The generation of neural network dynamics relies on the interactions between the intrinsic and synaptic properties of their neural components. Moreover, neuromodulators allow networks to change these properties and adjust their activity to specific challenges. Endogenous continuous ("tonic") neuromodulation can regulate and sometimes be indispensable for networks to produce basal activity. This seems to be the case for the inspiratory rhythm generator located in the preBötzinger complex (preBötC). This neural network is necessary and sufficient for generating inspiratory rhythms. The preBötC produces normal respiratory activity (eupnea) as well as sighs under normoxic conditions, and it generates gasping under hypoxic conditions after a reconfiguration process. The reconfiguration leading to gasping generation involves changes of synaptic and intrinsic properties that can be mediated by several neuromodulators. Over the past years, it has been shown that endogenous continuous neuromodulation of the preBötC may involve the continuous action of amines and peptides on extrasynaptic receptors. I will summarize the findings supporting the role of endogenous continuous neuromodulation in the generation and regulation of different inspiratory rhythms, exploring the possibility that these neuromodulatory actions involve extrasynaptic receptors along with evidence of glial modulation of preBötC activity.

Keywords: endogenous neuromodulation, glia, network activity, pacemaker neurons, reconfiguration, extrasynaptic
Adenosine is an inhibitory neuromodulator of the preBötC (Hülsmann et al., 2000; Ptak et al., 2009).

CONTINUOUS ("TONIC") NEUROMODULATION OF THE preBötC

The actions of endogenous neuromodulators on the inspiratory rhythm generator, including amines and peptides, were recently reviewed (Ballanyi, 2004; Peña and García, 2006; Doi and Ramírez, 2008; Peña, 2009). Therefore, I will focus on the evidence of endogenous continuous neuromodulations of the preBötC. In the CNS, several neuromodulators can be continuously released and act both at synaptic and extrasynaptic levels to regulate network function (Vizi et al., 2010). Extrasynaptic transmission was originally discovered for several monoamines that regulate the release of other neuromodulators and neurotransmitters despite the lack of synaptic contact between the two terminals (Vizi et al., 2010). In fact, the majority of monoaminergic and peptidergic neurons fail to make synaptical contacts and instead, they act on extrasynaptic receptors (Descarries and Mechawar, 2000; Vizi et al., 2010).

Such neuromodulators are preferentially, but not exclusively, accumulated in large, dense-core vesicles, and they require a strong depolarization or high frequency stimulation to be released (Torrealba and Carrasco, 2004; De-Migue1 and Trueba, 2005; Vizi et al., 2010). The fact that several neuromodulators, such as serotonin and adenosine, have been detected in the extracellular space of the preBötC by means of microdialysis (Richter et al., 1999), which detects neurotransmitters and neuromodulators that escaped the synaptic cleft (Peña and Tápia, 1999, 2000), suggests that they can reach extrasynaptic receptors and continuously modulate the preBötC. The extracellular concentration of these neuromodulators changes depending on the state of the network (i.e., hypoxia; Richter et al., 1999; Hehre et al., 2008) indicating that such continuous modulation adjusts the preBötC activity to fit particular demands. Next, I will present a catalog of neuromodulators that maintain a continuous neuromodulation of the preBötC, and discuss the possible involvement of extrasynaptic receptors or glial cells in this modulation. It is important to consider that respiratory rhythmogenesis is studied in a variety of experimental conditions ranging from behaving animals to preBötC islands (Ramírez-Jarquin et al., 2012). Thus, in most cases, the pharmacological manipulations could affect different respiratory circuits besides the preBötC (Zavala-Tecuapetla et al., 2008; Ramírez-Jarquin et al., 2012).

ADENOSINE

Adenosine is an inhibitory neuromodulator of the preBötC (Schmidt et al., 1995; Herlenius and Lagercrantz, 1999; Wilken et al., 2000; Huxtable et al., 2009) that can be directly released from neurons and glia or that can be extracellularly produced by the degradation of released ATP (Martin et al., 2007; Cunha, 2008; Zwickert et al., 2011). Ambient adenosine can exert its effects by diffusing far away from the release sites (Cunha, 2008; Vizi et al., 2010). An adenosinergic continuous modulation of the preBötC of mice has been evidenced by blocking adenosine-receptors with the non-selective, adenosine-receptor antagonist aminophylline (Wilken et al., 2000), which increases the frequency and amplitude of inspiratory rhythm in slices. This effect is similar to blocking the type 1 (A1) adenosine-receptor in rats with the specific antagonist DPCPX (Huxtable et al., 2009) These increases have also been observed in the brainstem-spinal cord preparation (also called the "en bloc") of rats (Herlenius and Lagercrantz, 1999) and in cats in vivo (Schmidt et al., 1995), where levels of adenosine increase in hypoxia (Richter et al., 1999), contributing to the respiratory depression observed during this condition. In fact, blocking A1-receptors attenuates hypoxia-induced breathing in the en bloc of rats (Kawai et al., 1995). Thus, it has been suggested that adenosine antagonists can be useful for the treatment of several respiratory dysfunctions (Mathew, 2011).

ATP

ATP excites the preBötC in vitro in rats (Huxtable et al., 2009; Zwickert et al., 2011) through the activation of P2Y-receptors (Lorier et al., 2007; Huxtable et al., 2009). Interestingly, blockade of endogenous activation of P2-receptors with suramin reduces inspiratory frequency in the slice preparation, while Cu^{2+}, an allosteric modulator of purinergic receptors, produced the opposite effect (Lorier et al., 2007, 2008). ATP is released during hypoxia, and blocking its tonic action on P2-receptors increases the hypoxia-induced slowing of the respiratory rhythm, suggesting that ATP is involved in maintaining respiration in hypoxia in rats (Gourine et al., 2005). Interestingly, the excitatory effect of exogenous ATP on the preBötC is precluded when glial cells are inhibited (Huxtable et al., 2009).

ACETYLCHOLINE

Acetylcholine (ACh) is another neuromodulator that tonically regulates preBötC activity in rats and mice (Shao and Feldman, 2009). Application of the acetylcholinesterase inhibitor physostigmine increases the frequency of rhythmic respiratory activity in the slice preparation involving the type-3-muscarinic and α4β2-nicotinic receptors in rats and mice, respectively (Shao and Feldman, 2005; Shao et al., 2008). Similarly, blockade of muscarinic-receptors with atropine reduces the amplitude and frequency of the respiratory rhythm in the en bloc from mice (Coddou et al., 2009). In the lamprey en bloc, physostigmine increases the respiratory frequency, while the nicotinic antagonists D-tubocurarine or bungarotoxin reduces it (Mutolo et al., 2011).

NORADRENALINE

Pre-Bötzinger complex activity is modulated by endogenous noradrenaline released from the A5, A6, A1C1, and A2C2 nuclei in rats and mice (Hilaire et al., 2004; Viemari, 2008). This continuous modulation involves activation of α-2-adrenoreceptors, since its blockade with yohimbine, piperoxane, or phentolamine decreases respiratory frequency in the en bloc in rats and mice (Errchidi et al., 1990; Zanella et al., 1990; Fujii and Arata, 2010) and abolishes gasping generation in slices from mice (Viemari et al., 2011). Accordingly, decreasing the extracellular noradrenaline concentration with pargyline, desipramine, or tyroside increases the frequency of the rhythm, while methyltyrosine, an inhibitor of noradrenaline biosynthesis, increases the en bloc respiratory frequency in rats and mice (Errchidi et al., 1990; Zanella et al., 2006). There is some evidence of a continuous modulation of the preBötC by histamine and dopamine. Thus, the histamine-type-1-receptor antagonist, pyrilamine, reduces the en bloc respiratory
SEROTONIN
The preBötC is modulated by 5-hydroxytryptamine (5-HT), which produces an excitatory effect mediated by 5-HT2-receptors and an inhibitory effect mediated by 5-HT1-receptors (Schwarzacher et al., 2002). The main source of 5-HT is the raphe nuclei (Richerson, 2004), whose projections can or cannot make synaptic contacts with their targets throughout the brain (Kosofsky and Molliver, 1987). In the preBötC, increasing the extracellular concentration of 5-HT with 5-HT-uptake inhibitors leads to an increase of respiratory activity in the en bloc from rats (Di Pasquale et al., 1994). In contrast, blocking 5-HT-receptors with the non-specific antagonist methysergide abolishes rhythmodogenesis in the en bloc and in slices from rats (Di Pasquale et al., 1994; Ptak et al., 2009). In these preparations, excitation of raphe neurons increases the frequency of the respiratory rhythm mediated by the activation of 5-HT2-receptors (Al-Zubaidy et al., 1996; Ptak et al., 2009). Accordingly, blocking either 5-HT2B-receptors (Günter et al., 2006), 5-HT2C-receptors (Ptak et al., 2009), or 5-HT2A receptors (Peña and Ramírez, 2002; Ptak et al., 2009) reduces the respiratory rhythm frequency and its regularity in slices from rats and mice. Such findings have been corroborated for 5-HT2A- and 5-HT2C-receptors in situ in rats (Ptak et al., 2009). Interestingly, low micromolar concentrations of 5-HT induce bursting activity in non-bursting preBötC neurons (Ptak et al., 2009), while blockade of 5-HT2A receptors abolishes the intrinsic bursting of the \textit{In}d\textit{dent}-dependent (hypoxia-resistant) pacemaker neurons (Peña and Ramírez, 2002; Tryba et al., 2006). Consequently, blockade of 5-HT2A receptors inhibits gasping generation in slices from mice (Tryba et al., 2006) and \textit{in situ} in rats (Bale and Solomon, 2010). These findings may have clinical relevance, since it has been hypothesized that a deficiency of the medullary 5-HT network is a potential cause of SIDS (Kinney et al., 2001).

PEPTIDES
Several neuropeptides may exert a continuous regulation of the preBötC. Neuropeptides are typical non-synaptic transmitters, which are released extrasynaptically (Torrealba and Carrasco, 2004; Wotjak et al., 2008). Blocking the endogenous activation of the opioid-receptors with naloxone increases the respiratory output in cats (Lawson et al., 1979) and reduces hypoxia-induced respiratory depression in rats (Schlenker and Inamdar, 1995). In mice, blocking endogenous activation of somatostatin-receptors increases the respiratory rhythm frequency and reduces its regularity, both in slices and \textit{in vivo} (Ramírez-Jarquín et al., 2012). Moreover, blockade of somatostatin-receptors, specifically subtype 2, prevents the reconfiguration of the preBötC during hypoxia \textit{in vitro} and reduces gasping generation and autoreexcitation \textit{in vivo} (Ramírez-Jarquín et al., 2012). In contrast, substance-P maintains an excitatory continuous modulation on the preBötC in rats and mice (Ptak et al., 2009; Doi and Ramírez, 2010). Blockade of the substance-P receptor (NK1) with SR 140333 or spantide inhibits rhythmodogenesis \textit{in vitro} and \textit{in situ} in mice and rats, respectively (Telgkamp et al., 2002; Ptak et al., 2009). Interestingly, in mice, inhibition of respiratory activity with NK1 antagonists has no significant respiratory effect when the levels of 5-HT or noradrenaline are increased by stimulating the raphe nucleus or locus coeruleus, respectively (Doi and Ramírez, 2010), indicating that the action of substance-P might be influenced by the neuropeudulatory state of the network (Doi and Ramírez, 2010).

POSSIBLE REGULATION OF THE preBötC BY GABA AND GLUTAMATE ACTING ON EXTRASYNAPTIC RECEPTORS
Glutamatergic and GABAergic neurons were thought to release their transmitters exclusively at synapses, where they mediate the classical “fast synaptic transmission” (Vizi et al., 2010). However, it has been shown that ambient GABA and glutamate can also tonically activate high-affinity, extrasynaptic receptors, suggesting their spillover from synaptic boutons, mediating a slower synaptic transmission (Semyanov et al., 2004; Farrant and Nusser, 2005; Aghajanian, 2009). Extrasynaptic GABA\textsubscript{A} inhibition can modulate the generation of hippocampal fast rhythms (Scanziani, 2000; Towers et al., 2004; Mann and Mody, 2010; Papatheodoropoulos and Koniaris, 2011), and it is likely that such modulation also occurs in the preBötC, where increasing the extracellular concentration of GABA, by inhibiting its uptake with nipeptocic acid, decreases the respiratory frequency (Ren and Greer, 2006). The presence of delta-subunit-containing-GABA\textsubscript{A}-receptors, which are mainly extrasynaptic (Nusser et al., 1998; Adkins et al., 2001; Brown et al., 2002) suggests a tonic GABAergic control of the preBötC. For instance, the application of the GABA\textsubscript{A}-receptor agonist THIP, which preferentially activates extrasynaptic GABA\textsubscript{A}-receptors containing delta-subunits (Nusser et al., 1998; Adkins et al., 2001; Brown et al., 2002), hyperpolarizes respiratory neurons and reduces the frequency of the respiratory rhythm (Shao and Feldman, 1997). Neurosteroids, which also target delta-containing, extrasynaptic GABA\textsubscript{A}-receptors (Stell et al., 2003; Beletti and Lambert, 2005; Scimemi et al., 2006), modulate GABA\textsubscript{A}-receptor-mediated hyperpolarization of respiratory neurons and the inhibition of rhythmodogenesis in slices (Ren and Greer, 2006).

Ambient glutamate can also activate extrasynaptic, NR2B-subunit-containing, NMDA-receptors and modulate neural network activity (Lambe and Aghajanian, 2006, 2007; Aghajanian, 2009). It is likely that extrasynaptic, NMDA-receptor-mediated excitation is also present in the preBötC, where inhibition of glutamate uptake with dihydrokainate increases rhythmodogenesis (Greer et al., 1991; Funk et al., 1993). Dihydrokainate can also restore rhythmodogenesis in substance-P-depleted slices, in which capsaicin abolishes rhythm generation (Morgado-Valle and Feldman, 2004). Similarly, releasing NMDA-receptors from their Mg\textsuperscript{2+}-blockade restores rhythmodogenesis in slices where the rhythm is abolished by AMPA-receptor blockade (Morgado-Valle and Feldman, 2007). This evidence supports the notion that a tone of extracellular glutamate can participate in rhythmodogenesis. Furthermore, the presence of the NR2B-receptor has been extensively documented in the preBötC (Watanabe et al., 1994; Paarmann et al., 2000, 2005; Liu and Wong-Riley, 2010).
GLIAL MODULATION OF THE preBötC

Glial cells are integral functional elements of neural networks, since it is argued that they can respond to and regulate neuronal activity (Araque and Navarrete, 2010). The respiratory network is not an exception (Gourine et al., 2010). Glial cells can sense preBötC activity, and a portion of them display a phase-locked rhythmic activity (Schnell et al., 2011). Moreover, glial cells are essential for rhythrogenesis, since both fluoroacetate, which selectively blocks the glial Krebs cycle, and methionine-sulfoxide, which blocks glutamine synthetase (Hülsmann et al., 2000; Young et al., 2005; Huxtable et al., 2010), inhibit rhythmic respiratory burst activity in slices. In these conditions, addition of isocitrate or glutamine restores the rhythmic network activity (Hülsmann et al., 2000). Accordingly, methionine-sulfoxide-treated pups displayed a reduced breathing frequency and a reduced responsiveness to hypercapnia (Young et al., 2005). Moreover, glial cells are required not only for maintaining rhythm generation but also for the response of the preBötC to neuromodulators or to metabolic demands (Gourine et al., 2010). For instance, fluoroacetate and methionine-sulfoxide reduce preBötC responsiveness to ATP (Huxtable et al., 2010), and preBötC glial cells can respond to preBötC neuromodulators including 5-HT and substance-P (Härtl et al., 2009).

I conclude that continuous neuromodulation exerts a powerful influence on the preBötC; to the extent that, in some cases, it is necessary for rhythm generation. Continuous neuromodulation tunes the excitability of the preBötC to respond to different demands and also determines the weight of specific neuronal types or specific synaptic interactions in the generation of network dynamics. This property could allow the preBötC to adopt an infinite number of conformations based on the same circuit (neural units and connections). Moreover, the evidence that one neuromodulator is determined by tonic control exerted by other neuromodulators, supports the notion that the intrinsic and synaptic properties of the preBötC are not fixed, but can change in a state-dependent manner. The levels of modulation in the preBötC would determine the availability of neural properties (intrinsic, synaptic, or both) that can participate in network dynamics or are susceptible to subsequent neuromodulation.

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