Neuroscience Research 197 (2023) 42–51

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.sciencedirect.com/journal/neuroscience-research

Review article

Astrocytes and brain-derived neurotrophic factor (BDNF)

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ARTICLE INFO

Keywords:
Astrocytes
Neurotrophins
Brain-derived neurotrophic factor (BDNF)

ABSTRACT

Astrocytes are emerging in the neuroscience field as crucial modulators of brain functions, from the molecular control of synaptic plasticity to orchestrating brain-wide circuit activity for cognitive processes. The cellular pathways through which astrocytes modulate neuronal activity and plasticity are quite diverse. In this review, we focus on neurotrophic pathways, mostly those mediated by brain-derived neurotrophic factor (BDNF). Neurotrophins are a well-known family of trophic factors with pleiotropic functions in neuronal survival, maturation and activity. Within the brain, BDNF is the most abundantly expressed and most studied of all neurotrophins. While we have detailed knowledge of the effect of BDNF on neurons, much less is known about its physiology on astroglia. However, over the last years new findings emerged demonstrating that astrocytes take an active part into BDNF physiology. In this work, we discuss the state-of-the-art knowledge about astrocytes and BDNF. Indeed, astrocytes sense extracellular BDNF through its specific TrkB receptors and activate intracellular responses that greatly vary depending on the brain area, stage of development and receptors expressed. Astrocytes also uptake and recycle BDNF / proBDNF at synapses contributing to synaptic plasticity. Finally, experimental evidence is now available describing deficits in astrocytic BDNF in several neuropathologies, suggesting that astrocytic BDNF may represent a promising target for clinical translation.

1. Introduction

1.1. Astrocytes

Astrocytes are the predominant class of neuroglia in the central nervous system (CNS). They represent around 50% of the total cells of the brain and play a key role in numerous functions within the CNS (Kim et al., 2019).

Astrocytes owe their name to their very complex, stellate morphology. The morphological structure of astrocytes has two functional roles: on one side they make contact with blood vessels, which allows for the absorption of energy substrates, on the other side they tightly enwrap most synapses, controlling the composition of the perineural interstitial fluid and therefore, indirectly, neuronal activity. They also offer trophic support to neurons by storing glucose in the form of glycogen granules, which can be metabolized to lactate and transferred to neurons. In neurons, lactate is transformed into pyruvate and finally used to produce ATP (Pellerin et al., 2007), to maintain their metabolic activity (Bonvento, Bolanos, 2021). Astrocytes also act as a primary defense against oxidative/nitrosative stress (Skowronska and Albrecht, 2013) and have a key role in neurogenesis by acting on synapse formation and elimination (Eroglu, Barres, 2010). One of the main functions of astrocytes is controlling the ionic homeostasis (i.e., Ca^{2+}, K^{+}, H^{+}), glutamate and water as they express several different channels and neurotransmitter receptors (Semyanov and Verkhratsky, 2021; Verkhratsky et al., 2020), including calcium channels. Ca^{2+} is a universal second messenger that regulates essential activities in all eukaryotic cells. In the CNS, Ca^{2+} regulates synaptic transmission (Sudhof, 2021), and modulation of intracellular Ca^{2+} concentration is a central feature of astrocyte physiology (Zorec et al., 2012). The processes that induce cytosolic Ca^{2+} transients in astrocytes are still not completely defined, but neuronal release of neurotransmitters seems to have an important role (Verkhratsky et al., 2020). Finally, astrocytes produce and secrete a rich repertoire of molecules, in a continuous dialogue with neurons and other CNS cells. Astrocyte-derived molecules include metabolic substrates, neurotransmitters and their precursors, as well as trophic factors such as neurotrophins (Pellerin et al., 2007; Bonvento and Bolanos, 2021).

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https://doi.org/10.1016/j.neures.2023.02.001
Received 29 September 2022; Received in revised form 17 January 2023; Accepted 2 February 2023
Available online 11 February 2023

1.2. Neurotrophins

Neurotrophins are a well-characterized family of neuronal trophic factors, which include nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4 or NT4/5). All neurotrophins are synthetized as proneurotrophins (pro NTs), which are either processed to the mature form within secretory vesicles (Seidah et al., 1996) or secreted and processed by proteases in the extracellular environment (Lee et al., 2001). Physiologically, neurotrophins exist as non-covalently associated dimers of about 27 kDa and serve a wide range of biological functions according to the set of receptors present on the target cell. The main classes of receptors are tropomyosin-related kinase (Trk) and p75 neurotrophin receptor ($p75^{NTR}$) (Lu et al., 2005). Each neurotrophin displays a binding specificity for a different class of receptors: TrkA for NGF, TrkB for BDNF and NT-4 and TrkC for NT-3 (Wiesmann et al., 1999; Ultsch et al., 1999). Upon NT binding, receptors dimerize and the subsequent cross-activation of the intracellular tyrosine kinase domains activates downstream signaling cascades such as the Ras-Raf-MAPK, PLC-γ-Ca^{2+} and PI3-kinase-Akt, which mediate neuronal survival, differentiation and plasticity depending on the context and cell type (Reichardt, 2006; Minichiello, 2009). Once formed, the NT-receptor complexes may be degraded, recycled or retrogradely transported along axons in organelles called signaling endosomes (Grimes et al., 1997; Howe et al., 2001; Yano et al., 2001). $p75^{NTR}$ modulates NT binding affinity and specificity for Trks acting as a coreceptor for multiple ligands (Teng et al., 2010). It promotes apoptosis or cell survival depending on the type of ligand (pro vs matureNT) and on the co-receptors expressed on cell membranes. Indeed, $p75^{NTR}$ can promote cell survival via its interaction with Trk receptors, or might induce cell death when associated with Sortilin (Nykjaer et al., 2004; Nykjaer et al., 2005; Teng et al., 2005). Within the developing and the adult brain, BDNF is the most abundant and most studied of all NTs; indeed, BDNF plays crucial roles at all stage of neuronal development and maturation, as well as in the establishment and maintenance of synaptic plasticity (Kowianski et al., 2018; Lu et al., 2014).

Most of our knowledge about neurotrophins' biology has been obtained through experiments performed on neurons, while limited and controversial information are available about the effect of those trophic factors in astrocytes. This review aims at summarizing the main studies describing the contribution of astroglial cells to neurotrophins' physiology, with a focus on the BDNF system.

2. Physiology of astroglial BDNF

2.1. An historical overview of the early experimental studies on neurotrophins and astrocytes

Among their various functions, astrocytes synthesize, release and reuptake trophic factors, including neurotrophins. Initial studies focused mostly on astroglia-derived NGF, and only later the scientific community addressed the function of astrocyte-derived BDNF. Indeed, the first proof that NGF was released from astrocytes was provided in 1979 (Lindsay, 1979) and several stimuli that induced astrocytes to produce neurotrophins were subsequently identified, including catecholamines (adrenaline, noradrenaline) (Furukawa et al., 1989). Since NGF-sensitive neurons in the brain are cholinergic, and cholinergic neurons are amongst the first to degenerate in Alzheimer's Diseases, astrocyte-derived NGF was proposed to be a possible therapeutic target to improve cholinergic neurons survival. This, unfortunately, did not translate into clinical applications (Saez et al., 2006). Secretion of NGF from astrocytes has been reported to be induced by interleukin-1 (Lindholm et al., 1987; Carman-Krzan et al., 1991), fibroblast growth factor (FGF), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGFβ-1) (see for example Yoshida and Gage, 1992) and acetylcholine (Mele and Juric, 2014). Interestingly, NGF expression is also induced by glutamate, suggesting its expression/secretion could be, under some circumstances, driven by neuronal activity (Pechan et al., 1993). Activation of PLC seems crucial to the induction of NGF in astrocytes (Laviada et al., 1995). Several evidence indicate that astrocytes constitutively secrete NGF (Carman-Krzan et al., 1991). NGF secretion is prominent in actively dividing astrocytes (Furukawa et al., 1987; Lu et al., 1991), suggesting that glia express the NGF gene, and presumably synthesize the trophic protein, only in an active growth state, such as during development or after injury. Indeed, activated astrocytes were identified as the major source of NGF upon neurotoxic injury in rat cholinergic basal forebrain neurons (Arendt et al., 1995). Astrocytes are also able to internalize NGF through TrkA-mediated internalization, and respond to exogenous NGF by acquiring a fibrous morphology (Hutton and Perez-Polo, 1995).

In 1992 Zafra and colleagues provided the first evidence about the capability of astrocytes to produce BDNF (Zafra et al., 1992) and two years later Schwartz and colleagues demonstrated that BDNF's release from astroglia could be induced by β-adrenergic receptor activation (Schwartz and Nishiyama, 1994). Subsequently, a growing body of literature supported the notion that astrocytes produce, bind, internalize and release BDNF (Alderson et al., 2000; Kinboshi et al., 2017). Some studies detected basal levels of BDNF expression in vitro in cultures of embryonic astrocytes (Zaheer et al., 1995) where, similarly to what was described for NGF, BDNF expression is induced by exposure to neurotransmitters, i.e., dopamine, epinephrine and norepinephrine (Inoue et al., 1997; Koppel et al., 2018).

2.2. Expression of TrkB in astrocytes

BDNF is the neurotrophin with the highest expression in the brain, where it plays a critical role in the regulation of synaptic physiology. It was first described as a survival factor for target cells; however, it is now known that BDNF regulates synaptic plasticity, memory, cognition and complex behaviors in the adult brain. Accordingly, BDNF deficits are linked to the development of many neurodegenerative and psychiatric diseases (see next section) (Krishnan and Nestler, 2008; Psychiatric et al., 2009; Gauthier et al., 2004; Ventriglia et al., 2002). TrkB has different splicing isoforms: full length (TrkB.FL), which presents a tyrosine kinase domain, and different truncated isoforms (TrkB.T) lacking this domain, such as TrkB.T1, the most abundant of them and consequently the most studied (Klein et al., 1990; Stoilov et al., 2002; Luberg et al., 2010). TrkB.T1 has a different expression pattern from the full-length receptor within the brain and was first identified as a dominant negative receptor for TrkB.FL, impairing its activation by sequestering BDNF. This was first demonstrated by Fryer and colleagues, who showed that the differentiation of SHSY5Y cells induced by BDNF was markedly reduced if cells were grown on a layer of cells expressing TrkB-T1, which were actually capable to bind and internalize the neurotrophin (Fryer et al., 1997).

Astrocytes express mainly TrkB.T1. Importantly, the expression of both TrkB.T1 and TrkB.FL is mediated by intracellular cAMP, indicating that the same stimuli are able to induce astroglia production, secretion of BDNF and TrkB expression (Deogracias et al., 2004). More recently, BDNF-TrkB.T1 signaling has been implicated in the morphological maturation of astrocytes (Holt et al., 2019). The intracellular pathways mediating this effect are still not described, however they may involve the activation of specific GTPases and cytoskeleton remodeling, as discussed later (Ohira et al., 2005). Reactive astrocytes were shown to express TrkB.FL in mice subjected to chronic cortical damage (McKeon et al., 1997) and viral encephalitis (Soontornniyomkij et al., 1998). There are also some reports that demonstrated a weak expression of TrkB.FL in cultured astrocytes (Condorelli et al., 1995; Jaudon et al., 2021). Crucially, the capacity of astrocytes to respond to BDNF stimuli seems to vary depending on the different brain areas, as recently demonstrated by Saba and colleagues (Saba et al., 2020).

2.3. BDNF vs pro-BDNF

Mature NTs and their precursors are both biologically active and the balance between the two is an important determinant of neuronal fate. Long-term synaptic modifications are regulated by the activity-dependent secretion of BDNF into the extracellular space (Poo, 2001), and this effect is dependent on whether the secreted form is proBDNF or mBDNF. Indeed, the two forms have a different affinity for the binding to $p75^{NTR}$ and TrkB, leading to opposite effects on synaptic strength (Lu et al., 2005). Moreover, the extracellular processing of proNTs can per se modulate synaptic efficacy (Pang et al., 2004). However, the physiological relevance of proBDNF is still a matter of debate [see, for example (Matsumoto et al., 2008)]. Of note, a similar case can be made for NGF. Indeed, the ratio between mNGF and proNGF plays an important role in neuronal physiology and its alterations affect the progression of neurodegeneration in diseases such as diabetic encephalopathy (Soligo et al., 2015) and Alzheimer's disease (Bruno and Cuello, 2006; Cuello et al., 2010; Fahnestock et al., 2001; Capsoni and Cattaneo, 2006; Chao et al., 2006; Cuello and Bruno, 2007).

Astrocytes have an important role in modulating synaptic availability of proBDNF through $p75^{NTR}$: proBDNF secreted during neuronal transmission is uptaken and subsequently recycled, regulating neurotrophin spatial and temporal availability. This process occurs similarly to the neurotransmitters removal from the synaptic cleft, suggesting a possible role of astrocytes in mediating synaptic plasticity, as discussed later (Bergami et al., 2008; Vignoli et al., 2016). Moreover, necroptotic astrocytes are able to induce neuronal apoptosis through the release of vesicles containing proBDNF (Chen et al., 2021).

2.4. Astrocytic TrkB signaling

In 2005, Ohira and colleagues demonstrated that TrkB.T1 is an active receptor of BDNF able to regulate astroglial morphology (Ohira et al., 2005). Drastic changes in astrocytes' morphology were associated with low levels of a negative repressor of Rho GTPases that directly binds TrkB.T1 at specific residues (named LFH). When the repressor is released from TrkB.T1, it decreases Rho GTPase activity, thus altering glial cytoskeleton. It is still unclear, though, which Rho protein is involved in the astrocyte morphological changes triggered by BDNF (Ohira et al., 2005).

Astrocytes are able to bind, internalize and release BDNF into the culture medium, a process likely involving clathrin-mediated internalization and the formation of multivesicular bodies, which do not seem to direct BDNF to lysosomes for degradation (Alderson et al., 2000). However, the scientific community does not agree about the astrocyte's ability to induce the activation of the BDNF's downstream signaling pathways through TrkB. Some studies demonstrated that astrocytes activate the MAPK pathway and c-fos expression, as well as intracellular Ca^{2+} transients, in response to BDNF similarly to what is observed in neurons. Initially the latter ability was attributed to the expression of TrkB.FL (Climent et al., 2000; Iulita, Cuello, 2014) but, in 2003, Rose and colleagues highlighted the contribution of TrkB.T1 to this pathway (Rose et al., 2003). BDNF binding to TrkB.T1 induced G-protein activation and activation of PLC-γ signaling, thus triggering the release of Ca^{2+} from glial intracellular stores (Rose et al., 2003). In astrocytes, Ca^{2+} release from intracellular stores lowers intra-ER Ca^{2+} concentration, which in turn activates the store-operated Ca^{2+} entry (SOCE) mechanism, essential to maintain Ca^{2+} homeostasis (Verkhratsky and Vladimir, 2014). SOCE controls Ca^{2+} signaling and gliosecretion in response to extracellular stimuli (Papanikolaou et al., 2017; Gao et al., 2016). Its activation is mediated through transient receptor potential (TRP) channels, a family of ion channels that permeate Ca^{2+} and monovalent cations (Ben Achour et al., 2010). Recently, Jaudon and colleagues reported that astrocytes were able to respond to BDNF inducing Ca^{2+} transient that were mostly mediated by TrkB-T, with only a small contribution of TrkB.FL (Jaudon et al., 2021). Moreover, they also confirmed PLC-γ involvement, supporting the idea that this protein is central to the induction of BDNF-dependent Ca^{2+} transients (Jaudon et al., 2021).

2.5. Astrocyte-derived BDNF in synaptic plasticity

The secretion of mature BDNF is induced by neuron depolarization and high frequency stimulation (HFS), which induces long-term potentiation (LTP) (Korte et al., 1995; Kang et al., 1997; Minichiello et al., 1999). It has been demonstrated that astrocytes play a pivotal role in synaptic plasticity (Allen, Lyons, 2018; Khakh and Sofroniew, 2015) regulating neurotransmitters and neuromodulators released from neighboring active synapses and, in response to these signals, modifying the extent of synaptic strengthening (Durkee, Araque, 2019). Even if they can bind BDNF, astrocyte involvement in the regulation of LTP is still debated. In 2016, Vignoli and colleagues demonstrated that cortical astrocytes play a role in LTP maintenance and memory consolidation through $p75^{NTR}$ that allows proBDNF internalization (Vignoli et al., 2016). Moreover, the same group further analyzed this process, reporting that astrocytic microdomains convert internalized proBDNF into mature BDNF for synaptic re-use (Vignoli et al., 2021), indicating the presence of local information storage in astrocytes for supporting memory circuits. The role of BDNF in synaptic strengthening is still a debated issue, partially due to the difficulties in unambiguously identifying the BDNF receptors through which astrocytes provide specific signaling for LTP. Some studies suggest that astrocytes mediate LTP sustainment through the internalization of mBDNF via TrkB.FL or TrkB.T1 (Han et al., 2021). Recently, the involvement of TrkB.FL in this process on peri-synaptic astrocytes has been excluded (Vignoli and Canossa, 2022).

The interplay between neurotransmitter transporters and TrkB also gives an important contribution to synaptic plasticity. For example, Adenosine A2A receptors (A2AR) modulate the action of BDNF on synaptic transmission and plasticity by controlling cholinergic currents and gamma-aminobutyric acid (GABA) transporters uptake (Sebastiao et al., 2011). A2AR activation transactivates TrkB and induces TrkB translocation to lipid rafts in a cAMP-dependent manner (Vaz et al., 2011). Astrocytes modulate synaptic transmission by controlling extracellular GABA levels through specific membrane GABA transporters (GAT1 and GAT3). These transporters are modulated by A2AR that can enhance or inhibit GABA uptake contributing to synaptic transmission (Cristovao-Ferreira et al., 2013). Astrocytic GATs are differentially modulated by BDNF. While GAT-3 is not influenced by BDNF, the regulation of GAT-1 expression at the plasma membrane involves TrkB-T, non-classic PLC-γ and MAPK pathways, and A2AR activation (Vaz et al., 2011). In fact, BDNF treatment stimulates GAT-1 mediated GABA internalization in astrocytes, thus controlling the clearance of GABA (Vaz et al., 2011). BDNF inhibits the internalization of GAT-1 through a dynamin-dependent process, boosting GABA uptake and accelerating the shutdown of GABAergic response (Vaz et al., 2011). In addition, GABA increases intracellular Ca^{2+} concentration in astrocytes, triggering the release of ATP, which might further contribute to the modulation of synaptic transmission (Vaz et al., 2011).

2.6. Astroglia BDNF response changes during cell maturation

Astrocytes undergo important physiological changes during the first 2–3 postnatal weeks, and their maturation accompanies and supports that of adjacent neurons (Felix et al., 2021). Recently, Jaudon and colleagues have reported that astrocytes modify their BDNF signaling competence at different developmental stages (Jaudon et al., 2021). They tested embryonic (E18.5) and postnatal astrocytes (P0–2) for the BDNF receptors and the activation of their downstream pathways, highlighting that embryonic glial cells express more TrkB.FL than postnatal cells, which on the contrary upregulate TrkB-T (Jaudon et al., 2021). At both stages of maturation, astrocytes are able to activate BDNF

dependent kinase-based signaling (i.e., MAPK, Akt and PLCγ) but the resulting magnitude of downstream protein phosphorylation was lower in postnatal cultures than in embryonic cells (Jaudon et al., 2021). This further supports the notion that astrocytes are competent in activating NT signaling during embryonic development while they mainly induce NT signaling cascades upon activation, in the presence of CNS injury or under pathological conditions, at the postnatal stage (Jaudon et al., 2021). On the other hand, postnatal astrocytes were more responsive in inducing Ca^{2+} transients upon BDNF stimulation compared to embryonic cells, a response that was mainly triggered by TrkB-T (Jaudon et al., 2021).

Another important difference between embryonic and postnatal astrocytes is the predominant type of metabolism. Indeed, one of the main functions of astrocytes is to provide metabolic support to neurons. Amongst the numerous astrocyte-derived molecules involved in this process, lactate plays a prominent role both as a metabolic and as a signaling molecule (Magistretti and Allaman, 2015). Interestingly, the production of lactate in wild-type postnatal cells is increased compared to that in embryonic cells, suggesting a predominant glycolytic mechanism, and this was observed both in cultured astrocytes (Jaudon et al., 2021) and in vivo (Zehnder et al., 2021). One protein that is ubiquitously expressed in neural cells and plays an important function supporting BDNF signaling is Kidins220 (Iglesias et al., 2000; Kong et al., 2001). Kidins220$^{-/-}$ embryonic astrocytes show altered SOCE mechanisms and increased expression of the Ca^{2+} channel TRPV4 both at mRNA and protein levels. TRPV4 is a thermo-, osmo-, and mechano-sensitive channel (Guler et al., 2002; Liedtke, Friedman, 2003; Mizuno et al., 2003) that mediates Ca^{2+} influx in primary astrocytes (Benfenati et al., 2007) and promotes Ca^{2+}-dependent Ca^{2+} release (Dunn et al., 2013, Benfenati et al., 2010). TRPV4 is expressed in cortical astrocytes and in complex with AQP4 regulates volume increase/decrease during osmotic shock (Benfenati et al., 2007). Interestingly, alteration of AQP4 mRNA levels was also observed upon BDNF chronic treatment, and a reduction of AQP4 has been described in a mouse model with reduced Kidins220 expression (Del Puerto et al., 2021), suggesting a complex interplay between Kidins220 and molecules involved in maintaining brain homeostasis at the level of astrocytes.

Because of its pleiotropic role in neuron and astrocytes physiology, alterations in BNDF/TrkB signaling have been observed in many human pathologies. In the next part of this review, we will focus on the astroglia contribution of BDNF in selected pathologies.

3. Physiopathology of astroglia BDNF

The role of astrocytes in the maintenance and functioning of the nervous system is emerging to be much larger than previously expected. Astrocytic malfunction has been shown to bear severe negative consequences across the CNS, and astrocytic involvement in pathologies has been widely documented with new, more detailed evidence emerging. Indeed, build-up of harmful factors (e.g., ROS, excessive Ca^{2+} or glutamate levels) or loss of regulatory function resulting in a cellular imbalance (e.g., loss of cell volume regulation, impaired astrocyte-neuron and neuron-neuron communication) has been connected with astrocytes' loss of their homeostatic and protective function (Lee et al., 2022). Astrocytes can also become reactive under pathological conditions, actively propagating the damage to the other cells of the nervous system (Jiwaji and Hardingham, 2022; Koizumi et al., 2021).

In the event of CNS injury, disease, or infection, the brain deploys its own protective mechanisms. As one of the first lines of defense, astrocytic cells become reactive and undergo morphological, molecular and functional remodeling (Sofroniew, 2020; Escartin et al., 2021). Reactive astrocytes do not simply restrict neuronal proliferation by forming a glial scar, a border formed by the astrocytes in order to seal off the healthy tissue from spreading lesions (Escartin et al., 2021), but also express an array of factors with heterogenous functions. Astrocytes increase the expression of classically neuroprotective factors such as BDNF and its receptor TrkB.FL in response to lesions (Stadelmann et al., 2002). Moreover, a recent transcriptomics study showed upregulation of NGF and BDNF in reactive astrocytes as well as downregulation of axonal inhibitory molecules (Teh et al., 2017). This was shown to vary by brain region illustrating a functional heterogeneity in astrocyte responses to neurotrophins and injury, further highlighting the complex function of reactive astrocytes (Cragnolini et al., 2018). Chun and colleagues even proposed two distinct categories of hypertrophic astrocytes depending on their proBDNF and GABA expression (Chun et al., 2018). "Active" astrocytes – induced by enriched environment – were showed to be pro-BDNF-positive/GABA-negative and support neuroplasticity, while "reactive" astrocytes – induced by acute brain injury – induced neuronal inhibition and were defined as GABA-positive/proBDNF-negative (Chun et al., 2018). As of today, the available data hints at the functional relevance of the BDNF system in the physiology of astroglial cells.

Table 1
Role of astrocytic BDNF, and proposed mechanism of action, in selected pathologies.

Pathology	Astrocytic involvement	BDNF action	Reference
Metabolic disorder	Indirect	Homeoostatic via TrkB.T1	Ameroso et al., 2022
Amyotrophic lateral sclerosis	Indirect	Homeostatic via TrkB.FL; Deleterious via TrkB.T1	Yanpallewar et al., 2012
Epilepsy	Indirect	Inconclusive	Vidaurre et al., 2012
Brain oedema	Direct	Inconclusive	Lu et al., 2022
Neuropathic pain	Direct	Deleterious via TrkB.T1	Matayas et al., 2017
Huntington's disease	Indirect	Diminished levels in the disease	Hong et al., 2016
Rett syndrome	Direct	Homeostatic function disturbed	Lioy et al., 2011
Retinal degeneration	Direct	Homeostatic via Trk.FL	Bales et al., 2022

Taken together, these studies suggest that neuroprotection, associated with BDNF / TrkB expression, might be the main astrocytic function at early stages of reactive astrogliosis. At this time, the pathology is considered as potentially resolvable, with the potential of reaching a state of chronic reactivity and leading to dysregulation of the neuroprotective mechanisms (Sofroniew, 2020). Hence, for the purpose of this review we will consider "reactive astrocytes" and their relationship with BDNF in the context of dysregulation of their neuroprotective mechanisms resulting in disease phenotypes.

Aberrant astrocytic BDNF signalling seems to be a key player in many astrocyte-related disorders. Several nervous system pathologies point to the imbalance in the astrocytic TrkB isoform expression patterns as a main culprit in disease development. TrkB.T1 is known to hinder BDNF stimulation via TrkB.FL inhibition (Yanpallewar et al., 2012) and propagate cell death (Dorsey et al., 2006). Whether direct, or indirect connection between astrocytes and BDNF-TrkB signalling in pathology has been made, it certainly is a common theme in nervous system disorders emphasising the role of astrocytes in CNS health and homeostasis. In the following paragraphs, we highlight the pathologies in which alterations of astroglia BDNF-TrkB signalling have been described, which are also summarized in Table 1.

3.1. Metabolic disorders

BDNF signalling via neuronal TrkB regulates synaptic transmission in brain metabolic circuits (Huang and Reichardt, 2003). Neuronal BDNF plays a critical role in maintaining energy and glucose balance within the CNS, as demonstrated by the fact that mice lacking BDNF are obese (Unger et al., 2007; Rios et al., 2001). A recent study investigated the role of astrocytic TrkB.T1 signalling in the ventromedial hypothalamus (VMH) control of energy homeostasis (Ameroso et al., 2022). VMH is a

central hub for regulating energy balance and the investigators demonstrated that BDNF signalling controls VMH neuron plasticity in response to changes in metabolic conditions. BDNF / TrkB.T1 signaling in hypothalamic astrocytes induced morphological changes in peri-synaptic astrocytic processes, resulting in increased glutamate uptake and altered neuronal excitability (Ameroso et al., 2022). By measuring blood glucose and serum insulin levels of TrkB.T1 KD mice, Ameroso and colleagues found that intact TrkB.T1 signalling in both VMH astrocytes and neurons is required for correct glycaemic control (Ameroso et al., 2022). However, BDNF signalling in VMH astrocytes had a predominant role in the regulation of feeding, energy expenditure and body weight (Ameroso et al., 2022). Those results uncover a metabolic role of the astrocytes not only at the cellular level but also for the entire body's energy homeostasis (Ameroso et al., 2022).

3.2. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative motor neuron disease resulting in progressive degeneration of motor neurons. A small number of ALS cases is hereditary (10%) but most of them have a sporadic aetiology (Nguyen et al., 2018). Despite years of research and many proposed mechanisms underlying neuronal death in ALS, the cause of this pathology is still not clear. Glutamate excitotoxicity, one of the mechanisms proposed, can arise from lack of inhibitory signalling, which can be regulated by the BDNF/TrkB pathway (Pradhan et al., 2019). However, whether BDNF has protective or detrimental effects in ALS pathology is still up for debate. While BDNF has been used for treatment in ALS models and in therapeutic trials (Gouel et al., 2019; Henriques et al., 2010), many failed to achieve satisfactory results. Enhancing BDNF transmission via TrkB modulation proved to be neuroprotective for neurons in vitro but these therapeutic effects were not replicated in vivo, where harmful effects on neuronal survival in conjunction with such treatments have been observed (Pradhan et al., 2019). A possible reason for this discrepancy could be the presence of TrkB.T1 receptors in in vivo models, hindering the neuroprotective actions of TrkB.FL signalling. Interestingly, specific deletion of TrkB.T1 in an ALS mouse model showed a delay in the disease onset similar to non-neurotrophic TrkB.FL activation (Yanpallewar et al., 2012). TrkB.T1 specific deletion in astrocytes showed rescue tendency and preserved muscle strength and coordination, contrary to what observed with a selective TrkB.T1 deletion in motor neurons, suggesting a non-cell autonomous mechanism to TrkB.T1-mediated effects in ALS (Yanpallewar et al., 2021). Attempts have been made at transplant of stem-cell-derived astrocytes for the treatment of ALS in animal models, with encouraging results (Lepore et al., 2008; Nicaise et al., 2015) strengthening the notion of astrocytes (Papadeas et al., 2011) and astrocytic BDNF as ALS therapeutic target.

3.3. Epilepsy

Epilepsy is a progressive CNS disorder characterised by abnormal firing patterns in the brain and spontaneous electrical discharges (Devinsky et al., 2018). Since astrocytes hold a regulatory function in the CNS, controlling not only metabolism but also neuronal activity, they have a prominent role in epilepsy pathology (Binder and Steinhauser, 2021). Models of temporal lobe epilepsy (TLE) have shown that inhibition of TrkB activation prevented seizures, rescued behavioural deficits, and prevented neuronal loss in the hippocampus (Liu et al., 2013). However, the BDNF-TrkB pathway can have multifaceted effects on neuronal survival depending on the specific TrkB isoforms or the signalling intensity. While a direct involvement of this molecule in the pathology of epilepsy is undeniable, a clear consensus on whether BDNF inhibits or promotes epileptogenesis has not yet been reached (Wang et al., 2021). TrkB.FL/TrkB.T1 imbalance in favour of TrkB.T1 can result in excitotoxicity (Vidaurre et al., 2012). Most recent research also shows that selective knockdown of TrkB in hippocampal astrocytes exerts neuroprotection in TLE models and results in stronger protection of cognitive function than TrkB knockdown in hippocampal neurons (Fernandez-Garcia et al., 2020). These results strongly suggest that a more precise role of astrocytic BDNF signalling in epilepsy should be explored further for possible therapeutic solutions.

3.4. Oedema

AQP4 and TRPV4 create a main system for water homeostasis in the CNS, as previously discussed. Together in volume regulator-osmosensor complexes, AQP4 and TRPV4 are chief proteins behind regulation of brain volume (Benfenati et al., 2011; Toft-Bertelsen and MacAulay, 2021). Cellular oedema is a primarily astroglial pathology. Indeed, astrocytes are not only responsible for brain volume regulation, but excessive astrocytic swelling linked to the TRPV4-AQP4 system can also trigger further damaging effects resulting in brain oedema (Jo et al., 2015). A recent study by Lu and colleagues linked astrocytic, AQP4-mediated cellular oedema with TNF-α and the NF-kB pathways (Lu et al., 2022). The NF-kB pathway and p65 binding enhance AQP4 overexpression which in turn negatively impacts astrocytic viability (Lu et al., 2022). A direct link has not yet been made, but it is known that TNF-α induces BDNF expression via NF-kB in astrocytes (Saha et al., 2006) and neurons (Balkowiec-Iskra et al., 2011). It is also important to note that astrocytic TRPV4 is strongly involved in the process of inflammation, inducing the production of TNF-α via activation of the NF-kB pathway (Liu et al., 2018). TRPV4+ astrocytes, upon activation, can also activate other astrocytes, both TRPV4+ and TRPV4- (Shibasaki et al., 2014). Thus, while experimental evidence suggests the role of astrocytic BDNF in the onset and development of oedema, further study is required to elucidate this connection.

3.5. Neuropathic pain

It is well-established that BDNF is an important modulator of pain in the CNS. Reactive astrocytes also contribute to inflammation and neuropathies under pathological conditions (Linnerbauer and Rothhammer, 2020). TrkB.T1 was found to participate in the development and maintenance of BDNF-mediated pain (Renn et al., 2009) and deletion of TrkB.T1 reduced spinal cord injury (SCI)-related abnormalities, including the pain component (Wu et al., 2013). The same study also revealed that TrkB.T1 was responsible for upregulating cell cycle pathways in SCI. As mentioned earlier, TrkB.T1 is abundantly expressed in astrocytes and reactive astrocytes are one of the key components of the glial scar and inflammatory reaction (Lee, MacLean, 2015). Indeed, TrkB.T1 was found to control astrocytic proliferation, migration and inflammation and its deletion reduced astrocytic reactivity after SCI (Matyas et al., 2017), in agreement with the heavy reliance of astrocytes on the maintenance of balance between astrocytic TrkB isoforms to regulate their physiological signalling outpout (Cao et al., 2020). It is also worth considering the possible involvement of the vanilloid receptor family members, such as TRPV1 or TRPV4, in the development and maintenance of astrocyte-mediated neuropathic pain. Expression of TRPV1 in astrocytes has been shown to mediate astrocytic activation (Yang et al., 2019; Wang et al., 2019), whereas TrkB.T1 deletion attenuated behavioural reaction to the capsaicin treatment, which is a strong TRPV1 agonist (Renn et al., 2009). TRPV4 inhibition also showed attenuation of inflammation and glial reactivity (Liu et al., 2018). No direct link between those factors has been explored so far but it could be worth examining since both TrkB.T1 and TRPV1 represent promising therapeutic targets.

3.6. Huntington's disease

Huntington's disease (HD) is a hereditary neurodegenerative disease caused by an autosomal dominant mutation in the *Huntingtin* (*Htt*) gene resulting in the production of aberrant huntingtin protein (mHtt)

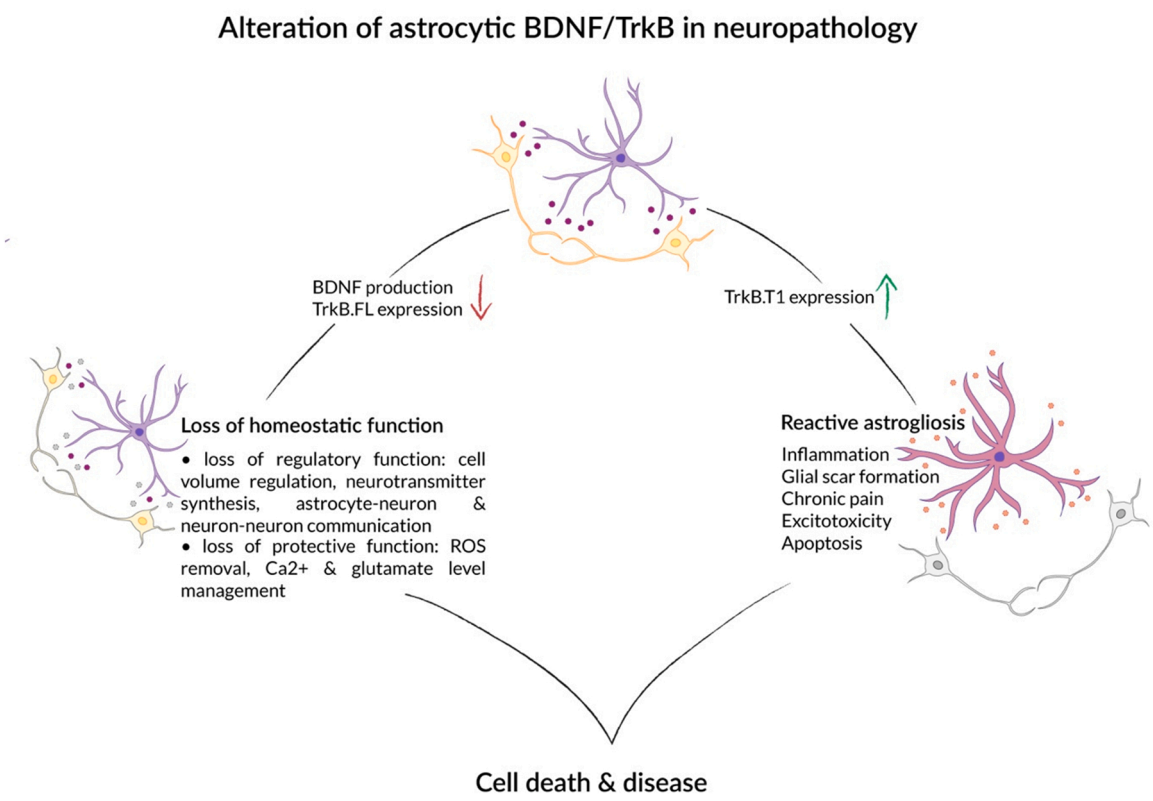

Fig. 1. Alteration of astrocytic BDNF/TrkB signalling axis in neuropathology.

(McColgan and Tabrizi, 2018). Expression of the mutant protein affects both neuronal and glial cells across the brain (Palpagama et al., 2019) and HD astrocytes are characterised by lowered expression of glutamate transporters and potassium channels resulting in excitotoxicity (Shin et al., 2005; Tong et al., 2014). BDNF levels were also found to be affected in HD patients (Zuccato et al., 2001; Zuccato, Cattaneo, 2007) and BDNF administration in transgenic HD mice provided some level of neuroprotection against the development of the disease (Zuccato et al., 2005; Simmons et al., 2009). Since neurons are the main source of BDNF, most of the studies on BDNF in HD focused on this cell type, however astrocytes not only react to BDNF but also release it themselves (Zafra et al., 1992; Alderson et al., 2000; Kinboshi et al., 2017). In fact, astrocytes overexpressing mHtt show significantly lower BDNF levels (Wang et al., 2012). Further, another study demonstrated that mHtt does not affect production of BDNF in astrocytes itself but instead binds to Rab3a – a secretory vesicle GTPase – and prevents it from executing its function, effectively halting BDNF secretion. Overexpression of Rab3a in the same astrocytes was enough to rescue BDNF secretion (Hong et al., 2016) making the astrocytic BDNF release an important component of HD pathology.

3.7. Rett syndrome

Rett syndrome is an X-linked disorder belonging to the ASD spectrum caused by a loss of function (*lof*) mutation in the MECP2 gene (Collins and Neul, 2022). MECP2 is present in most tissues, however since neurological disorders are the main *lof* manifestations, most Rett syndrome studies have been performed on neurons and glia. In fact, selective re-expression of *Mecp2* in astrocytes of MeCP2-deficient mice rescued their locomotion and alleviated anxiety as well as restored correct respiratory control (Lioy et al., 2011). Additionally, restoration of MeCP2 in astrocytes also had positive effects on mutant neurons showing that glia plays a key role in the Rett syndrome pathology (Lioy et al., 2011). In fact, MeCP2-deficient astrocytes not only present abnormal BDNF regulation, but they can also spread the MeCP2 deficiency via gap-junctions to other astrocytes (Maezawa et al., 2009). Through its signalling, BDNF also acts as a neuronal modulator of respiratory drive. Thus, a model of astrocytic-BDNF respiration control was proposed (Caravagna et al., 2013), which is relevant as alteration of the breathing pattern is one of the main manifestation of Rett pathology. The aforementioned studies suggest a strong involvement of astrocytic-BDNF in development and propagation of Rett syndrome dysfunction.

3.8. Retinal degeneration

The cause of progressive neuronal death in retinal degeneration is still not precisely described. Photoreceptors exposed to various insults, such as phototoxicity, undergo apoptosis (Xu et al., 1997). This can happen either under physiological conditions, when excessive light levels are sufficient to damage retinal cells, but also in pathologies when light can propagate the spreading of the photoreceptor death (Heckenlively et al., 1991; Coussa et al., 2019). Retinal ganglion cells (RGCs) are supported not only by astrocytes and microglia but also by Muller cells, retina-specific radial glial cells thought to protect RGC from apoptosis (Telegina et al., 2018). The role of neurotrophins in RGC protection has been subjected to intensive study. Indeed, axonal transport of BDNF is disturbed in RGC axons of a glaucoma model (Pease et al., 2000) and both absence and blockade of $p75^{NTR}$ was sufficient to block light-induced photoreceptor apoptosis in vivo (Harada et al., 2000). Phototoxicity was shown to upregulate expression of TrkC and $p75^{NTR}$ in both Muller glia and photoreceptors (Harada et al., 2000). Both knockouts of glial TrkB and neuronal TrkB showed increased glutamate-induced retinal degeneration (Harada et al., 2011). This was further supported by another study showing that TrkB activation drives trophic factor upregulation and inhibits reduction of GDNF in response to optic nerve injury, ultimately leading to RGC protection at early stages after insult (Harada et al., 2015). This relationship was explored

as a therapeutic target in a recent study that assessed the positive impact of treadmill exercise on astrocytes health in a light-induced retinal degeneration (LIRD) model. Exercise showed to increase retinal BDNF-astrocyte interaction, with a positive impact on astrocytic and retinal health. The active animal group also had a higher TrkB.FL/TrkB.T1 ratio, whereas inactive animals showed significant increase in TrkB-T1 expression (Bales et al., 2022).

4. Conclusions

Most of our knowledge about neurotrophin and BDNF function is derived from studies performed in neurons. However, we now know that astrocytes actively participate to neurotrophin physiology. Indeed, astrocytes produce, uptake and recycle BDNF / proBDNF, which plays an especially important role in the modulation of synaptic efficacy. Moreover, BDNF binding to astrocytic Trk receptors activates specific intracellular pathways that control astrocytic morphology and affect neuronal excitability. A relevant example is provided by a recent work showing the impact of altering hypothalamic astrocytes' morphology on the energetic metabolism of the whole body (Ameroso et al., 2022). As we have discussed, the molecular and cellular pathways that astrocytes activate upon BDNF stimuli are very diverse and depend on the brain area, stage of development and on the TrkB isoform mainly expressed. Thus, it is not possible yet to extrapolate a general scheme of astrocytic BDNF-dependent signalling, to the same extent of what we have for neurons (see, for example, Minichiello, 2009), as we still lack a good deal of mechanistic information that we will only acquire through dedicated lines of research. Nevertheless, an increasing body of evidence is highlighting the contribution of astroglial BDNF in several neuropathologies, which we have summarized in Fig. 1. Interestingly, a number of studies have started to explore the therapeutic potential of selectively targeting the BDNF system in astroglia, to provide long-term support to diseased neurons, with some promising results. Future studies should aim at dissecting such pathways in greater details, as they might represent interesting targets for clinical translation.

Data availability

References are provided for all data described in this Manuscript.

Acknowledgements

We thank Prof. Benfenati (University of Genova, Italy) and Prof. Ferroni (University of Bologna, Italy) for the critical reading of the manuscript.

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