations in cortical astrocytes. *Glia* 64, 363–373. doi: 10.1002/glia.22933

Masmoudi-Kouki, O., Gandolfo, P., Castel, H., Leprince, J., Fournier, A., Dejda, A., et al. (2007). Role of PACAP and VIP in astroglial functions. *Peptides* 28, 1753–1760. doi: 10.1016/j.peptides.2007.05.015

Massengill, C. I., Day-Cooney, J., Mao, T., and Zhong, H. (2021). Genetically encoded sensors towards imaging cAMP and PKA activity *in vivo*. *J. Neurosci. Methods* 362:109298. doi: 10.1016/j.jneumeth.2021.109298

Matias, I., Morgado, J., and Gomes, F. C. A. (2019). Astrocyte heterogeneity: impact to brain aging and disease. *Front. Aging Neurosci.* 11:59. doi: 10.3389/fnagi.2019.00059

Matos, M., Augusto, E., Machado, N. J., dos Santos-Rodrigues, A., Cunha, R. A., and Agostinho, P. (2012). Astrocytic adenosine A2A receptors control the amyloid-β peptide-induced decrease of glutamate uptake. *J. Alzheimer's Dis.* 31, 555–567. doi: 10.3233/JAD-2012-120469

Michel, P. P., Toulorge, D., Guerreiro, S., and Hirsch, E. C. (2013). Specific needs of dopamine neurons for stimulation in order to survive: implication for Parkinson's disease. *FASEB J.* 27, 3414–3423. doi: 10.1096/fj.12-220418

Migliore, M. M., Ortiz, R., Dye, S., Campbell, R. B., Amiji, M. M., and Waszczak, B. L. (2014). Neurotrophic and neuroprotective efficacy of intranasal GDNF in a rat model of Parkinson's disease. *Neuroscience* 274, 11–23. doi: 10.1016/j.neuroscience.2014.05.019

Modi, K. K., Sendtner, M., and Pahan, K. (2013). Up-regulation of ciliary neurotrophic factor in astrocytes by aspirin. *J. Biol. Chem.* 288, 18533–18545. doi: 10.1074/jbc.M112.447268

Mogi, M., Togari, A., Kondo, T., Mizuno, Y., Komure, O., Kuno, S., et al. (1999). Brain-derived growth factor and nerve growth factor concentrations are decreased in the substantia nigra in Parkinson's disease. *Neurosci. Lett.* 270, 45–48. doi: 10.1016/S0304-3940(99)00463-2

Müller, M. S., Fox, R., Schousboe, A., Waagepetersen, H. S., and Bak, L. K. (2014). Astrocyte glycogenolysis is triggered by store-operated calcium entry and provides metabolic energy for cellular calcium homeostasis. *Glia* 62, 526–534. doi: 10.1002/glia.22623

Nagai, J., Rajbhandari, A. K., Gangwani, M. R., Hachisuka, A., Coppola, G., Masmanidis, S. C., et al. (2019). Hyperactivity with disrupted attention by activation of an astrocyte synaptogenic cue. *Cell* 177, 1280–1292.e20. doi: 10.1016/j.cell.2019.03.019

Navarrete, M., Perea, G., Fernandez de Sevilla, D., Gómez-Gonzalo, M., Núñez, A., Martín, E. D., et al. (2012). Astrocytes mediate *in vivo* cholinergic-induced synaptic plasticity. *PLoS Biol.* 10:e1001259. doi: 10.1371/journal.pbio.1001259

Oberheim, N. A., Goldman, S. A., and Nedergaard, M. (2012). Heterogeneity of astrocytic form and function. *Methods Mol. Biol.* 814, 23–45. doi: 10.1007/978-1-61779-452-0_3

Oe, Y., Wang, X., Patriarchi, T., Konno, A., Ozawa, K., Yahagi, K., et al. (2020). Distinct temporal integration of noradrenaline signaling by astrocytic second messengers during vigilance. *Nat. Commun.* 11:471. doi: 10.1038/s41467-020-14378-x

Ofori, E., Pasternak, O., Planetta, P. J., Burciu, R., Snyder, A., Febo, M., et al. (2015). Increased free-water in the substantia nigra of Parkinson's disease: a single-site and multi-site study. *Neurobiol. Aging* 36, 1097–1104. doi: 10.1016/j.neurobiolaging.2014.10.029

Okubo, Y., Kanemaru, K., Suzuki, J., Kobayashi, K., Hirose, K., and Iino, M. (2019). Inositol 1,4,5-trisphosphate receptor type 2-independent Ca²⁺ release from the endoplasmic reticulum in astrocytes. *Glia* 67, 113–124. doi: 10.1002/glia.23531

Paco, S., Hummel, M., Plá, V., Sumoy, L., and Aguado, F. (2016). Cyclic AMP signaling restricts activation and promotes maturation and antioxidant defenses in astrocytes. *BMC Genom.* 17:304. doi: 10.1186/s12864-016-2623-4

Padmashri, R., Suresh, A., Boska, M. D., and Dunaevsky, A. (2015). Motor-skill learning is dependent on astrocytic activity. *Neural Plast.* 2015:938023. doi: 10.1155/2015/938023

Paiva, I., Carvalho, K., Santos, P., Cellai, L., Pavlou, M. A. S., Jain, G., et al. (2019). A2A R-induced transcriptional deregulation in astrocytes: an *in vitro* study. *Glia* 67, 2329–2342. doi: 10.1002/glia.23688

Palasz, E., Wysocka, A., Gasiorowska, A., Chalimoniuk, M., Niewiadomski, W., and Niewiadomska, G. (2020). BDNF as a promising therapeutic agent in Parkinson's disease. *Int. J. Mol. Sci.* 21:1170. doi: 10.3390/ijms21031170

Palygin, O., Lalo, U., and Pankratov, Y. (2011). Distinct pharmacological and functional properties of NMDA receptors in mouse cortical astrocytes. *Br. J. Pharmacol.* 163, 1755–1766. doi: 10.1111/j.1476-5381.2011.01374.x

Palygin, O., Lalo, U., Verkhratsky, A., and Pankratov, Y. (2010). Ionotropic NMDA and P2X1/5 receptors mediate synaptically induced Ca²⁺ signalling in cortical astrocytes. *Cell Calcium* 48, 225–231. doi: 10.1016/j.ceca.2010.09.004

Panatier, A., Vallée, J., Haber, M., Murai, K. K., Lacaille, J.-C., and Robitaille, R. (2011). Astrocytes are endogenous regulators of basal transmission at central synapses. *Cell* 146, 785–798. doi: 10.1016/j.cell.2011.07.022

Pankratov, Y., and Lalo, U. (2015). Role for astroglial α1-adrenoreceptors in gliotransmission and control of synaptic plasticity in the neocortex. *Front. Cell. Neurosci.* 9:230. doi: 10.3389/fncel.2015.00230

Papouin, T., Dunphy, J., Tolman, M., Dineley, K. T., and Haydon, P. G. (2017). Septal cholinergic neuromodulation tunes the astrocyte-dependent gating of hippocampal NMDA receptors to wakefulness. *Neuron* 94, 840-854.e7. doi: 10.1016/j.neuron.2017.04.021

Pekny, M., Pekna, M., Messing, A., Steinhäuser, C., Lee, J.-M., Parpura, V., et al. (2016). Astrocytes: a central element in neurological diseases. *Acta Neuropathol.* 131, 323–345. doi: 10.1007/s00401-015-1513-1

Peng, L., and Huang, J. (2012). Astrocytic 5-HT(2B) receptor as *in vitro* and *in vivo* target of SSRIs. *Recent Pat. CNS Drug Discov.* 7, 243–253. doi: 10.2174/157488912803252078

Perez-Alvarez, A., Navarrete, M., Covelo, A., Martin, E. D., and Araque, A. (2014). Structural and functional plasticity of astrocyte processes

and dendritic spine interactions. *J. Neurosci.* 34, 12738–12744. doi: 10.1523/JNEUROSCI.2401-14.2014

Petravicz, J., Boyt, K. M., and McCarthy, K. D. (2014). Astrocyte IP3R2-dependent Ca^{2+} signaling is not a major modulator of neuronal pathways governing behavior. *Front. Behav. Neurosci.* 8:384. doi: 10.3389/fnbeh.2014.00384

Petravicz, J., Fiacco, T. A., and McCarthy, K. D. (2008). Loss of IP3 receptor-dependent Ca^{2+} increases in hippocampal astrocytes does not affect baseline CA1 pyramidal neuron synaptic activity. *J. Neurosci.* 28, 4967–4973. doi: 10.1523/JNEUROSCI.5572-07.2008

Pham, C., Hérault, K., Oheim, M., Maldera, S., Vialou, V., Cauli, B., et al. (2021). Astrocytes respond to a neurotoxic Aβ fragment with state-dependent Ca^{2+} alteration and multiphasic transmitter release. *Acta Neuropathol. Commun.* 9:44. doi: 10.1186/s40478-021-01146-1

Pöyhönen, S., Er, S., Domanskyi, A., and Airavaara, M. (2019). Effects of neurotrophic factors in glial cells in the central nervous system: expression and properties in neurodegeneration and injury. *Front. Physiol.* 10:486. doi: 10.3389/fphys.2019.00486

Ramos, B. P., and Arnsten, A. F. T. (2007). Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacol. Ther.* 113, 523–536. doi: 10.1016/j.pharmthera.2006.11.006

Raskin, J., Cummings, J., Hardy, J., Schuh, K., and Dean, R. A. (2015). Neurobiology of Alzheimer's disease: integrated molecular, physiological, anatomical, biomarker, and cognitive dimensions. *Curr. Alzheimer's Res.* 12, 712–722. doi: 10.2174/1567205012666150701103107

Reeves, A. M. B., Shigetomi, E., and Khakh, B. S. (2011). Bulk loading of calcium indicator dyes to study astrocyte physiology: key limitations and improvements using morphological maps. *J. Neurosci.* 31, 9353–9358. doi: 10.1523/JNEUROSCI.0127-11.2011

Requardt, R. P., Wilhelm, F., Rillich, J., Winkler, U., and Hirrlinger, J. (2010). The biphasic NAD(P)H fluorescence response of astrocytes to dopamine reflects the metabolic actions of oxidative phosphorylation and glycolysis. *J. Neurochem.* 115, 483–492. doi: 10.1111/j.1471-4159.2010.06940.x

Reuschlein, A.-K., Jakobsen, E., Mertz, C., and Bak, L. K. (2019). Aspects of astrocytic cAMP signaling with an emphasis on the putative power of compartmentalized signals in health and disease. *Glia* 67, 1625–1636. doi: 10.1002/glia.23622

Robertson, J. M. (2018). The gliocentric brain. *Int. J. Mol. Sci.* 19:3033. doi: 10.3390/ijms19103033

Rodríguez-Matellán, A., Avila, J., and Hernández, F. (2020). Overexpression of GSK-3β in adult tet-OFF GSK-3β transgenic mice, and not during embryonic or postnatal development, induces tau phosphorylation, neurodegeneration and learning deficits. *Front. Mol. Neurosci.* 13:175. doi: 10.3389/fnmol.2020.561470

Rodríguez-Prados, M., Rojo-Ruiz, J., García-Sancho, J., and Alonso, M. T. (2020). Direct monitoring of ER Ca^{2+} dynamics reveals that Ca^{2+} entry induces ER-Ca^{2+} release in astrocytes. *Pflugers Arch.* 472, 439–448. doi: 10.1007/s00424-020-02364-7

Rose, C. R., Ziemens, D., and Verkhratsky, A. (2020). On the special role of NCX in astrocytes: translating Na+-transients into intracellular Ca^{2+} signals. *Cell Calcium* 86:102154. doi: 10.1016/j.ceca.2019.102154

Rossello, X., Igbavboa, U., Weisman, G. A., Sun, G. Y., and Wood, W. G. (2012). AP-2β regulates amyloid beta-protein stimulation of apolipoprotein E transcription in astrocytes. *Brain Res.* 1444, 87–95. doi: 10.1016/j.brainres.2012.01.017

Santello, M., Bezzi, P., and Volterra, A. (2011). TNFα controls glutamatergic gliotransmission in the hippocampal dentate gyrus. *Neuron* 69, 988–1001. doi: 10.1016/j.neuron.2011.02.003

Scemes, E., and Giaume, C. (2006). Astrocyte calcium waves. *Glia* 54, 716–725. doi: 10.1002/glia.20374

Schmid, A., Meili, D., and Salathe, M. (2014). Soluble adenylyl cyclase in health and disease. *Biochim. Biophys. Acta* 1842, 2584–2592. doi: 10.1016/j.bbadis.2014.07.010

Scott, J. D., and Santana, L. F. (2010). A-kinase anchoring proteins: getting to the heart of the matter. *Circulation* 121, 1264–1271. doi: 10.1161/CIRCULATIONAHA.109.896357

Semyanov, A., Henneberger, C., and Agarwal, A. (2020). Making sense of astrocytic calcium signals — from acquisition to interpretation. *Nat. Rev. Neurosci.* 21, 551–564. doi: 10.1038/s41583-020-0361-8

Shanmughapriya, S., Rajan, S., Hoffman, N. E., Zhang, X., Guo, S., Kolesar, J. E., et al. (2015). Ca^{2+} signals regulate mitochondrial metabolism by stimulating CREB-mediated expression of the mitochondrial Ca^{2+} uniporter gene mcu. *Sci. Signal* 8:ra23. doi: 10.1126/scisignal.2005673

Sharma, A., Kazim, S. F., Larson, C. S., Ramakrishnan, A., Gray, J. D., McEwen, B. S., et al. (2019). Divergent roles of astrocytic vs. neuronal EAAT2 deficiency on cognition and overlap with aging and Alzheimer's molecular signatures. *Proc. Natl. Acad. Sci. U. S. A.* 116, 21800–21811. doi: 10.1073/pnas.1903566116

Sherwood, M. W., Arizono, M., Hisatsune, C., Bannai, H., Ebisui, E., Sherwood, J. L., et al. (2017). Astrocytic IP3 Rs: contribution to Ca^{2+} signalling and hippocampal LTP. *Glia* 65, 502–513. doi: 10.1002/glia.23107

Sherwood, M. W., Arizono, M., Panatier, A., Mikoshiba, K., and Oliet, S. H. R. (2021). Astrocytic IP3Rs: beyond IP3R2. *Front. Cell Neurosci.* 15:695817. doi: 10.3389/fncel.2021.695817

Shigetomi, E., Jackson-Weaver, O., Huckstepp, R. T., O'Dell, T. J., and Khakh, B. S. (2013). TRPA1 channels are regulators of astrocyte basal calcium levels and long-term potentiation *via* constitutive d-serine release. *J. Neurosci.* 33, 10143–10153. doi: 10.1523/JNEUROSCI.5779-12.2013

Shigetomi, E., Tong, X., Kwan, K. Y., Corey, D. P., and Khakh, B. S. (2011). TRPA1 channels regulate astrocyte resting calcium and inhibitory synapse efficacy through GAT-3. *Nat. Neurosci.* 15, 70–80. doi: 10.1038/nn.3000

Singh, P. K., Chen, Z.-L., Ghosh, D., Strickland, S., and Norris, E. H. (2020). Increased plasma bradykinin level is associated with cognitive impairment in Alzheimer's patients. *Neurobiol. Dis.* 139:104833. doi: 10.1016/j.nbd.2020.104833

Skowrońska, K., Kozłowska, H., and Albrecht, J. (2020). Neuron-derived factors negatively modulate ryanodine receptor-mediated calcium release in cultured mouse astrocytes. *Cell Calcium* 92:102304. doi: 10.1016/j.ceca.2020.102304

Song, Y., and Gunnarson, E. (2012). Potassium dependent regulation of astrocyte water permeability is mediated by cAMP signaling. *PLoS ONE* 7:e34936. doi: 10.1371/journal.pone.0034936

Steeland, S., Gorlé, N., Vandendriessche, C., Balusu, S., Brkic, M., Van Cauwenberghe, C., et al. (2018). Counteracting the effects of TNF receptor-1 has therapeutic potential in Alzheimer's disease. *EMBO Mol. Med.* 10:e8300. doi: 10.15252/emmm.201708300

Stenovec, M. (2021). Ketamine alters functional plasticity of astroglia: an implication for antidepressant effect. *Life* 11:573. doi: 10.3390/life11060573

Stenovec, M., Li, B., Verkhratsky, A., and Zorec, R. (2020). Astrocytes in rapid ketamine antidepressant action. *Neuropharmacology* 173:108158. doi: 10.1016/j.neuropharm.2020.108158

Stephen, T.-L., Gupta-Agarwal, S., and Kittler, J. T. (2014). Mitochondrial dynamics in astrocytes. *Biochem. Soc. Trans.* 42, 1302–1310. doi: 10.1042/BST20140乙337

Su, Z., Leszczyniecka, M., Kang, D., Sarkar, D., Chao, W., Volsky, D. J., et al. (2003). Insights into glutamate transport regulation in human astrocytes: cloning of the promoter for excitatory amino acid transporter 2 (EAAT2). *Proc. Natl. Acad. Sci. U. S. A.* 100, 1955–1960. doi: 10.1073/pnas.0136555100

Sun, H., Liang, R., Yang, B., Zhou, Y., Liu, M., Fang, F., et al. (2016). Aquaporin-4 mediates communication between astrocyte and microglia: implications of neuroinflammation in experimental Parkinson's disease. *Neuroscience* 317, 65–75. doi: 10.1016/j.neuroscience.2016.01.003

Sun, W., McConnell, E., Pare, J.-F., Xu, Q., Chen, M., Peng, W., et al. (2013). Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. *Science* 339, 197–200. doi: 10.1126/science.1226740

Takata, N., Mishima, T., Hisatsune, C., Nagai, T., Ebisui, E., Mikoshiba, K., et al. (2011). Astrocyte calcium signaling transforms cholinergic modulation to cortical plasticity *in vivo*. *J. Neurosci.* 31, 18155–18165. doi: 10.1523/JNEUROSCI.5289-11.2011

Taylor, C. W. (2017). Regulation of IP3 receptors by cyclic AMP. *Cell Calcium* 63, 48–52. doi: 10.1016/j.ceca.2016.10.005

Tenner, B., Getz, M., Ross, B., Ohadi, D., Bohrer, C. H., Greenwald, E., et al. (2020). Spatially compartmentalized phase regulation of a Ca^{2+}-cAMP-PKA oscillatory circuit. *eLife* 9:e55013. doi: 10.7554/eLife.55013.sa2

Tresguerres, M., Levin, L. R., and Buck, J. (2011). Intracellular cAMP signaling by soluble adenylyl cyclase. *Kidney Int.* 79, 1277–1288. doi: 10.1038/ki.2011.95

Turunen, T., and Koskelainen, A. (2021). Functional modulation of phosphodiesterase-6 by calcium in mouse rod photoreceptors. *Sci. Rep.* 11:8938. doi: 10.1038/s41598-021-88140-8

Ujita, S., Sasaki, T., Asada, A., Funayama, K., Gao, M., Mikoshiba, K., et al. (2017). cAMP-dependent calcium oscillations of astrocytes: an implication for pathology. *Cerebr. Cortex* 27, 1602–1614. doi: 10.1093/cercor/bhv310

Valenza, M., Facchinetti, R., Steardo, L., and Scuderi, C. (2020). Altered waste disposal system in aging and Alzheimer's disease: focus on astrocytic aquaporin-4. *Front. Pharmacol.* 10:1656. doi: 10.3389/fphar.2019.01656

Vandecaetsbeek, I., Vangheluwe, P., Raeymaekers, L., Wuytack, F., and Vanoevelen, J. (2011). The Ca^{2+} pumps of the endoplasmic reticulum and golgi apparatus. *Cold Spring Harb. Perspect. Biol.* 3:a004184. doi: 10.1101/cshperspect.a004184

Veinbergs, I., Everson, A., Sagara, Y., and Masliah, E. (2002). Neurotoxic effects of apolipoprotein E4 are mediated *via* dysregulation of calcium homeostasis. *J. Neurosci. Res.* 67, 379–387. doi: 10.1002/jnr.10138

Velebit, J., Horvat, A., Smoli,č, T., Prpar Mihevc, S., Rogelj, B., Zorec, R., et al. (2020). Astrocytes with TDP-43 inclusions exhibit reduced noradrenergic cAMP and Ca2+ signaling and dysregulated cell metabolism. *Sci. Rep.* 10:6003. doi: 10.1038/s41598-020-62864-5

Verkhratsky, A., and Nedergaard, M. (2018). Physiology of astroglia. *Physiol. Rev.* 98, 239–389. doi: 10.1152/physrev.00042.2016

Verkhratsky, A., Zorec, R., Rodríguez, J. J., and Parpura, V. (2016). Astroglia dynamics in ageing and Alzheimer's disease. *Curr. Opin. Pharmacol.* 26, 74–79. doi: 10.1016/j.coph.2015.09.011

von Bartheld, C. S., Bahney, J., and Herculano-Houzel, S. (2016). The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. *J. Comp. Neurol.* 524, 3865–3895. doi: 10.1002/cne.24040

Wild, A. R., and Dell'Acqua, M. L. (2018). Potential for therapeutic targeting of AKAP signaling complexes in nervous system disorders. *Pharmacol. Ther.* 185, 99–121. doi: 10.1016/j.pharmthera.2017.12.004

Willoughby, D., Everett, K. L., Halls, M. L., Pacheco, J., Skroblin, P., Vaca, L., et al. (2012a). Direct binding between Orai1 and AC8 mediates dynamic interplay between Ca^{2+} and cAMP signaling. *Sci. Signal* 5:ra29. doi: 10.1126/scisignal.2002299

Willoughby, D., Halls, M. L., Everett, K. L., Ciruela, A., Skroblin, P., Klussmann, E., et al. (2012b). A key phosphorylation site in AC8 mediates regulation of Ca2+-dependent cAMP dynamics by an AC8–AKAP79–PKA signalling complex. *J. Cell Sci.* 125, 5850–5859. doi: 10.1242/jcs.111427

Xin, W., and Bonci, A. (2018). Functional astrocyte heterogeneity and implications for their role in shaping neurotransmission. *Front. Cell Neurosci.* 12:141. doi: 10.3389/fncel.2018.00141

Xin, W., Schuebel, K. E., Jair, K., Cimbro, R., De Biase, L. M., Goldman, D., et al. (2019). Ventral midbrain astrocytes display unique physiological features and sensitivity to dopamine D2 receptor signaling. *Neuropsychopharmacology* 44, 344–355. doi: 10.1038/s41386-018-0151-4

Xu, Z., Xiao, N., Chen, Y., Huang, H., Marshall, C., Gao, J., et al. (2015). Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Aβ accumulation and memory deficits. *Mol. Neurodegener.* 10:58. doi: 10.1186/s13024-015-0056-1

Yu, J. T., Tan, L., and Hardy, J. (2014). Apolipoprotein E in Alzheimer's disease: an update. *Annu. Rev. Neurosci.* 37, 79–100. doi: 10.1146/annurev-neuro-071013-014300

Zeinstra, E. M., Wilczak, N., Wilschut, J. C., Glazenburg, L., Chesik, D., Kroese, F. G. M., et al. (2006). 5HT4 agonists inhibit interferon-γ-induced MHC class II and B7 costimulatory molecules expression on cultured astrocytes. *J. Neuroimmunol.* 179, 191–195. doi: 10.1016/j.jneuroim.2006.06.012

Zhang, Y., Meng, X., Jiao, Z., Liu, Y., Zhang, X., and Qu, S. (2020). Generation of a novel mouse model of Parkinson's disease *via* targeted knockdown of glutamate transporter GLT-1 in the Substantia Nigra. *ACS Chem. Neurosci.* 11, 406–417. doi: 10.1021/acschemneuro.9b00609

Zhao, N., Attrebi, O. N., Ren, Y., Qiao, W., Sonustun, B., Martens, Y. A., et al. (2020). APOE4 exacerbates α-synuclein pathology and related toxicity independent of amyloid. *Sci. Transl. Med.* 12:eaay1809. doi: 10.1126/scitranslmed.aay1809

Zhou, Z., Okamoto, K., Onodera, J., Hiragi, T., Andoh, M., Ikawa, M., et al. (2021). Astrocytic cAMP modulates memory *via* synaptic plasticity. *Proc. Natl. Acad. Sci. U. S. A.* 118:e2016584118. doi: 10.1073/pnas.2016584118

Zumkehr, J., Rodriguez-Ortiz, C. J., Cheng, D., Kieu, Z., Wai, T., Hawkins, C., et al. (2015). Ceftriaxone ameliorates tau pathology and cognitive decline *via* restoration of glial glutamate transporter in a mouse model of Alzheimer's disease. *Neurobiol. Aging* 36, 2260–2271. doi: 10.1016/j.neurobiolaging.2015.04.005