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Astrocytes as new targets to improve cognitive functions

Glenn Dallérac *, Nathalie Rouach *

Neuroglial Interactions in Cerebral Physiopathology, Center for Interdisciplinary Research in Biology, Collège de France, Centre National de la Recherche Scientifique UMR 7241, Institut National de la Santé et de la Recherche Médicale U1050, Labex Memolife, PSL Research University, Paris, France

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ABSTRACT

Astrocytes are now viewed as key elements of brain wiring as well as neuronal communication. Indeed, they not only bridge the gap between metabolic supplies by blood vessels and neurons, but also allow fine control of neurotransmission by providing appropriate signaling molecules and insulation through a tight enwrapping of synapses. Recognition that astroglia is essential to neuronal communication is nevertheless fairly recent and the large body of evidence dissecting such role has focused on the synaptic level by identifying neuro- and gliotransmitters uptaken and released at synaptic or extrasynaptic sites. Yet, more integrated research deciphering the impact of astroglial functions on neuronal network activity have led to the reasonable assumption that the role of astrocytes in supervising synaptic activity translates in influencing neuronal processing and cognitive functions. Several investigations using recent genetic tools now support this notion by showing that inactivating or boosting astroglial function directly affects cognitive abilities. Accordingly, brain diseases resulting in impaired cognitive functions have seen their physiopathological mechanisms revisited in light of this primary protagonist of brain processing. We here provide a review of the current knowledge on the role of astrocytes in cognition and in several brain diseases including neurodegenerative disorders, psychiatric illnesses, as well as other conditions such as epilepsy. Potential astroglial therapeutic targets are also discussed.

Contents

Abbreviations: AAV, adeno-associated viral vectors; ALS, amyotrophic lateral sclerosis; ApoE, apolipoprotein E; AQP4, aquaporin-4; AD, Alzheimer's disease; ASD, autism spectrum disorders; BBB, blood brain barrier; BD, bipolar disorder; Ca^{2+}, calcium; CALHM1, calcium homeostasis modulator 1; CUS, chronic unpredictable stress; Cx, connexin; DAAO, D-amino acid oxidase; DBS, deep brain stimulation; Disc1, disrupted-in-schizophrenia; EAAT2, excitatory amino acid transporter; ECS, electroconvulsive stimulation; EC-SOD, extracellular SOD; FXS, Fragile X syndrome; GFAP, glial fibrillary acidic protein; GJ, gap junction channel; GLT, glutamate transporter; GPCs, glial progenitor cells; GPx, glutathione peroxidase; GR, glucocorticoid receptors; GST, glutathione-S-transferase; HD, Huntington's disease; HO-1, heme oxygenase 1; IP3R2, inositol triphosphate receptor 2; K^+, potassium; Kir4.1, inward rectifier K^+ channel 4.1; L-AAA, L-α-aminoadipate; LDH, lactate dehydrogenase enzyme; MCT, monocarboxylate transporters; LTD, long-term depression; LTP, long-term potentiation; MD, major depression; MeCP2, methyl-CpG-binding protein-2; MSNs, medium spiny neurons; mPFC, medial prefrontal cortex; NAAMFs, neuronal activity associated magnetic fields; NCX, sodium/calcium exchangers; NFAT, nuclear factor of activated T-cells; NG2, nerve-glia antigen 2; NO, nitric oxide; NOR, novel object recognition; NT-3, neurotrophin-3; O_2^-, superoxide; OHC, hydroxycholesterol; $ONOO^-$, peroxynitrite; PD, Parkinson's disease; PLC, phospholipase C; RTT, Rett syndrome; ROS, reactive oxygen species; SOC, store operated channels; SOD, superoxide dismutase; SWA, slow wave sleep activity; TeNT, tetanus neurotoxin; TNFα, tumor necrosis factor α; TMS, trans-magnetic stimulation; TRPC, transient potential channels; UPS, ubiquitin-proteasome degradation system; VGCC, voltage-gated calcium channels.

* Corresponding authors.
E-mail addresses: glenn.dallerac@college-de-france.fr (G. Dallérac), nathalie.rouach@college-de-france.fr (N. Rouach).

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1. Introduction

Brain information processing is traditionally perceived as a neuronal performance. Recent data nevertheless point to an important role of astrocytes in behavioral states, cerebral pathologies and cognitive functions, including learning and memory (Fields et al., 2013; Halassa and Haydon, 2010; Halassa et al., 2009; Pannasch and Rouach, 2013; Pereira and Furlan, 2010; Scuderi et al., 2013). This explains the increasing interest within the neuroscience community, in the relatively underexplored area of neuroglial interactions. Astrocytes are indeed now viewed as crucial elements of the brain circuitry which regulate the formation, maturation, activity and plasticity of neuronal networks involved in processing of sensory, emotional or cognitive information. Astrocytes not only modulate neuronal excitability, synaptic activity and plasticity, but also rhythm generation and neuronal network patterns (Dallérac et al., 2013; Fellin et al., 2009; Lee et al., 2014; Sasaki et al., 2014; Wang et al., 2012a). In particular, astrocytes have been reported to contribute to slow oscillations (Fellin et al., 2009; Poskanzer and Yuste, 2011), gamma oscillations (Lee et al., 2014) and sleep (Halassa and Haydon, 2010; Halassa et al., 2009), in part through modulations of excitatory synaptic activity by releasing gliotransmitters such as glutamate or adenosine. Indeed, numerous astroglial factors and properties are thought to regulate neurotransmission and plasticity. How do astrocytes operate?

Astrocytes are dynamic signaling elements of the brain (Bernardinelli et al., 2014; Haber et al., 2006). They can sense neuronal inputs through membrane ion channels, transporters and receptors. They can also respond by transduction pathways, involving for instance calcium (Ca^{2+}) signaling, and modulate in turn adjacent neuronal elements by various mechanisms, including uptake or release of neuroactive factors, contact-mediated signaling or plastic physical coverage of neurons (Araque et al., 2014; Bernardinelli et al., 2014; Clarke and Barres, 2013; Dallérac et al., 2013). In particular, astrocytes can regulate the formation and stability of synapses, receptor trafficking and the moment-to-moment synaptic activity by releasing for instance gliotransmitters such as glutamate, ATP or D-serine, acting on pre- or postsynaptic receptors (Araque et al., 2014). They can also modify efficacy of synapses by controlling extracellular glutamate concentration *via* clearance through their transporters (Dallérac et al., 2013; Oliet et al., 2001; Pannasch et al., 2014, 2011) or by changing the extracellular space volume as a result of plastic physical coverage of neurons (Piet et al., 2004). However, comprehensive molecular description of such regulations, their occurrence and impact during physiological or pathological conditions remains to be further described. Indeed, deciphering the specific and direct contribution of astrocytes to neuronal activity and cognitive functions is challenging, due to the scarcity of tools interfering selectively with astroglial pathways. In fact, a major technical limit to the study of neuroglial interactions is to act selectively on astrocytes, as they possess many receptors, transporters and transmitters identical to the neuronal ones. Consequently, elucidating the nature, molecular mechanisms and significance of astroglial contribution to cognitive functions represents an emerging and promising field of research. Unraveling how astrocytes control the activity of neuronal circuits is important, not only to advance our comprehension of cognitive function, but also to provide a novel framework for identifying dysfunction underlying neurological disorders as well as alternative therapeutic targets. Indeed astrocyte degeneration has been described in several pathological conditions such as depressive disorders or dementia (Rodriguez et al., 2009). In particular, reactive astrogliosis and dystrophy accompany these diseases, events which may directly contribute to early alterations in synaptic transmission and cognitive processes that occur prior to neurodegeneration. In addition, astroglial cell loss described at later stages of several neurodegenerative diseases is also likely to indirectly alter neuronal function and survival by compromising glial physiological support and modulation of neuronal activity, and may thereby accelerate the course of pathologies (Rossi et al., 2008; Rodriguez et al., 2009; Martorana et al., 2012).

Here, we review recent findings on the role of astrocytes in cognitive functions, focusing on their novel neurophysiological and behavioral roles, as well as the experimental approaches used. In addition, future directions and prospects in unraveling the physiological and pathological relevance of astrocytes in cognitive functions are also discussed.

2. Astroglial contribution to cognitive functions

Evolutionary advanced brains are endowed with information processing abilities that enable them to perform decision making, planning, learning as well as storage of memories. These highly developed cognitive functions have recently been defined as the competence of "thinking and knowing" (Heyes, 2012). The physiology behind such complex processes has been investigated at different levels of complexity, from the interactions between brain areas to specific neuronal network activities and involvement of synaptic plasticity. Research in cell physiology unveiling astrocytes as active partners of neurotransmission processes has recently drawn attention to the role that astroglial networks undertake in higher integrated brain functions. Indeed, a wealth of investigations now shows that astrocytes regulate processes considered as cellular substrates for handling information and memory formation. Basal synaptic transmission and synaptic plasticity, which are believed to be at the root of information processing and mnesic function, depend on the astrocytes ability to control extracellular levels of neurotransmitters and ions, in

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particular the glutamate and potassium (K^+) released during excitatory neurotransmission and neuronal activity (Dallérac et al., 2013; Sibille et al., 2014). Neuroactive molecules are also released from astrocytes through various mechanisms, namely Ca^{2+}-dependent or -independent vesicular or non-vesicular liberations. These so-called gliotransmitters also influence synaptic function and can display excitatory as well as inhibitory effects depending on the released factor, the brain region and the developmental stage considered. Primary examples involve the regulation of long-term potentiation (LTP) and long-term depression (LTD) by astroglial glutamate (Park et al., 2015), D-serine (Henneberger et al., 2010; Mothet et al., 2015; Panatier et al., 2006; Papouin et al., 2012; Yang et al., 2003), ATP (Chen et al., 2013; Lee et al., 2013a; Rasooli-Nejad et al., 2014) and adenosine (Fujii et al., 2014; Pascual et al., 2005). Recent work also reports that astroglial responses to neuronal activity show several forms of plasticity including glutamate and K^+ uptake as well as Ca^{2+} signaling (Sibille et al., 2015a,b, 2014), highlighting the active role played by astrocytes in information processing.

2.1. Astrocytes and cognition: early clues and correlative data

Insofar as brain oscillations are regarded as physiological correlates of cognitive functions and are driven by the fine interactions between excitation and inhibition, the reasonable assumption has long been that the roles of astrocytes in modulating synaptic and neuronal activities translate in influencing cognitive processes. However, convincing experimental evidence showing such integrated function are only recent. Early investigations have pointed out a possible role of astrocyte metabolism in passive avoidance learning of chicks. Injection of glial metabolic blockers such as fluoroacetate, fluorocitrate (Hertz et al., 1996), methionine sulfoximine (Gibbs et al., 1996), or ethacrynic acid (Gibbs, 1991) either before or after the one-trial passive avoidance learning session indeed impairs the intermediate stage of memory formation (Hertz et al., 1996). Similar results were obtained by injecting antisera against the glial proteins S100α/S100β immediately after training of the chicks (O'Dowd et al., 1997). However, the methodologies employed to inhibit astroglia in these studies are nowadays criticized with regard to their specificity (Anlauf and Derouiche, 2013; Steiner et al., 2007; Wenker, 2010). Recent behavioral work in rats similarly indicates that poisoning of medial prefrontal cortex (mPFC) astrocytes with L-α-aminoadipate (L-AAA) impairs mPFC associated cognitive functions, *i.e.* attentional set-shifting, working memory and reversal learning (Lima et al., 2014). However, although L-AAA is a metabolic blocker that primarily affects astrocytes, such targeting only relies on its preferential transport in glia (Huck et al., 1984) and therefore lacks sufficient specificity. Likewise, a mouse model of Alexander's disease presenting a mutation in the gene encoding the astroglial marker glial fibrillary acidic protein (*Gfap*) (Hagemann et al., 2006) shows deficiencies in spatial memory as assessed in the Morris water maze. Yet, such effect is likely attributable to the deficit in adult neurogenesis concomitantly reported as GFAP is also expressed in proliferating progenitors (Hagemann et al., 2013). Correlative data showing activation of astroglial marker and increase in astrocytes density after learning also support the idea that astrocytes are recruited during cognition (Brockett et al., 2015; Gómez-Pinilla et al., 1998; Sampedro-Piquero et al., 2014).

2.2. Role of gliotransmission and metabolic support in cognition

One of the first compelling clues indicating that astrocytes are at play in learning and memory came from the study of Halassa and collaborators showing that the conditional astrocyte selective expression of the SNARE domain of the protein synaptobrevin II (dnSNARE), preventing astroglial vesicular release in mice, impairs sleep and affects memory. Effectively, slow wave sleep activity (SWA; 0.5–4 Hz power spectrum density) is markedly reduced in dnSNARE mice and, as a result, novel object recognition memory defects associated with sleep deprivation is not observed in these mice; interestingly however, novel object recognition (NOR) memory is unaffected in normal conditions (Halassa et al., 2009). It should be noted that the use of dnSNARE mice as an accurate tool to specifically assess the role of vesicular gliotransmission is currently highly debated since it has recently been reported that expression of the dominant negative SNARE transgene also occurs in neurons (Fujita et al., 2014). Using a different mouse model consisting in the inducible conditional expression of a transgene coding for the blocker of vesicular release tetanus neurotoxin (TeNT) in astrocytes, Lee and collaborators reported that fast oscillations in the gamma frequencies (low gamma range, 20–40 Hz) show a significantly reduced power in mice expressing astroglial TeNT in the awake phases but not during sleep (Lee et al., 2014). These results somewhat contrast with the above-mentioned reduction in SWA during sleep of dnSNARE mice (Fellin et al., 2009; Halassa et al., 2009), although the analyzed frequencies differ. Also in contrast with the study of Halassa and collaborators, the reduction in gamma power was here accompanied with deficits in novel recognition memory, indicating that vesicular release in astrocytes is an essential contributor to memory formation and consolidation. Explanation for the discrepancies between results obtained with astroglial TeNT mice *vs* dnSNARE animals may lie in the different methodologies used to generate the transgenic mice with altered astroglial function. Both transgenic lines use the Tet-Off system enabling to turn off expression of the gene of interest (*i.e.* dnSNARE or TeNT) upon the presence of a tetracycline analog such as doxycycline. The TeNT line, in contrast to the dnSNARE, however further controls expression of the TeNT transgene through a cre-lox system and thus requires tamoxifen administration to activate the cre-recombinase and triggers gene expression (Lee et al., 2014). Given the reported side effects of the tamoxifen, including marked disturbances of the digestive system (Huh et al., 2012) and modification of important signaling molecules such as tumor necrosis factor α (TNF α) or Interleukin-1β (IL-1β) (Sun et al., 2013a), it is plausible that non-specific effects of this inducer foster the discrepancies. Another major difference of the two models is the genetically controlled enzymatic approach used in the TeNT line *vs* the dominant negative transgene expressed in dnSNARE mice. Could it be that the tetanus neurotoxin leaks to surrounding neurons or synapses? Although synaptic transmission appears to be normal in TeNT mice (Lee et al., 2014), it is difficult to rule out such possibility. Finally, Fujita and collaborators recently stressed that the GFAP promoter used in both lines would not be specific to astrocyte and would also drive expression of the transgene in neurons (Fujita et al., 2014). Differential results between the lines may thus also originate from unequal "leakage" of transgene expression driven by the broadly used GFAP promoter.

Nevertheless, release of neuromodulators by astrocytes regulating synaptic activity has recently been shown to also involve a non-vesicular liberation by means of connexin hemichannels (Chever et al., 2014). Indeed, inter-astrocytes communication occurs through passage of small cytoplasmic molecules *via* gap junction channels (GJs), each formed by 2 hemichannels, composed of 6 connexin (Cx) proteins (Giaume et al., 2010). When hemichannels are not apposed to form intercellular GJs, they provide a mean of exchange between intra- and extracellular media (Cheung et al., 2014; Giaume et al., 2013). The recently identified physiological role of astroglial hemichannels (formed by Cx43 proteins) provides new lights on the previous finding that

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blocking these channels by infusing specific peptides (TAT-Cx43L2 or GAP27) in the basolateral amygdala affects auditory fear conditioning by selectively impairing memory consolidation, but not short-term memory nor rats behavior and reactivity (Stehberg et al., 2012). Interestingly, this echoes with a recent investigation showing that similar conditioning paradigms results in the retraction of astrocytes from synapses in the lateral amygdala (Ostroff et al., 2014; Fig. 1A–C). Moreover, such regulation may involve connexin proteins as our laboratory identified that removing Cx30 from mouse astrocytes results in the invasion of the synaptic cleft by glial processes, which consequently uptake more glutamate through glutamate transporters (GLT) and thereby downregulate excitatory synaptic transmission (Pannasch et al., 2014; Fig. 1D–I). The opposite phenomenon is thus readily conceivable after learning: retraction of astroglial processes from relevant synapses may be part of morphological changes necessary to sustain memory consolidation. Altogether, these findings therefore indicate that memory formation requires uptake and supply of neuroactive molecules by astrocytes, which clearly involve multiple pathways.

Besides the apparent role of gliotransmission in cognition, neuroglial metabolic coupling, essential to sustain high neuronal demands (Pellerin et al., 2007; Rouach et al., 2008), has been found to play a crucial role in memory consolidation (Suzuki et al., 2011). In the latter study, the authors elegantly show that pharmacological blockade of glycogenolysis, *i.e.* breakdown of the glycogen exclusively stored in astrocytes into glucose, during the early but not later phase of memory storage impairs retention of a simple inhibitory avoidance task. Most interestingly, such impairment could be rescued by lactate, but not glucose administration, indicating that glycogenolysis is the relevant energy source during memory consolidation. Further, blocking lactate transport out of astrocytes or intake into neurons *via* antisense oligonucleotides (directed against astroglial monocarboxylate transporters 4, MCT4 or neuronal MCT2, respectively) in effect blocked memory retention and could be rescued by exogenous lactate administration in the former case (astroglial MCT4 blockade) but not the latter (neuronal MCT2 blockade), thus providing direct evidence for an involvement of the astrocyte-neuron lactate shuttle in memory consolidation. Such results are consistent with previous investigations reporting that astrocyte-derived lactate is necessary for passive avoidance in chicks (Gibbs and Hertz, 2008; Gibbs et al., 2007). Remarkably matching data were also obtained using an alternation task of spatial working memory (Newman et al., 2011), suggesting that the role of astroglial lactate on memory formation is a fundamental need not restricted to one type of memory. Worth mentioning, mice deficient for the astroglial protein aquaporin-4 (AQP4), major player in the regulation of water homeostasis, also display a marked impairment of spatial learning in the Morris water maze (Zhang et al., 2013). This is likely attributable to metabolic abnormalities as AQP4 loss

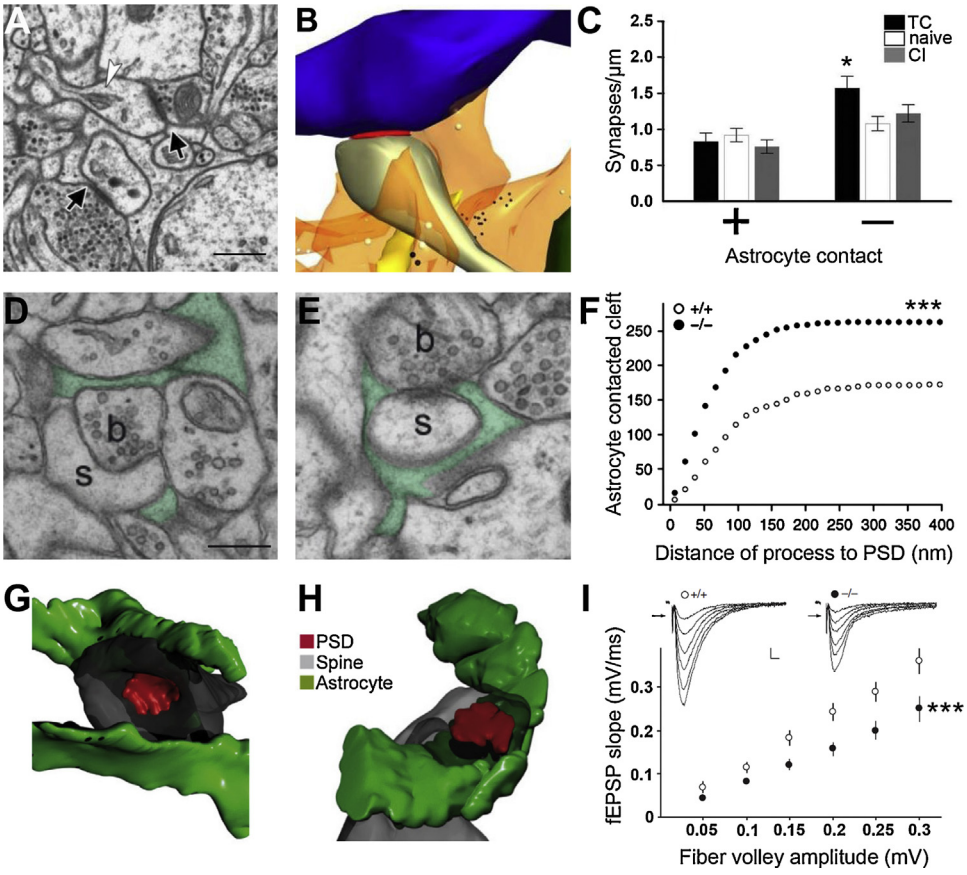

Fig. 1. Regulation of perisynaptic astrocytic processes contact to synapses. (A–C) Aversive conditioning reduces the number of synapses contacted by astrocytes. (A) Electron microscopy micrograph showing contact between astrocytic process and the synaptic cleft (black arrows) at spines with a spine apparatus (white arrowhead). Scale bar: 500 nm. (B) Three-dimensional reconstruction used to quantify morphological parameters of analyzed synapses. (C) Quantification of the number of synapses with or without astrocytic contact after aversive conditioning (TC: threat conditioning) compared to control (Cl) and naive animal. (D–I) The number of hippocampal synapses contacted by astroglial processes and the proximity of the latter to synaptic clefts is regulated by the astroglial protein connexin 30 (Cx30). Astrocytes (green) lacking Cx30 (E, H) come closer to the synaptic cleft than wild-type astrocytes expressing Cx30 (D, G). b: bouton, s: spine. (F) In the absence of Cx30 more synapses are contacted by astrocytes and their processes are markedly closer to the cleft than in wild-type controls. (I) Invasion of the synaptic cleft by astroglial processes results in the uptake of synaptic glutamate leading to a reduced synaptic transmission, as illustrated here using extracellular field recordings of excitatory postsynaptic potentials.
Adapted with permission from Ostroff et al. (2014) (A–C) and Pannasch et al. (2014) (D–I).

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provokes an edema of astroglial endfeet and, as a result, compromise blood brain barrier integrity (Zhou et al., 2008).

2.3. Do astrocytes underlie cognitive performance?

Most interestingly, Han and collaborators engrafted mice with human glial progenitor cells (GPCs), resulting in the replacement of the majority of forebrain glia (Han et al., 2013). Astrocytes derived from human GPCs show larger and more complex features than the endogenous mouse ones and this differentiation occurs in a cell autonomous fashion. "Human astrocytes" however integrate well in the mouse brain and confer advantages to the chimeric brain. Indeed, Ca^{2+} signaling was found to propagate 3-fold faster in astrocytes derived from the transplant and this is associated with an increase in basal transmission and synaptic plasticity, as assessed by inducing long-term potentiation in acute hippocampal slices. Strikingly, such changes behaviorally translate in enhanced cognitive abilities as tested in the Barnes maze and object location spatial memory tasks, as well as contextual and tone fear conditioning. Authors indicate that transferrin immunostaining failed to reveal oligodentrocytes derived from human GPC, meaning that most of the latter differentiated into astrocytes as suggested by previous report on the fate of human GPC transplanted in a normal mouse brain (Sim et al., 2009). Thus, results obtained by assessing these chimeric mice strongly support the astrocentric view of cognitive abilities by highlighting the fact that the sole replacement of astrocytes in a murine brain with an "enhanced human astroglia" is sufficient to improve cognition and plasticity. Based on the observation that protoplasmic astrocytes form polyhedral tesselating domains that greatly complexifies with evolution, the astrocentric hypothesis indeed proposes that cognition, and even consciousness, are supported by the seamless three-dimensional matrix formed by astroglial networks (Robertson, 2013, 2002). Of course, the aptitude of sustaining an engram is certainly not a solely glial feature and most probably resides in the interaction between neuronal and astrocytic networks. Yet the body of work showing that astrocytes are key elements in complex brain processes rightly promote the role of these brain cells to the level of that of neurons.

Finally, quite aside from the classical neurochemical view of brain functioning, interesting alternative hypotheses on the role of astrocytes in memory formation have emerged by considering the biophysical properties of neuronal and astroglial matrices. Notably, analyses of the electromagnetic neuronal and glial activities led to the proposal that the intensity, frequency and spatial orientation of time-varying neuronal activity associated magnetic fields (NAAMFs) modulate the intensity and orientation of the static magnetic fields in neighboring astrocytes (Banaclocha, 2007). Astroglial magnetic fields are here hypothesized to influence neuronal activity on a large scale and its static nature would allow for long-term storage of memory. This integrated view of neuro-glial interaction is supported by a cellular automata modeling investigation showing that neurons using astrocytes as information sink is indeed a viable system and that this information would remain available to neurons for extended periods of time. Interestingly however, the study predicts that such storage system does not rely on physically binding information to any specific structure such as a synapse, but instead relies on ion channels expression and distribution as well as the syncitium properties of astroglial networks (Caudle, 2006). The astrocentric vision of memory storage therefore appears to be incompatible with the concept of a tripartite synapse being at the root of cognition. Such conclusion suggests that the latter hypothesis is rather extreme and that more comprehensive modeling investigations, encompassing synaptic plasticity mechanisms and synaptic assemblies, are needed in the field of neuroglial interactions and cognition.

3. Neuroglial interactions in neurodegenerative diseases

The evident hallmark of diseases falling into this category is the degeneration and eventual loss of the sufferer neurons. One persistent question though, is why certain neurons die in certain brain regions while others do not. In Huntington's disease (HD), neuronal loss mainly concerns medium spiny neurons (MSNs) of the striatum (Vonsattel et al., 1985) while midbrain dopaminergic neurons are exclusively affected in Parkinson's disease (PD) and hippocampal cells are primary targets of Alzheimer's disease (AD) (Thompson and Vinters, 2012). The etiology of such selective neuronal death is likely to differ between different neurodegenerative disorders. Yet one important consideration that has long been ignored in all these diseases is the cellular environment influencing dying or surviving neurons. A better understanding of how changes in neuroglial interactions alter brain activity has recently emerged and is starting to bring lights to the conundrum. How neurons die has been subject to several hypotheses in different neurodegenerative disorders and mainly concerns excitotoxicity, oxidative damages and proteins aggregation (Fig. 2).

3.1. Excitotoxicity

Excitotoxicity is one of the major mechanisms put forward in HD, PD and AD (Gardoni and Di Luca, 2006). It corresponds to the triggering of apoptotic programmed cell death due to abnormally high neuronal activation. Given that in many instances astrocytes actually bridle neurotransmission, loss of such function could unleash aberrant activity. One important insight described in this regard is the downregulation of GLT1 (Fig. 2A), a transporter enabling clearance of glutamate from excitatory synapses. This appears to be a common feature of neurodegenerative disorders as it was found in HD (Behrens et al., 2002; Liévens et al., 2001), AD (Cassano et al., 2012) and downregulating nigral excitatory amino-acid transporters recapitulated the phenotype of PD mouse models (Assous et al., 2014). Most interestingly, deficient GLT1 expression in amyotrophic lateral sclerosis (ALS), a severe condition caused by degeneration of motor neurons, has also been proposed to be an important neuroglial factor promoting excitotoxicity (Howland et al., 2002; Pardo et al., 2006; Rothstein et al., 1992). In support of such hypothesis, abnormally high glutamate levels have been reported in the cerebro-spinal fluid of ALS patients (Rothstein et al., 1990) and administration of translational activators such as the Beta-lactam antibiotic Ceftriaxone offered neuroprotection (Rothstein et al., 2005). Similarly, up-regulation of GLT1 expression in the severe R6/2 mouse model of HD was sufficient to normalize striatal glutamate uptake and attenuate pathological phenotype (Miller et al., 2008). Treated mice indeed showed less hind limb clasping, a typical motor phenotype upon tail suspension associated with R6 mouse models, and recovered normal behavior as assessed in the open field and plus-maze. This suggests that targeting re-expression of GLT1 in astroglia could alleviate cognitive symptoms and neuronal death in neurodegenerative disorders. Supporting this notion, it was found that the beneficial effect of a classical neuroprotective drug, riluzole, is actually attributable to the up-regulation of GLT1 expression in astrocytes (Fumagalli et al., 2008).

Furthermore, the signal triggering excitotoxic death is known to be a high influx of Ca^{2+} ensuing from overactivation of ionotropic glutamate receptors (Arundine and Tymianski, 2003). Astrocytes play an important role in Ca^{2+} homeostasis, a function altered in HD, PD and AD (Heeman et al., 2011; Kuchibhotla et al., 2008; Lim et al., 2008; Zhang et al., 2008). An increase in extracellular Ca^{2+} concentration indeed strengthens the driving force for Ca^{2+} influx into neurons during synaptic transmission, and thus favors excitotoxicity. Regulation of Ca^{2+} concentrations relies on several

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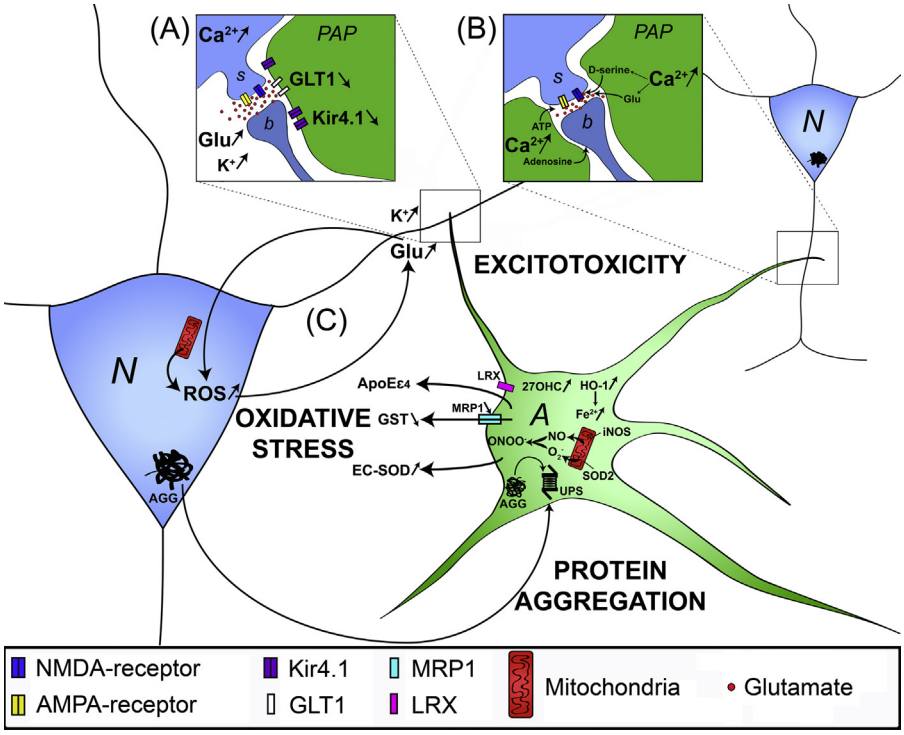

Fig. 2. Major neuroglial interactions involved in neurodegenerative diseases. The three main processes leading to neuronal death, namely excitotoxicity, oxidative stress and proteins aggregation, are influenced by astrocytes. *Excitotoxicity*: (A) Excitotoxicity is exacerbated by the reduced expression of glutamate transporters GLT1 and K^+ channels Kir4.1, leading to increased glutamate spillover and extracellular K^+ levels. (B) Excitotoxicity is also favored by the increase in astroglial Ca^{2+} that triggers release of gliotransmitter enhancing gliotransmission such as D-serine, glutamate or ATP. These changes indeed promote activation of the ionotropic NMDA and AMPA/kainate receptors, which not only support excitotoxicity, but also the production of reactive oxygen species (ROS), thus increasing neuronal oxidative stress. Insofar as the latter can induce glutamate release and decrease its reuptake, a vicious cycle between excitotoxicity and oxidative stress is set. (C) *Oxidative stress*: The main ROS involved in neurodegenerative diseases are nitric oxide (NO) and superoxide (O_2^-), which interact to produce the highly damaging peroxynitrite ($ONOO^-$). Inducible nitric oxide synthase (iNOS) activation first result in the transport of glutathione-S-transferase (GST, the major antioxidant of the brain) toward neurons, but this effect does not hold for chronic activation as GST levels have been found to decrease in neurodegenerative disorders as well as its transporter multiple resistance drug 1 (MRP1). An interesting protective potential of astrocytes is that enhanced liberation of extracellular superoxide dismutase (EC-SOD), the O_2^- scavenging enzyme goes hand in hand with neuroprotection and reduction of neurological symptoms in Parkinson's disease. Enhancing the mitochondrial superoxide dismutase SOD2 has also been found to result in a neuroprotective effect. One important factor promoting the formation of ROS is free iron. Important amounts of Fe^{2+} are generated by the activation of HO-1 in neurodegenerative conditions, an enzyme barely detectable in astrocytes from non-pathological tissue. Cholesterol, produced in astrocytes, its oxidized product 27OHC and regulators of its transport to neurons such as the aplipoprotein E (notably the ApoEε4 allele) and the liver X receptor (LRX) have also been found be associated with neurodegenerative disorders including Alzheimer and Huntington's disease. *Protein aggregation*: Finally, astrocytes may also play a detoxification role, to some extend counteracting protein aggregation (AGG), as their Ubiquitin Proteasome System (UPS) have been found to be more efficient than the neuronal ones. A: Astrocyte, N: Neuron, PAP: perisynaptic astrocytic process, b: bouton, s: spine.

astroglial elements including the Ca^{2+} homeostasis modulator 1 (CALHM1) and Na^+/Ca^{2+} exchangers (NCX), which have been associated with AD (Aqdam et al., 2010; Castaldo et al., 2009; Wu et al., 1997) and proposed as valuable neuroprotective targets in neurodegenerative diseases (Gomez-Villafuertes et al., 2007; Molinaro et al., 2013). Besides extracellular Ca^{2+} concentration, activation of many astroglial mechanisms depends on intracellular Ca^{2+} signaling (Verkhratsky et al., 2012a,b). The latter is also markedly altered in neurodegenerative diseases as increase in spontaneous intracellular Ca^{2+} elevation and oscillations have been reported in PD and AD (Bosson et al., 2015; Kuchibhotla et al., 2009), yet not in HD (Lee et al., 2013b) although astroglial Ca^{2+} buffering is dysfunctional (Oliveira, 2010). Release of excitatory molecules that depends on Ca^{2+} activation such as glutamate, D-serine or ATP (Mothet et al., 2005; Bezzi et al., 1998; Parpura et al., 1994; Pangrsic et al., 2007) is consequently greater in these pathological conditions and thus provide an environment favoring neuronal activation and excitotoxicity (Lee et al., 2013b). For instance, increase in Ca^{2+}-dependent release of glutamate from astrocytes leads to neuronal damage, both in cell cultures and *in vivo* (Bezzi and Volterra, 2001). Ca^{2+} waves have been shown to spread in the astroglial network across long distances and this phenomenon would imply the release of gliotransmitters (Scemes and Giaume, 2006) (Fig. 2B). Increase in spontaneous intracellular Ca^{2+} signaling and gliotransmitter release could hence allow dispersion of excitotoxic death. Ca^{2+} signaling involves entry through several astroglial channels including transient potential channels (TRPC), NCX, voltage-gated Ca^{2+} channels (VGCC), ionotropic Ca^{2+} permeable channels, store operated channels (SOC), as well as discharge from intracellular stores *via* a phospholipase C/inositol triphosphate receptor 2 (PLC/IP3R2) dependent mechanisms (Verkhratsky et al., 2012a). Although normalizing astroglial Ca^{2+} activity in neurodegenerative diseases by targeting these receptors would most likely be beneficial to cognitive symptoms and neuronal loss, the complexity and regionalization of such signaling in astrocytes renders this aim difficult to reach with sufficient accuracy. Nevertheless, aiming at reversing the deleterious consequences of Ca^{2+} rise in astrocytes may be a more feasible approach. For example in AD, pathological activation of the Ca^{2+}-dependent phosphatase calcineurin (Norris et al., 2005) results in the nuclear translocation of the nuclear factor of activated T-cells (NFAT) transcription factor inducing the expression of genes favoring inflammation (Hudry et al., 2012; Wu et al., 2012). Strikingly, interfering with NFAT in AD mice astrocytes is sufficient to reduce cognitive symptoms and gliosis (Furman et al., 2012). Such mechanism may be also relevant in other neurological disorders as calcineurin/NFAT pathway has been

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found to play a role in PD (Luo et al., 2014) although activation of NFAT appears to prevent protein aggregation in HD (Hayashida et al., 2010).

Another important ion of which homeostasis is regulated by astrocytes is K^+. Neurons release large amounts of K^+ upon firing and synaptic transmission; astrocytes are able to buffer and redistribute this K^+, thus ensuring an extracellular K^+ content optimal for brain activity (Laming, 2000). When K^+ concentration increases, neurons typically depolarize and become more readily excitable, hence vulnerable to excitotoxicity. Dysregulation of extracellular K^+ has been reported in HD (Ariano et al., 2005), and PD (Strauss et al., 2008), although in the latter case baseline levels were not altered and only clearance rate was reported to slow down in the mouse 6-hydroxydopamine lesion model of PD. In AD no change in basal K^+ content has been reported, but a positive correlation between K^+ concentration and the occurrence of the well-known pathological β-amyloid aggregates was described in post-mortem tissues of severe AD patients (Graham et al., 2015). A recent study unraveled that the main K^+ channel through which astrocytes uptake K^+, Kir4.1 (inward rectifier K^+ channel 4.1), is markedly downregulated in a severe mouse model of HD (R6/2) and in the late stages of the disease in a milder mouse model (Q175) (Tong et al., 2014). Remarkably, restoring Kir4.1 expression in astrocytes restored normal astrocytic functional properties and, importantly, rescued R6/2 MSNs resting membrane potential to control levels, markedly reduced their degenerative features, as well as R6/2 mice motor phenotype and survival. Seeking restoration of physiological astroglial Kir4.1 expression/function in HD and potentially other neurodegenerative disorders (Wang et al., 2008; Xu et al., 2002) should thus be an efficient strategy for delaying excitotoxic mechanisms, onset of cognitive and motor symptoms and disease progression (Fig. 2A).

3.2. Oxidative stress

The second major cause of cell death in neurodegenerative diseases is the oxidative damages undergone by all types of brain cells. The brain is particularly vulnerable to free radicals due to high oxygen consumption, high iron content that increases with aging (Beard et al., 1993) coupled to low iron ions binding capacity of the cerebro-spinal fluid (Halliwell, 1992), and oxidation of neurotransmitters such as dopamine and serotonin (Spencer et al., 1998). Regrettably, oxidative damage also represents a complication of excitotoxicity as prolonged activations of ionotropic glutamate receptors provoke the formations of free radicals (Dong et al., 2009) and excess of cell free radicals can induce glutamate releases (Gilgun-Sherki et al., 2001) and impairs astroglial glutamate uptake (Volterra et al., 1994). The end result is that the two major cell killers work in concert in a deadly vicious cycle (Fig. 2C). Reactive oxygen species (ROS) are the main free radicals and are mainly produced in mitochondria where they are of prime importance in the redox reaction of the respiratory chain. Mitochondrial dysfunctions in neurodegenerative diseases lead to the overproduction of ROS, thereby disturbing the balance of oxidant *vs* antioxidant. The main reactive molecules provoking oxidative stress in neurodegenerative diseases are nitric oxide (NO) (Calabrese et al., 2009), superoxide (O_2^-) (Maier and Chan, 2002), and the product of their interaction, peroxynitrite ($ONOO^-$) (Lipton et al., 1993). The astroglial NO synthase isoform (iNOS) does not work constitutively like neuronal cNOS, and is instead inducible. Its activation is independent of Ca^{2+} concentration but requires astrocyte stimulation; the inflammation associated with neurodegenerative disorders enables such activation in a chronic fashion (Murphy et al., 1993). Interestingly, altering astroglial iNOS activity could be an efficient way of reducing oxidative stress and thus delay cognitive symptoms. However, iNOS activation has been suggested to display neuroprotective as well as neurodegenerative effects. Indeed, activated iNOS initially stimulates the production and transfer of glutathione-S-transferase (GST, the major antioxidant of the brain), but this effects does not hold for chronic exposure to NO (Heales et al., 2004) such that GST levels have actually been found to be reduced in AD and PD (Mazzetti et al., 2015) and the transporter enabling the astrocyte-neuron shuttle of GST, namely multidrug resistance protein 1 (Mrp1) is downregulated in HD (Ribeiro et al., 2012). It therefore appears that downregulating iNOS expression would be beneficial to neurodegenerative conditions, yet at the expense of the neuroprotective effect of NO production through GST stimulation.

Superoxide dismutase (SOD) is the enzyme converting O_2^- into H_2O_2 and the latter is then converted to H_2O and O_2 by glutathione peroxidase (GPx). SOD dysfunction has extensively been investigated in amyotrophic lateral sclerosis (ALS), as 20% of ALS patients present a mutation on the *Sod* gene (Kato et al., 2000; Rossi, 2015), but not so much in HD, PD and AD. Interestingly however, astrocytes are able to release extracellular SOD (EC-SOD) (Stewart et al., 2002; Takano et al., 2013), which would permit neuroprotection (Fukui et al., 2003). In accordance with an important role of astrocyte release of EC-SOD in the treatment of neurodegenerative disorders, EC-SOD levels have been found to increase in Parkinsonians undergoing deep brain stimulation (DBS) and, remarkably, levels dropped down upon interruption of the DBS treatment (Wang et al., 2013). Further, increasing astroglial release of EC-SOD is likely to alleviate cognitive disturbances in neurodegenerative disorders as age-related cognitive decline was found to be attenuated by increased EC-SOD and the resulting quenching of free radicals (Levin, 2005). Finally, overexpression of mitochondrial SOD (SOD2) could also be beneficial as astroglial specific overexpression of SOD2 (under control of the *Gfap* promoter) was found to reduce neuronal vulnerability after forebrain ischemia (Xu et al., 2010). A similar strategy could thus result in neuroprotection in HD, PD and AD.

Another important factor in the oxidative stress implicated in neurodegenerative processes is the iron content of the brain, known to increase with aging (Beard et al., 1993) and to be abnormally high in these disorders (Ward et al., 2014). As for metabolites, astrocytes are ideally positioned to take up iron from the blood and distribute it to the neuropil. How this iron is handled is physiologically tightly controlled as free Fe^{2+} and Fe^{3+} are known to catalyze many ROS producing reactions and the resulting oxidative stress provokes memory impairment (De Lima et al., 2005). Despite an increased expression of ferritin, the main iron-sequestering molecule, in HD, PD and AD (Bartzokis and Tishler, 2000; Yang et al., 2013), these disorders are all associated with an excess of free iron, known to exacerbate oxidative stress (Kruszewski, 2003). One interesting lead regarding the role of astroglia in generating iron overload is the abnormally high activation of heme oxygenase 1 (HO-1), an astroglial enzyme that degrades heme into carbon monoxide, free iron (Fe^{2+}) and biliverdin (Chen, 2014). Indeed HO-1 is normally hardly detectable in basal conditions, such high activation thus represents an important new source of free Fe^{2+} for the cell. Interestingly, HO-1 expression was showed to be associated with impaired global cognition (Schipper et al., 2006) and it was thus suggested that downregulating glial HO-1 could be a valuable therapeutic strategy to alleviate oxidative stress related cognitive impairment in AD (Schipper et al., 2009) and could also be beneficial to other neurodegenerative disorders (Schipper and Song, 2015).

A recently identified player in the oxidative products involved in the pathogenesis of neurodegenerative disorders is cholesterol and its oxidized products. In the adult brain, neurons do not produce cholesterol and fully rely on the astroglial synthesis pathway. Cholesterol is then transported from astrocytes to

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neurons by means of a carrier protein, the apolipoprotein ApoE. The *ApoEε4* allele is known to be an important risk factor in AD as it would confer a faulty cholesterol metabolism, although this is still under debate (Gamba et al., 2015). Targeting this protein or regulators of its expression, such as the liver X receptor (LRX), may thus be of interest in AD treatment. Since cholesterol does not cross the blood brain barrier (BBB), excess of brain cholesterol needs to be converted to oxidized products, oxysterols, which do traverse the BBB, to be expelled from the brain. The two main oxysterols involved in brain cholesterol homeostasis are 24-hydroxycholesterol (24OHC), produced in neurons and 27-hydroxycholesterol (27OHC) produced in astrocytes, and the ratio between these is of prime importance in cholesterol homeostasis. Interestingly these oxidized cholesterol species have been found to be altered in AD (Gamba et al., 2015; Shafaati et al., 2011), HD (Leoni et al., 2011; Valenza and Cattaneo, 2011) and PD (Björkhem et al., 2013). Accordingly, increase in 27OHC appears to result in memory disturbances (Heverin et al., 2015; Zhang et al., 2015). Deciphering how the neuronal 24OHC *vs* astroglial 27OHC balance could be restored should thus be beneficial in the treatment of these diseases.

3.3. Protein aggregates

The neuropathology of HD, AD or PD is characterized by the formation of protein aggregates, which are thought to sequester proteins important for cellular functioning, such as for example transcription factors. HD belongs to the polyglutamine family of trinucleotide repeat diseases as it is attributable to a repeat CAG codon within the first exon of the gene encoding the protein huntingtin (Paulsen et al., 2001). Akin to all proteins presenting a polyglutamine expansion, mutant huntingtin (mHtt) self-aggregates and sticks to other cellular proteins, with a preference for other polyglutamines. AD neural tissue typically exhibits β-amyloid filaments or Tau deposits and intracellular neurofibrillary tangles of which the accumulation is thought to be at the root of neuronal and cognitive dysfunctions (Hardy and Selkoe, 2002). PD brains display protein aggregates mainly containing α-synuclein and called Lewy bodies in the dopaminergic neurons as part of the degenerative process (Gundersen, 2010). Insofar as they are associated with brain disorders in which there is a clear neuronal loss, intracellular inclusions have been assumed to be toxic for neurons. Yet, such view has been questioned as aggregates may actually represent a cellular sequestering mechanism protecting the cell from the noxious effects of soluble mutated proteins; *i.e.* mHtt, α-synuclein, β-amyloid, or Tau (Cowan and Mudher, 2013; Sisodia, 1998). Both scenarios most likely co-exist in that aggregation likely protects neurons from pernicious diffusible mutant proteins by sequestering them, but a no-return situation might arise at the point where the proteasome fails to degrade intracellular inclusions (Falsone and Falsone, 2015).

With regard to astrocytes, an interesting piece of data is the finding that exogenous astrocytes are attracted to amyloid, migrate toward it and eventually degrades it, *in vitro* as well as *in vivo*; digestive properties that are lost in the disease state since endogenous astrocytes are unable to remove plaques (Wyss-Coray et al., 2003). Thus, understanding the astroglial processes impaired in AD would potentially enable to render astrocytes such competence for detoxification and thus delay the course of the disease. An important observation is also that, in HD, glial cells contain less mHtt aggregates than neurons (Shin et al., 2005), and this would be attributable to the fact that neurons are endowed with a lower ubiquitin-proteasome degradation system (UPS) than astrocytes. Additionally, the age-dependent decrease in UPS activity is faster and larger in neurons (Tydlacka et al., 2008). These observations are consistent with prominent digestive/detoxification roles of astrocytes. Finally, α-synuclein has been shown to directly transfer from neurons to astrocytes in pathological conditions, suggesting that, in PD too, one astroglial function is to take up and attempt clearance of misfolded/toxic proteins. Such transfer was however found to induce noxious inflammatory responses in glial cells (Lee et al., 2010). Therefore, the purifying potential of astrocytes toward aggregates is disturbed in the disease process but may just need a little hand to efficiently overcome the appalling cognitive symptoms associated with neurodegenerative disorders.

4. Astroglia as therapeutic targets in psychiatric disorders

Since the advent of the tripartite synapse and the recognition that atrocytes play a key role in higher brain functions, the neurobiology of most complex disorders has been revisited with a more integrated view, taking into account this major partner. Hence, psychiatric diseases, including major depression (MD), bipolar disorder (BD), schizophrenia, and autism spectrum disorders (ASD), have all seen their field of research transformed in light of data describing alterations in neuro-glial communications or unveiling neglected/unknown effects of classical drugs on astroglial function.

4.1. Major depression

Among the strong changes associated with these diseases, the number of astrocytes has been shown to decrease, mainly in prefrontal areas, hippocampus and amygdala of post-mortem (Cotter et al., 2001; Harrison, 2002; Rajkowska and Miguel-Hidalgo, 2007) and preclinical tissue of MD patients (Banasr and Duman, 2008) as well as in animal models of depression (Czéh et al., 2006; Iwata et al., 2011). Besides, GFAP staining persistently decreases (Si et al., 2004; Nagy et al., 2015) and the morphology of GFAP stained cells is also altered in depression, indicating degenerative changes that likely underlie the brain shrinkage associated with this psychiatric condition. Interestingly, evidence suggest that existing therapeutic strategies capable of alleviating depressive states could reverse the abovementioned glial pathology. Notably, antidepressants have been found to normalize glial cell number (Czéh et al., 2006) and GFAP staining (Czéh et al., 2007; Liu et al., 2009). In line with this, electroconvulsive stimulation (ECS) and trans-magnetic stimulation (TMS) treatments also result in an up-regulation of the GFAP marker in rodent and non-human primates (Dwork et al., 2004; Fujiki and Steward, 1997; Kragh et al., 1993; Steward, 1994). The cause of reduction in astrocytes number, GFAP expression and the gliodegenerative changes associated with MD however remains uncertain. One hypothesis proposes that the impaired glial function is attributable to increased level of glucocorticoids as MD patients exhibit increased concentrations of cortisol in plasma, urine, and cerebrospinal fluid (Cotter et al., 2001) and that elevated levels of glucocorticoids are known to downregulate astroglial activation, as measured by reduced GFAP expression (Laping et al., 1994), and inhibit glucose uptake, thus leading to impaired function and degeneration (Virgin et al., 1991). This effect would be mediated through astrocytic glucocorticoid receptors (GR) activation (Crossin et al., 1997) and may involve regulation of genes expression (Bohn et al., 1994). If the glucocorticoid hypothesis of MD indeed accounts for most of the neuropathology and symptoms of the disease, downregulating astroglial GR may be a good antidepressant strategy, although facilitation of GR has been suggested to be involved in the antidepressant effect of desipramine *via* feedback inhibition of glucocorticoid synthesis by the hypothalamic-pituitary-adrenal axis (Pariante et al., 1997). Accordingly, GR antagonists such as mifepristone have been proposed as antidepressant (Gallagher and

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Young, 2006) and have been showed to reverse depressive-like behavior (on the sucrose preference test and novelty suppressed feeding test) in the chronic unpredictable stress (CUS) rat model of depression (Sun et al., 2012). Of interest, this investigation provides further insight into the molecular determinant of astroglial dysfunction in MD as it shows that CUS decreases Cx43 mediated coupling and, conversely hindering Cx43 coupling in the PFC is sufficient to induce depressive-like behavior. Crucially, mifeprisone was found to reverse impairment of Cx43 coupling concomitantly to depressive-like behavior, suggesting that one primary factor inducing/favoring MD is astroglial GJs function. Also supportive of this notion, expression of Cx30, the other major astroglial gap junction subunit, has been found to be reduced in a cohort of 12 MD patients (Bernard et al., 2011). Thus, although specific agonists of astrocytic GJs are not currently available, their development could also represent a potent approach to treat MD.

4.2. Schizophrenia and bipolar disorders

In schizophrenia and BD the astroglial pathology appears less consistent, with studies reporting an increase in PFC glial number and/or GFAP expression (Feresten et al., 2013; Gomes et al., 2015; Rajkowska et al., 2002) and some reporting reductions (Altshuler et al., 2010; Steffek et al., 2008; Webster et al., 2005; Williams et al., 2013) or no difference (Falkai et al., 1999). Such disparities may be due to the inflammatory status of the animal models or post-mortem brains analyzed, as astrogliosis was recently proposed to underlie morphological and quantitative astroglial changes in schizophrenia (Catts et al., 2014). Inflammatory processes are expected to interfere with all sorts of astroglial functions but more specific findings have recently emerged. Indeed, one of the foremost hypotheses of schizophrenia is hypofunction of NMDA receptors of the PFC (Tsai and Coyle, 2002). D-Serine is an endogenous co-agonist of these receptors and is one of the main gliotransmitters thus far identified (Fossat et al., 2011). Most interestingly, adjunction of D-serine has been found to be beneficial to the treatment of schizophrenic patients, and conversely, inhibition of the D-serine degrading enzyme D-amino acid oxidase (DAAO) also results in a positive outcome (Heresco-Levy et al., 2005; Lane et al., 2013; Fig. 3B). The main genetic link described in schizoprenia is the Disrupted-in-schizophrenia (*Disc1*) gene, of which the resulting protein has strikingly been found to stabilize the D-serine producing enzyme serine racemase in astrocytes (Ma et al., 2013; Fig. 3A). Furthermore, inducible expression of a human mutant DISC1 in astrocytes (under the control of the GFAP promoter) downregulates endogenous DISC1, prevents stabilization of serine racemase protein levels, and produces schizophrenic like features. Specifically, mutant mice display greater responses to an NMDA antagonist, MK-801, in the open field and pre-pulse inhibition of the acoustic startle tests and are significantly more sensitive to the ameliorative effects of D-serine (Ma et al., 2013). Together, these findings suggest that deficiency in astroglial production of D-serine is at the core of the etiology of schizophrenia. Normalizing such production is now therefore of prime interest to design better treatments against schizophrenia and associated conditions such as BD. Another relevant finding regarding the role of astrocytes in schizophrenia is an increased expression of the excitatory amino acid transporter EAAT2 (Matute et al., 2005; Smith et al., 2001) which could, to some extent, explain hypoglutamatergic states associated with this mental illness. The pertinence of these alterations is supported by *in vivo* and *in vitro* (cultured astrocytes) data showing that the clozapine antipsychotic decreases GLT1 expression in astrocytes (Melone et al., 2001; Vallejo-Illarramendi et al., 2005), hence suggesting that this effect on astroglia accounts, at least in part, for its efficacy.

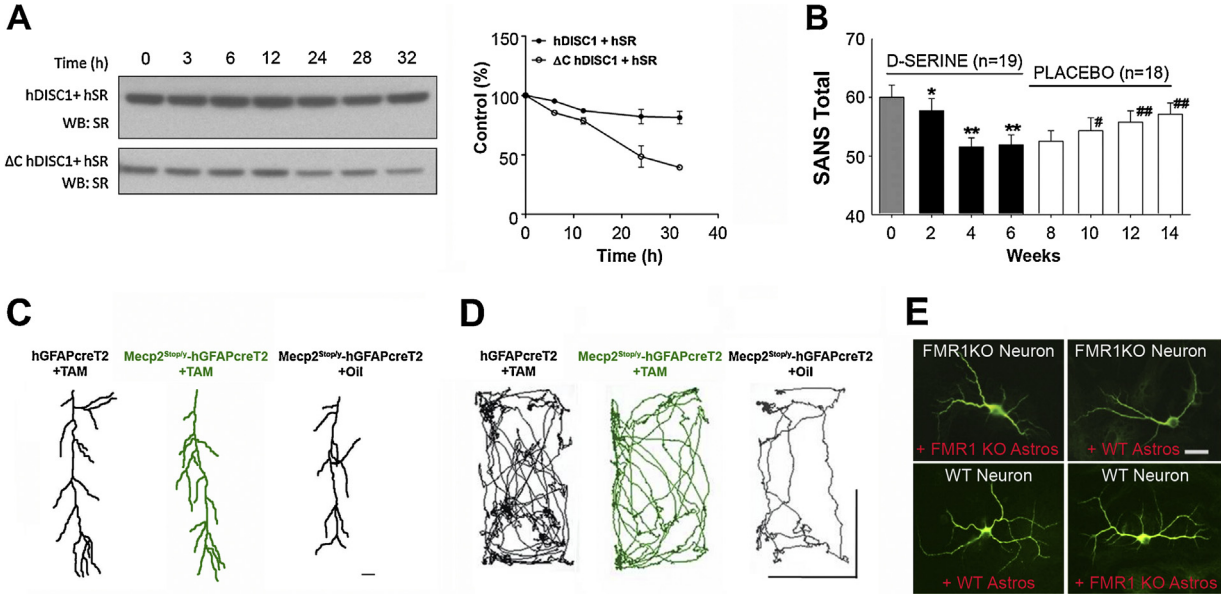

Fig. 3. Therapeutic potential of astrocytes in schizophrenia and autism spectrum disorders. (A, B) The gliotransmitter D-serine is involved in schizophrenia. (A) Mutation of the *Disrupted in schizophrenia* gene (hDisc1 → ΔC hDisc1) in astrocytes results in a destabilization of the D-serine producing enzyme serine racemase (hSR) as shown by the rapidly decaying level of astroglial hSR in the presence of the protein synthesis blocker cycloheximide for 32 h, suggesting that D-serine levels are reduced in schizophrenia. (B) Accordingly, adjunction of D-serine to the treatment of schizophrenic patients markedly improves scores on the Scale for Assessment of Negative Symtoms (SANS). (C, D) Wild type astrocytes suffice to rescue neuronal morphological phenotype in Fragile X and Rett syndrome. (C) Removal of the dominant mutant Mecp2 mutation in astrocyte (Mecp2$^{Stop/y}$-hGFAPcreT2 + TAM, in green) rescues the normal dendritic morphology as compared to control (hGFAPcreT2 + TAM) and mutant (Mecp2$^{Stop/y}$-hGFAPcreT2 + oil) mice. (D) Removal of the dominant mutant Mecp2 mutation in astrocyte (Mecp2$^{Stop/y}$-hGFAPcreT2 + TAM, in green) rescues the normal behavioral phenotype assessed in the open field as compared to control (hGFAPcreT2 + TAM) and mutant (Mecp2$^{Stop/y}$ hGFAPcreT2 + oil) mice. (E) *Top panels*: wild type astrocytes rescue the dendritic phenotype of FMR1 knockout neurons in culture. *Bottom panels*: FMR1 astrocytes induce Fragile X dendritic phenotype in wild type cultured neurons. Adapted with permission from Ma et al. (2013) (A), Heresco-Levy et al. (2005) (B), Lioy et al. (2011) (C, D) and Jacobs and Doering (2010) (E).

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4.3. Autism spectrum disorders

ASD are neurodevelopmental psychiatric diseases characterized by various degrees of impairment in social interaction and communication skills as well as repetitive behaviors. Brains of ASD patients present on average a larger size and a larger number of cells, including astrocytes (Herbert, 2005). The increased number of astrocytes is also accompanied by an augmented expression of GFAP and morphological alterations associated with reactive astroglia (Laurence and Fatemi, 2005; Vargas et al., 2005; Yuskaitis et al., 2010), such as cell swelling and decreased arborization (Nguyen et al., 2012). These observations are consistent with the view that ASD are conditions in which inflammatory processes, including astrogliosis, play a central role (McDougle et al., 2014; Rossignol and Frye, 2014). Etiology in ASD is however a very complex matter as it depends on many genetic and environmental factors at given neurodevelopmental time periods. Exposition to noxious compounds before birth is actually thought to suffice for engendering autism. Ethanol exposure before birth has been reported to induce autism (Aronson et al., 1997) as well as fetal alcohol spectrum disorders, which exhibit symptoms reminiscent of ASD, such as attention deficits, language development defects, and inadequate social perception (Dörrie et al., 2014). Recent evidence indicate that prenatal introduction of ethanol inhibits astroglial M3 muscarinic receptors, which are consequently unable to stimulate the release of fibronectin, laminin, and plasminogen activator inhibitor-1, normally causing neurite outgrowth in hippocampal neurons (Guizzetti et al., 2010). Accordingly, lack of neuritogenesis is a strong neuropathological correlate of ASD (Bakos et al., 2015). Therefore, counteracting ethanol inhibition of astroglial M3 receptors before birth in a context at risk may be an efficient strategy to avoid ethanol induced neurodevelopmental disorders. Another major environmental risk for ASD is prenatal exposure to the anticonvulsant valproic acid (Christianson et al., 1994) such that administration of this compound before birth is a frequent model of autism in rodents (Ingram et al., 2000). Strikingly, valproic acid induces neuronal death through a non-cell autonomous effect by inducing astrocytic morphological changes and release of the tumor necrosis factor α (TNFα) (Wang et al., 2011). Interestingly, exposition to ozone has also been shown to enhance astroglial expression of TNFα (Araneda et al., 2008), thus supporting the view that prenatal exposure to air pollution is a serious risk of neurodevelopmental defects such as ASD (Block and Calderón-Garcidueñas, 2009). Limiting TNFα signaling in astrocytes may thus be salvatory in cases of prenatal exposure to valproic acid or toxic air compounds. Naturally, genetic predispositions interfere with these environmental aggressions and the resulting pathological outcomes are highly variable (Lecavalier, 2014).

Autistic syndromes that are attributed to specific genetic mutations have been subject to more intense research and mainly include Rett and Fragile X syndromes. Rett syndrome (RTT) is due to the loss of function mutation in the gene encoding the epigenetic factor methyl-CpG-binding protein-2 (MeCP2). The function of the protein is unclear but would participate in the regulation of gene expression through chromatin conformational modifications. As for many other disorders, the neurocentric vision of the physiopathology behind brain deficits was challenged relatively recently by Ballas and collaborators who investigated whether non-cell autonomous mechanism could participate to the etiology of RTT and discovered that glial cells, including astrocytes, also express MeCP2 and are also affected by the mutation in a RTT mouse model (Ballas et al., 2009). A striking result of this study is that neurons co-cultured with astrocytes carrying the mutation display impaired dendritic morphology. Insofar as similar observations were obtained simply using culture medium conditioned with RTT astrocytes the loss of MeCP2 was proposed to result in the aberrant secretion of soluble factors. The latter have not so far been identified, although secretion of cytokines in response to inflammation have been showed to be reduced in RTT astrocyte, potentially due to a constitutive activation of the p38MAPK pathway, suggesting that in RTT inflammatory pathways are activated in basal conditions (Maezawa et al., 2009). However, other factors may be at play as MeCP2 was recently reported to up- or downregulate at least 118 genes in astrocytes, comprising the glutamine transporter *Snat1*, the growth-suppressing transcription factor *Ndn*, the AMPA receptor subunit *Gria1*, the platelet derived growth factor *Pdgfb*, the protein phosphatase 2 *Ppp2r2b*, or the early growth response 1 *Egr1* (Yasui et al., 2013), all of which may be involved in the non-cell autonomous impairment in neuronal growth. Interestingly, the same group reported that the loss of MeCP2 spreads between astrocytes *via* gap junctions as blocking the latter with the non-specific drug carbenoxolone or using specific blockade of Cx43 channel *via* RNAi prevents contagion of the MeCP2 loss to neighboring cells (Maezawa et al., 2009). It should be noted that such effect may be mediated by the release of soluble factors through hemichannels, although the authors ward off this possibility by showing that mutant astrocytes conditioned medium does not affect MeCP2 expression in cultures of wild type astrocytes (Maezawa et al., 2009). Finally, a recent important finding is the demonstration that in a RTT mouse model where all cells express mutant MeCP2, re-expressing MeCP2 preferentially in astrocytes exerts this time a positive non-cell-autonomous effect on mutant neurons *in vivo*, as normal neuronal features, including dendritic morphology, were restored (Fig. 3C). Crucially, such positive influence of wild type MeCP2 in astrocytes improved locomotion and anxiety levels, alleviated respiratory abnormalities, and substantially prolonged lifespan (Lioy et al., 2011; Fig. 3D). Altogether these recent advances in the understanding of RTT point toward astroglia as a promising target for reducing RTT symptoms.

Fragile X syndrome (FXS) is an inherited form of ASD associated with intellectual disabilities as well as, in some cases, motor symptoms. The disorder is owed to the CGG trinucleotide expansion mutation of the protein FMRP, a translational regulator that binds to synaptic mRNA and plays important neurodevelopmental roles in synaptogenesis (Bassell and Warren, 2008). Thence, akin to RTT, loss of FMRP function in FXS neurons has been found to result in growth abnormalities, including reduced dendritic length and hyperabundance of dendritic spines with a long, thin, and otherwise immature morphology which confers abnormal synaptic plasticity properties (Bassell and Warren, 2008). Only relatively recently, FMRP was found to be expressed in astrocytes too, *in vitro* (Pacey and Doering, 2007) and *in vivo* (Gholizadeh et al., 2015) using GFAP and S100β astroglial markers, respectively. Most interestingly, using a co-culture system, Jacobs and Doering found that wild-type neurons cultured in the presence of FMRP knock out astrocytes soon displayed the typical neuronal abnormalities associated with FXS suggesting a causative role for astroglial dysfunction in the disease neuropathology (Fig. 3E). Further support of this interpretation was the observation that, reciprocally, co-culture of FMRP knockout neurons with wild type astrocytes reverse the dendritic and spine aberrations present at DIV 0 (Jacobs and Doering, 2010; Fig. 3E). Together these data strongly support a non-cell autonomous effect of FMRP, and unveil the possibility that astrocytes may be a target of choice to prevent neurodevelopmental defects in FXS. Still, these observations need to be ascertained *in vivo*, as the transfer of specific molecules may occur differently in a culture system and *in situ*. Re-expression of FMRP *in vivo* in the *Fmr1* knock out mouse model of FXS has already been performed in neurons, using adeno-associated viral vectors (AAV9) containing the FMRP transgene under the control of the

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neuronal specific promoter synapsin-1 (Gholizadeh et al., 2014). Strikingly, 50% of FMRP re-expression was sufficient to reduce the repetitive behavior and deficit in social dominance normally overt in FXS mice. If such recovery is attributable to neuroglial FMRP signaling, similar or better rescue may be obtained by gene therapy strategies directed toward astrocytes alone (*e.g.* using GFAP or GLAST promoters) or both neurons and astrocytes; however, these experiments have yet to be accomplished. An important finding giving insight into the factors involved in the altered neuroglial dialogue is that astroglial FMRP binds to neurotrophin-3 (NT-3, a nerve growth factor) mRNA and that NT-3 release from FMRP deficient astrocytes is enhanced. Remarkably, knocking down NT-3 translation using shRNA injection in the PFC rescued trace fear memory deficits in FMRP knockout mice (Yang et al., 2012). With regard to other astroglial genes that would be regulated by FMRP, information is still lacking, although a post-mortem study found up-regulation of both GFAP and metabotropic glutamate receptor 5 (mGluR5) associated with a diminution of FMRP expression in the PFC of 20 autistic patients compared to 10 controls (Fatemi and Folsom, 2011). A leading hypothesis of the molecular mechanisms at play in FXS physiopathology implicates group 1 mGluRs (mGluR1 and mGluR5) in the complications associated with FMRP loss of function. Specifically, genes that are known to respond to mGluRs stimulation, such as microtubule associated protein 1b or postsynaptic density protein 95 kDa or the *Fmr1* gene itself, are also targets of FMRP. The proposed mechanism supposes that mGluRs activation activates FMRP and stimulates local translation of Fmr1 mRNA, which would then up- or downregulate translation of synaptic proteins (Ronesi and Huber, 2008). The latter would include mGluRs, since a negative feedback loop is thought to be missing in FXS mice displaying enhanced mGluRs dependent long-term depression (Huber et al., 2002). In this context, it is interesting to point out that mGluR5 is well known to be present in astrocytes during development and early postnatal period (up to 3 weeks) (Sun et al., 2013b) and to sense synaptic activities (Panatier and Robitaille, 2015), which enable proper neuroglial dialogue, eventually shaping the pattern of neuronal inputs. If FMRP is indeed a major regulator of mGluRs-induced mRNA translation in astrocytes too, its role in the astroglial regulation of synaptic development would be determinant. Although further investigation needs to be carried out to validate this hypothesis, one may already foresee a powerful target to overcome neurodevelopmental defects associated with FXS.

5. Astroglial therapeutic potential in epileptic conditions

Epilepsy, affecting about 1% of the population, is a common but poorly understood group of neurological disorders characterized by the periodic occurrence of seizures, which disrupt normal brain function. More than half of the epileptic patients have seen their first seizures initiated in childhood during which critical periods of postnatal brain development take place. The disastrous consequence of childhood epilepsy is indeed that it strongly interferes with these critical periods, leading to major negative impact on cognitive outcome such that patients will carry a lifelong perspective of disability and reduced quality of life. Even in adult refractory epilepsy, cognitive impairment has long been recognized as a common co-morbidity (Hermann et al., 2009). Determining new antiepileptic targets remains of prime importance to relieve patients from the burden of the sequels of seizures.

Epileptic seizures are generated by hypersynchronous neuronal firing. How such large population of neurons becomes synchronized remains unknown, although it is thought to result from an imbalance between excitatory and inhibitory synaptic inputs and changes in intrinsic excitability (Losi et al., 2012; McNamara, 1994). Despite treatment with currently available antiepileptic drugs, mostly modulators of neuronal GABAergic signaling and voltage-dependent sodium channels, one-third of patients with epilepsy are pharmacoresistant, making it crucial to develop novel therapies on new targets. Epileptiform activity is traditionally assumed to be generated exclusively in and by neurons. However, since 1986 a non-neuronal source of excitation has been proposed to contribute to seizures (Jefferys, 1995; Konnerth et al., 1986). The view that epilepsy is a neurocentric disorder has now given way to an instead astrocytic basis for this disorder (Bedner et al., 2015; Tian et al., 2005). This provocative vision has recently been put forward, but is in fact still under intense and critical investigation. Numerous studies have reported morphological and functional changes in astrocytes, which become reactive in epileptic tissue (Fig. 4A), as described in several comprehensive reviews (Coulter and Steinhauser, 2015; Crunelli and Carmignoto, 2013; Losi et al., 2012; Wetherington et al., 2008). These data, despite contradictory on several instances, mostly do suggest that astrocytes contribute to the pathology. However in most cases, studies report correlations between astroglial properties alterations and epilepsy, especially in seizure foci from surgically-removed human epileptic tissue, while only few works performed in animal models of epilepsy actually demonstrate a causal link.

5.1. Alteration of astroglial phenotype by epileptiform activity

At the morphological level, a typical feature of astrocytes during epilepsy is their swelling and loss of non-overlapping domain organization (Oberheim et al., 2008) (Fig. 4A and B). Indeed astrocytes normally tile during development to occupy in the healthy brain independent spatial territories, and thereby individually control thousands of synapses (Bushong et al., 2002; Halassa et al., 2007). Remarkably, in normal conditions synapses are only contacted by a single astrocyte, while in several animal models of epilepsy, multiple astrocytes overlap their fine processes to contact the same synapses. The functional impact of this anatomical remodeling in epilepsy is yet unclear, but one might speculate that excessive astroglial inputs onto synapses contribute to recurrent excitation in chronic epileptic brain. Multiple functional astroglial changes occur during epileptiform activity. Notably, glutamate-induced Ca^{2+} oscillations (Fig. 4C) and intercellular Ca^{2+} waves (Ding et al., 2007; Fellin et al., 2006; Gómez-Gonzalo et al., 2010; Lee et al., 1995; Tian et al., 2005) have been reported, although their origin and maintenance are unclear as, once induced by epileptiform activity, they outlast the period of neuronal activity (Fellin et al., 2006; Tian et al., 2005). Such intracellular Ca^{2+} signaling contributes *in vivo* to neuronal excitotoxicity (Ding et al., 2007), and may also modulate extracellular K^+ uptake (Wang et al., 2012a,b). Another significant change occurring during epileptiform events is a marked membrane depolarization (Fig. 4D) (Dichter et al., 1972; Grossman and Hampton, 1968), which can be synchronized to $[K^+]_e$ changes (Amzica and Steriade, 2000; Amzica et al., 2002). Intriguingly, action potential generation has also been reported in astrocytes from human epileptic foci in response to depolarization, although astrocytes might have been mistaken for NG2 (nerve-glia antigen 2) cells in these studies, which were performed at a time where the complexity of the glial lineage was not clearly set (Bordey and Sontheimer, 1998; O'Connor et al., 1998). Finally, the classic functions of neurotransmitter precursor synthesis (glutamine), regulation of extracellular homeostasis, including glutamate and K^+ uptake, interstitial volume, and ammonia detoxification (David et al., 2009; Jabs et al., 2008; Verkhratsky et al., 2012b; Wetherington et al., 2008) have all been found to be altered in epileptic conditions. Remarkably hyperammonia, which can result from impairment in ammonia detoxification, has been shown to trigger neuronal disinhibition

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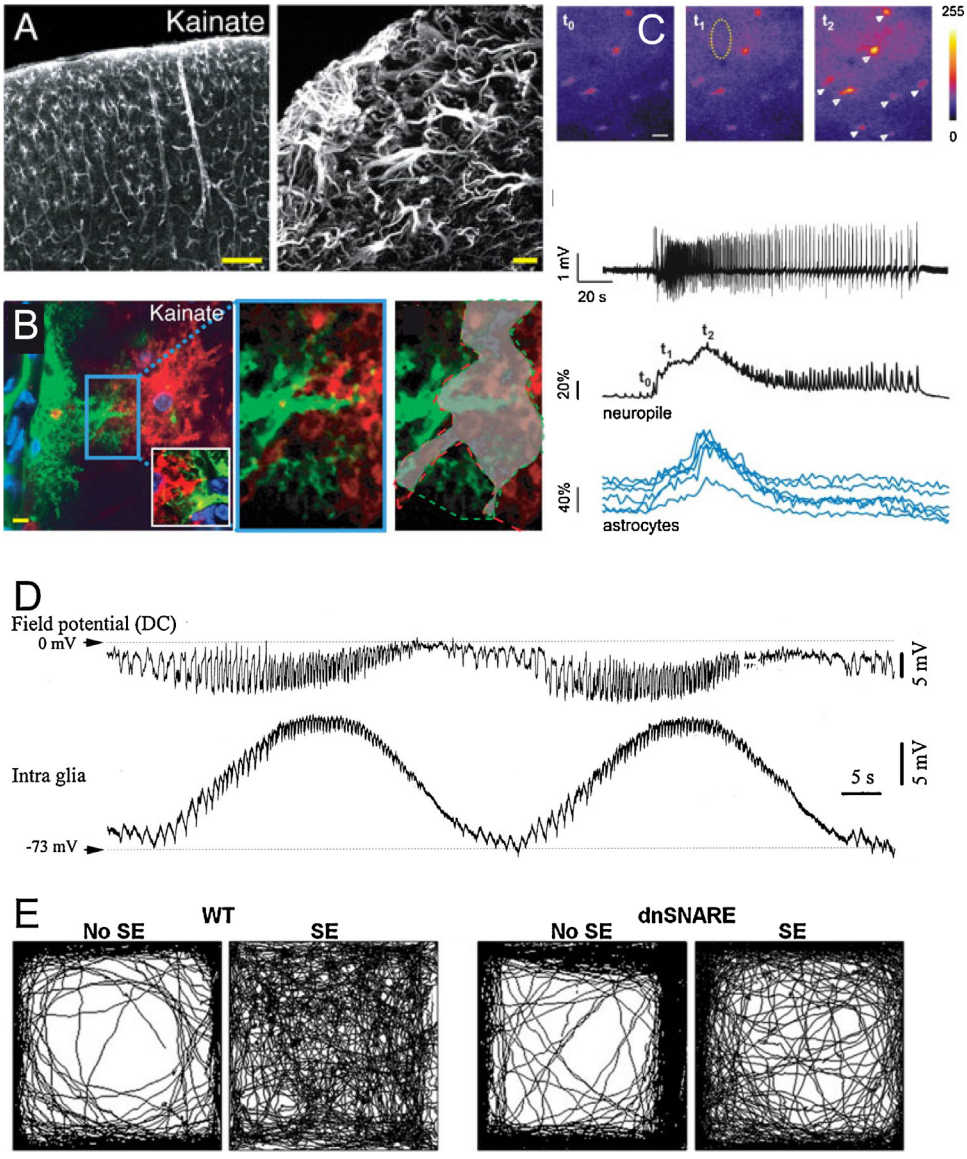

Fig. 4. Alterations and impact of astrocytes in animal models of epilepsy. (A) Low and high-power images illustrating the presence of reactive hypertrophic astrocytes labeled with GFAP in the sensory-motor cortex of a kainate mouse model of epilepsy, 6 months after exposure to kainate. Scale bars: left, 100 μm; right, 10 μm. (B) Loss of domain organization in hypertrophic astrocytes revealed by diolistic labeling showing overlap of processes from two reactive astrocytes in the cortex of a kainate mouse. Scale bar, 10 μm. *Inset*: Overlapping processes of two astrocytes in the hippocampal CA3 area. High-power images of blue box demonstrating overlapping area and processes of cortical astrocytes in a kainate mouse. (C) 2-photon calcium imaging in guinea pig entorhinal cortex before (t0) and during the development (t1 and t2) of an ictal discharge induced by arterial perfusion with bicuculline. Scale bar: 20 μm. Field potential and calcium signal changes from neuropile (dashed circle in C) and astrocytes (arrowheads in C) during an ictal discharge. (D) Relationship between glial membrane potential and recurrent seizures. Intraglial and field potentials recordings were measured at short distance (1 mm) in the suprasylvian gyrus. During seizures, glia displayed steady depolarization. (E) Astrocytic dnSNARE expression attenuates behavioral consequences of epilepsy. Representative 30 min of track plots of control no-SE (status epilepticus) and SE-experienced WT and dnSNARE mice placed in the open field 8 months after pilocarpine treatment.
Adapted with permission, from Oberheim et al. (2008) (A, B), Gómez-Gonzalo et al. (2010) (C), Amzica et al. (2002) and Clasadonte et al. (2013) (E).

and seizures by itself through impairment of astrocytic K^+ buffering (Rangroo Thrane et al., 2013).

5.2. Molecular determinants and impact on epilepsy

Changes in astroglial function most likely relies on alterations in the expression and activity of various membrane channels, such as K^+ (Kir4.1), water (aquaporin 4) or gap junction channels (connexins), as well as receptors (*e.g.* mGluRs), transporters (*e.g.* GLT-1 and GLAST for glutamate, GAT3 for GABA), and astroglial specific enzymes such as glutamine synthetase or glutamate and lactate dehydrogenase, as extensively described (Coulter and Steinhauser, 2015; Crunelli and Carmignoto, 2013; Jabs et al., 2008; Losi et al., 2012; Verkhratsky et al., 2012b; Wetherington et al., 2008). In particular, a decrease in astrocytic glutamine synthetase activity has been reported in seizure foci of sclerotic hippocampi (Eid et al., 2004), and proposed to alter the glutamine-glutamate cycle, which would increase extracellular glutamate levels (During and Spencer, 1993). However, enhanced glutamate levels can also result from decreased expression of astroglial glutamate transporters, as well as from increased glutamate release due to astroglial swelling induced by reduced expression of aquaporin 4 water channels (De Lanerolle et al., 2010; Verkhratsky et al., 2012b). In addition, increased extracellular K^+ levels reported during epilepsy are thought to result from impaired expression of astroglial Kir4.1 channels, aquaporin water channels (AQP4) and

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connexin gap junction channels, which altogether lead to reduced fluxes of water and impaired K^+ buffering (Crunelli and Carmignoto, 2013; Jabs et al., 2008; Verkhratsky et al., 2012b). Accordingly, knockout mice for Kir4.1 or AQP4 channels display increased seizure susceptibility (Binder et al., 2004; Djukic et al., 2007) Epilepsy is also associated with an increase in astroglial release of several neuroactive factors with excitatory, inflammatory or immune functions, such as glutamate, chemokines, cytokines and complement factors, which may contribute to hyperexcitability and excitotoxicity (Devinsky et al., 2013; Verkhratsky et al., 2012b). Furthermore, astrocytes can alter the vasculature by increasing its permeability, thereby enabling seizure prone factors such as albumin to penetrate the brain (Kovacs et al., 2012). However, in several cases, inconsistencies about the type of protein alterations and underlying functions are evident. This is probably due to differences in epilepsy models, *i.e.* acute *versus* chronic and different stages of the disease studied in animal models or human tissue, as well as to the complexity of protein functions. Still, potential astroglial targets that could help alleviating epileptic conditions consistently include K^+ and water homeostasis through Kir4.1, AQP4 and connexin channels.

A typical feature of astrocytes is their high intercellular communication through gap junction channels formed by connexin subunits, Cx43 and Cx30. These channels mediate long-range intercellular exchange of numerous ions, metabolites and neuroactive substances, ensuring energy substrates delivery, extracellular ionic and space volume homeostasis, hydric balance and neurotransmitter clearance (Pannasch and Rouach, 2013). Astrocytic networks therefore promote K^+ and glutamate uptake, as well as neuronal energy supply (Amzica et al., 2002; Pannasch et al., 2011). Confusingly, increase, decrease and unchanged levels of Cx43 and associated gap junctional communication have been reported in different animal models of epilepsy (Giaume et al., 2010). In addition, although astrocytic connexins decrease the susceptibility for epileptiform events by partially accounting for K^+ buffering (Wallraff et al., 2006), we have recently shown that they can also sustain epileptiform activity by supplying energy metabolites through astroglial networks (Rouach et al., 2008). In support of this latter finding, a role for astroglial gap junction channels in promoting epileptiform activity has been reported in organotypic hippocampal slice cultures using Cx43 mimetic peptides (Samoilova et al., 2008) and in the hippocampus *ex vivo* and *in vivo* using knockout mice for astroglial connexins (Chever et al., 2016). Thus, downregulation or blockade of connexin channels may be sufficient to reduce seizure occurrence and/or duration. However a very recent study, performed in human epileptic tissue and animal model of epilepsy, suggested an anticonvulsant effect of astrocytic gap junctions (Bedner et al., 2015). In this work, astrocyte uncoupling is proposed to be a cause of human temporal lobe epilepsy, based on correlative data. These data show both, a lack of gap junction coupling in astrocytes from human epileptic tissue with sclerosis, and that uncoupling impairs K^+ buffering and precedes neuronal death and seizures in an animal model of epilepsy. Yet, in this study uncoupling was not directly induced by connexin deletion or selective inhibition, but through activation of inflammatory pathways, well known to reach multiple targets. Therefore, more work is necessary to accurately decipher with selective tools the role of astrocyte gap junction channels in chronic epilepsy.

Noteworthy, impaired brain energy metabolism may also be involved in seizures, as insufficient glucose availability during brain development leads to infantile epilepsy (Pascual et al., 2007) and ketogenic diet (Sirven et al., 1999), a high fat (85%) and low carbohydrate diet, as well as antiglycolytic compounds (Garriga-Canut et al., 2006), display antiepileptic properties. Interestingly, first developed in the early 1900s, the ketogenic diet offers significant anticonvulsant benefits in some children with severe epilepsy. Designed to mimic many of the metabolic effects of starvation, the ketogenic diet provides exogenous fats combined with restricted carbohydrates and calories, which results in moderate hypoglycemia, accumulation of ketone bodies (the products of incompletely burned fats) and increased ATP, the cell energy molecule (DeVivo et al., 1978; Nakazawa et al., 1983). This metabolic therapy is still successfully used today as an alternative but transitory cure for medically refractory epilepsy, particularly in children (Neal et al., 2008; Wilder, 1921) and suppresses or decreases seizure in about two third of the treated patients (Freeman et al., 1998). However, the key mechanism underlying efficiency of the ketogenic diet is still currently unknown. In addition, this therapy is only used transitorily as adhering to this diet is difficult and long term risks include hyperlipidemia, lethargy, kidney stones, pancreatitis, liver dysfunction and metabolic acidosis (Neal et al., 2008). Therefore, deciphering the cellular and molecular mechanisms underlying the anti-epileptic effect of the ketogenic diet is a major challenge since it should contribute to better understand seizure generation from a metabolic point of view and to develop new anti-epileptic strategies by directly targeting the involved pathways. In support of this, a recent major contribution found that simply inhibiting the lactate dehydrogenase enzyme (LDH) in neurons or astrocytes is sufficient to hyperpolarize neurons and suppress epileptic seizures. How this effect is mediated remains however unknown. Still, authors identified an existing anti-epileptic drug, stiripentol, as a mild inhibitor of LDH and designed an analog, isosafrole, with better LDH inhibitory properties. Both drugs proved to be efficient in reducing epileptiform activities (Sada et al., 2015).

Epileptic discharges are characterized by an intense neuronal activity responsible for a high energy demand, but between seizures the epileptic zones are hypometabolic, as shown by fluorodeoxyglucose PET studies (Wieser, 2004), questioning the role of perturbed brain metabolism in seizure generation. Given the evidence that glucose is the major brain metabolic substrate and is metabolized predominantly in astrocytes through glycolysis, followed by transfer of lactate to neurons to fuel their energy demands, glycolysis inhibition and possibly local ketogenesis in astroglial metabolic networks induced by carbohydrate restriction in the ketogenic diet may therefore play a key role in controlling epileptiform activity. This hypothesis is supported by our previous work demonstrating that hypoglycemia suppresses epileptiform activity *in vitro*, an effect inhibited by supply of glucose directly to gap junction-mediated astrocytic networks (Rouach et al., 2008). Up to now, the reported brain energy deficits in epilepsies not only include glucose hypometabolism (Hetherington et al., 2002; Lamusuo et al., 2001; Sadzot et al., 1992), but also poor glucose utilization and high lactate levels (Cavus et al., 2005), which could impair the energetically costly astroglial glutamate uptake and glutamate-glutamine cycling (Eid et al., 2004; Petroff et al., 2002) and lead to extracellular glutamate accumulation and seizures. As astrocytes play a key role in energy metabolism and glutamate homeostasis, it is tempting to speculate that plastic activity-dependent metabolic changes in astrocytes, already proposed to occur during synaptic plasticity (Magistretti, 2006), contribute to seizures.

Ca^{2+}-dependent glutamate release by astrocytes is another way proposed to contribute to seizure genesis (Gómez-Gonzalo et al., 2010; Kang et al., 2005; Tian et al., 2005). Indeed, by activating NMDARs (slow inward currents), astroglial glutamate release can synchronize neurons (Angulo et al., 2004; Fellin et al., 2004) and generate paroxysmal depolarization shifts, underlying interictal bursts (Kang et al., 2005; Tian et al., 2005). This hypothesis is also supported by a study showing the importance of astroglial Ca^{2+} signaling in driving neurons to seizure threshold (Gómez-Gonzalo et al., 2010). Hence an astrocentric view of epileptogenesis has emerged (Tian et al., 2005), corroborated by several lines of

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evidence: (1) some proconvulsants evoke astroglial Ca^{2+} signaling, while anticonvulsants attenuate it (Tian et al., 2005); (2) pathologic tissues from epileptic patients show altered spontaneous intracellular $Ca^{2+}{}_i$ oscillations (Manning and Sontheimer, 1997); (3) epileptic discharges are associated with astroglial Ca^{2+} waves (Ding et al., 2007; Lee et al., 1995). However, these data describe mostly correlations between astroglial Ca^{2+} signaling and neuronal epileptic discharges, but no causal link. Indeed, another study showed that astrocytic glutamate is actually not necessary for the initiation and maintenance of epileptiform activity, although it does evoke neuronal depolarization and action potentials, and modulate the strength of interictal and ictal events (Fellin et al., 2006). Noteworthy, it was recently shown *in vivo* using genetic manipulations targeting specifically astrocytes, that snare-dependent gliotransmitter release, traditionally thought to be Ca^{2+}-dependent, contributes to seizures, hippocampal damage and behavioral deficits associated to epileptic discharges (Fig. 4E) (Clasadonte et al., 2013). Therefore, more work is necessary to decipher which type of astroglial Ca^{2+} signaling is involved in seizure activity.

Contradictory results have occasionally emerged in the literature on the role of astrocytes in epilepsy, probably due to the diversity of the models, and also to several limitations. In particular, a major technical limit to the study of neuroglial interactions is to act selectively on astrocytes, as they possess many receptors, transporters and transmitters identical to the neuronal ones. In addition, since the physiopathological consequences of the bidirectional communication between neurons and astrocytes are not fully understood, it is sometimes unclear whether astrocytic changes cause, worsen, fight the disease, or rather represent an accompanying phenomenon. Still, in all, the multiple morphological and functional alterations of astrocytes come along with and likely contribute to seizures in the epileptic brain. This view is supported by a few modeling studies of epilepsy. Although most modeling studies have only considered the contribution of neurons (Lytton, 2008), a few models predict seizures in the case of increased expression of mGluRs (Nadkarni and Jung, 2005, 2003) or reduced K^+ clearance (David et al., 2009; Sibille et al., 2015a) by astrocytes.

6. Conclusions

Investigations of the multiple roles of astrocytes in the brain have gradually transformed the field of neuroscience research. This started from the molecular and cellular levels, by showing that astrocytes are able to uptake and release neuroactive molecules with more complex purposes than provide trophic and clearance support, passing by physiological appreciations of the neuroglial interactions *via* characterization of astroglial responses to synaptic activity and how they influence neurotransmission, all the way through the realization that these electrically silent cells are actually major players in the regulation of neural circuits activities, notably by forming long-distance communication networks (Pannasch and Rouach, 2013). Recent advances now show that the physiological roles of astrocytes do translate at the behavioral and cognitive level to an extent beyond expectation. Indeed, they not only help, but subtend cognition since disturbing them results in major impairment of key functions such as sleep (Halassa et al., 2009) and memory consolidation (*e.g.* recognition memory) (Lee et al., 2014), associative memory (Gibbs et al., 2008; Stehberg et al., 2012). Moreover, their prevalent impact in evolution that has long been suspected because of their increase in number and complexification in advanced brains (Oberheim et al., 2006) has recently been supported by direct evidence revealing that replacement of the mouse astrocytic population by human astroglia markedly ameliorates plasticity and cognitive functions (Han et al., 2013). Such striking findings indicate that the purpose of improving cognition could be better served by aiming at influencing astroglial processes. In the physiological context, this could mean developing pro-cognitive agents counteracting cognitive decline associated to overstrain or simply aging. More importantly, many brain diseases result in intellectual disabilities, and would likely benefit from new therapeutic strategies targeting astrocytes. Disorders characterized by the loss of neurons undergo harmful processes that manipulated astrocytes may well soften. Namely, excitotoxicity is promoted by impaired clearance of glutamate *via* GLT1 and K^+ *via* Kir4.1 in most neurodegenerative conditions, restoring these astroglial functions should thus result in a neuroprotective effect delaying cognitive symptoms. Oxidative stress is also a major affliction in these diseases and regulating the expression of ROS producing or scavenging enzymes in astrocytes such as NOS and SOD, respectively, or enzymes influencing iron content like HO-1, may be salvatory. Finally, astrocytes appear to be endowed with the powerful ability to detoxify degenerating neurons by degrading protein aggregates (*e.g.* amyloid plaques, mHtt aggregates (Tydlacka et al., 2008; Wyss-Coray et al., 2003)) associated with AD, HD and PD. Promoting such function may be enough to protect neurons from premature death. The more subtle brain diseases represented by neuropsychiatric disorders would also see their treatment benefit from astroglial based strategy. Incidentally, antidepressant drugs already correct reported astroglial defects, although the process behind such effect remains poorly understood. Likewise, schizophrenia treatments presently encompass adjunction of the gliotransmitter D-serine or inhibitor of its degrading enzyme DAAO. ASD is in fact a plural disease and may be more complex to apprehend. Nevertheless, several lines of evidence suggest that limiting TNFα signaling specifically in astrocytes might be favorable to the relief of autistic symptoms. Remarkably, current data obtained on animal models of RTT and FXS suggest that timely administrated gene therapy on astrocytes may suffice to suppress neuropathology and symptoms associated with these genetic forms of ASD. This could be advantageous as the spread of a therapeutic transgene should be facilitated by the high GJs coupling of astroglial networks. Finally, research on the brain damaging epileptic conditions points to a possible role of astrocytes in epileptogenesis and/or maintenance of epileptic activities. Although several discrepancies have been found on this matter, Kir4.1, AQP4 and connexins channels have by and large been found to be major players in the mechanisms regulating seizures and could thus represent key targets to appease epileptic brains.

As a whole, the current knowledge of the role of astrocytes in normal information processing and in the major brain diseases known to generate cognitive dysfunction enables to point out several promising astrocytic elements that influence brain function or that may be able to help delaying cognitive decline or rehabilitating normal intellectual capacities. Nevertheless, neuroglial interactions are tremendously complex and many shadows remain in our appreciation of how astroglial and neuronal network work in concert to handle and process information. Similarly, revision of our understanding of the brain diseases in light of the relatively new roles ascribed to astroglia is still at its infancy and further development are needed to beat these appaling disorders.

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References

Altshuler, L.L., Abulseoud, O.A., Foland-Ross, L., Bartzokis, G., Chang, S., Mintz, J., Hellemann, G., Vinters, H.V., 2010. Amygdala astrocyte reduction in subjects with major depressive disorder but not bipolar disorder. Bipolar Disord. 12, 541–549, http://dx.doi.org/10.1111/j.1399-5618.2010.00838.x.

Amzica, F., Massimini, M., Manfridi, A., 2002. Spatial buffering during slow and paroxysmal sleep oscillations in cortical networks of glial cells in vivo. J. Neurosci. 22, 1042–1053.

Amzica, F., Steriade, M., 2000. Neuronal and glial membrane potentials during sleep and paroxysmal oscillations in the neocortex. J. Neurosci. 20, 6648–6665.

Angulo, M.C., Kozlov, A.S., Charpak, S., Audinat, E., 2004. Glutamate released from glial cells synchronizes neuronal activity in the hippocampus. J. Neurosci. 24, 6920–6927, http://dx.doi.org/10.1523/JNEUROSCI.0473-04.2004.

Anlauf, E., Derouiche, A., 2013. Glutamine synthetase as an astrocytic marker: its cell type and vesicle localization. Front. Endocrinol. (Lausanne) 4, 144, http://dx.doi.org/10.3389/fendo.2013.00144.

Aqdam, M.J., Kamali, K., Rahgozar, M., Ohadi, M., Manoochehri, M., Tahami, A., Bostanshirin, L., Khorshid, H.R.K., 2010. Association of CALHM1 gene polymorphism with late onset Alzheimer's disease in Iranian population. Avicenna J. Med. Biotechnol. 2, 153–157.

Araneda, S., Commin, L., Atlagich, M., Kitahama, K., Parraguez, V.H., Pequignot, J.-M., Dalmaz, Y., 2008. VEGF overexpression in the astroglial cells of rat brainstem following ozone exposure. Neurotoxicology 29, 920–927, http://dx.doi.org/10.1016/j.neuro.2008.09.006.

Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H.R., Robitaille, R., Volterra, A., 2014. Gliotransmitters travel in time and space. Neuron 81, 728–739, http://dx.doi.org/10.1016/j.neuron.2014.02.007.

Ariano, M.A., Cepeda, C., Calvert, C.R., Flores-Hernandez, J., Hernandez-Echeagaray, E., Klapstein, G.J., Chandler, S.H., Aronin, N., DiFiglia, M., Levine, M.S., Flores-Hernández, J., Hernández-Echeagaray, E., 2005. Striatal potassium channel dysfunction in Huntington's disease transgenic mice. J. Neurophysiol. 93, 2565–2574, http://dx.doi.org/10.1152/jn.00791.2004.

Aronson, M., Hagberg, B., Gillberg, C., 1997. Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: a follow-up study. Dev. Med. Child Neurol. 39, 583–587.

Arundine, M., Tymianski, M., 2003. Molecular mechanisms of calcium-dependent neurodegeneration in excitotoxicity. Cell Calcium 34, 325–337.

Assous, M., Had-Aissouni, L., Gubellini, P., Melon, C., Nafia, I., Salin, P., Kerkerian-Le-Goff, L., Kachidian, P., 2014. Progressive Parkinsonism by acute dysfunction of excitatory amino acid transporters in the rat substantia nigra. Neurobiol. Dis. 65, 69–81, http://dx.doi.org/10.1016/j.nbd.2014.01.011.

Bakos, J., Bacova, Z., Grant, S.G., Castejon, A.M., Ostatnikova, D., 2015. Are molecules involved in neuritogenesis and axon guidance related to autism pathogenesis? Neuromol. Med. 17, 297–304, http://dx.doi.org/10.1007/s12017-015-8357-7.

Ballas, N., Lioy, D.T., Grunseich, C., Mandel, G., 2009. Non-cell autonomous influence of MeCP2-deficient glia on neuronal dendritic morphology. Nat. Neurosci. 12, 311–317, http://dx.doi.org/10.1038/nn.2275.

Banaclocha, M.A.M., 2007. Neuromagnetic dialogue between neuronal minicolumns and astroglial network: a new approach for memory and cerebral computation. Brain Res. Bull. 73, 21–27, http://dx.doi.org/10.1016/j.brainresbull.2007.01.012.

Banasr, M., Duman, R.S., 2008. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. Biol. Psychiatry 64, 863–870, http://dx.doi.org/10.1016/j.biopsych.2008.06.008.

Bartzokis, G., Tishler, T.A., 2000. MRI evaluation of basal ganglia ferritin iron and neurotoxicity in Alzheimer's and Huntingon's disease. Cell. Mol. Biol. (Noisy-le-grand) 46, 821–833.

Bassell, G.J., Warren, S.T., 2008. Fragile X syndrome: loss of local mRNA regulation alters synaptic development and function. Neuron 60, 201–214, http://dx.doi.org/10.1016/j.neuron.2008.10.004.

Beard, J.L., Connor, J.R., Jones, B.C., 1993. Iron in the brain. Nutr. Rev. 51, 157–170.

Bedner, P., Dupper, A., Huttmann, K., Muller, J., Herde, M.K., Dublin, P., Deshpande, T., Schramm, J., Haussler, U., Haas, C.A., Henneberger, C., Theis, M., Steinhauser, C., 2015. Astrocyte uncoupling as a cause of human temporal lobe epilepsy. Brain 138, 1208–1222, http://dx.doi.org/10.1093/brain/awv067.

Behrens, P.F., Franz, P., Woodman, B., Lindenberg, K.S., Landwehrmeyer, G.B., 2002. Impaired glutamate transport and glutamate-glutamine cycling: downstream effects of the Huntington mutation. Brain 125, 1908–1922.

Bernard, R., Kerman, I.A., Thompson, R.C., Jones, E.G., Bunney, W.E., Barchas, J.D., Schatzberg, A.F., Myers, R.M., Akil, H., Watson, S.J., 2011. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Mol. Psychiatry 16, 634–646, http://dx.doi.org/10.1038/mp.2010.44.

Bernardinelli, Y., Muller, D., Nikonenko, I., 2014. Astrocyte-synapse structural plasticity. Neural Plast. 2014, 232105, http://dx.doi.org/10.1155/2014/232105.

Bezzi, P., Carmignoto, G., Pasti, L., Vesce, S., Rossi, D., Rizzini, B.L., Pozzan, T., Volterra, A., 1998. Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. Nature 391, 281–285.

Bezzi, P., Volterra, A., 2001. A neuron-glia signalling network in the active brain. Curr. Opin. Neurobiol. 11, 387–394.

Binder, D.K., Oshio, K., Ma, T., Verkman, A.S., Manley, G.T., 2004. Increased seizure threshold in mice lacking aquaporin-4 water channels. Neuroreport 15, 259–262, http://dx.doi.org/10.1097/00001756-200402090-00009.

Björkhem, I., Lövgren-Sandblom, A., Leoni, V., Meaney, S., Brodin, L., Salveson, L., Winge, K., Pålhagen, S., Svenningsson, P., 2013. Oxysterols and Parkinson's disease: evidence that levels of 24S-hydroxycholesterol in cerebrospinal fluid correlates with the duration of the disease. Neurosci. Lett. 555, 102–105, http://dx.doi.org/10.1016/j.neulet.2013.09.003.

Block, M.L., Calderón-Garcidueñas, L., 2009. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 32, 506–516, http://dx.doi.org/10.1016/j.tins.2009.05.009.

Bohn, M.C., O'Banion, M.K., Young, D.A., Giuliano, R., Hussain, S., Dean, D.O., Cunningham, L.A., 1994. In vitro studies of glucocorticoid effects on neurons and astrocytes. Ann. N. Y. Acad. Sci. 746, 243–258, discussion 258–9, 289–93.

Bordey, A., Sontheimer, H., 1998. Properties of human glial cells associated with epileptic seizure foci. Epilepsy Res. 32, 286–303, http://dx.doi.org/10.1016/S0920-1211(98)00059-X.

Bosson, A., Boisseau, S., Buisson, A., Savasta, M., Albrieux, M., 2015. Disruption of dopaminergic transmission remodels tripartite synapse morphology and astrocytic calcium activity within substantia nigra pars reticulata. Glia 63, 673–683, http://dx.doi.org/10.1002/glia.22777.

Brockett, A.T., LaMarca, E.A., Gould, E., 2015. Physical exercise enhances cognitive flexibility as well as astrocytic and synaptic markers in the Medial Prefrontal Cortex. PLOS ONE 10, e0124859, http://dx.doi.org/10.1371/journal.pone.0124859.

Bushong, E.A., Martone, M.E., Jones, Y.Z., Ellisman, M.H., 2002. Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. J. Neurosci. 22, 183–192.

Calabrese, V., Cornelius, C., Rizzarelli, E., Owen, J.B., Dinkova-Kostova, A.T., Butterfield, D.A., 2009. Nitric oxide in cell survival: a janus molecule. Antioxid. Redox Signal. 11, 2717–2739, http://dx.doi.org/10.1089/ARS.2009.2721.

Cassano, T., Serviddio, G., Gaetani, S., Romano, A., Dipasquale, P., Cianci, S., Bellanti, F., Laconca, L., Romano, A.D., Padalino, I., LaFerla, F.M., Nicoletti, F., Cuomo, V., Vendemiale, G., 2012. Glutamatergic alterations and mitochondrial impairment in a murine model of Alzheimer disease. Neurobiol. Aging 33, 1121.e1–1121.e12, http://dx.doi.org/10.1016/j.neurobiolaging.2011.09.021.

Castaldo, P., Cataldi, M., Magi, S., Lariccia, V., Arcangeli, S., Amoroso, S., 2009. Role of the mitochondrial sodium/calcium exchanger in neuronal physiology and in the pathogenesis of neurological diseases. Prog. Neurobiol. 87, 58–79, http://dx.doi.org/10.1016/j.pneurobio.2008.09.017.

Catts, V.S., Wong, J., Fillman, S.G., Fung, S.J., Shannon Weickert, C., 2014. Increased expression of astrocyte markers in schizophrenia: association with neuroinflammation. Aust. N. Z. J. Psychiatry 48, 722–734, http://dx.doi.org/10.1177/0004867414531078.

Caudle, R.M., 2006. Memory in astrocytes: a hypothesis. Theor. Biol. Med. Model. 3, 2.

Cavus, I., Kasoff, W.S., Cassaday, M.P., Jacob, R., Gueorguieva, R., Sherwin, R.S., Krystal, J.H., Spencer, D.D., Abi-Saab, W.M., 2005. Extracellular metabolites in the cortex and hippocampus of epileptic patients. Ann. Neurol. 57, 226–235.

Chen, J., 2014. Heme oxygenase in neuroprotection: from mechanisms to therapeutic implications. Rev. Neurosci. 25, 269–280, http://dx.doi.org/10.1515/revneuro-2013-0046.

Chen, J., Tan, Z., Zeng, L., Zhang, X., He, Y., Gao, W., Wu, X., Li, Y., Bu, B., Wang, W., Duan, S., 2013. Heterosynaptic long-term depression mediated by ATP released from astrocytes. Glia 61, 178–191, http://dx.doi.org/10.1002/glia.22425.

Cheung, G., Chever, O., Rouach, N., 2014. Connexons and pannexons: newcomers in neurophysiology. Front. Cell. Neurosci. 8, 348, http://dx.doi.org/10.3389/fncel.2014.00348.

Chever, O., Lee, C.-Y., Rouach, N., 2014. Astroglial connexin43 hemichannels tune basal excitatory synaptic transmission. J. Neurosci. 34, 11228–11232, http://dx.doi.org/10.1523/JNEUROSCI.0015-14.2014.

Chever, O., Dossi, E., Pannasch, U., Derangeon, M., Rouach, N., 2016. Astroglial networks promote neuronal coordination. Sci. Signal. 9, ra6, http://dx.doi.org/10.1126/scisignal.aad3066.

Christianson, A.L., Chesler, N., Kromberg, J.G., 1994. Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev. Med. Child Neurol. 36, 361–369.

Clarke, L.E., Barres, B.A., 2013. Glia keep synapse distribution under wraps. Cell 154, 267–268, http://dx.doi.org/10.1016/j.cell.2013.06.045.

Clasadonte, J., Dong, J., Hines, D.J., Haydon, P.G., 2013. Astrocyte control of synaptic NMDA receptors contributes to the progressive development of temporal lobe epilepsy. Proc. Natl. Acad. Sci. U. S. A. 110, 17540–17545, http://dx.doi.org/10.1073/pnas.1311967110.

Cotter, D.R., Pariante, C.M., Everall, I.P., 2001. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. Brain Res. Bull. 55, 585–595, http://dx.doi.org/10.1016/S0361-9230(01)00527-5.

Coulter, D.A., Steinhauser, C., 2015. Role of astrocytes in epilepsy. Cold Spring Harb. Perspect. Med. 5, a022434, http://dx.doi.org/10.1101/cshperspect.a022434.

Cowan, C.M., Mudher, A., 2013. Are tau aggregates toxic or protective in tauopathies? Front. Neurol. 4, 114, http://dx.doi.org/10.3389/fneur.2013.00114.

Crossin, K.L., Tai, M.H., Krushel, L.A., Mauro, V.P., Edelman, G.M., 1997. Glucocorticoid receptor pathways are involved in the inhibition of astrocyte proliferation. Proc. Natl. Acad. Sci. U. S. A. 94, 2687–2692.

Crunelli, V., Carmignoto, G., 2013. New vistas on astroglia in convulsive and non-convulsive epilepsy highlight novel astrocytic targets for treatment. J. Physiol. 591, 775–785, http://dx.doi.org/10.1113/jphysiol.2012.243378.

Czéh, B., Müller-Keuker, J.I.H., Rygula, R., Abumaria, N., Hiemke, C., Domenici, E., Fuchs, E., 2007. Chronic social stress inhibits cell proliferation in the adult medial prefrontal cortex: hemispheric asymmetry and reversal by fluoxetine treatment. Neuropsychopharmacology 32, 1490–1503, http://dx.doi.org/10.1038/sj.npp.1301275.

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Czéh, B., Simon, M., Schmelting, B., Hiemke, C., Fuchs, E., 2006. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. Neuropsychopharmacology 31, 1616–1626, http://dx.doi.org/10.1038/sj.npp.1300982.

Dallérac, G., Chever, O., Rouach, N., 2013. How do astrocytes shape synaptic transmission? Insights from electrophysiology. Front. Cell. Neurosci. 7, 159, http://dx.doi.org/10.3389/fncel.2013.00159.

David, Y., Cacheaux, L.P., Ivens, S., Lapilover, E., Heinemann, U., Kaufer, D., Friedman, A., 2009. Astrocytic dysfunction in epileptogenesis: consequence of altered potassium and glutamate homeostasis? J. Neurosci. 29, 10588–10599, http://dx.doi.org/10.1523/JNEUROSCI.2323-09.2009.

De Lanerolle, N.C., Lee, T.S., Spencer, D.D., 2010. Astrocytes and epilepsy. Neurotherapeutics 7, 424–438, http://dx.doi.org/10.1016/j.nurt.2010.08.002, pii:S1933-7213(10)00113-3.

De Lima, M.N.M., Polydoro, M., Laranja, D.C., Bonatto, F., Bromberg, E., Moreira, J.C.F., Dal-Pizzol, F., Schröder, N., 2005. Recognition memory impairment and brain oxidative stress induced by postnatal iron administration. Eur. J. Neurosci. 21, 2521–2528, http://dx.doi.org/10.1111/j.1460-9568.2005.04083.x.

Devinsky, O., Vezzani, A., Najjar, S., De Lanerolle, N.C., Rogawski, M.A., 2013. Glia and epilepsy: excitability and inflammation. Trends Neurosci. 36, 174–184, http://dx.doi.org/10.1016/j.tins.2012.11.008, pii:S0166-2236(12)00205-6.

DeVivo, D.C., Leckie, M.P., Ferrendelli, J.S., McDougal, D.B., 1978. Chronic ketosis and cerebral metabolism. Ann. Neurol. 3, 331–337, http://dx.doi.org/10.1002/ana.410030410.

Dichter, M.A., Herman, C.J., Selzer, M., 1972. Silent cells during interictal discharges and seizures in hippocampal penicillin foci. Evidence for the role of extracellular K^+ in the transition from the interictal state to seizures. Brain Res. 48, 173–183.

Ding, S., Fellin, T., Zhu, Y., Lee, S.-Y., Auberson, Y.P., Meaney, D.F., Coulter, D.A., Carmignoto, G., Haydon, P.G., 2007. Enhanced astrocytic Ca^{2+} signals contribute to neuronal excitotoxicity after status epilepticus. J. Neurosci. 27, 10674–10684, http://dx.doi.org/10.1523/JNEUROSCI.2001-07.2007.

Djukic, B., Casper, K.B., Philpot, B.D., Chin, L.-S., McCarthy, K.D., 2007. Conditional knock-out of Kir4.1 leads to glial membrane depolarization, inhibition of potassium and glutamate uptake, and enhanced short-term synaptic potentiation. J. Neurosci. 27, 11354–11365, http://dx.doi.org/10.1523/JNEUROSCI.0723-07.2007.

Dong, X., Wang, Y., Qin, Z., 2009. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol. Sin. 30, 379–387, http://dx.doi.org/10.1038/aps.2009.24.

Dörrie, N., Föcker, M., Freunscht, I., Hebebrand, J., 2014. Fetal alcohol spectrum disorders. Eur. Child Adolesc. Psychiatry 23, 863–875, http://dx.doi.org/10.1007/s00787-014-0571-6.

During, M.J., Spencer, D.D., 1993. Extracellular hippocampal glutamate and spontaneous seizure in the conscious human brain. Lancet 341, 1607–1610, http://dx.doi.org/10.1016/0140-6736(93)90754-5.

Dwork, A.J., Arango, V., Underwood, M., Ilievski, B., Rosoklija, G., Sackeim, H.A., Lisanby, S.H., 2004. Absence of histological lesions in primate models of ECT and magnetic seizure therapy. Am. J. Psychiatry 161, 576–578.

Eid, T., Thomas, M.J., Spencer, D.D., Runden-Pran, E., Lai, J.C., Malthankar, G.V., Kim, J.H., Danbolt, N.C., Ottersen, O.P., de Lanerolle, N.C., 2004. Loss of glutamine synthetase in the human epileptogenic hippocampus: possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. Lancet 363, 28–37.

Falkai, P., Honer, W.G., David, S., Bogerts, B., Majtenyi, C., Bayer, T.A., 1999. No evidence for astrogliosis in brains of schizophrenic patients. A post-mortem study. Neuropathol. Appl. Neurobiol. 25, 48–53.

Falsone, A., Falsone, S.F., 2015. Legal but lethal: functional protein aggregation at the verge of toxicity. Front. Cell. Neurosci. 9, 45, http://dx.doi.org/10.3389/fncel.2015.00045.

Fatemi, S.H., Folsom, T.D., 2011. Dysregulation of fragile × mental retardation protein and metabotropic glutamate receptor 5 in superior frontal cortex of individuals with autism: a postmortem brain study. Mol. Autism 2, 6, http://dx.doi.org/10.1186/2040-2392-2-6.

Fellin, T., Gomez-Gonzalo, M., Gobbo, S., Carmignoto, G., Haydon, P.G., 2006. Astrocytic glutamate is not necessary for the generation of epileptiform neuronal activity in hippocampal slices. J. Neurosci. 26, 9312–9322, http://dx.doi.org/10.1523/JNEUROSCI.2836-06.2006.

Fellin, T., Halassa, M.M., Terunuma, M., Succol, F., Takano, H., Frank, M., Moss, S.J., Haydon, P.G., 2009. Endogenous nonneuronal modulators of synaptic transmission control cortical slow oscillations in vivo. Proc. Natl. Acad. Sci. U. S. A. 106, 15037–15042, http://dx.doi.org/10.1073/pnas.0906419106.

Fellin, T., Pascual, O., Gobbo, S., Pozzan, T., Haydon, P.G., Carmignoto, G., 2004. Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. Neuron 43, 729–743, http://dx.doi.org/10.1016/j.neuron.2004.08.011.

Feresten, A.H., Barakauskas, V., Ypsilanti, A., Barr, A.M., Beasley, C.L., 2013. Increased expression of glial fibrillary acidic protein in prefrontal cortex in psychotic illness. Schizophr. Res. 150, 252–257, http://dx.doi.org/10.1016/j.schres.2013.07.024.

Fields, R.D., Araque, A., Johansen-Berg, H., Lim, S.-S., Lynch, G., Nave, K.-A., Nedergaard, M., Perez, R., Sejnowski, T., Wake, H., 2013. Glial biology in learning and cognition. Neuroscientist, http://dx.doi.org/10.1177/1073858413504465.

Fossat, P., Turpin, F.R., Sacchi, S., Dulong, J., Shi, T., Rivet, J.-M., Sweedler, J.V., Pollegioni, L., Millan, M.J., Oliet, S.H.R., Mothet, J.-P., 2011. Glial D-serine gates NMDA receptors at excitatory synapses in prefrontal cortex. Cereb. Cortex 1–12, http://dx.doi.org/10.1093/cercor/bhr130.

Freeman, J.M., Vining, E.P., Pillas, D.J., Pyzik, P.L., Casey, J.C., Kelly, L.M., 1998. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics 102, 1358–1363.

Fujii, S., Tanaka, K.F., Ikenaka, K., Yamazaki, Y., 2014. Increased adenosine levels in mice expressing mutant glial fibrillary acidic protein in astrocytes result in failure of induction of LTP reversal (depotentiation) in hippocampal CA1 neurons. Brain Res. 1578, 1–13, http://dx.doi.org/10.1016/j.brainres.2014.07.005.

Fujiki, M., Steward, O., 1997. High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astroglial gene expression in the murine CNS. Brain Res. Mol. Brain Res. 44, 301–308.

Fujita, T., Chen, M.J., Li, B., Smith, N.A., Peng, W., Sun, W., Toner, M.J., Kress, B.T., Wang, L., Benraiss, A., Takano, T., Wang, S., Nedergaard, M., 2014. Neuronal transgene expression in dominant-negative SNARE mice. J. Neurosci. 34, 16594–16604, http://dx.doi.org/10.1523/JNEUROSCI.2585-14.2014.

Fukui, S., Nawashiro, H., Ookawara, T., Suzuki, K., Otani, N., Ooigawa, H., Shima, K., 2003. Extracellular superoxide dismutase following cerebral ischemia in mice. Acta Neurochir. Suppl. 86, 83–85.

Fumagalli, E., Funicello, M., Rauen, T., Gobbi, M., Mennini, T., 2008. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. Eur. J. Pharmacol. 578, 171–176.

Furman, J.L., Sama, D.M., Gant, J.C., Beckett, T.L., Murphy, M.P., Bachstetter, A.D., Van Eldik, L.J., Norris, C.M., 2012. Targeting astrocytes ameliorates neurologic changes in a mouse model of Alzheimer's disease. J. Neurosci. 32, 16129–16140.

Gallagher, P., Young, A.H., 2006. Mifepristone (RU-486) treatment for depression and psychosis: a review of the therapeutic implications. Neuropsychiatr. Dis. Treat. 2, 33–42.

Gamba, P., Testa, G., Gargiulo, S., Staurenghi, E., Poli, G., Leonarduzzi, G., 2015. Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. Front. Aging Neurosci. 7, 1–21, http://dx.doi.org/10.3389/fnagi.2015.00119.

Gardoni, F., Di Luca, M., 2006. New targets for pharmacological intervention in the glutamatergic synapse. Eur. J. Pharmacol. 545, 2–10, http://dx.doi.org/10.1016/j.ejphar.2006.06.022.

Garriga-Canut, M., Schoenike, B., Qazi, R., Bergendahl, K., Daley, T.J., Pfender, R.M., Morrison, J.F., Ockuly, J., Stafstrom, C., Sutula, T., Roopra, A., 2006. 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure. Nat. Neurosci. 9, 1382–1387, http://dx.doi.org/10.1038/nn1791.

Gholizadeh, S., Arsenault, J., Xuan, I.C.Y., Pacey, L.K., Hampson, D.R., 2014. Reduced phenotypic severity following adeno-associated virus-mediated Fmr1 gene delivery in fragile X mice. Neuropsychopharmacology 39, 3100–3111, http://dx.doi.org/10.1038/npp.2014.167.

Gholizadeh, S., Halder, S.K., Hampson, D.R., 2015. Expression of fragile X mental retardation protein in neurons and glia of the developing and adult mouse brain. Brain Res. 1596, 22–30, http://dx.doi.org/10.1016/j.brainres.2014.11.023.

Giaume, C., Koulakoff, A., Roux, L., Holcman, D., Rouach, N., 2010. Astroglial networks: a step further in neuroglial and gliovascular interactions. Nat. Rev. Neurosci. 11, 87–99, http://dx.doi.org/10.1038/nrn2757.

Giaume, C., Leybaert, L., Naus, C.C., Sáez, J.C., 2013. Connexin and pannexin hemichannels in brain glial cells: properties, pharmacology, and roles. Front. Pharmacol. 4, 88, http://dx.doi.org/10.3389/fphar.2013.00088.

Gibbs, M.E., 1991. Behavioral and pharmacological unravelling of memory formation. Neurochem. Res. 16, 715–726.

Gibbs, M.E., Hertz, L., 2008. Inhibition of astrocytic energy metabolism by D-lactate exposure impairs memory. Neurochem. Int. 52, 1012–1018, http://dx.doi.org/10.1016/j.neuint.2007.10.014.

Gibbs, M.E., Hutchinson, D., Hertz, L., 2008. Astrocytic involvement in learning and memory consolidation. Neurosci. Biobehav. Rev. 32, 927–944, http://dx.doi.org/10.1016/j.neubiorev.2008.02.001.

Gibbs, M.E., Lloyd, H.G.E., Santa, T., Hertz, L., 2007. Glycogen is a preferred glutamate precursor during learning in 1-day-old chick: biochemical and behavioral evidence. J. Neurosci. Res. 85, 3326–3333, http://dx.doi.org/10.1002/jnr.21307.

Gibbs, M.E., O'Dowd, B.S., Hertz, L., Robinson, S.R., Sedman, G.L., Ng, K.T., 1996. Inhibition of glutamine synthetase activity prevents memory consolidation. Brain Res. Cogn. Brain Res. 4, 57–64.

Gilgun-Sherki, Y., Melamed, E., Offen, D., 2001. Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. Neuropharmacology 40, 959–975.

Gomes, F.V., Llorente, R., Del Bel, E.A., Viveros, M.-P., López-Gallardo, M., Guimarães, F.S., 2015. Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol. Schizophr. Res. 164, 155–163, http://dx.doi.org/10.1016/j.schres.2015.01.015.

Gómez-Gonzalo, M., Losi, G., Chiavegato, A., Zonta, M., Cammarota, M., Brondi, M., Vetri, F., Uva, L., Pozzan, T., de Curtis, M., Ratto, G.M., Carmignoto, G., 2010. An excitatory loop with astrocytes contributes to drive neurons to seizure threshold. PLoS Biol. 8, e1000352, http://dx.doi.org/10.1371/journal.pbio.1000352.

Gómez-Pinilla, F., So, V., Kesslak, J.P., 1998. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. Neuroscience 85, 53–61, http://dx.doi.org/10.1016/S0306-4522(97)00576-9.

Gomez-Villafuertes, R., Mellström, B., Naranjo, J.R., 2007. Searching for a role of NCX/NCKX exchangers in neurodegeneration. Mol. Neurobiol. 35, 195–202.

Graham, S.F., Nasarauddin, M.B., Carey, M., McGuinness, B., Holscher, C., Kehoe, P.G., Love, S., Passmore, A.P., Elliott, C.T., Meharg, A., Green, B.D., 2015. Quantitative

Please cite this article in press as: Dallérac, G., Rouach, N., Astrocytes as new targets to improve cognitive functions. Prog. Neurobiol. (2016), http://dx.doi.org/10.1016/j.pneurobio.2016.01.003

measurement of [Na+] and [K+] in postmortem human brain tissue indicates disturbances in subjects with Alzheimer's disease and dementia with Lewy bodies. J. Alzheimers Dis. 44, 851–857, http://dx.doi.org/10.3233/JAD-141869.
Grossman, R.G., Hampton, T., 1968. Depolarization of cortical glial cells during electrocortical activity. Brain Res. 11, 316–324.
Guizzetti, M., Moore, N.H., Giordano, G., VanDeMark, K.L., Costa, L.G., 2010. Ethanol inhibits neuritogenesis induced by astrocyte muscarinic receptors. Glia 58, 1395–1406, http://dx.doi.org/10.1002/glia.21015.
Gundersen, V., 2010. Protein aggregation in Parkinson's disease. Acta Neurol. Scand. Suppl. 82–87 , http://dx.doi.org/10.1111/j.1600-0404.2010.01382.x.
Haber, M., Zhou, L., Murai, K.K., 2006. Cooperative astrocyte and dendritic spine dynamics at hippocampal excitatory synapses. J. Neurosci. 26, 8881–8891, http://dx.doi.org/10.1523/JNEUROSCI.1302-06.2006.
Hagemann, T.L., Connor, J.X., Messing, A., 2006. Alexander disease-associated glial fibrillary acidic protein mutations in mice induce Rosenthal fiber formation and a white matter stress response. J. Neurosci. 26, 11162–11173, http://dx.doi.org/10.1523/JNEUROSCI.3260-06.2006.
Hagemann, T.L., Paylor, R., Messing, A., 2013. Deficits in adult neurogenesis, contextual fear conditioning, and spatial learning in a Gfap mutant mouse model of Alexander disease. J. Neurosci. 33, 18698–18706, http://dx.doi.org/10.1523/JNEUROSCI.3693-13.2013.
Halassa, M.M., Fellin, T., Takano, H., Dong, J.-H., Haydon, P.G., 2007. Synaptic islands defined by the territory of a single astrocyte. J. Neurosci. 27, 6473–6477, http://dx.doi.org/10.1523/JNEUROSCI.1419-07.2007.
Halassa, M.M., Florian, C., Fellin, T., Munoz, J.R., Lee, S.-Y., Abel, T., Haydon, P.G., Frank, M.G., 2009. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 61, 213–219, http://dx.doi.org/10.1016/j.neuron.2008.11.024.
Halassa, M.M., Haydon, P.G., 2010. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. Annu. Rev. Physiol. 72, 335–355, http://dx.doi.org/10.1146/annurev-physiol-021909-135843.
Halliwell, B., 1992. Reactive oxygen species and the central nervous system. J. Neurochem. 59, 1609–1623.
Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S., Xu, Q., Oberheim, N.A., Bekar, L., Betstadt, S., Silva, A.J., Takano, T., Goldman, S.A., Nedergaard, M., 2013. Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell 12, 342–353, http://dx.doi.org/10.1016/j.stem.2012.12.015.
Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356, http://dx.doi.org/10.1126/science.1072994.
Harrison, P.J., 2002. The neuropathology of primary mood disorder. Brain.
Hayashida, N., Fujimoto, M., Tan, K., Prakasam, R., Shinkawa, T., Li, L., Ichikawa, H., Takii, R., Nakai, A., 2010. Heat shock factor 1 ameliorates proteotoxicity in cooperation with the transcription factor NFAT. EMBO J. 29, 3459–3469, http://dx.doi.org/10.1038/emboj.2010.225.
Heales, S.J.R., Lam, A.A.J., Duncan, A.J., Land, J.M., 2004. Neurodegeneration or neuroprotection: the pivotal role of astrocytes. Neurochem. Res. 29, 513–519, http://dx.doi.org/10.1023/B:NERE.0000014822.69384.0f.
Heeman, B., Van den Haute, C., Aelvoet, S.-A., Valsecchi, F., Rodenburg, R.J., Reumers, V., Debyser, Z., Callewaert, G., Koopman, W.J.H., Willems, P.H.G.M., Baekelandt, V., 2011. Depletion of PINK1 affects mitochondrial metabolism, calcium homeostasis and energy maintenance. J. Cell Sci. 124, 1115–1125, http://dx.doi.org/10.1242/jcs.078303.
Henneberger, C., Papouin, T., Oliet, S.H.R., Dmitri, A., Rusakov, D.A., 2010. Long-term potentiation depends on release of D-serine from astrocytes. Nature 463, 232–236, http://dx.doi.org/10.1038/nature08673.
Herbert, M.R., 2005. Large brains in autism: the challenge of pervasive abnormality. Neuroscientist 11, 417–440, http://dx.doi.org/10.1177/0091270005278866.
Heresco-Levy, U., Javitt, D.C., Ebstein, R., Vass, A., Lichtenberg, P., Bar, G., Catinari, S., Ermilov, M., 2005. D-Serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. Biol. Psychiatry 57, 577–585, http://dx.doi.org/10.1016/j.biopsych.2004.12.037.
Hermann, B.P., Lin, J.J., Jones, J.E., Seidenberg, M., 2009. The emerging architecture of neuropsychological impairment in epilepsy. Neurol. Clin. 27, 881–907, http://dx.doi.org/10.1016/j.ncl.2009.08.001.
Hertz, L., Gibbs, M.E., O'Dowd, B.S., Sedman, G.L., Robinson, S.R., Syková, E., Hajek, I., Hertz, E., Peng, L., Huang, R., Ng, K.T., 1996. Astrocyte-neuron interaction during one-trial aversive learning in the neonate chick. Neurosci. Biobehav. Rev. 20, 537–551.
Hetherington, H.P., Pan, J.W., Spencer, D.D., 2002. 1H and 31P spectroscopy and bioenergetics in the lateralization of seizures in temporal lobe epilepsy. J. Magn. Reson. Imaging 16, 477–483.
Heverin, M., Maioli, S., Pham, T., Mateos, L., Camporesi, E., Ali, Z., Winblad, B., Cedazo-Minguez, A., Björkhem, I., 2015. 27-Hydroxycholesterol mediates negative effects of dietary cholesterol on cognition in mice. Behav. Brain Res. 278, 356–359, http://dx.doi.org/10.1016/j.bbr.2014.10.018.
Heyes, C., 2012. New thinking: the evolution of human cognition. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 367, 2091–2096, http://dx.doi.org/10.1098/rstb.2012.0111.
Howland, D.S., Liu, J., She, Y., Goad, B., Maragakis, N.J., Kim, B., Erickson, J., Kulik, J., DeVito, L., Psaltis, G., DeGennaro, L.J., Cleveland, D.W., Rothstein, J.D., 2002. Focal loss of the glutamate transporter EAAT2 in a transgenic rat model of SOD1 mutant-mediated amyotrophic lateral sclerosis (ALS). Proc. Natl. Acad. Sci. U. S. A. 99, 1604–1609, http://dx.doi.org/10.1073/pnas.032539299.
Huber, K.M., Gallagher, S.M., Warren, S.T., Bear, M.F., 2002. Altered synaptic plasticity in a mouse model of fragile X mental retardation. Proc. Natl. Acad. Sci. U. S. A. 99, 7746–7750, http://dx.doi.org/10.1073/pnas.122205699.
Huck, S., Grass, F., Hörtnagl, H., 1984. The glutamate analogue alpha-aminoadipic acid is taken up by astrocytes before exerting its gliotoxic effect in vitro. J. Neurosci. 4, 2650–2657.
Hudry, E., Wu, H.-Y., Arbel-Ornath, M., Hashimoto, T., Matsouaka, R., Fan, Z., Spires-Jones, T.L., Betensky, R.A., Bacskai, B.J., Hyman, B.T., 2012. Inhibition of the NFAT pathway alleviates amyloid β neurotoxicity in a mouse model of Alzheimer's disease. J. Neurosci. 32, 3176–3192.
Huh, W.J., Khurana, S.S., Geahlen, J.H., Kohli, K., Waller, R.A., Mills, J.C., 2012. Tamoxifen induces rapid, reversible atrophy, and metaplasia in mouse stomach. Gastroenterology 142,, 21–24.e7.
Ingram, J.L., Peckham, S.M., Tisdale, B., Rodier, P.M., 2000. Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. Neurotoxicol. Teratol. 22, 319–324.
Iwata, M., Shirayama, Y., Ishida, H., Hazama, G.I., Nakagome, K., 2011. Hippocampal astrocytes are necessary for antidepressant treatment of learned helplessness rats. Hippocampus 21, 877–884, http://dx.doi.org/10.1002/hipo.20803.
Jabs, R., Seifert, G., Steinhauser, C., 2008. Astrocytic function and its alteration in the epileptic brain. Epilepsia 49 (Suppl. 2), 3–12.
Jacobs, S., Doering, L.C., 2010. Astrocytes prevent abnormal neuronal development in the fragile × mouse. J. Neurosci. 30, 4508–4514, http://dx.doi.org/10.1523/JNEUROSCI.5027-09.2010.
Jefferys, J.G., 1995. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. Physiol. Rev. 75, 689–723.
Kang, N., Xu, J., Xu, Q., Nedergaard, M., Kang, J., 2005. Astrocytic glutamate release-induced transient depolarization and epileptiform discharges in hippocampal CA1 pyramidal neurons. J. Neurophysiol. 94, 4121–4130, http://dx.doi.org/10.1152/jn.00448.2005.
Kato, S., Takikawa, M., Nakashima, K., Hirano, A., Cleveland, D.W., Kusaka, H., Shibata, N., Kato, M., Nakano, I., Ohama, E., 2000. New consensus research on neuropathological aspects of familial amyotrophic lateral sclerosis with superoxide dismutase 1 (SOD1) gene mutations: inclusions containing SOD1 in neurons and astrocytes. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1, 163–184.
Konnerth, A., Heinemann, U., Yaari, Y., 1986. Nonsynaptic epileptogenesis in the mammalian hippocampus in vitro. I. Development of seizurelike activity in low extracellular calcium. J. Neurophysiol. 56, 409–423.
Kovacs, R., Heinemann, U., Steinhauser, C., 2012. Mechanisms underlying blood–brain barrier dysfunction in brain pathology and epileptogenesis: role of astroglia. Epilepsia 53 (Suppl. 6), 53–59, http://dx.doi.org/10.1111/j.1528-1167.2012.03703.x.
Kragh, J., Bolwig, T.G., Woldbye, D.P., Jørgensen, O.S., 1993. Electroconvulsive shock and lidocaine-induced seizures in the rat activate astrocytes as measured by glial fibrillary acidic protein. Biol. Psychiatry 33, 794–800.
Kruszewski, M., 2003. Labile iron pool: the main determinant of cellular response to oxidative stress. Mutat. Res. 531, 81–92.
Kuchibhotla, K.V., Goldman, S.T., Lattarulo, C.R., Wu, H.-Y., Hyman, B.T., Bacskai, B.J., 2008. Abeta plaques lead to aberrant regulation of calcium homeostasis in vivo resulting in structural and functional disruption of neuronal networks. Neuron 59, 214–225, http://dx.doi.org/10.1016/j.neuron.2008.06.008.
Kuchibhotla, K.V., Lattarulo, C.R., Hyman, B.T., Bacskai, B.J., 2009. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science 323, 1211–1215, http://dx.doi.org/10.1126/science.1169096.
Laming, P.R., 2000. Potassium signalling in the brain: its role in behaviour. Neurochem. Int. 36, 271–290, http://dx.doi.org/10.1016/S0197-0186(99)00136-9.
Lamusuo, S., Jutila, L., Ylinen, A., Kalviainen, R., Mervaala, E., Haaparanta, M., Jaaskelainen, S., Partanen, K., Vapalahti, M., Rinne, J., 2001. [18F]FDG-PET reveals temporal hypometabolism in patients with temporal lobe epilepsy even when quantitative MRI and histopathological analysis show only mild hippocampal damage. Arch. Neurol. 58, 933–939.
Lane, H.-Y., Lin, C.-H., Green, M.F., Hellemann, G., Huang, C.-C., Chen, P.-W., Tun, R., Chang, Y.-C., Tsai, G.E., 2013. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry 70, 1267–1275, http://dx.doi.org/10.1001/jamapsychiatry.2013.2159.
Laping, N.J., Teter, B., Nichols, N.R., Rozovsky, I., Finch, C.E., 1994. Glial fibrillary acidic protein: regulation by hormones, cytokines, and growth factors. Brain Pathol. 4, 259–275.
Laurence, J.A., Fatemi, S.H., 2005. Glial fibrillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects. Cerebellum 4, 206–210, http://dx.doi.org/10.1080/14734220500208846.
Lecavalier, L., 2014. Handbook of Autism and Anxiety, http://dx.doi.org/10.1007/978-3-319-06796-4.
Lee, H.-J., Suk, J.-E., Patrick, C., Bae, E.-J., Cho, J.-H., Rho, S., Hwang, D., Masliah, E., Lee, S.-J., 2010. Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. J. Biol. Chem. 285, 9262–9272, http://dx.doi.org/10.1074/jbc.M109.081125.
Lee, H.S., Ghetti, A., Pinto-Duarte, A., Wang, X., Dziewczapolski, G., Galimi, F., Huitron-Resendiz, S., Pina-Crespo, J.C., Roberts, A.J., Verma, I.M., Sejnowski, T.J., Heinemann, S.F., 2014. Astrocytes contribute to gamma oscillations and recognition memory. Proc. Natl. Acad. Sci. U. S. A. 111, E3343–E3352, http://dx.doi.org/10.1073/pnas.1410893111.
Lee, H.U., Yamazaki, Y., Tanaka, K.F., Furuya, K., Sokabe, M., Hida, H., Takao, K., Miyakawa, T., Fujii, S., Ikenaka, K., 2013a. Increased astrocytic ATP release

Please cite this article in press as: Dallérac, G., Rouach, N., Astrocytes as new targets to improve cognitive functions. Prog. Neurobiol. (2016), http://dx.doi.org/10.1016/j.pneurobio.2016.01.003

results in enhanced excitability of the hippocampus. Glia 61, 210–224, http://dx.doi.org/10.1002/glia.22427.

Lee, S.H., Magge, S., Spencer, D.D., Sontheimer, H., Cornell-Bell, A.H., 1995. Human epileptic astrocytes exhibit increased gap junction coupling. Glia 15, 195–202.

Lee, W., Reyes, R.C., Gottipati, M.K., Lewis, K., Lesort, M., Parpura, V., Gray, M., 2013b. Enhanced Ca(2+)-dependent glutamate release from astrocytes of the BACHD Huntington's disease mouse model. Neurobiol. Dis. 58, 192–199, http://dx.doi.org/10.1016/j.nbd.2013.06.002.

Leoni, V., Mariotti, C., Nanetti, L., Salvatore, E., Squitieri, F., Bentivoglio, A.R., Bandettini di Poggio, M., Bandettini Del Poggio, M., Piacentini, S., Monza, D., Valenza, M., Cattaneo, E., Di Donato, S., 2011. Whole body cholesterol metabolism is impaired in Huntington's disease. Neurosci. Lett. 494, 245–249, http://dx.doi.org/10.1016/j.neulet.2011.03.025.

Levin, E.D., 2005. Extracellular superoxide dismutase (EC-SOD) quenches free radicals and attenuates age-related cognitive decline: opportunities for novel drug development in aging. Curr. Alzheimer Res. 2, 191–196.

Liévens, J.C., Woodman, B., Mahal, A., Spasic-Boscovic, O., Samuel, D., Kerkerian-Le Goff, L., Bates, G.P., 2001. Impaired glutamate uptake in the R6 Huntington's disease transgenic mice. Neurobiol. Dis. 8, 807–821, http://dx.doi.org/10.1006/nbdi.2001.0430.

Lim, D., Fedrizzi, L., Tartari, M., Zuccato, C., Cattaneo, E., Brini, M., Carafoli, E., 2008. Calcium homeostasis and mitochondrial dysfunction in striatal neurons of Huntington disease. J. Biol. Chem. 283, 5780–5789, http://dx.doi.org/10.1074/jbc.M704704200.

Lima, A., Sardinha, V.M., Oliveira, A.F., Reis, M., Mota, C., Silva, M.A., Marques, F., Cerqueira, J.J., Pinto, L., Sousa, N., Oliveira, J.F., 2014. Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats. Mol. Psychiatry 19, 834–841, http://dx.doi.org/10.1038/mp.2013.182.

Lioy, D.T., Garg, S.K., Monaghan, C.E., Raber, J., Foust, K.D., Kaspar, B.K., Hirrlinger, P.G., Kirchhoff, F., Bissonnette, J.M., Ballas, N., Mandel, G., 2011. A role for glia in the progression of Rett's syndrome. Nature 475, 497–500, http://dx.doi.org/10.1038/nature10214.

Lipton, S.A., Choi, Y.B., Pan, Z.H., Lei, S.Z., Chen, H.S., Sucher, N.J., Loscalzo, J., Singel, D.J., Stamler, J.S., 1993. A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. Nature 364, 626–632, http://dx.doi.org/10.1038/364626a0.

Liu, Q., Li, B., Zhu, H.-Y., Wang, Y.-Q., Yu, J., Wu, G.-C., 2009. Clomipramine treatment reversed the glial pathology in a chronic unpredictable stress-induced rat model of depression. Eur. Neuropsychopharmacol. 19, 796–805, http://dx.doi.org/10.1016/j.euroneuro.2009.06.010.

Losi, G., Cammarota, M., Carmignoto, G., 2012. The role of astroglia in the epileptic brain. Front. Pharmacol. 3, 132, http://dx.doi.org/10.3389/fphar.2012.00132.

Luo, J., Sun, L., Lin, X., Liu, G., Yu, J., Parisiadou, L., Xie, C., Ding, J., Cai, H., 2014. A calcineurin- and NFAT-dependent pathway is involved in α-synuclein-induced degeneration of midbrain dopaminergic neurons. Hum. Mol. Genet. 23, 6567–6574, http://dx.doi.org/10.1093/hmg/ddu377.

Lytton, W.W., 2008. Computer modelling of epilepsy. Nat. Rev. Neurosci. 9, 626–637, http://dx.doi.org/10.1038/nrn2416.

Ma, T.M., Abazyan, S., Abazyan, B., Nomura, J., Yang, C., Seshadri, S., Sawa, A., Snyder, S.H., Pletnikov, M.V., 2013. Pathogenic disruption of DISC1-serine racemase binding elicits schizophrenia-like behavior via D-serine depletion. Mol. Psychiatry 18, 557–567, http://dx.doi.org/10.1038/mp.2012.97.

Maezawa, I., Swanberg, S., Harvey, D., LaSalle, J.M., Jin, L.-W., 2009. Rett syndrome astrocytes are abnormal and spread MeCP2 deficiency through gap junctions. J. Neurosci. 29, 5051–5061, http://dx.doi.org/10.1523/JNEUROSCI.0324-09.2009.

Magistretti, P.J., 2006. Neuron-glia metabolic coupling and plasticity. J. Exp. Biol. 209, 2304–2311, http://dx.doi.org/10.1242/jeb.02208.

Maier, C.M., Chan, P.H., 2002. Role of superoxide dismutases in oxidative damage and neurodegenerative disorders. Neuroscientist 8, 323–334.

Manning Jr., T.J., Sontheimer, H., 1997. Spontaneous intracellular calcium oscillations in cortical astrocytes from a patient with intractable childhood epilepsy (Rasmussen's encephalitis). Glia 21, 332–337.

Martorana, F., Brambilla, L., Valori, C.F., Bergamaschi, C., Roncoroni, C., Aronica, E., Volterra, A., Bezzi, P., Rossi, D., 2012. The BH4 domain of Bcl-X(L) rescues astrocyte degeneration in amyotrophic lateral sclerosis by modulating intracellular calcium signals. Hum. Mol. Genet. 21, 826–840.

Matute, C., Melone, M., Vallejo-Illarramendi, A., Conti, F., 2005. Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenics. Glia 49, 451–455, http://dx.doi.org/10.1002/glia.20119.

Mazzetti, A.P., Fiorile, M.C., Primavera, A., Lo Bello, M., 2015. Glutathione transferases and neurodegenerative diseases. Neurochem. Int. 82, 10–18, http://dx.doi.org/10.1016/j.neuint.2015.01.008.

McDougle, C.J., Landino, S.M., Vahabzadeh, A., O'Rourke, J., Zurcher, N.R., Finger, B.C., Palumbo, M.L., Helt, J., Mullett, J.E., Hooker, J.M., Carlezon, W.A., 2014. Toward an immune-mediated subtype of autism spectrum disorder. Brain Res. 1617, 72–92, http://dx.doi.org/10.1016/j.brainres.2014.09.048.

McNamara, J.O., 1994. Cellular and molecular basis of epilepsy. J. Neurosci. 14, 3413–3425.

Melone, M., Vitellaro-Zuccarello, L., Vallejo-Illarramendi, A., Pérez-Samartin, A., Matute, C., Cozzi, A., Pellegrini-Giampietro, D.E., Rothstein, J.D., Conti, F., 2001. The expression of glutamate transporter GLT-1 in the rat cerebral cortex is down-regulated by the antipsychotic drug clozapine. Mol. Psychiatry 6, 380–386, http://dx.doi.org/10.1038/sj.mp.4000880.

Miller, B.R., Dorner, J.L., Shou, M., Sari, Y., Barton, S.J., Sengelaub, D.R., Kennedy, R.T., Rebec, G.V., 2008. Up-regulation of GLT1 expression increases glutamate uptake and attenuates the Huntington's disease phenotype in the R6/2 mouse. Neuroscience 153, 329–337.

Molinaro, P., Cataldi, M., Cuomo, O., Viggiano, D., Pignataro, G., Sirabella, R., Secondo, A., Boscia, F., Pannaccione, A., Scorziello, A., Sokolow, S., Herchuelz, A., Di Renzo, G., Annunziato, L., 2013. Genetically modified mice as a strategy to unravel the role played by the Na(+)/Ca (2+) exchanger in brain ischemia and in spatial learning and memory deficits. Adv. Exp. Med. Biol. 961, 213–222, http://dx.doi.org/10.1007/978-1-4614-4756-6_18.

Mothet, J.-P., Pollegioni, L., Ouanounou, G., Martineau, M., Fossier, P., Baux, G., 2005. Glutamate receptor activation triggers a calcium-dependent and SNARE protein-dependent release of the gliotransmitter D-serine. Proc. Natl. Acad. Sci. U. S. A. 102, 5606–5611.

Mothet, J.-P., Le Bail, M., Billard, J.-M., 2015. Time and space profiling of NMDA receptor co-agonist functions. J. Neurochem., http://dx.doi.org/10.1111/jnc.13204.

Murphy, S., Simmons, M.L., Agullo, L., Garcia, A., Feinstein, D.L., Galea, E., Reis, D.J., Minc-Golomb, D., Schwartz, J.P., 1993. Synthesis of nitric oxide in CNS glial cells. Trends Neurosci. 16, 323–328.

Nadkarni, S., Jung, P., 2003. Spontaneous oscillations of dressed neurons: a new mechanism for epilepsy? Phys. Rev. Lett. 91, 268101.

Nadkarni, S., Jung, P., 2005. Synaptic inhibition and pathologic hyperexcitability through enhanced neuron-astrocyte interaction: a modeling study. J. Integr. Neurosci. 4, 207–226.

Nagy, C., Suderman, M., Yang, J., Szyf, M., Mechawar, N., Ernst, C., Turecki, G., 2015. Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. Mol. Psychiatry 20, 320–328.

Nakazawa, M., Kodama, S., Matsuo, T., 1983. Effects of ketogenic diet on electroconvulsive threshold and brain contents of adenosine nucleotides. Brain Dev. 5, 375–380.

Neal, E.G., Chaffe, H., Schwartz, R.H., Lawson, M.S., Edwards, N., Fitzsimmons, G., Whitney, A., Cross, J.H., 2008. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 7, 500–506, http://dx.doi.org/10.1016/S1474-4422(08)70092-9.

Newman, L.A., Korol, D.L., Gold, P.E., 2011. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS ONE 6, e28427, http://dx.doi.org/10.1371/journal.pone.0028427.

Nguyen, M.V.C., Du, F., Felice, C.A., Shan, X., Nigam, A., Mandel, G., Robinson, J.K., Ballas, N., 2012. MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development and in the mature adult brain. J. Neurosci. 32, 10021–10034, http://dx.doi.org/10.1523/JNEUROSCI.1316-12.2012.

Norris, C.M., Kadish, I., Blalock, E.M., Chen, K.-C., Thibault, V., Porter, N.M., Landfield, P.W., Kraner, S.D., 2005. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. J. Neurosci. 25, 4649–4658.

O'Connor, E.R., Sontheimer, H., Spencer, D.D., de Lanerolle, N.C., 1998. Astrocytes from human hippocampal epileptogenic foci exhibit action potential-like responses. Epilepsia 39, 347–354.

O'Dowd, B.S., Zhao, W.Q., Ng, K.T., Robinson, S.R., 1997. Chicks injected with antisera to either S-100 alpha or S-100 beta protein develop amnesia for a passive avoidance task. Neurobiol. Learn. Mem. 67, 197–206, http://dx.doi.org/10.1006/nlme.1997.3766.

Oberheim, N.A., Tian, G.F., Han, X., Peng, W., Takano, T., Ransom, B., Nedergaard, M., 2008. Loss of astrocytic domain organization in the epileptic brain. J. Neurosci. 28, 3264–3276.

Oberheim, N.A., Wang, X., Goldman, S., Nedergaard, M., 2006. Astrocytic complexity distinguishes the human brain. Trends Neurosci. 29, 547–553, http://dx.doi.org/10.1016/j.tins.2006.08.004.

Oliet, S.H., Piet, R., Poulain, D.A., 2001. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science 292, 923–926, http://dx.doi.org/10.1126/science.1059162.

Oliveira, J.M.A., 2010. Mitochondrial bioenergetics and dynamics in Huntington's disease: tripartite synapses and selective striatal degeneration. J. Bioenergy Biomembr. 42, 227–234, http://dx.doi.org/10.1007/s10863-010-9287-6.

Ostroff, L.E., Manzur, M.K., Cain, C.K., Ledoux, J.E., 2014. Synapses lacking astrocyte appear in the amygdala during consolidation of Pavlovian threat conditioning. J. Comp. Neurol. 522, 2152–2163, http://dx.doi.org/10.1002/cne.23523.

Pacey, L.K.K., Doering, L.C., 2007. Developmental expression of FMRP in the astrocyte lineage: implications for fragile X syndrome. Glia 55, 1601–1609, http://dx.doi.org/10.1002/glia.20573.

Panatier, A., Robitaille, R., 2015. Astrocytic mGluR5s and the tripartite synapse. Neuroscience, http://dx.doi.org/10.1016/j.neuroscience.2015.03.063.

Panatier, A., Theodosis, D.T., Mothet, J.-P., Touquet, B., Pollegioni, L., Poulain, D.A., Oliet, S.H.R., 2006. Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell 125, 775–784, http://dx.doi.org/10.1016/j.cell.2006.02.051.

Pangrsic, T., Potokar, M., Stenovec, M., Kreft, M., Fabbretti, E., Nistri, A., Pryazhnikov, E., Khiroug, L., Giniatullin, R., Zorec, R., 2007. Exocytotic release of ATP from cultured astrocytes. J. Biol. Chem. 282, 28749–28758.

Pannasch, U., Freche, D., Dallérac, G., Ghézali, G., Escartin, C., Ezan, P., Cohen-Salmon, M., Benchenane, K., Abudara, V., Dufour, A., Lübke, J.H.R., Déglon, N., Knott, G., Holcman, D., Rouach, N., 2014. Connexin 30 sets synaptic strength by controlling astroglial synapse invasion. Nat. Neurosci., http://dx.doi.org/10.1038/nn.3662.

Pannasch, U., Rouach, N., 2013. Emerging role for astroglial networks in information processing: from synapse to behavior. Trends Neurosci. 36, 405–417, http://dx.doi.org/10.1016/j.tins.2013.04.004.

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Pannasch, U., Vargová, L., Reingruber, J., Ezan, P., Holcman, D., Giaume, C., Syková, E., Rouach, N., 2011. Astroglial networks scale synaptic activity and plasticity. Proc. Natl. Acad. Sci. U. S. A. 108, 8467–8472, http://dx.doi.org/10.1073/pnas.1016650108.

Papouin, T., Ladépêche, L., Ruel, J., Sacchi, S., Labasque, M., Hanini, M., Groc, L., Pollegioni, L., Mothet, J.-P., Oliet, S.H.R., 2012. Synaptic and extrasynaptic NMDA receptors are gated by different endogenous coagonists. Cell 150, 633–646, http://dx.doi.org/10.1016/j.cell.2012.06.029.

Pardo, A.C., Wong, V., Benson, L.M., Dykes, M., Tanaka, K., Rothstein, J.D., Maragakis, N.J., 2006. Loss of the astrocyte glutamate transporter GLT1 modifies disease in SOD1(G93A) mice. Exp. Neurol. 201, 120–130.

Pariante, C.M., Pearce, B.D., Pisell, T.L., Owens, M.J., Miller, A.H., 1997. Steroid-independent translocation of the glucocorticoid receptor by the antidepressant desipramine. Mol. Pharmacol. 52, 571–581.

Park, H., Han, K.-S., Seo, J., Lee, J., Dravid, S.M., Woo, J., Chun, H., Cho, S., Bae, J.Y., An, H., Koh, W., Yoon, B.-E., Berlinguer-Palmini, R., Mannaioni, G., Traynelis, S.F., Bae, Y.C., Choi, S.-Y., Lee, C.J., 2015. Channel-mediated astrocytic glutamate modulates hippocampal synaptic plasticity by activating postsynaptic NMDA receptors. Mol. Brain 8, 7, http://dx.doi.org/10.1186/s13041-015-0097-y.

Parpura, V., Basarsky, T.A., Liu, F., Jeftinija, K., Jeftinija, S., Haydon, P.G., 1994. Glutamate-mediated astrocyte-neuron signalling. Nature 369, 744–747.

Pascual, J.M., Wang, D., Hinton, V., Engelstad, K., Saxena, C.M., Van Heertum, R.L., De Vivo, D.C., 2007. Brain glucose supply and the syndrome of infantile neuroglycopenia. Arch. Neurol. 64, 507–513.

Pascual, O., Casper, K.B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J.-Y., Takano, H., Moss, S.J., McCarthy, K., Haydon, P.G., 2005. Astrocytic purinergic signaling coordinates synaptic networks. Science 310, 113–116, http://dx.doi.org/10.1126/science.1116916.

Paulsen, J.S., Ready, R.E., Hamilton, J.M., Mega, M.S., Cummings, J.L., 2001. Neuropsychiatric aspects of Huntington's disease. J. Neurol. Neurosurg. Psychiatry 71, 310–314, http://dx.doi.org/10.1136/jnnp.71.3.310.

Pellerin, L., Bouzier-Sore, A.-K., Aubert, A., Serres, S., Merle, M., Costalat, R., Magistretti, P.J., 2007. Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55, 1251–1262, http://dx.doi.org/10.1002/glia.20528.

Pereira, A., Furlan, F.A., 2010. Astrocytes and human cognition: modeling information integration and modulation of neuronal activity. Prog. Neurobiol. 92, 405–420, http://dx.doi.org/10.1016/j.pneurobio.2010.07.001.

Petroff, O.A., Errante, L.D., Rothman, D.L., Kim, J.H., Spencer, D.D., 2002. Glutamate–glutamine cycling in the epileptic human hippocampus. Epilepsia 43, 703–710.

Piet, R., Vargová, L., Syková, E., Poulain, D.A., Oliet, S.H.R., 2004. Physiological contribution of the astrocytic environment of neurons to intersynaptic crosstalk. Proc. Natl. Acad. Sci. U. S. A. 101, 2151–2155, http://dx.doi.org/10.1073/pnas.0308408100.

Poskanzer, K.E., Yuste, R., 2011. Astrocytic regulation of cortical UP states. Proc. Natl. Acad. Sci. U. S. A. 108, 18453–18458, http://dx.doi.org/10.1073/pnas.1112378108.

Rajkowska, G., Miguel-Hidalgo, J.J., 2007. Gliogenesis and glial pathology in depression. CNS Neurol. Disord. Drug Targets 6, 219–233.

Rajkowska, G., Miguel-Hidalgo, J.J., Makkos, Z., Meltzer, H., Overholser, J., Stockmeier, C., 2002. Layer-specific reductions in GFAP-reactive astroglia in the dorsolateral prefrontal cortex in schizophrenia. Schizophr. Res. 57, 127–138.

Rangroo Thrane, V., Thrane, A.S., Wang, F., Cotrina, M.L., Smith, N.A., Chen, M., Xu, Q., Kang, N., Fujita, T., Nagelhus, E.A., Nedergaard, M., 2013. Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. Nat. Med. 19, 1643–1648, http://dx.doi.org/10.1038/nm.3400.

Rasooli-Nejad, S., Palygin, O., Lalo, U., Pankratov, Y., 2014. Cannabinoid receptors contribute to astroglial Ca2+-signalling and control of synaptic plasticity in the neocortex. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 369, 20140077, http://dx.doi.org/10.1098/rstb.2014.0077.

Ribeiro, M., Rosenstock, T.R., Cunha-Oliveira, T., Ferreira, I.L., Oliveira, C.R., Rego, A.C., 2012. Glutathione redox cycle dysregulation in Huntington's disease knock-in striatal cells. Free Radic. Biol. Med. 53, 1857–1867, http://dx.doi.org/10.1016/j.freeradbiomed.2012.09.004.

Robertson, J.M., 2002. The astrocentric hypothesis: proposed role of astrocytes in consciousness and memory formation. J. Physiol. Paris 96, 251–255, http://dx.doi.org/10.1016/S0928-4257(02)00013-X.

Robertson, J.M., 2013. Astrocyte domains and the three-dimensional and seamless expression of consciousness and explicit memories. Med. Hypotheses 81, 1017–1024, http://dx.doi.org/10.1016/j.mehy.2013.09.021.

Rodriguez, J.J., Olabarria, M., Chvatal, A., Verkhratsky, A., 2009. Astroglia in dementia and Alzheimer's disease. Cell Death Differ. 16, 378–385.

Ronesi, J.A., Huber, K.M., 2008. Metabotropic glutamate receptors and fragile X mental retardation protein: partners in translational regulation at the synapse. Sci. Signal. 1–4.

Rossi, D., Brambilla, L., Valori, C.F., Roncoroni, C., Crugnola, A., Yokota, T., Bredesen, D.E., Volterra, A., 2008. Focal degeneration of astrocytes in amyotrophic lateral sclerosis. Cell Death Differ. 15, 1691–1700.

Rossi, D., 2015. Astrocyte physiopathology: at the crossroads of intercellular networking, inflammation and cell death. Prog. Neurobiol. 130, 86–120, http://dx.doi.org/10.1016/j.pneurobio.2015.04.003.

Rossignol, D.A., Frye, R.E., 2014. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front. Physiol. 5, 150, http://dx.doi.org/10.3389/fphys.2014.00150.

Rothstein, J.D., Martin, L.J., Kuncl, R.W., 1992. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. N. Engl. J. Med. 326, 1464–1468.

Rothstein, J.D., Patel, S., Regan, M.R., Haenggeli, C., Huang, Y.H., Bergles, D.E., Jin, L., Dykes Hoberg, M., Vidensky, S., Chung, D.S., Toan, S.V., Bruijn, L.I., Su, Z.-Z., Gupta, P., Fisher, P.B., 2005. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 433, 73–77.

Rothstein, J.D., Tsai, G., Kuncl, R.W., Clawson, L., Cornblath, D.R., Drachman, D.B., Pestronk, A., Stauch, B.L., Coyle, J.T., 1990. Abnormal excitatory amino acid metabolism in amyotrophic lateral sclerosis. Ann. Neurol. 28, 18–25.

Rouach, N., Koulakoff, A., Abudara, V., Willecke, K., Giaume, C., 2008. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science 322, 1551–1555, http://dx.doi.org/10.1126/science.1164022.

Sada, N., Lee, S., Katsu, T., Otsuki, T., Inoue, T., 2015. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. Science 347, 1362–1367, http://dx.doi.org/10.1126/science.aaa1299.

Sadzot, B., Debets, R.M., Maquet, P., van Veelen, C.W., Salmon, E., van Emde Boas, W., Velis, D.N., van Huffelen, A.C., Franck, G., 1992. Regional brain glucose metabolism in patients with complex partial seizures investigated by intracranial EEG. Epilepsy Res. 12, 121–129.

Samoilova, M., Wentlandt, K., Adamchik, Y., Velumian, A.A., Carlen, P.L., 2008. Connexin 43 mimetic peptides inhibit spontaneous epileptiform activity in organotypic hippocampal slice cultures. Exp. Neurol. 210, 762–775.

Sampedro-Piquero, P., De Bartolo, P., Petrosini, L., Zancada-Menendez, C., Arias, J.L., Begega, A., 2014. Astrocytic plasticity as a possible mediator of the cognitive improvements after environmental enrichment in aged rats. Neurobiol. Learn. Mem. 114, 16–25, http://dx.doi.org/10.1016/j.nlm.2014.04.002.

Sasaki, T., Ishikawa, T., Abe, R., Nakayama, R., Asada, A., Matsuki, N., Ikegaya, Y., 2014. Astrocyte calcium signalling orchestrates neuronal synchronization in organotypic hippocampal slices. J. Physiol. 592, 2771–2783, http://dx.doi.org/10.1113/jphysiol.2014.272864.

Scemes, E., Giaume, C., 2006. Astrocyte calcium waves: what they are and what they do. Glia 54, 716–725, http://dx.doi.org/10.1002/glia.20374.

Schipper, H.M., Bennett, D.A., Liberman, A., Bienias, J.L., Schneider, J.A., Kelly, J., Arvanitakis, Z., 2006. Glial heme oxygenase-1 expression in Alzheimer disease and mild cognitive impairment. Neurobiol. Aging 27, 252–261, http://dx.doi.org/10.1016/j.neurobiolaging.2005.01.016.

Schipper, H.M., Gupta, A., Szarek, W.A., 2009. Suppression of glial HO-1 activity as a potential neurotherapeutic intervention in AD. Curr. Alzheimer Res. 6, 424–430.

Schipper, H.M., Song, W., 2015. A heme oxygenase-1 transducer model of degenerative and developmental brain disorders. Int. J. Mol. Sci. 16, 5400–5419, http://dx.doi.org/10.3390/ijms16035400.

Scuderi, C., Stecca, C., Iacomino, A., Steardo, L., 2013. Role of astrocytes in major neurological disorders: the evidence and implications. IUBMB Life 65, 957–961, http://dx.doi.org/10.1002/iub.1223.

Shafaati, M., Marutle, A., Pettersson, H., Lövgren-Sandblom, A., Olin, M., Pikuleva, I., Winblad, B., Nordberg, A., Björkhem, I., 2011. Marked accumulation of 27-hydroxycholesterol in the brains of Alzheimer's patients with the Swedish APP 670/671 mutation. J. Lipid Res. 52, 1004–1010, http://dx.doi.org/10.1194/jlr.M014548.

Shin, J.-Y., Fang, Z.-H., Yu, Z.-X., Wang, C.-E., Li, S.-H., Li, X.-J., 2005. Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J. Cell Biol. 171, 1001–1012, http://dx.doi.org/10.1083/jcb.200508072.

Si, X., Miguel-Hidalgo, J.J., O'Dwyer, G., Stockmeier, C.A., Rajkowska, G., 2004. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacology 29, 2088–2096.

Sibille, J., Dao Duc, K., Holcman, D., Rouach, N., 2015a. The neuroglial potassium cycle during neurotransmission: role of Kir4.1 channels. PLoS Comput. Biol. 11, e1004137, http://dx.doi.org/10.1371/journal.pcbi.1004137.

Sibille, J., Pannasch, U., Rouach, N., 2014. Astroglial potassium clearance contributes to short-term plasticity of synaptically evoked currents at the tripartite synapse. J. Physiol. 592, 87–102, http://dx.doi.org/10.1113/jphysiol.2013.261735.

Sibille, J., Zapata, J., Teillon, J., Rouach, N., 2015b. Astroglial calcium signaling displays short-term plasticity and adjusts synaptic efficacy. Front. Cell. Neurosci. 9, 189, http://dx.doi.org/10.3389/fncel.2015.00189.

Sim, F.J., Windrem, M.S., Goldman, S.A., 2009. Fate determination of adult human glial progenitor cells. Neuron Glia Biol. 5, 45–55, http://dx.doi.org/10.1017/S1740925X09990317.

Sirven, J., Whedon, B., Caplan, D., Liporace, J., Glosser, D., O'Dwyer, J., Sperling, M.R., 1999. The ketogenic diet for intractable epilepsy in adults: preliminary results. Epilepsia 40, 1721–1726.

Sisodia, S.S., 1998. Nuclear inclusions in glutamine repeat disorders: are they pernicious, coincidental, or beneficial? Cell 95, 1–4.

Smith, R.E., Haroutunian, V., Davis, K.L., Meador-Woodruff, J.H., 2001. Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. Am. J. Psychiatry 158, 1393–1399.

Spencer, J.P., Jenner, P., Daniel, S.E., Lees, A.J., Marsden, D.C., Halliwell, B., 1998. Conjugates of catecholamines with cysteine and GSH in Parkinson's disease: possible mechanisms of formation involving reactive oxygen species. J. Neurochem. 71, 2112–2122.

Steffek, A.E., McCullumsmith, R.E., Haroutunian, V., Meador-Woodruff, J.H., 2008. Cortical expression of glial fibrillary acidic protein and glutamine synthetase is decreased in schizophrenia. Schizophr. Res. 103, 71–82, http://dx.doi.org/10.1016/j.schres.2008.04.032.

Stehberg, J., Moraga-Amaro, R., Salazar, C., Becerra, A., Echeverría, C., Orellana, J.A., Bultynck, G., Ponsaerts, R., Leybaert, L., Simon, F., Sáez, J.C., Retamal, M.A., 2012. Release of gliotransmitters through astroglial connexin 43 hemichannels is necessary for fear memory consolidation in the basolateral amygdala. FASEB J. 26, 3649–3657, http://dx.doi.org/10.1096/fj.11-198416.

Please cite this article in press as: Dallérac, G., Rouach, N., Astrocytes as new targets to improve cognitive functions. Prog. Neurobiol. (2016), http://dx.doi.org/10.1016/j.pneurobio.2016.01.003

Steiner, J., Bernstein, H.-G., Bielau, H., Berndt, A., Brisch, R., Mawrin, C., Keilhoff, G., Bogerts, B., 2007. Evidence for a wide extra-astrocytic distribution of S100B in human brain. BMC Neurosci. 8, 2, http://dx.doi.org/10.1186/1471-2202-8-2.

Steward, O., 1994. Electroconvulsive seizures upregulate astroglial gene expression selectively in the dentate gyrus. Brain Res. Mol. Brain Res. 25, 217–224.

Stewart, V.C., Stone, R., Gegg, M.E., Sharpe, M.A., Hurst, R.D., Clark, J.B., Heales, S.J.R., 2002. Preservation of extracellular glutathione by an astrocyte derived factor with properties comparable to extracellular superoxide dismutase. J. Neurochem. 83, 984–991.

Strauss, U., Zhou, F.-W., Henning, J., Battefeld, A., Wree, A., Köhling, R., Haas, S.J.-P., Benecke, R., Rolfs, A., Gimsa, U., 2008. Increasing extracellular potassium results in subthalamic neuron activity resembling that seen in a 6-hydroxydopamine lesion. J. Neurophysiol. 99, 2902–2915, http://dx.doi.org/10.1152/jn.00402.2007.

Sun, X., Ji, C., Hu, T., Wang, Z., Chen, G., 2013a. Tamoxifen as an effective neuroprotectant against early brain injury and learning deficits induced by subarachnoid hemorrhage: possible involvement of inflammatory signaling. J. Neuroinflamm. 10, 157.

Sun, J.-D., Liu, Y., Yuan, Y.-H., Li, J., Chen, N.-H., 2012. Gap junction dysfunction in the prefrontal cortex induces depressive-like behaviors in rats. Neuropsychopharmacology 37, 1305–1320, http://dx.doi.org/10.1038/npp.2011.319.

Sun, W., McConnell, E., Pare, J.-F., Xu, Q., Chen, M., Peng, W., Lovatt, D., Han, X., Smith, Y., Nedergaard, M., 2013b. Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. Science 339, 197–200, http://dx.doi.org/10.1126/science.1226740.

Suzuki, A., Stern, S.A., Bozdagi, O., Huntley, G.W., Walker, R.H., Magistretti, P.J., Alberini, C.M., 2011. Astrocyte–neuron lactate transport is required for long-term memory formation. Cell 144, 810–823, http://dx.doi.org/10.1016/j.cell.2011.02.018.

Takano, K., Tanaka, N., Kawabe, K., Moriyama, M., Nakamura, Y., 2013. Extracellular superoxide dismutase induced by dopamine in cultured astrocytes. Neurochem. Res. 38, 32–41, http://dx.doi.org/10.1007/s11064-012-0882-2.

Thompson, P.M., Vinters, H.V., 2012. Pathologic lesions in neurodegenerative diseases. Prog. Mol. Biol. Transl. Sci. 107, 1–40, http://dx.doi.org/10.1016/B978-0-12-385883-2.00009-6.

Tian, G.-F., Azmi, H., Takano, T., Xu, Q., Peng, W., Lin, J., Oberheim, N., Lou, N., Wang, X., Zielke, H.R., Kang, J., Nedergaard, M., 2005. An astrocytic basis of epilepsy. Nat. Med. 11, 973–981, http://dx.doi.org/10.1038/nm1277.

Tong, X., Ao, Y., Faas, G.C., Nwaobi, S.E., Xu, J., Haustein, M.D., Anderson, M.A., Mody, I., Olsen, M.L., Sofroniew, M.V., Khakh, B.S., 2014. Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. Nat. Neurosci. 17, 694–703.

Tsai, G., Coyle, J.T., 2002. Glutamatergic mechanisms in schizophrenia. Annu. Rev. Pharmacol. Toxicol. 42, 165–179, http://dx.doi.org/10.1146/annurev.pharmtox.42.082701.160735.

Tydlacka, S., Wang, C.-E., Wang, X., Li, S., Li, X.-J., 2008. Differential activities of the ubiquitin-proteasome system in neurons versus glia may account for the preferential accumulation of misfolded proteins in neurons. J. Neurosci. 28, 13285–13295, http://dx.doi.org/10.1523/JNEUROSCI.4393-08.2008.

Valenza, M., Cattaneo, E., 2011. Emerging roles for cholesterol in Huntington's disease. Trends Neurosci. 34, 474–486, http://dx.doi.org/10.1016/j.tins.2011.06.005.

Vallejo-Illarramendi, A., Torres-Ramos, M., Melone, M., Conti, F., Matute, C., 2005. Clozapine reduces GLT-1 expression and glutamate uptake in astrocyte cultures. Glia 50, 276–279, http://dx.doi.org/10.1002/glia.20172.

Vargas, D.L., Nascimbene, C., Krishnan, C., Zimmerman, A.W., Pardo, C.A., 2005. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann. Neurol. 57, 67–81, http://dx.doi.org/10.1002/ana.20315.

Verkhratsky, A., Rodríguez, J.J., Parpura, V., 2012a. Calcium signalling in astroglia. Mol. Cell. Endocrinol. 353, 45–56, http://dx.doi.org/10.1016/j.mce.2011.08.039.

Verkhratsky, A., Sofroniew, M.V., Messing, A., deLanerolle, N.C., Rempe, D., Rodriguez, J.J., Nedergaard, M., 2012b. Neurological diseases as primary gliopathies: a reassessment of neurocentrism. ASN Neuro 4 , http://dx.doi.org/10.1042/AN20120010.

Virgin, C.E., Ha, T.P., Packan, D.R., Tombaugh, G.C., Yang, S.H., Horner, H.C., Sapolsky, R.M., 1991. Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity. J. Neurochem. 57, 1422–1428.

Volterra, A., Trotti, D., Tromba, C., Floridi, S., Racagni, G., 1994. Glutamate uptake inhibition by oxygen free radicals in rat cortical astrocytes. J. Neurosci. 14, 2924–2932.

Vonsattel, J.P., Myers, R.H., Stevens, T.J., Ferrante, R.J., Bird, E.D., Richardson Jr., E.P., 1985. Neuropathological classification of Huntington's disease. J. Neuropathol. Exp. Neurol. 44, 559–577.

Wallraff, A., Köhling, R., Heinemann, U., Theis, M., Willecke, K., Steinhäuser, C., 2006. The impact of astrocytic gap junctional coupling on potassium buffering in the hippocampus. J. Neurosci. 26, 5438–5447, http://dx.doi.org/10.1523/JNEUROSCI.0037-06.2006.

Wang, C., Luan, Z., Yang, Y., Wang, Z., Cui, Y., Gu, G., 2011. Valproic acid induces apoptosis in differentiating hippocampal neurons by the release of tumor necrosis factor-α from activated astrocytes. Neurosci. Lett. 497, 122–127, http://dx.doi.org/10.1016/j.neulet.2011.04.044.

Wang, E.-S., Yao, H.-B., Chen, Y.-H., Wang, G., Gao, W.-W., Sun, Y.-R., Guo, J.-G., Hu, J.-W., Jiang, C.-C., Hu, J., 2013. Proteomic analysis of the cerebrospinal fluid of Parkinson's disease patients pre- and post-deep brain stimulation. Cell. Physiol. Biochem. 31, 625–637, http://dx.doi.org/10.1159/000350082.

Wang, F., Smith, N., Xu, Q., Fujita, T., Baba, A., Matsuda, T., Takano, T., Bekar, L., Nedergaard, M., 2012a. Astrocytes modulate neural network activity by Ca2+-dependent uptake of extracellular K+. Sci. Signal. 5, ra26, http://dx.doi.org/10.1126/scisignal.2002334.

Wang, F., Xu, Q., Wang, W., Takano, T., Nedergaard, M.B., 2012b. Bergmann glia modulate cerebellar Purkinje cell bistability via Ca2+-dependent K+ uptake. Proc. Natl. Acad. Sci. U. S. A. 109, 7911–7916, http://dx.doi.org/10.1073/pnas.1120380109.

Wang, Y., Yang, P., Tang, J., Lin, J., Cai, X., Wang, X., Zheng, G., 2008. Potassium channels: possible new therapeutic targets in Parkinson's disease. Med. Hypotheses 71, 546–550, http://dx.doi.org/10.1016/j.mehy.2008.05.021.

Ward, R.J., Zucca, F.A., Duyn, J.H., Crichton, R.R., Zecca, L., 2014. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol. 13, 1045–1060, http://dx.doi.org/10.1016/S1474-4422(14)70117-6.

Webster, M.J., O'Grady, J., Kleinman, J.E., Weickert, C.S., 2005. Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder and schizophrenia. Neuroscience 133, 453–461, http://dx.doi.org/10.1016/j.neuroscience.2005.02.037.

Wenker, I., 2010. An active role for astrocytes in synaptic plasticity? J. Neurophysiol. 104, 1216–1218, http://dx.doi.org/10.1152/jn.00429.2010.

Wetherington, J., Serrano, G., Dingledine, R., 2008. Astrocytes in the epileptic brain. Neuron 58, 168–178, http://dx.doi.org/10.1016/j.neuron.2008.04.002.

Wieser, H.-G., 2004. ILAE Commission Report. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 45, 695–714, http://dx.doi.org/10.1111/j.0013-9580.2004.09004.x.

Wilder, R.M., 1921. The effects of ketonemia on the course of epilepsy. Mayo Clin. Proc. 2, 307–308.

Williams, M.R., Hampton, T., Pearce, R.K.B., Hirsch, S.R., Ansorge, O., Thom, M., Maier, M., 2013. Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 263, 41–52, http://dx.doi.org/10.1007/s00406-012-0328-5.

Wu, A., Derrico, C.A., Hatem, L., Colvin, R.A., 1997. Alzheimer's amyloid-beta peptide inhibits sodium/calcium exchange measured in rat and human brain plasma membrane vesicles. Neuroscience 80, 675–684.

Wu, H.-Y., Hudry, E., Hashimoto, T., Uemura, K., Fan, Z.-Y., Berezovska, O., Grosskreutz, C.L., Bacskai, B.J., Hyman, B.T., 2012. Distinct dendritic spine and nuclear phases of calcineurin activation after exposure to amyloid-β revealed by a novel fluorescence resonance energy transfer assay. J. Neurosci. 32, 5298–5309.

Wyss-Coray, T., Loike, J.D., Brionne, T.C., Lu, E., Anankov, R., Yan, F., Silverstein, S.C., Husemann, J., 2003. Adult mouse astrocytes degrade amyloid-beta in vitro and in situ. Nat. Med. 9, 453–457, http://dx.doi.org/10.1038/nm838.

Xu, L., Emery, J.F., Ouyang, Y.-B., Voloboueva, L.A., Giffard, R.G., 2010. Astrocyte targeted overexpression of Hsp72 or SOD2 reduces neuronal vulnerability to forebrain ischemia. Glia 58, 1042–1049, http://dx.doi.org/10.1002/glia.20985.

Xu, X.-H., Pan, Y.-P., Wang, X.-L., 2002. mRNA expression alterations of inward rectifier potassium channels in rat brain with cholinergic impairment. Neurosci. Lett. 322, 25–28.

Yang, H., Yang, M., Guan, H., Liu, Z., Zhao, S., Takeuchi, S., Yanagisawa, D., Tooyama, I., 2013. Mitochondrial ferritin in neurodegenerative diseases. Neurosci. Res. 77, 1–7, http://dx.doi.org/10.1016/j.neures.2013.07.005.

Yang, Q., Feng, B., Zhang, K., Guo, Y., Liu, S., Wu, Y., Li, X., Zhao, M., 2012. Excessive astrocyte-derived neurotrophin-3 contributes to the abnormal neuronal dendritic development in a mouse model of fragile X syndrome. PLoS Genet. 8, e1003172, http://dx.doi.org/10.1371/journal.pgen.1003172.

Yang, Y., Ge, W., Chen, Y., Zhang, Z., Shen, W., Wu, C., Poo, M., Duan, S., 2003. Contribution of astrocytes to hippocampal long-term potentiation through release of D-serine. Proc. Natl. Acad. Sci. U. S. A. 100, 15194–15199, http://dx.doi.org/10.1073/pnas.2431073100.

Yasui, D.H., Xu, H., Dunaway, K.W., Lasalle, J.M., Jin, L.-W., Maezawa, I., 2013. MeCP2 modulates gene expression pathways in astrocytes. Mol. Autism 4, 3, http://dx.doi.org/10.1186/2040-2392-4-3.

Yuskaitis, C.J., Beurel, E., Jope, R.S., 2010. Evidence of reactive astrocytes but not peripheral immune system activation in a mouse model of Fragile X syndrome. Biochim. Biophys. Acta 1802, 1006–1012, http://dx.doi.org/10.1016/j.bbadis.2010.06.015.

Zhang, D.-D., Yu, H.-L., Ma, W.-W., Liu, Q.-R., Han, J., Wang, H., Xiao, R., 2015. 27-Hydroxycholesterol contributes to disruptive effects on learning and memory by modulating cholesterol metabolism in the rat brain. Neuroscience 300, 163–173, http://dx.doi.org/10.1016/j.neuroscience.2015.05.022.

Zhang, H., Li, Q., Graham, R.K., Slow, E., Hayden, M.R., Bezprozvanny, I., 2008. Full length mutant huntingtin is required for altered Ca2+ signaling and apoptosis of striatal neurons in the YAC mouse model of Huntington's disease. Neurobiol. Dis. 31, 80–88, http://dx.doi.org/10.1016/j.nbd.2008.03.010.

Zhang, J., Li, Y., Chen, Z.G., Dang, H., Ding, J.H., Fan, Y., Hu, G., 2013. Glia protein aquaporin-4 regulates aversive motivation of spatial memory in morris water maze. CNS Neurosci. Ther. 19, 937–944, http://dx.doi.org/10.1111/cns.12191.

Zhou, J., Kong, H., Hua, X., Xiao, M., Ding, J., Hu, G., 2008. Altered blood–brain barrier integrity in adult aquaporin-4 knockout mice. Neuroreport 19, 1–5, http://dx.doi.org/10.1097/WNR.0b013e3282f2b4eb.

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