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REVIEW

Astrocytes and synaptic plasticity in health and disease

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Abstract Activity-dependent synaptic plasticity phenomena such as long-term potentiation and long-term depression are candidate mechanisms for storing information in the brain. Regulation of synaptic plasticity is critical for healthy cognition and learning and this is provided in part by metaplasticity, which can act to maintain synaptic transmission within a dynamic range and potentially prevent excitotoxicity. Metaplasticity mechanisms also allow neurons to integrate plasticity-associated signals over time. Interestingly, astrocytes appear to be critical for certain forms of synaptic plasticity and metaplasticity mechanisms. Synaptic dysfunction is increasingly viewed as an early feature of AD that is correlated with the severity of cognitive decline, and the development of these pathologies is correlated with a rise in reactive astrocytes. This review focuses on the contributions of astrocytes to synaptic plasticity and metaplasticity in normal tissue, and addresses whether astroglial pathology may lead to aberrant engagement of these mechanisms in neurological diseases such as Alzheimer's disease.

Keywords Synaptic plasticity · Astrocytes · Metaplasticity · Alzheimer's disease

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Introduction

It has widely been accepted that memories are stored at least in part as changes in the strength of the synaptic connections between neurons, i.e., via synaptic plasticity. Metaplasticity regulates synaptic plasticity across time and among other things can help keep synaptic weights within a dynamic range by modifying the thresholds for long-term potentiation (LTP) and long-term depression (LTD) (Abraham 2008). Mounting evidence also suggests that the communication between neurons and astrocytes is critical for healthy brain functions. Notably, in this context, astrocytes can respond to neural activity and release gliotransmitters which feedback to neurons and regulate LTP and LTD, in part through generating metaplasticity (Gordon et al. 2009; Jones et al. 2013). Moreover, several studies have demonstrated the active participation of astrocytes in memory formation (Gibbs et al. 2008; Zorec et al. 2015).

Under neurodegenerative disease conditions, such as Alzheimer's disease (AD), synaptic alterations in the hippocampus and association cortices are an early feature and correlate with the severity of cognitive decline (DeKosky et al. 1996). Astrocytes become activated under these conditions, undertaking amyloid-β (Aβ) clearance and degradation through reactive astrogliosis which is a complex, multistage pathological response. Astrocytes thus provide nutritional support and stability to neurons and isolate them from the amyloid plaque deposition in the brain (Rossner et al. 2005). However, signaling in astrocytes and calcium homeostasis is disrupted in transgenic mouse models of AD (Kuchibhotla et al. 2009; Takano et al. 2006), and such pathological astrocyte function might also be directly involved in the early stages of neuronal pathophysiology in AD. This may also occur in other neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), where

astrocytes contribute to degeneration and death of motor neurons (Vargas and Johnson 2010; Haidet-Phillips et al. 2011).

This review addresses the astrocytic regulation of synaptic plasticity, including metaplasticity, focusing primarily in the hippocampus. We will also discuss whether the normal regulation of synaptic function becomes aberrant during pathological states, potentially contributing to the synaptic deficits in these pathologies, with a focus on Alzheimer's disease. We will also consider whether astrocytes or gliotransmitters are potential targets for treating AD or other neurological disorders.

Astrocyte communication and signaling

Astrocytes encase many synaptic contacts and thus help to ensure normal neuronal excitability by maintaining extracellular ion homeostasis through clearing glutamate and potassium ions from the regions around synapses. Astrocytes, by synthesizing glutamine which is utilized by neurons to form glutamate, also contribute significantly to neuronal metabolic homeostasis. Importantly, astrocytes are well equipped to communicate bidirectionally with neurons at tripartite synapses (Araque et al. 1999). In the hippocampus, one astrocyte is in close vicinity to approximately 100 neurons (Agulhon et al. 2008; Hamilton and Attwell 2010) and can connect to thousands of synapses (Bushong et al. 2002). It is well established that neurotransmitters released from the neurons can induce elevations in astrocytic calcium levels. For example, activation of pyramidal neurons in the hippocampus induces elevations in astrocytic Ca^{2+} levels by stimulation of astrocytic metabotropic glutamate receptors (Porter and McCarthy 1996). This activation state can be communicated to neighboring astrocytes via gap junctions or release of extracellular signaling molecules (Giaume et al. 2010). In retina and the embryonic ventricular zone, for example, induction of intracellular calcium signals in astrocytes leads to Ca^{2+} waves that spread across astrocytic networks (Weissman et al. 2004). In turn, either electrical or mechanical stimulation of a single astrocyte raises their intracellular calcium levels causing extrasynaptic glutamate release and resulting in elevated calcium levels in neighboring neurons (Charles et al. 1991; Parpura et al. 1994). Through release of a variety of gliotransmitters such as glutamate, D-serine, ATP, GABA, tumor necrosis factor-α (TNF-α), and endocannabinoids, astrocytes are also capable of regulating synaptic plasticity (see Fig. 1).

Although the molecular mechanisms underlying release of these gliotransmitters from astrocyte are not well understood, both Ca^{2+}-dependent exocytosis and Ca^{2+}-independent mechanisms have been reported. Studies report that Ca^{2+}-dependent release of gliotransmitter is based on Ca^{2+} and SNARE protein-dependent mechanisms (Bezzi et al. 2004; Araque et al. 2000) and through astrocytic vesicular compartments (Bezzi et al. 2004; Mothet et al. 2005) or lysosomal exocytosis (Jaiswal et al. 2007; Zhang et al. 2007). Such release can be triggered by activation of astrocytic G-protein coupled receptors (GPCRs) that couple by Gq to phospholipase C, the hydrolysis of which generates the second messenger IP_3 which binds with the Type 2 IP_3 receptor in the membrane of the astrocytic smooth endoplasmic reticulum to open Ca^{2+} channels and raise intracellular free calcium levels (Parpura and Zorec 2010; Pascual et al. 2005). Surprisingly, calcium-dependent entry of astrocytic mitochondria into neighboring neurons is also possible and this entry is believed to be vital for enhancing neuronal survival signals (Hayakawa et al. 2016). In certain cases, Ca^{2+}-independent mechanisms for the release of gliotransmitters appear to coexist with Ca^{2+}-dependent mechanisms. Such mechanisms include release through astrocytic hemi-channels (Ye et al. 2003), release by vesicles (Parpura et al. 1994), backward transport of Na^+- dependent glutamate uptake (Anderson and Swanson 2000; Nicholls and Attwell 1990), through the channel pore of P2X7 receptors (Duan et al. 2003), and by volume regulated anion/Cl^- channels (Kimelberg et al. 2006; Ye et al. 2009). Ca^{2+}-independent mechanisms are known to occur in cultured astrocytic cells, but their relevance in vivo remains inconclusive.

In summary, astrocytes are in close contact with neurons, regulating neuronal function at the synaptic and network levels and thus are well placed to respond to neural network activity, and impose a significant impact on that activity under both physiological and pathological conditions.

Astrocytes and the regulation of synaptic transmission

Numerous studies have demonstrated that gliotransmitters released from astrocytes can modulate synaptic transmission. Astrocytic glutamate release modulates brain networks in multiple brain regions in situ including hippocampus, thalamus, etc. Slow inward currents are evoked by astrocytic glutamate in CA1 hippocampal pyramidal neurons by activating extrasynaptic NMDARs (Araque et al. 1998; Fellin et al. 2004; Angulo et al. 2004; Perea and Araque 2005; De Pitta and Brunel 2016). Astrocytic glutamate has been shown to synchronously excite hippocampal pyramidal neurons, indicating that gliotransmission may contribute to the coordinated neuronal firing patterns of neurons (Angulo et al. 2004). Moreover, activation of astrocytic CB1 receptors potentiates synaptic transmission via calcium-dependent release of glutamate

(Navarrete and Araque 2010). ATP released from astrocytes during neuronal activity is able to influence synaptic transmission by acting on P2X or P2Y receptors (Palygin et al. 2010). Alternatively, ATP can be converted to adenosine by ectonucleotidases to act on pre-synaptic adenosine receptors (A1/A2) to increase (A2) or decrease (A1) transmitter release (Guthrie et al. 1999; Palygin et al. 2010). In the hypothalamus, the afferent activity-induced activation of astrocytes causes an enhancement in the amplitude of synaptic currents at glutamate synapses that depend on the release of glial ATP (Gordon et al. 2009). At CA3-CA1 synapses, astrocyte-derived ATP causes a quick and short-lasting form of pre-synaptic depression (Zhang et al. 2003). However, astrocytes can also regulate inhibitory synaptic transmission (Kang et al. 1998). Astrocytes may release ATP to stimulate interneuron excitability by acting on P2Y1 receptors and thereby potentiate GABAergic synaptic transmission (Bowser and Khakh 2004). Conversely, glutamate release from astrocytes in CA1 can promote pre-synaptic inhibition of inhibitory interneurons via activation of Group II/III mGluRs, although activation of neuronal kainate receptors by astrocyte-derived glutamate can counterbalance this inhibitory state and enhance inhibitory neurotransmission (Liu et al. 2004). In a nutshell, astrocytic-mediated gliotransmitter signaling regulates diverse synaptic and network functions under normal physiological conditions.

Astrocytic contribution to synaptic plasticity

The activation of mGluR and muscarinic cholinergic receptors generates LTP in the hippocampus in vivo and in vitro, an effect that requires simultaneous postsynaptic activity and astrocyte glutamate release and hence activation of neuronal mGluRs (Navarrete et al. 2012). Stimulation of single astrocytes in the hippocampus can cause glutamate release that elicits slow inward NMDAR-mediated currents, enhances the probability of glutamate release, and induces Group I mGluR-mediated LTP (Perea and Araque 2007). Conversely, the high affinity glutamate transporter-1 (GLT-1) coexists with aquaporin (AQP4) and reduced GLT-1 levels in AQP4-null mice results in decreased glutamate uptake by astrocytes and impaired LTP (Zeng et al. 2007).

Besides glutamate, D-serine, traditionally considered to be released from astrocytes, enables LTP induction in cultures and acute hippocampal slices (Henneberger et al. 2010; Yang et al. 2003) and is essential for NMDA receptor-dependent synaptic plasticity in the supraoptic nucleus (Panatier et al. 2006). For example, local LTP induction at Schaffer collateral synapses in CA1 was abolished by clamping intracellular Ca^{2+} levels within a single nearby astrocyte. This LTP was rescued by bath application of D-serine (Henneberger et al. 2010). Similarly, blocking glial cell activation with fluoroacetate (a metabolic inhibitor) blocked LTP in the prefrontal cortex by attenuating the amount of D-serine present extrasynaptically (Fossat et al. 2012). D-Serine is a product of serine racemase, an enzyme first found in astrocytes (Schell et al. 1995) but later discovered to be primarily found in neurons (Kartvelishvily et al. 2006; Miya et al. 2008). In contrast to the traditional view therefore, it appears that it is L-serine that is synthesized and released by astrocytes and this is used by serine racemase in neurons to synthesize D-serine, which then modulates synaptic plasticity (Wolosker et al. 2016). In accord with this model, neuronal serine racemase conditional knockout mice display a significant reduction in LTP and reduced NMDAR currents, whereas astrocytic serine racemase conditional knockout mice show neither effect (Benneyworth et al. 2012). Taken together, these data indicate a key contribution by astrocytes to the D-serine regulation of LTP, but that this is an indirect role via the production and release of the precursor L-serine.

ATP release has also been implicated in hippocampal LTP (Wieraszko and Ehrlich 1994). ATP released from astrocytes, when converted to adenosine via ectonucleotidases, tonically suppressed synaptic transmission and subsequently enhanced the dynamic range for long-term potentiation and associated transient heterosynaptic depression in CA1 (Pascual et al. 2005). Glial ATP, when converted to adenosine, can also generate heterosynaptic LTD, thus amplifying the effect of the homosynaptically induced LTP, akin to lateral inhibition (Chen et al. 2013).

Another key set of gliotransmitters is cytokines. For example, TNF-α, possibly released from astrocytes in developing visual cortex, is essential for experience-dependent change in synaptic transmission (Kaneko et al. 2008). Mice deficient in TNF-α exhibited not only the normal loss of deprived eye responses following monocular visual deprivation, but also a lack of subsequent enhancement in open eye responses (Kaneko et al. 2008). Interestingly, acute application of TNF-α increased surface expression of AMPARs in both hippocampal culture and acute slices, resulting in increased synaptic strength and modulation of neuronal activity (Beattie et al. 2002). Even in the presence of tetrodotoxin, TNF-α upregulates postsynaptic AMPAR surface expression in culture, suggesting that astrocyte-derived TNF-α may be a crucial signal for synaptic up-scaling (Stellwagen and Malenka 2006). Similarly, interleukins can modulate synaptic plasticity in the brain. Treatment of hippocampal slices with recombinant human interleukin-6 (IL-6) impaired LTP in the CA1 (Li et al. 1997) and there was impaired LTP in a mouse model over-expressing IL-6 release from astrocytes in the dentate gyrus (Bellinger et al. 1995). Similarly, human recombinant IL-2 (Tancredi et al. 1990) and IL-1β inhibit hippocampal

LTP (Bellinger et al. 1993), while IL-10 antagonizes the LTP inhibition by IL-1β (Kelly et al. 2001). Besides interleukins, intracerebroventricular injection of interferon gamma (IFN-ϒ) (Maher et al. 2006) and bath application of IFN-α (Mendoza-Fernandez et al. 2000) attenuates LTP in rat hippocampus. Thus, it is clear that cytokines play an active role in modulating synaptic plasticity, and although astrocytes (as well as microglia) are capable of releasing cytokines, the conditions under which astrocytes are stimulated to do so *in vivo* remain unclear.

Astrocytes and metaplasticity

How are LTP and LTD balanced in the healthy brain? One contributing mechanism is metaplasticity, whereby neural activity results in a change in neural state that alters the cell's response to subsequent plasticity-inducing events (Abraham and Bear 1996). Metaplasticity mechanisms are capable of regulating events across time and space (from minutes to hours) to maintain synaptic plasticity and neuronal homeostasis inside the brain. Classical examples of metaplasticity are the ability of transient NMDAR activation (by weak HFS or by LFS) to inhibit subsequent LTP induction in hippocampal CA1, an effect lasting for less than an hour (Coan et al. 1989; Fujii et al. 1991), or the activation of Group I mGluRs to facilitate and prolong LTP (Raymond et al. 2000). Metaplasticity-like mechanisms have also been reported in human cortex (Bocci et al. 2014; Muller-Dahlhaus and Ziemann 2015), *Xenopus* (Dunfield and Haas 2009), and *Aplysia* (Fischer et al. 1997).

Metaplasticity phenomena can be broadly divided into homosynaptic and heterosynaptic subtypes. Homosynaptic metaplasticity is expressed at synapses that participate in the initial bout of priming activity, while heterosynaptic metaplasticity occurs when an episodic priming event at one set of synapses regulates subsequent plasticity at synapses in either nearby dendritic compartments or throughout the cell (Abraham 2008). In one recently studied example of heterosynaptic metaplasticity in hippocampal area CA1, high-frequency priming stimulation of one set of synapses caused a cell-wide shift in plasticity thresholds, such that subsequent LTD was enhanced and LTP was impaired (Hulme et al. 2012; Wang and Wagner 1999). This phenomenon appears to be mediated via astrocytes as the effect did not require postsynaptic neuronal depolarization, but involves release of calcium from intracellular stores by IP_3, the opening of connexin-43 channels or hemi-channels located on astrocytes, the release and extracellular conversion of ATP to adenosine, and subsequent activation of adenosine type 2 receptors (A2Rs) (Hulme et al. 2012; Jones et al. 2013). Moreover, the stratum radiatum astrocytes were widely activated by priming stimulation in the stratum oriens, an effect that was almost completely blocked by an inhibitor of gap junctions and hemi-channels (Hulme et al. 2014). This range of evidence strongly supports the potential role of astrocytes in mediating at this type of heterosynaptic metaplasticity, although which glial transmitter may be exerting the plasticity regulation remains to be determined. Other examples of astrocyte-mediated metaplasticity have recently been reviewed (Jones 2015).

Astrocytic signaling in disease conditions

Neurodegenerative diseases are characterized by synaptic dysfunction, apoptotic cell death, and neuroinflammation, and are typically associated with severe cognitive decline and/or motor deficits. Accumulating evidence suggests a role for dysfunction in astrocyte-neuron signaling as an important contributor to pathology for most neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), and ALS. There is in particular substantial evidence for a role of astrocytes in AD and this section will focus mainly on how astrocytes are affected in AD and may contribute to the disease pathophysiology.

Three-dimensional reconstructions of amyloid plaques demonstrated that astrocytes are well placed to play a major role in amyloid-β (Aβ) degradation (Wegiel et al. 2000). Astrocytes degrade Aβ deposition by two ways—either by phagocytosis or by Aβ degrading proteases. There is substantial evidence that adult mouse astrocytes can phagocytose and degrade Aβ deposits in vitro (Wyss-Coray et al. 2003). Similarly, Aβ degrading proteases such as neprilysin display ability to degrade both $Aβ_{1–40}$ and $Aβ_{1–42}$ (Iwata et al. 2000; Leal et al. 2006). However, aberrant activity by astrocytes in disease conditions might also aggravate the pathophysiology. Abnormal astrocytic calcium signaling is seen in various pathological states including epilepsy, AD, stroke, and traumatic brain injury (Rodriguez et al. 2009). Calcium homeostasis and signaling in astrocytes are also disrupted in transgenic mouse models of AD (Kuchibhotla et al. 2009; Takano et al. 2006) and in astrocytes cultured with Aβ peptides (Haughey and Mattson 2003). Indeed, high levels of extracellular Aβ induce sporadic Ca^{2+} signals in astrocytes but not in isolated neurons, which may be due to differences in their membrane lipid composition (Abramov et al. 2003). The aberrant astrocytic calcium signaling begins near Aβ plaques and spreads for long distances through the cortex, suggesting that the astrocytic calcium signaling can be widespread. The ability of Aβ to dysregulate astrocytic calcium signaling in vitro and in vivo suggests the potential for astrocytes to contribute to the early stages of pathogenesis in AD (Kuchibhotla et al. 2009).

Astrocytic networks in aged transgenic mice are aberrantly coupled by submissive intercellular diffusion/spread through gap junctions (Kuchibhotla et al. 2009) particularly in the neocortex (Peters et al. 2009).

Differences of pre-synaptic function in adult AD mice (APP/PS1) can arise from an altered calcium dynamic caused by the FAD-linked mutation in presenilin 1, which is known to enhance Ca^{2+} release from the endoplasmic reticulum (Megill et al. 2015). Hyperactive spontaneous short-lived astrocytic calcium waves, independent of neural activity and seen in many transgenic mice models, might influence neuronal signaling at synapses (Takano et al. 2006). Although the amyloid plaques have been one of the cardinal neuropathological feature of AD, it is now recognised that soluble Aβ oligomers are themselves toxic and lead to synaptic deterioration early in the disease process (Coleman et al. 2004). Of particular interest here, soluble Aβ oligomers contribute to impairments in astrocytic metabolism (Tarczyluk et al. 2015) and enhanced astrogliosis (Carrero et al. 2012). Atrophic astrocytes appear in the entorhinal cortex, hippocampus, and prefrontal cortex of 3xTg AD mice even before occurrence of extracellular β-amyloid depositions (Olabarria et al. 2010; Yeh et al. 2011) indicating a possible response to soluble Aβ oligomers.

Another neuropathological feature is reactive astrocytosis, during which astrocytes proliferate in response to ischaemia, injury, or disease, and show hypertrophy of the cell soma and increased gene expression of glial fibrillary acidic protein (GFAP) (Wisniewski and Wegiel 1991). Interestingly, hyperactive calcium signaling occurs in astrocytes that surround plaques, while atrophy occurs further away from plaques (Rodriguez et al. 2009), indicating that there is a complex alteration of astrocytic function in AD. Moreover, morphological atrophy of astrocytes results in reduced ability to envelop synapses which may lead to thinning and reduced numbers of synaptic contacts and thus decline in synaptic function (Coleman et al. 2004; Terry 2000). Reactive astrocytes along with microglia release proinflammatory cytokines, including interleukin-1β, interferon-γ, cyclooxygenase-2 (COX-2), interleukin-6, and TNF-α (Benzing et al. 1999; McGeer and McGeer 2010), noted above as being potent inhibitors of LTP. It is interesting, therefore, that although murine AD models differ in the temporal profile of astrocytosis and the onset of LTP deficits, the development of these features goes hand in hand (Table 1). While not conclusive, this correlation suggests that astrocytosis may be a major contributor to the LTP deficits and associated cognitive decline.

Early impairment of microvasculature may be another functional outcome of altered astrocyte calcium signaling in AD as astrocytic control of the microvasculature is altered in 3xTg, Dutch/Iowa mutants, and Tg2576 mouse models of AD mice at early stages of the disease, well

Table 1 Parallel age-dependence of astrogliosis and impaired LTP in AD transgenic mice

Animal model	Age (months)	Astrogliosis	Impaired LTP
Tg2576	2–5	Rodriguez-Vieitez et al. (2015)	Jacobsen et al. (2006) and Ma et al. (2010)
	5–10	Hsiao et al. (1996) and Rodriguez-Vieitez et al. (2015)	
	>10	Apelt and Schliebs (2001), Jacobsen et al. (2006), Rossner et al. (2001) and Terai et al. (2001)	Chapman et al. (1999) and Jung et al. (2011)
PDAPP	2–5	Games et al. (1995)	Larson et al. (1999)
	5–12	Heneka et al. (2005)	Dewachter et al. (2002)
	>12		Giacchino et al. (2000)
APP/PS1	2–5	Poisnel et al. (2012) and Ruan et al. (2009)	Gong et al. (2004) and Trinchese et al. (2004)
	5–12	Kamphuis et al. (2012) and Poisnel et al. (2012)	Trinchese et al. (2004) and Volianskis et al. (2010)
	>12	Jo et al. (2014) and Poisnel et al. (2012)	Jo et al. (2014) and Volianskis et al. (2010)
J20	2–5	Beauquis et al. (2013)	Harris et al. (2010) and Saganich et al. (2006)
	5–10	Beauquis et al. (2013) and Wright et al. (2013)	Dewachter et al. (2002)
	>10	Moechars et al. (1999)	
3xTg	2–5	Rodriguez et al. (2009) and Yeh et al. (2011)	
	5–12	Caruso et al. (2013), Kulijewicz-Nawrot et al. (2012), Sancheti et al. (2014) and Yeh et al. (2011)	Oddo et al. (2003) and Sancheti et al. (2013)
	>12	Kulijewicz-Nawrot et al. (2012), Oddo et al. (2003), Olabarria et al. (2010) and Yeh et al. (2011)	Oddo et al. (2003) and Sancheti et al. (2013)
5xFAD	2–5	Aytan et al. (2016) and Oakley et al. (2006)	
	5–10	Huttenrauch et al. (2015), Oakley et al. (2006) and Wu et al. (2014)	Crouzin et al. (2013), Kimura et al. (2010) and Kimura and Ohno (2009)
	>10	Jo et al. (2014)	

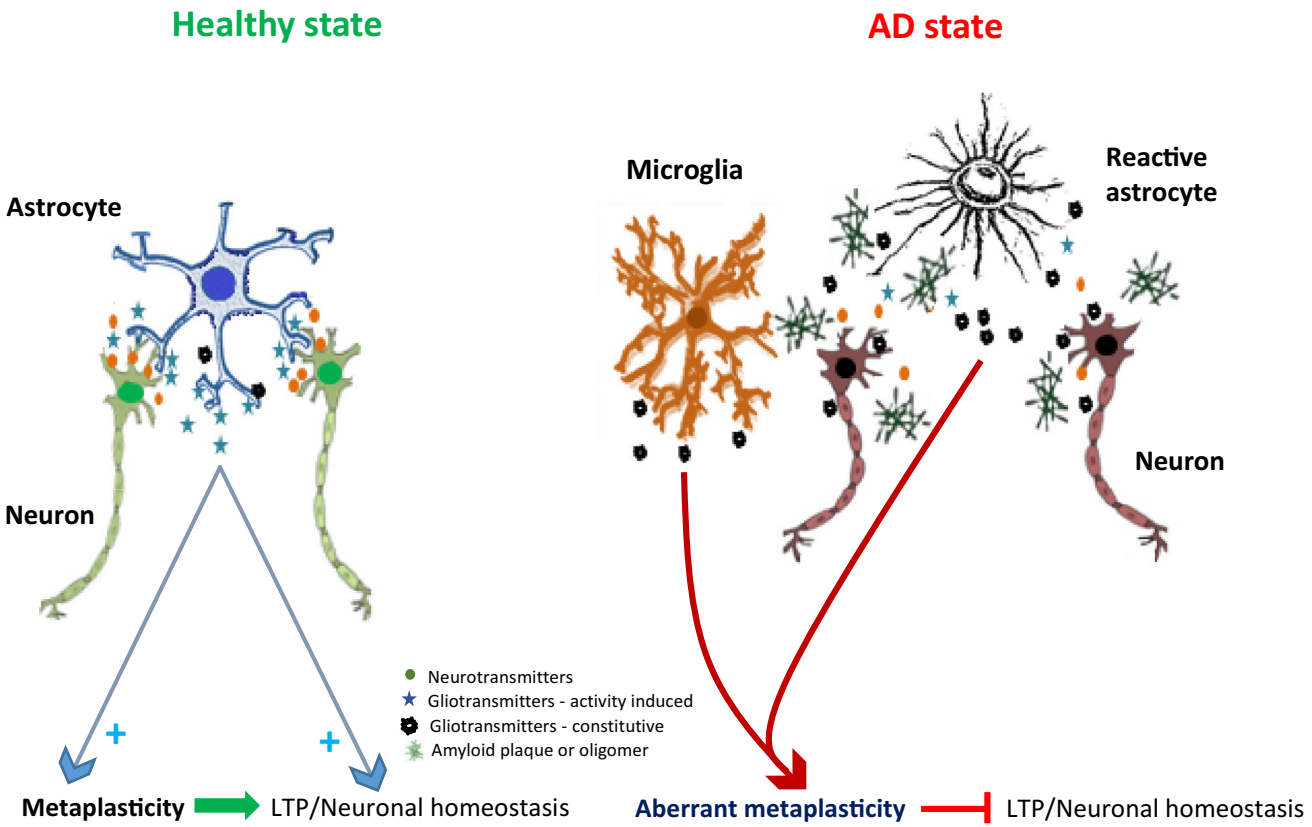

Fig. 1 Astroglial regulation of plasticity in healthy vs diseased states. In the healthy state, activity-mediated release of gliotransmitters (such as D-serine, ATP, glutamate, TNF-α etc) from astrocytes regulates (+) LTP and metaplasticity, balancing synaptic plasticity with neuronal homeostasis. In AD, astrocytes are less able to sense the neuronal activity and withdraw their processes from synapses due to the presence of extrasynaptic amyloid plaque and neuroinflammation. Furthermore, reactive astrocytes and microglia increase the constitutive release of gliotransmitters (such as glutamate, GABA, S100β, IL-1β, TNF-α, etc.). This may induce aberrant metaplasticity states which result in impairments in LTP and neuronal homeostasis

prior to Aβ production, and loss of synapses (Takano et al. 2007). Moreover, astrocytes are well known to regulate glycogen processing, but development of AD induces progressive loss of glucose usage in the brain, contributing to a nutritional collapse that may have dire consequences on neuronal survival and synaptic plasticity (Allaman et al. 2010). These additional features of the AD brain add support to the concept that dysfunctional astrocytic signaling contributes to altered synaptic plasticity and thus cognition in AD.

Aberrant metaplasticity in disease condition

As discussed above, strong afferent activity can cause widespread-synchronous calcium elevations in astrocytes that drive the release of gliotransmitters to dampen LTP and enhance LTD throughout a neural network. The fact that spontaneous astrocytic and neuronal calcium waves are reported in AD models (Chakroborty et al. 2012; Kuchibhotla et al. 2009; Mattson and Chan 2003) is suggestive of endogenous hyper-activation of brain cells due to the disease and thus an excessive release of gliotransmitters. This raises the possibility that there may be an associated aberrant constitutive engagement of inhibitory metaplasticity mechanisms that underpin the impairment of LTP that is common to most mouse models of AD (Jones 2015).

The possible aberrant engagement of metaplasticity mechanisms in AD models was first supported by the finding that NMDAR-mediated inhibition of LTP was absent in APP23 mice, even before the onset of extracellular plaques (Balducci et al. 2010), suggesting that this mechanism was already active and mediating LTP inhibition basally. This could explain in part the therapeutic efficacy of memantine in AD. Memantine is a partial NMDAR antagonist that can rescue the attenuated LTP induction/expression due to application of low concentrations of NMDA in CA1 (Frankiewicz and Parsons 1999; Izumi et al. 1992; Zajaczkowski et al. 1997; Zorumski and Izumi 2012). The fact that cognitive deficits, like the altered synaptic

metaplasticity, occur before the onset of plaques in the APP23 mice (Balducci et al. 2010) supports the important role played by soluble Aβ oligomers in synaptic dysfunction, and is consistent with the fact that the oligomers can enhance activation of the GluN2B-containing NMDARs that are targets of astrocytically released glutamate, thereby inhibiting LTP and favoring LTD (Li et al. 2011).

Targeting astrocytes may have therapeutic potential

Given the established role of astrocytes in regulating synaptic activity and metaplasticity, aberrations in astrocyte signaling may contribute to the progression of impairments in synaptic plasticity corresponding to cognitive decline in AD. In particular, it is worth paying attention to possible aberrant engagement of the inhibitory metaplasticity mechanisms in AD models. Understanding the mechanisms by which astrocyte regulates plasticity and generates metaplasticity in diseased states may suggest new therapeutic targets that are so urgently needed in this field. For example, an enhanced level of TNF-α (as produced by reactive astrocytes and no doubt activated microglia) not only causes impairments in LTP but also triggers a cascade of neuronal dysfunction and neurotoxicity as well as contributing to altered APP processing and plaque formation. Thus, antiTNF-α therapy has gained much attention in treating AD symptoms. Clinically, infliximab treatment can improve cognitive impairment and regulate $A\beta_{1\text{-}42}$/p-tau levels in the cerebrospinal fluid (Shi et al. 2011). Other clinical antiTNF-α therapy such as and pentoxifylline (Sha and Callahan 2003) has been promising in treating severe cognitive decline in AD. Hence, targeting the TNF-α protein, its receptor or TNF-α converting enzyme (TACE) might be possible therapeutic interventions for the treatment of AD, although an early clinical trial with etanercept was inconclusive (Butchart et al. 2015). Thus the optimal agent, dose, and means of administration remain to be investigated further (Clark and Vissel 2016). In addition, considering the role played by p38 MAP kinase and NF-κB in TNF-α production in AD patients, inhibition of these molecules may be useful in treating neurodegeneration. Treatments against other inflammatory cytokines should also be considered, as well as the upregulation of the LTP pro-acting D-serine (Zou et al. 2016). Recent studies indicate that exogenous ATP may also be a therapeutic target as it helps in restoring LTP and protects dendritic loss as seen in AD (Jung et al. 2012). Finally, astrocytes themselves could be the direct target of gene therapies, as over-expression of the master autophagy/lysosome gene transcription factor EB in astrocytes facilitated Aβ clearance and reduced plaque formation in a mouse model of AD (Xiao et al. 2015). In summary, although anti-Aβ treatments have received the bulk of attention as Alzheimer's treatment, the direct or indirect effects of aberrant astrocyte activity may also offer attractive targets as treatment options for rescuing at least the impairment in plasticity-associated memory and cognition.

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