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REVIEW
Brain-derived neurotrophic factor interacts with astrocytes and neurons to control respiration

Céline Caravagna, Jorge Soliz and Tommy Seaborn
Department of Pediatrics, Laval University, Centre de Recherche du Centre Hospitalier Universitaire (CHU) de Québec, Hôpital St-François d'Assise, 10 Rue de l'Espinay, Room D0-742, Québec, QC, Canada

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Abstract

Respiratory rhythm is generated and modulated in the brainstem. Neuronal involvement in respiratory control and rhythmogenesis is now clearly established. However, glial cells have also been shown to modulate the activity of brainstem respiratory groups. Although the potential involvement of other glial cell type(s) cannot be excluded, astrocytes are clearly involved in this modulation. In parallel, brain-derived neurotrophic factor (BDNF) also modulates respiratory rhythm. The currently available data on the respective roles of astrocytes and BDNF in respiratory control and rhythmogenesis lead us to hypothesize that there is BDNF-mediated control of the communication between neurons and astrocytes in the maintenance of a proper neuronal network capable of generating a stable respiratory rhythm. According to this hypothesis, progression of Rett syndrome, an autism spectrum disease with disordered breathing, can be stabilized in mouse models by re-expressing the normal gene pattern in astrocytes or microglia, as well as by stimulating the BDNF signaling pathway. These results illustrate how the signaling mechanisms by which glia exerts its effects in brainstem respiratory groups is of great interest for pathologies associated with neurological respiratory disorders.

Introduction

In vertebrates, breathing movements are initiated by the central nervous system (CNS), and their frequency and amplitude are regulated to match the organism's metabolic requirements (O_2 consumption and CO_2 excretion). Neurons associated with respiratory rhythm are located in the two main parts of the brainstem, namely the pons and the medulla oblongata (Ramirez & Richter, 1996; Feldman & Del Negro, 2006). Because of their crucial importance in physiology and pathophysiology, the anatomy of the respiratory neuronal groups and the mechanisms underlying central respiratory control have been extensively studied (Blanchi & Sieweke, 2005; Alheid & McCrimmon, 2008; Feldman *et al.*, 2012). The respiratory central pattern generator is located in the brainstem and has a dual origin, comprising two distinct interacting oscillators, namely the preBötzinger complex (preBötC) (Arata *et al.*, 1990; Smith *et al.*, 1991) and the retrotrapezoid nucleus (RTN)/parafacial respiratory group (pFRG) (Janczewski & Feldman, 2006). The preBötC is located in the ventrolateral part of the medulla oblongata, and is characterized by the presence of inspiratory rhythmic neurons (Johnson *et al.*, 1994). On the other hand, active expiratory rhythm is generated by the RTN/pFRG, which is located in the rostral part of the ventrolateral medulla oblongata. The RTN/pFRG also has the ability to increase breathing frequency and stabilize respiratory rhythm (e.g. by alleviating apneas) (Thoby-Brisson *et al.*, 2009). In addition to those responsible for the respiratory rhythmogenesis, other brainstem neuronal groups are involved in respiratory control. For instance: (i) the nucleus tractus solitarii (NTS) integrates the peripheral afferences (e.g. from lungs and carotid bodies) (Spyer, 2009); (ii) pontine A5/A6 catecholaminergic nuclei (Hilaire *et al.*, 2004) and the Kölliker–Fuse nucleus (Spyer, 2009) constitute a source of massive projections to medulla oblongata respiratory areas, having complex actions depending on the species and age; and (iii) the caudal ventral respiratory group acts as the premotor output by sending the rhythmic motor command to the effector muscles (Rybak *et al.*, 2007). The relative positions of the brainstem respiratory centers that we consider in this review are schematically summarized in Fig. 1.

Using biochemical and electrophysiological approaches, most of the published studies investigated respiratory control by focusing on the involvement of neurons in this process (Ezure, 2004; Feldman *et al.*, 2012). However, the CNS is composed of not only neurons but also glial cells. Among the several functions in which glial cells are involved (Vernadakis, 1988; Barres, 2008), they play a crucial role in the brain by maintaining homeostasis and providing support and protection to neurons. To date, little is known about the specific involvement of glial cells in respiratory control. Thus, the objective of this review is to underline the importance of astrocytes in the respiratory control that occurs in brainstem, by emphasizing the potential brain-derived neurotrophic factor (BDNF)-mediated control of the communication between astrocytes and neurons.

Involvement of glial cells in respiratory control

Glial cells

There are different types of glial cell, each having specific roles. Glia is divided in two main groups of cells: microglia and

Correspondence: Tommy Seaborn, as above.
E-mail: Tommy.Seaborn@crchuq.ulaval.ca

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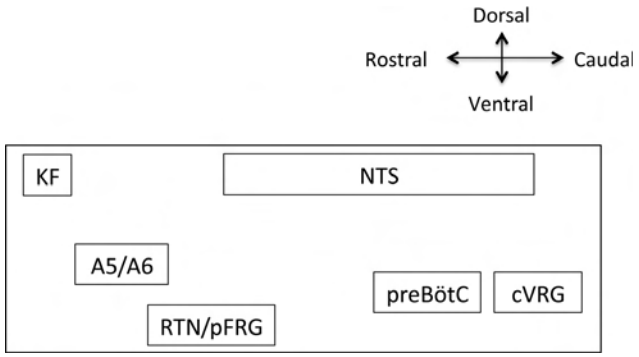

FIG. 1. Schematic representation of brainstem respiratory centers in which glia and/or BDNF are involved in breathing control. These respiratory groups are depicted on a sagittal section to represent their relative positions on the dorsoventral and rostrocaudal axes, without considering their relative lateral distributions. BDNF and/or glial action has been demonstrated in the Kölliker–Fuse nucleus (KF), pontic catecholaminergic groups (A5/A6), NTS, RTN, pFRG, preBötC, and caudal ventral respiratory group (cVRG).

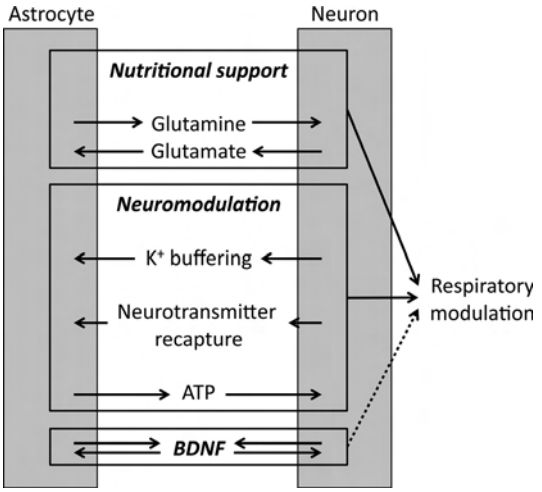

FIG. 2. Link between neurons and astrocytes in respiratory control and rhythmogenesis. By providing nutritional support and being involved in neuromodulation, astrocytes support neurons in exerting their normal activity. This intercellular communication is involved in respiratory regulation by neurons located in the brainstem. Both neurons and astrocytes express BDNF and the potent BDNF receptor TrkB, making possible bidirectional signaling between the two cell types. However, it is not determined whether this signaling occurs via autocrine and/or paracrine communication, and which cell type releases and/or receives the BDNF ligand. The precise role of this communication in respiratory control and rhythmogenesis remains to be determined, and we hypothesize that BDNF release by astrocytes modulates the activity of the neurons responsible for respiratory control (dashed arrow).

macroglia. Microglial cells are derived from primitive macrophages that arise during early development and are maintained in the CNS independently of circulating monocytes (Ginhoux *et al.*, 2010). Stresses such as hypoxia/ischemia or infection activate microglial cells, which contribute to protecting and cleaning the brain by phagocytosing cell debris, apoptotic cells, and infectious agents (Neumann *et al.*, 2009). In contrast to microglial cells, macroglial cells arise from neural precursors (Kukekov *et al.*, 1999). Five types of macroglial cell have been identified to date in the CNS (Krawczyk & Jaworska-Adamu, 2010; Robel *et al.*, 2011), namely astrocytes, oligodendrocytes, ependymocytes, synantocytes, and radial glial cells. Astrocytes mainly provide physical and nutritional support to neurons, and recent evidence has shown their involvement in regulating synaptic signaling by neurotransmitter recapture and/or release (Santello *et al.*, 2012). Oligodendrocytes provide myelin insulation of axons in the CNS (De Robertis *et al.*, 1958). Ependymocytes are ciliated cells bordering the cavities of the CNS and making up the walls of the ventricles that are responsible for the synthesis and secretion of the cerebrospinal fluid (Del Bigio, 2010). The recently identified synantocytes participate in neuronal cytoskeleton stabilization and the formation of glial scars, and mediate the response of oligodendrocytes to neuronal damage (Krawczyk & Jaworska-Adamu, 2010). Finally, the radial glial cells are the ubiquitous glial cell type during the development of vertebrate brains, and act as stem and progenitor cells (Robel *et al.*, 2011). They are the major source of neurons in the mouse brain, but are largely absent from the adult mammalian brain (Robel *et al.*, 2011). Among these five glial cell types, astrocytes are undoubtedly the most studied, including in the field of respiratory neurobiology.

Astrocytic neuronal regulation by gliotransmitters

Astrocytes are involved in the regulation of synaptic signaling in several ways (Santello *et al.*, 2012). For example, they can modulate neuron activity by spatial K^+ buffering (Kofuji & Newman, 2004) or regulate extracellular neurotransmitter concentrations via recapture and release (Hamilton & Attwell, 2010). On the other hand, it is now recognized that astrocytes can express neurotransmitters by themselves (Hamilton & Attwell, 2010). These 'gliotransmitters' are defined as glia-secreted molecules modulating neuronal activity in response to a stimulus (Santello *et al.*, 2012). Gliotransmitters can be amino acids (e.g. glutamate and D-serine), nucleotides or nucleosides (e.g. ATP), growth factors (e.g. BDNF and insulin-like growth factor) (Honda *et al.*, 2011), vascular endothelial growth factor (Perrin *et al.*, 2009), or other molecules such as cytokines or prostaglandins (Ji *et al.*, 2013; Liu *et al.*, 2013). Although the existence of these astrocyte-released gliotransmitters is now established, their effects and release mechanisms are still controversial (Hamilton & Attwell, 2010; Kasymov *et al.*, 2013). Among these gliotransmitters, some have been demonstrated to be involved in breathing control (Fig. 2).

Astrocytic respiratory regulation via glutamine synthesis

Glial involvement in respiratory rhythmogenesis was demonstrated for the first time by Hulsmann *et al.* (2000). By using fluoroacetate, a selective antagonist of the glial Krebs cycle, they showed that blockade of glial metabolism depresses rhythmic activity in the respiratory network of medullary slices from neonatal mice. During normal metabolism, astrocytes synthesize glutamine from extracellular glutamate, and provide this essential nutriment to neurons via exocytosis, contributing to the stabilization of respiratory neuronal network activity (Stobart & Anderson, 2013). Thus, the main explanation suggested by Hülsmann *et al.* for the observed inhibitory effect is that the deletion in astrocyte-to-neuron glutamine coupling leads to a reduction in respiratory network activity (Fig. 2). However, other functions of astrocytes or of other glial cells could contribute to the respiratory pattern resulting from the uncoupling between glia and neurons.

Astrocytic respiratory regulation via ATP release

Although ATP is mainly known as the major cellular energy source, it also has the ability to act as a positive regulator of respiratory

rhythmogenesis (Lorier *et al.*, 2008; Funk, 2010; Moraes *et al.*, 2011). Moreover, ATP receptors are expressed at the astrocyte membrane (Funk *et al.*, 2008; Koles *et al.*, 2011). On the basis of these two observations, a role for astrocytes in respiratory rhythm modulation has been hypothesized. Accordingly, modulation of inspiratory network activity by ATP in the preBötC is mediated not only through neurons, but also through glia, as shown by the use of specific glial toxins (e.g. fluoroacetate) that suppress the increase in respiratory frequency that normally occurs in response to ATP stimulation (Huxtable *et al.*, 2010).

In addition, ventral brainstem astrocytes, including those located in the RTN, are themselves chemosensitive (Gourine *et al.*, 2010; Kasymov *et al.*, 2013). Indeed, experimental extracellular acidification evokes Ca^{2+} ionic waves in these astrocytes, which, in turn, release ATP that propagates pH-induced Ca^{2+} excitation among the neighboring astrocytes (Gourine *et al.*, 2010). This cell communication results in amplification of ATP release into the extracellular milieu, and neurons expressing the ATP receptors in the respiratory groups of the ventral medulla, mainly in the RTN, are therefore stimulated (Gourine *et al.*, 2010). These data provide great support to the idea of astrocytic involvement in respiratory control in an important respiratory nucleus.

BDNF as a neuronal respiratory modulator

BDNF signaling

Brain-derived neurotrophic factor is a member of the neurotrophin family, along with nerve growth factor, neurotrophin-3, and neurotrophin-4 (Huang & Reichardt, 2001). BDNF is mainly known as a neurotrophic factor involved in neuronal survival and differentiation (Huang & Reichardt, 2001; Bath *et al.*, 2012), and its main receptor is tyrosine kinase receptor B (TrkB) (Soppet *et al.*, 1991; Squinto *et al.*, 1991). TrkB can be expressed as full-length or truncated forms, the latter lacking the intracellular catalytic tyrosine protein kinase domain (Klein *et al.*, 1990). Binding of BDNF to TrkB stimulates various intracellular signaling pathways, including the mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/Erk), phospholipase Cγ and phosphoinositide 3-kinase pathways (Numakawa *et al.*, 2010). Alternatively, BDNF and the other neurotrophins can also bind with lower affinity to the p75 neurotrophin receptor (p75NTR) (Rodriguez-Tebar *et al.*, 1990; Reichardt, 2006; Sandhya *et al.*, 2013).

BDNF and its receptors in brainstem respiratory groups

Both BDNF expression and TrkB expression have been reported in various respiratory groups located in the brainstem. For instance, expression of BDNF and TrkB was detected in the NTS neurons of rats (Liu & Wong-Riley, 2013), as well as in the preBötC neurons of both mice (Thoby-Brisson *et al.*, 2003) and rats (Liu & Wong-Riley, 2013). Similarly, neurons of the RTN/pFRG of rats showed expression of both BDNF and TrkB (Liu & Wong-Riley, 2013). Protein expression of p75NTR in the respiratory groups remains to be demonstrated, although its mRNA has been detected in the preBötC neurons of mice (Thoby-Brisson *et al.*, 2004). As p75NTR has a lower affinity for BDNF than TrkB (Rodriguez-Tebar *et al.*, 1990), its activation may require a higher concentration of BDNF. Also, if BDNF actually acted in the respiratory groups via p75NTR activation, the downstream mechanisms induced and the resulting biological effects would probably be different, at least in part, from those resulting from TrkB activation (Hempstead, 2002; Chapleau & Pozzo-Miller, 2012).

Functional involvement of BDNF in respiratory control

Experiments performed in BDNF-deficient mice demonstrated BDNF involvement in respiratory control (Erickson *et al.*, 1996; Balkowiec & Katz, 1998). These mice show severe abnormal ventilation characterized by reduced respiratory frequency and tidal volume, and induced respiratory instability (Erickson *et al.*, 1996). Indeed, systemic BDNF deletion results in a loss of peripheral chemoafferent neurons, which probably contributes to the erratic respiratory pattern of these mice. However, electrophysiological recordings on isolated brainstem preparations from these BDNF-deficient mice confirmed a central origin for the major part of the observed respiratory perturbations (Balkowiec & Katz, 1998). Nevertheless, it is not clear whether these respiratory perturbations result from neurodevelopmental deficits or postnatal neuromodulatory effects.

Most recently, electrophysiological experiments performed on fetal brainstem preparations from wild-type mice showed that incubation of brainstems with BDNF results in an increased burst frequency of the preBötC neurons, which occurs via TrkB activation (Bouvier *et al.*, 2008). However, patch clamp recordings performed by the same laboratory on individual neurons from brainstem slices of wild-type newborn mice revealed a significant decrease in the discharge frequency of preBötC neurons in response to incubation in BDNF (Thoby-Brisson *et al.*, 2003). The authors concluded, from the apparent discrepancy between results obtained from prenatal and postnatal brainstem preparations, that there is a developmental switch in the effect of BDNF on respiratory frequency (Thoby-Brisson *et al.*, 2003). Similarly, an age-dependent effect of BDNF on the modulation of synaptic glutamatergic transmission (Kron *et al.*, 2007a) and inhibitory synapses (Kron *et al.*, 2007b) has also been observed in the Kölliker–Fuse nucleus of rat.

The *in vivo* recordings from BDNF-deficient mice and *in vitro* recordings from wild-type mice brainstem slices seem conflicting. Indeed, *in vivo* recordings from BDNF-deficient mice showed abnormal ventilation with decreased frequency, whereas BDNF incubation of brainstem slices from wild-type mice decreased burst frequency. In these experimental contexts, both lack of BDNF and addition of exogenous BDNF seem to decrease the respiratory rhythm. These conflicting results may be explained by the major differences between the two experimental protocols. First, peripheral afferences are missing in brainstem slices, and BDNF is known to participate in the integration of anoxic afferent messages from the carotid bodies (Clark *et al.*, 2011; Montero *et al.*, 2012). Thus, suppressing these afferences might have altered the BDNF action on breathing. Second, the *in vivo* breathing signal was obtained from the whole animal, whereas the *in vitro* recording from brainstem slice was from a single neuron, and the effect of treatment of an isolated neuron does not necessarily reflect the effect of treatment on the entire network. For example, if BDNF has inhibitory activity on inhibitory neurons, the net result at the network level will be respiratory stimulation. Finally, BDNF-deficient mice show neurodevelopmental deficits that affect the normal breathing pattern at birth (Erickson *et al.*, 1996). Thus, the neurodevelopmental impact of chronic BDNF depletion is not in conflict with an inhibitory effect of acute exposure to BDNF after birth.

Taken together, the *in vivo* and *in vitro* results indicate that respiratory control and rhythmogenesis are directly linked to BDNF action, making BDNF a significant player in the regulation of respiration. However, it is unknown whether this BDNF action occurs on neurons only or also on astrocytes.

Potential role for astrocytic BDNF signaling in respiratory control

On the basis of the involvement of glial cells, especially astrocytes, and BDNF in respiratory control and rhythmogenesis, we hypothesize that astrocytic action on neuronal respiratory control occurs, at least partially, via BDNF and TrkB signaling. However, BDNF expression and TrkB expression have not yet been formally demonstrated in glial cells of the respiratory centers. Although this knowledge would be necessary to support our hypothesis, there are some available data concerning the expression of BDNF and TrkB by glial cells. For instance, primate hippocampal astrocytes express BDNF and TrkB following experimental cerebral ischemia (Tonchev, 2011), and microglial cells express BDNF in a rat spinal cord injury model (Lu *et al.*, 2009). In healthy animals, primary cultures of cortical astrocytes express TrkB, and respond to BDNF stimulation with induction of Ca^{2+} waves (Climent *et al.*, 2000). In hippocampal mixed cultures of neurons and astrocytes, inhibitory synapse formation driven by autocrine/paracrine neuronal BDNF release and TrkB signaling is promoted by one or more unidentified protein(s) released by astrocytes (Elmariah *et al.*, 2005; Hughes *et al.*, 2010). Similarly, the BDNF switch from promoting to inhibiting NTS neuronal dendritogenesis upon glia depletion was reported in primary mixed cultures from the NTS of newborn rats (Martin *et al.*, 2012). This latter observation strongly suggests a functional link between BDNF signaling and glia in a brainstem nucleus involved in respiratory control.

Although the peripheral and neurodevelopmental actions of BDNF are very important to consider in the context of breathing control, a model outlining a mechanism for the specific action of astrocytic BDNF on neurons can be proposed (Fig. 3). This model suggests that astrocytes release BDNF in standard conditions, maintaining normal neuronal activity by inhibiting rhythmic neurons. This hypothesis is supported by the demonstrated inhibitory effect of exogenous BDNF on the respiratory activity of mouse brainstem slices (Thoby-Brisson *et al.*, 2003). Futhermore, a stimulatory effect on respiratory drive has been observed following administration of BDNF (Bouvier *et al.*, 2008) or TrkB agonists (Johnson *et al.*, 2012; Schmid *et al.*, 2012), suggesting that the inhibitory effect of BDNF signaling occurs on inhibitory neurons. Thus, astrocytic BDNF signaling, by inhibiting the activity of respiratory inhibitory neurons, could result in a stimulatory effect on respiratory drive. Accordingly, BDNF was shown to reduce the action of inhibitory neurons in the Kölliker–Fuse nucleus of rat (Kron *et al.*, 2007b). Moreover, blockade of the glial Krebs cycle in mouse brainstem slices leads to rhythmic activity depression (Hulsmann *et al.*, 2000). As mentioned previously, the authors suggested that this inhibitory effect on breathing is caused by a lack of glutamine–glutamate coupling between astrocytes and respiratory neurons. Alternatively, the reported finding could be explained by the model we are proposing as a reduction in neuronal inhibition resulting from a decrease in BDNF release by glial cells.

As preBötC and RTN/pFRG neurons express BDNF, expression of TrkB by astrocytes in the respiratory groups would potentially generate a BDNF effect on these glial cells. Indeed, cultured astrocytes respond to exogenous BDNF by inducing Ca^{2+} waves (Climent *et al.*, 2000). Activation of astrocytes has functional consequences, including neuronal modulation, and thus contributes to their network regulatory functions (Scemes & Giaume, 2006). A recent study suggested that preinspiratory astrocytes are actively involved in respiratory rhythm generation via coupling between Ca^{2+} waves and neuronal rhythmic activities (Okada *et al.*, 2012), but another group concluded that there was no synchronization between Ca^{2+} rises in astrocytes and burst generation (Schnell *et al.*, 2011). Thus, further investigations are necessary to elucidate the potential coupling between respiration and astrocytic Ca^{2+} waves.

Finally, if BDNF and TrkB are expressed by both neurons and astocytes, potential autocrine or paracrine neuron–neuron and/or astrocyte–astrocyte BDNF signaling in the respiratory centers, as has been reported in other contexts, cannot be excluded (Wei *et al.*, 2010; Cheng *et al.*, 2011; Kuribara *et al.*, 2011). However, it is difficult at this point to speculate about the physiological results of this potential cell signaling on respiratory control.

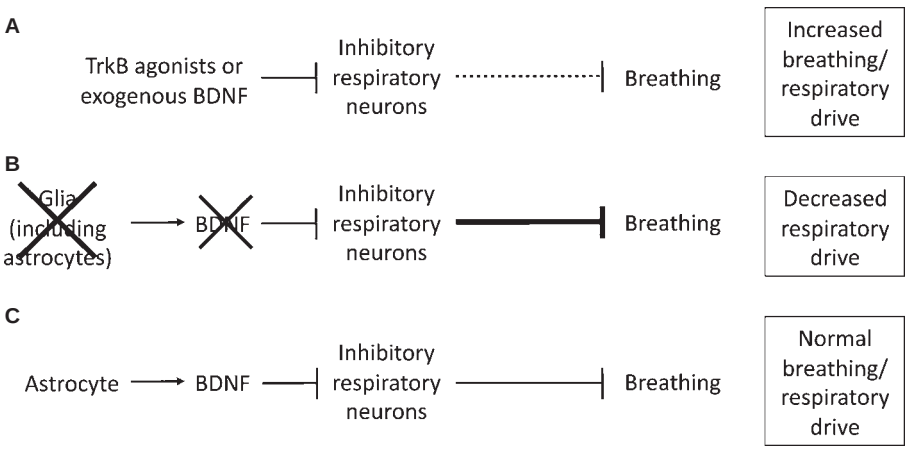

FIG. 3. Proposed model for astrocytic BDNF action on breathing control. (A) BDNF was reported to inhibit respiratory neurons in brainstem slices (Thoby-Brisson *et al.*, 2003). If these inhibited neurons are themselves inhibitory, as supported by the reported BDNF-reduced activity of inhibitory neurons in the Kölliker–Fuse nucleus (Kron *et al.*, 2007b), the effect on breathing will be a decrease in inhibition. Accordingly, exogenous BDNF treatment of isolated brainstems (Bouvier *et al.*, 2008) and treatment of mice with TrkB agonists (Johnson *et al.*, 2012; Schmid *et al.*, 2012) were reported to increase ventilatory drive and *in vivo* respiratory frequency, respectively. (B) In addition to inhibiting glial conversion of glutamate into glutamine (Hulsmann *et al.*, 2000), *in vitro* glial blockade could also prevent glial BDNF release, thus indirectly decreasing respiratory drive. (C) In an attempt to unify the results reported in this review, including those illustrated in A and B, we are proposing a model outlining mechanisms for the specific action of astrocytic BDNF on neurons in breathing control. Lines with arrowheads: extracellular release. Solid lines with bars: inhibition. Thick line with bar: enhanced inhibition. Dotted line with bar: decreased inhibition.

Rett syndrome as an example of a respiratory disorder

Pathogenesis of Rett syndrome

Rett syndrome can be used as an example to illustrate the potential BDNF-mediated control of communication between astrocytes and neurons in respiratory control and rhythmogenesis. Rett syndrome is a genetic disease caused, in most cases, by mutation(s) in the gene encoding methyl-CpG-binding protein 2 (MeCP2) (Amir *et al.*, 1999). It is an autism spectrum developmental disorder affecting 1 per 10 000 female babies (the gene is on the X chromosome, and mutation is lethal for hemizygous males and homozygous females) (Hagberg, 1985). This disease results in normal postnatal development until 6 months of age, when regression occurs (e.g. severe motor, autonomic and respiratory dysfunctions) (Rett, 1986). Thereafter, Rett patients show a post-regression pseudo-stationary phase, but cognitive deficits usually persist (Katz *et al.*, 2009), and a significant proportion of the patients never develop normal language, motor and respiratory functions (Halbach *et al.*, 2012).

Glial involvement in Rett syndrome

The involvement of neurons in Rett syndrome is well characterized. Indeed, specific neuronal mutation of *Mecp2* in mice reproduces most of the respiratory symptoms associated with Rett syndrome (e.g. hyperventilation during wakefulness, forced expiration, and apneas) (Na *et al.*, 2013). However, both wild-type and mutated *Mecp2* alleles are also expressed by astrocytes in humans (Ballas *et al.*, 2009; Maezawa *et al.*, 2009). In addition, in conditional mutant mice with general deletion and specific inducible re-expression of *Mecp2* in astrocytes, it has been elegantly demonstrated that MeCP2 deletion generates respiratory Rett-like symptoms, whereas MeCP2 re-expression specifically in the astrocytes stabilizes these symptoms (Lioy *et al.*, 2011). Without denying the importance of neurons in Rett syndrome, this model highlights the importance of astrocytes in the Rett-associated symptoms, including for the respiratory phenotype. Moreover, microglial cells seem to be also implicated in Rett syndrome pathogenesis, as shown by the arrest of disease development in *Mecp2*-null mice expressing the normal gene in microglial cells only (Derecki *et al.*, 2012). Thus, Rett syndrome studies corroborate, from a functional pathogenetic point of view, the importance of glia in the control of respiration. On this basis, the gliotransmitters shown to be secreted by astrocytes (Hamilton & Attwell, 2010; Santello *et al.*, 2012) could potentially play a role in Rett syndrome pathogenesis (Tropea *et al.*, 2009). Among them, BDNF has been shown to be involved in the syndrome.

BDNF involvement in Rett syndrome

As BDNF expression is regulated by MeCP2 (Martinowich *et al.*, 2003), Rett syndrome represents an interesting and relevant context in which to study the role of BDNF in respiratory control. BDNF levels are lowered in the brain of a mouse model of Rett syndrome (*Mecp2*-null mice), and there are respiratory phenotypic similarities between mice carrying BDNF and MeCP2 deficiencies, both showing a decrease in their brain weight and relative size of hippocampal neurons (Chang *et al.*, 2006). Moreover, BDNF overexpression in the brains of *Mecp2*-null mutant mice delays the onset of Rett syndrome and improves physical and cognitive functions as well as survival, which is normally decreased in mutants (Chang *et al.*, 2006). Similarly, TrkB agonist treatment (administered via drinking water or intraperitoneal injection) decreases Rett symptoms in *Mecp2*-null mice (Johnson *et al.*, 2012; Schmid *et al.*, 2012). This effect seems to be in conflict with the above-described BDNF effect on brainstem slices, i.e. a decrease in burst frequency in response to exogenous BDNF application. This apparent contradiction may be explained, at least in part, by potential TrkB agonist actions on other organs, such as lungs (Prakash *et al.*, 2010), in the *in vivo* context. Also, the amount of TrkB agonist crossing the blood–brain barrier in the *in vivo* experiments is not precisely known. Finally, the durations of the treatment in the two experimental models are not comparable (weeks vs. minutes). In addition, both these *in vitro* and *in vivo* experiments may contribute to supporting the model that we are proposing to describe astrocytic BDNF action on breathing control (Fig. 3).

Taken together, these studies using cerebral BDNF overexpression and TrkB activation highlight potential interesting therapeutic avenues to explore in an attempt to treat the symptoms associated with Rett syndrome. More precisely, the tested TrkB agonists improve respiratory function in the Rett mouse model by restoring breathing frequency to the wild-type level (Schmid *et al.*, 2012), partially improving breathing pattern irregularities, and returning tidal volumes to near wild-type levels (Johnson *et al.*, 2012). The Rett mouse model allows the demonstration of BDNF involvement in perturbations of respiratory control and rhythmogenesis in a pathological context.

Moreover, the disturbances in Ca^{2+} homeostasis observed during the early postnatal development of *Mecp2*-null mice are restored after incubation of brainstem slices from these mice in BDNF solution (Mironov *et al.*, 2009), providing a potential mechanism to explain how BDNF could be involved in the development of the respiratory abnormalities associated with Rett syndrome. This observation reveals a possible mechanism by which BDNF, by regulating Ca^{2+} homeostasis, contributes to the maintenance of a proper neuronal network that is capable of generating a stable respiratory rhythm.

Potential astrocytic signaling via the BDNF–TrkB pathway in Rett syndrome

As mentioned previously, a decrease in BDNF cerebral expression was reported in the Rett mouse model (Chang *et al.*, 2006). Accordingly, MeCP2 deficiency in mouse cultured astrocytes causes a significant decrease in *Bdnf* transcription (Maezawa *et al.*, 2009). These results suggest that the lack of normal MeCP2 expression in astrocytes is responsible, at least partially, for the decrease in cerebral BDNF expression observed in the Rett mouse model.

The exact role of MeCP2 in glia is still undetermined. However, as BDNF and MeCP2 are both expressed by astrocytes (Climent *et al.*, 2000; Ballas *et al.*, 2009; Maezawa *et al.*, 2009), it is possible, considering the physiological and electrophysiological respiratory dysfunctions reported in mouse models of Rett syndrome and BDNF deficiency, that astrocytes expressing BDNF and MeCP2 are located in the respiratory groups. If confirmed, this hypothesis would contribute to explaining the respiratory deficiencies observed in Rett mouse models and Rett patients by providing a functional link between *Mecp2* mutation and the physiological and electrophysiological observations.

The model that we propose to explain the mechanism by which BDNF released by astrocytes acts on respiratory control (Fig. 3) could also be used to explain how BDNF can be involved in Rett syndrome pathogenesis. As Rett syndrome has a developmental origin, it is also important to consider BDNF neurodevelopmental effects in relation to the observed respiratory symptoms. Accord-

ingly, overexpression of BDNF in the brains of *Mecp2*-null mice delays the onset of Rett syndrome, including the respiratory disorders (Chang *et al.*, 2006). On the other hand, acute postnatal TrkB agonist treatment decreases Rett symptoms in *Mecp2*-null mice (Johnson *et al.*, 2012; Schmid *et al.*, 2012). Taken together, these observations suggest that Rett syndrome results from both neurodevelopmental effects and direct effect of BDNF on neuronal activity. Thus, understanding the BDNF-mediated control of communication between astrocytes and neurons has the potential to improve postnatal management of the respiratory symptoms in Rett patients.

Other relevant respiratory disorder-associated syndromes

Knowledge of the link between glia, BDNF and respiratory control has the potential to be very helpful in understanding some other respiratory pathologies (Table 1). For instance, pathological observations of victims of sudden infant death syndrome revealed lowered BDNF levels in the caudal NTS and increased TrkB levels in the caudal dorsal motor nucleus of the vagus (Tang *et al.*, 2012). This altered expression of BDNF reported in the NTS may have important physiological implications, especially regarding respiratory and cardiac control, given the role that NTS has in these functions (Boscan *et al.*, 2002).

In addition, abnormality in the RTN/pFRG is now considered to be a cause of Ondine syndrome, which is formally known as idiopathic congenital central hypoventilation syndrome (Amiel *et al.*, 2009). Moreover, a trend towards lowered BDNF expression was reported in the cerebrospinal fluid of infants suffering from the syndrome (Chiaretti *et al.*, 2005). Although this latter result is preliminary and remains to be confirmed, these two observations on the Ondine syndrome reinforce the idea that studying BDNF in the RTN/pFRG (and in other respiratory centers) is a promising avenue to explore in order to better understand respiratory disturbances.

Conclusion

We have reviewed here the respective roles of glial cells and BDNF in respiratory control and rhythmogenesis. On the basis of the available data, we hypothesize that there is BDNF-mediated control of the communication between neurons and astrocytes in the brainstem respiratory groups (Fig. 2). This hypothesis is strongly supported by the current knowledge on the pathogenesis of Rett syndrome. Accordingly, it is necessary to test this hypothesis, as our knowledge of the signaling mechanisms by which astrocytes are involved in respiratory control and rhythmogenesis is still incomplete. For example, application of BDNF to brainstem slices in which glial metabolism has been blocked could provide crucial evidence regarding the type of glial-to-neuron communication occurring in respiratory centers. Understanding the link between glial cells and BDNF signaling in respiratory control and rhythmogenesis would undoubtedly be helpful in refining our understanding of pathologies associated with respiratory disturbances.

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Abbreviations

BDNF, brain-derived neurotrophic factor; CNS, central nervous system; MeCP2, methyl-CpG-binding protein 2; NTS, nucleus tractus solitarii; p75NTR, p75 neurotrophin receptor; preBötC, preBötzinger complex; pFRG, parafacial respiratory group; RTN, retrotrapezoid nucleus; TrkB, tyrosine kinase receptor B.

TABLE 1. Syndromes associated with a respiratory control disturbance in which glia and/or brain-derived neurotrophic factor (BDNF) are involved

Syndrome Mutated gene(s) Respiratory-associated symptoms	Glia involvement	BDNF involvement
Rett syndrome (Rett, 1986) *Mecp2* mutation Hyperventilation, apnea	Astrocytes express MeCP2 (Maezawa *et al.*, 2009)	BDNF is decreased in the brain of a mouse model of Rett syndrome and is a transcriptional target of MeCP2 (Chang *et al.*, 2006)
Ondine syndrome (Healy & Marcus, 2011) *Phox2b* mutation Hypoventilation	Not demonstrated	BDNF is decreased in cerebrospinal fluid (Chiaretti *et al.*, 2005)
Sudden infant death syndrome (Thach, 2005) No mutation identified Apnea	Proliferation of astrocytes and microglial activation is increased in the NTS (Biondo *et al.*, 2004)	BDNF is increased and TrkB is decreased in the caudal brainstem (Tang *et al.*, 2012)
Pitt–Hopkins syndrome (Ouvrier, 2008) *Tcf4* mutation Hyperventilation	Glial cells express TCF4 (Yi *et al.*, 2012)	BDNF is a transcriptional target of TCF4 (Yi *et al.*, 2012)
Prader–Willi syndrome (Nixon & Brouillette, 2002) Mutations in chromosomal region 15q11–q13 Abnormal ventilatory responses to hypercapnia and hyperoxia	Primitive neuroglial progenitor cells express the genes whose mutation induces the syndrome (McGuckin *et al.*, 2004)	Neuronal response to BDNF is defective (Bush & Wevrick, 2010)

TCF4, transcription factor 4.

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