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25

Possible Role of Respiratory Pacemaker Neurons in the Generation of Different Breathing Patterns

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1. Introduction

Rhythmic output is a common feature of several neuronal networks throughout the brain (Arshavsky 2003; Llinas 1988; Buzsaki & Draguhn 2004; Ramirez et al., 2004; Selverston 1999; Harris-Warrick & Marder 1991). Despite the fact that rhythmogenic networks were initially described for simple motor behaviors produced by invertebrates (Selverston 1999; Harris-Warrick & Marder 1991), there is increasing evidence suggesting that basic mechanisms revealed in these simple networks are conserved in mammalian circuits in the neocortex or other subcortical networks involved in more complex behaviors (Ramirez et al. 2004; Yuste et al., 2005). Recent findings indicate that network oscillations determine synaptic input selection, neuronal assemblies formation as well as synaptic plasticity (for a review see Buzsaki & Draguhn 2004). Rhythmic network activity emerges from the combination of synaptic network interactions and intrinsic cellular properties (Vergara et al., 2005; Peña et al., 2004; Cunningham et al., 2004; Yuste et al. 2005; Peña & Ramirez 2005; Peña et al., 2006; Mellen & Mishra, 2010). However the relative contribution of those mechanisms may be state dependent (Llinas 1988; Yuste et al. 2005; Peña & Ramirez 2005; Doi & Ramirez, 2010). Examples of state-dependency in neuronal network activity can be observed during sleep/wake states in the cortex or normoxia/hypoxia in the respiratory network (Llinas 1988; Yuste et al. 2005; Peña & Ramirez 2005; Peña & Aguileta, 2007). Moreover, neuronal network properties may be altered by several intracellular and extracellular environmental conditions (i.e. the action of neuromodulatory systems; Steriade 2004; Traub et al., 2003; Peña & Ramirez 2002; 2004; Johnson et al., 2003; van den Top et al., 2004; Doi & Ramirez, 2008). Regardless of the old dilemma on the relative contribution of intrinsic and synaptic properties to circuit activity (Vergara et al. 2003; Egorov et al., 2002; Shu et al., 2003; 2006; Cunningham et al. 2004; Cardin et al., 2005), there is increasing evidence supporting the participation of intrinsic pacemaker neurons in the generation of network rhythmic activity (Llinas & Sugimori 1980; Schwindt & Crill 1982; Freund & Antal 1988; King et al., 1998; Stewart & Fox 1989; 1990; Leresche et al., 1991; Tresch & Kiehn 2000; Wang 2002; Sotty et al., 2003; Cunningham et al. 2004; Peña et al. 2004; Ramirez et al. 2004; Sipilä et al., 2005).

2. Pacemaker neurons

Pacemaker neurons can be considered as neurons with the intrinsic ability to generate bursts of action potentials at regular intervals (in the absence of synaptic interactions; Ramirez & Peña, 2005; Peña, 2008). Pacemaker neurons posses a particular combination of ion currents, that allows them to amplify synaptic inputs, as well as to promote general network excitation and synchrony (Llinas & Sugimori 1980; Llinas 1988; Del Negro et al. 2002; Arshavsky 2003; Ramirez et al. 2004; Schwindt & Crill 1982; Tresch & Kiehn 2000; Harris-Warrick 2002; Shu et al. 2006). The well stablished role of pacemaker neurons commanding rhythmic neuronal networks in invertebrates (Selverston 1999; Harris-Warrick & Marder 1991; Ramirez et al. 2004), is now been suggested for mammalian neuronal networks as well. For instance, GABAergic pacemaker neurons from the medial septum seem to be essential for theta rhythm generation (Freund & Antal 1988; Stewart & Fox, 1989; 1990; King et al. 1998; Sotty et al. 2003; Wang 2002); bursting CA3 pyramidal neurons seem to be responsible for spontaneous rhythmic activity observed in the newborn hippocampus (Sipilä et al. 2005), bursting reticular thalamic neurons might be responsible for generation of several thalamocortical rhythms (Leresche et al. 1991) and fast rhythmic bursting neurons seem to be essential for gamma rhythm generation in the cortex (Cunningham et al. 2004). Pacemaker neurons may also be involved in generation of different breathing patterns.

3. Respiratory rhythms generation

Ventilation of the lungs as consequence of rhythmic contractions of the respiratory muscles constitutes a complex neuromuscular function that involves several brainstem and spinal cord circuits, several muscles such as the diaphragm, intercostal, laryngeal and pharyngeal muscles, as well as the lungs and the vasculature (Richter, 1982; Bianchi et al., 1995; Feldman, 1995) A reduction in such function can cause hypoxia, that evokes a response of the respiratory network that leads to the generation of gasping, which is considered to be the 'last-resort' respiratory effort to autoresuscitate and sustain life (Poets et al., 1999; Sridhar et al., 2003; Peña, 2009). Indeed, failure to respond to severe hypoxia via gasping and autoresuscitation can result in death. Thus, dysregulation of the generation of gasping rhythm and/or autoresuscitation has been hypothesised to contribute to Sudden Infant Death Syndrome (SIDS; Poets et al., 1999; Sridhar et al., 2003; Peña, 2009).

Breathing is commanded and regulated by the respiratory centres of the brainstem (Richter, 1982; Bianchi et al., 1995; Feldman, 1995). The central respiratory pattern generator consists of two interacting oscillators, one controlling inspiration (the pre-Bötzinger complex; PreBötC) and other, located in the parafacial respiratory group (pFRG), possibly controlling active expiration (Smith et al., 1991; Onimaru & Homma, 2006; Janczewski & Feldman, 2006; Peña, 2009). In contrast with the pFRG, the vital role of the PreBötC in the generation of respiratory rhythms is supported by a variety of experimental data. First, during embryonic development there is a coincidence between the appearance of the PreBötC and initial respiratory rhythmic activity *in vitro* (Pagliardini et al., 2003; Thoby-Brisson et al., 2005; Greer et al., 2006). Second, brain stem rhythmic respiratory output is eliminated when the PreBötC is ablated (Smith et al., 1991; Ramirez et al., 1998; Wenninger et al., 2004). Finally, perturbations of neuronal function in and around the PreBötC severely disrupt breathing in mammals (Ramirez et al., 1998; Gray et al., 2001; Wenninger et al., 2004).

We have been characterizing pacemaker activity in the PreBötC in a slice preparation, which is able to produce, in normoxic conditions, the neural correlate of two respiratory rhythms observed *in vivo*: fictive eupneic activity and fictive sighs. If this preparation is challenged with hypoxia, fictive eupnea and sighs are supplanted by another rhythm called fictive gasping (Lieske et al. 2000; Ramirez & Lieske 2003). It has been proposed that the PreBötC is a multifunctional neural network, able to produce multiple rhythmic activities by the reconfiguration of network interactions (Lieske et al. 2000; Peña et al., 2004).

4. Respiratory pacemaker neurons

The PreBötC contains several types of neurons, including expiratory, inspiratory and postinspiratory neurons (Peña & Ramirez, 2002; Peña et al., 2004; Ramirez et al., 1997). Based just on their intrinsic properties and their ability to burst in synaptic isolation, we can distinguish two major types of neurons: pacemaker and non-pacemaker neurons (Thoby-Brisson & Ramirez 2001; Del Negro et al. 2002; Peña et al. 2004). Regardless of the evidence that there is a *continuum* between the intrinsic properties of pacemaker and non pacemaker neurons (Ramirez et al. 2004); most respiratory neurons in the PreBötC have been considered non-pacemakers (Ramirez et al. 1997; Peña et al. 2004). On the other hand, PreBötC pacemaker neurons reported so far, express a quite variable range of interburst and intraburst frequencies; amplitude of the plateau potential underlying bursting firing; as well as the voltage trajectory of such plateau (Thoby-Brisson & Ramirez 2001; Del Negro et al. 2002; 2005; Peña et al. 2004; Viemari & Ramirez 2006; Tryba et al. 2006, Mellen & Mishra, 2010, Table 1).

An initial pharmacological characterization has shown that there are at least two types of respiratory pacemakers neurons in the PreBötC (Thoby-Brisson & Ramirez 2001; Peña et al. 2004; Del Negro et al. 2005; Table 1). Despite the fact that all of them are sensitive to tetrodotoxin (TTX) (Thoby-Brisson & Ramirez 2001), two groups have been identified based on their sensitivity to the general calcium channel blocker Cd^{2+} (Elsen & Ramirez 1998): One group of pacemakers stop bursting in the presence of Cd^{2+}, whereas another group continued bursting in the same conditions. Such pacemaker neurons were originally identified as Type II (or Cd^{2+}-sensitive) and Type I (or Cd^{2+}-insensitive) pacemaker neurons, respectively (Thoby-Brisson & Ramirez 2001, Table 1). In the last two decades, some other differences have also been identified: In general, type I pacemaker neurons produce bursts of shorter duration than type II pacemaker neurons (Thoby-Brisson & Ramirez 2001; Peña & Ramirez 2002; 2004; Peña et al. 2004). Whereas type I pacemaker neurons are present during all postnatal development, it seems like type II pacemakers are scarce at early postnatal age (P0-P5) and increase their presence afterwards (Peña et al. 2004, Table 1).

The identification of the ion channels involved in bursting properties of these groups of respiratory pacemaker neurons, has provided us with some pharmacological tools that have helped to test the role of these neurons in the generation of the different respiratory rhythms (Del Negro et al. 2002; 2005; Peña et al. 2004; Paton et al., 2006; Tryba et al. 2006). The sensitivity of PreBötC pacemaker neurons to either Cd^{2+} or TTX (Thoby-Brisson & Ramirez 2001), does not help much for this purpose, since both channel blockers produce a generalized disturbance of neuronal firing and neurotransmitter release (Onimaru et al. 1989; Peña & Tapia 2000; Peña et al., 2002). Further pharmacological characterization revealed that most type I (or Cd^{2+}-insensitive) pacemaker neurons rely on the activity of a

persistent Na^+ current and that bursting activity of most of them might be abolished by persistent Na^+ current blockers, including riluzole (Del Negro et al. 2002; 2005; Peña et al. 2004; Tryba et al. 2006). It is important to mention that around 25 % of type I (or Cd^{2+}-insensitive) pacemaker neurons were not sensitive neither to riluzole nor to Cd^{2+} (Peña et al. 2004).

	Type I Pacemaker	**Type II Pacemaker**	**References**
Blocked by tetrodotoxin	Yes	Yes	Thoby-Brisson & Ramirez, 2001 Peña et al. 2004
Blocked by Cd^{2+}	No	Yes	Thoby-Brisson & Ramirez, 2001 Peña et al. 2004 Tryba et al. 2006
Presence at: P0-P5	Scarce	Yes	Peña et al. 2004 Del Negro et al. 2002; 2005
Presence at: >P5	Yes	Yes	Peña et al. 2004 Del Negro et al. 2002; 2005
Blocked by riluzole	Yes (around 75 % of them*)	No	Peña et al. 2004 Del Negro et al. 2002; 2005 Paton et al. 2006 Tryba et al. 2006
Blocked by FFA	No	Yes (around 90 % of them*)	Peña et al. 2004 Del Negro et al. 2005 Tryba et al. 2006
5-HT_{2A}R-dependent	Yes	No	Peña et al. 2004 Tryba et al. 2006
Substance P-potentiated	No	Yes	Peña et al. 2004 Ben-Mabrouk & Tryba, 2008
Noradrenaline-potentiated	No	Yes	Viemari & Ramirez, 2006
Necessary for eupnea generation	Yes[a]	Yes[a]	Peña et al. 2004 Tryba et al., 2006 Peña and Aguileta, 2007
Bursting in hypoxia	Yes	No	Thoby-Brisson & Ramirez, 2000 Peña et al. 2004 Paton et al. 2006 Tryba et al. 2006
Necessary for gasping generation	Yes	No	Peña et al. 2004 Paton et al. 2006 Tryba et al. 2006 Peña and Aguileta, 2007

Abbreviations: FFA: flufenamic acid; 5-HT_{2A}R: 5-HT_{2A} receptors. *From data reported in Peña et al. 2004.[a]Both populations have to be blocked to abolish eupnea.

Table 1. Properties of pacemaker neurons localized in the preBötC.

On the other hand, type II pacemaker neurons, which are both TTX and Cd^{2+}-sensitive, seem to rely on a Ca^{2+}-activated unspecific cationic current (ICAN) (Peña et al. 2004; Del Negro et al. 2005; Tryba et al. 2006; Ben-Mabrouk & Tryba, 2010), which may arise from TRP channels (Ben-Mabrouk & Tryba, 2010). This is supported by the fact that around 90% of these pacemakers were blocked by the ICAN blocker flufenamic acid (FFA) (Peña et al. 2004; Ben-Mabrouk & Tryba, 2010). Remarkably, none of the type I pacemaker neurons are affected by FFA and no type II pacemaker neurons are affected by riluzole, which allows using such channel blockers to diminish the activity of a specific population of respiratory pacemaker neurons, without affecting others (Peña et al. 2004).

5. Role of pacemaker neurons in respiratory rhythm generation is state dependent

Although both riluzole and FFA may have several unspecific effects, mainly when used at high concentrations (Peña & Tapia 2000; Del Negro et al. 2005; Wang et al., 2006), both drugs have been used to test the role of specific pacemaker neurons on the activity of the preBötC. The evidence has shown that riluzole, at the concentration that blocks most of type I pacemaker neurons, affects but does not abolishes the generation of fictive eupnea (Del Negro et al. 2002; Peña et al. 2004). Certainly riluzole abolishes generation of fictive sighs (Peña et al. 2004; Table 1). A similar effect was observed when FFA was applied, at the concentration that blocks most of type II pacemaker neurons (elimination of sighs but maintenance of fictive eupnea generation, Peña et al. 2004, Table 1). However when both drugs are applied, no rhythm activity is recorded in the PreBötC (Peña et al. 2004; Del Negro et al. 2005). Even though a report showed that rhythmic activity can be restored upon application of substance P (Del Negro et al. 2005), we failed to consistently reproduce this finding (Tryba et al. 2006; Ben-Mabrouk & Tryba, 2008). In fact, we have been able to reproduce all our findings *in vivo*, where we found that neither riluzole nor FFA were able to block eupnea by themselves but abolished respiration when applied simultaneously (Peña & Aguileta, 2007). Furthermore we found that substance P was not able to recorver eupnea generation *in vivo* (Peña & Aguileta, 2007). Taken together, the evidence suggests that eupnea produced by the PreBötC *in vitro* can be maintained if one population of pacemaker neurons is blocked either with riluzole or with FFA, but when most type I and type II pacemaker neurons are blocked with both drugs, the PreBötC is not longer able to produce any physiologically meaningful rhythmic activity (Peña et al. 2004; Tryba et al. 2006).

Another seems to be the scenery during gasping generation. As previously mentioned, the PreBötC undergoes a reconfiguration process during hypoxia to generate gasping (Lieske et al. 2000; Peña, 2009). Three major changes occur during hypoxic conditions in this network: The first involves a generalized reduction of inhibitory synaptic transmission (Richter et al., 1991; Lieske et al. 2000), the second involves the shutdown of most of the non-pacemaker neurons (Ballanyi et al., 1994; Thoby-Brisson & Ramirez 2000), and the third involves a differential effect of hypoxia on pacemaker neurons. Type II (or Cd^{2+}-sensitive) pacemaker neurons cease to produce rhythmic bursting activity in hypoxic conditions, whereas a major subset of type I (or Cd^{2+}-insensitive) pacemaker neurons maintain their bursting activity in hypoxia (Thoby-Brisson & Ramirez 2000; Peña et al. 2004; Tryba et al. 2006; Table 1). This evidence suggests that type I (or Cd^{2+}-insensitive) pacemaker neurons may play a major role in the generation of gasping in hypoxia (Thoby-Brisson & Ramirez 2000; Peña et al. 2004;

Tryba et al. 2006). Consistent with this idea we showed that riluzole, but not FFA, specifically blocks gasping generation both *in vitro* (Peña et al. 2004) and *in vivo* (Peña & Aguileta, 2007). Our conclusion that riluzole-sensitive pacemaker activity is necessary for gasping generation, but not eupnea, has been corroborated in the *in situ* preparation as well as *in vivo* by other authors (Paton et al. 2006; St. John et al., 2006). This leads to some important conclusions: First, type I (or Cd^{2+}-insensitive) pacemaker neurons cannot be considered as the principal drivers of the more complex respiratory network operating during normoxia, but they become the sole drivers of gasping. Second, hypoxia renders the respiratory network more vulnerable to the blockade of a single ionic mechanism: namely, the persistent Na^{+} current (Peña & Ramirez 2002; Tryba et al. 2006). Gasping is an important autoresuscitation mechanism that seems to fail in victims of sudden infant death syndrome (SIDS, Poets et al., 1999; Sridhar et al., 2003). Consistent with a change in configuration of the respiratory network, SIDS victims breathe normally during normoxia, but do not gasp effectively when exposed to hypoxic conditions (Poets et al., 1999; Sridhar et al. 2003).

6. Respiratory pacemaker neurons as targets of neuromodulation

Respiratory function, as most of brain functions are regulated by neuromodulatory systems, which change the functionality of the respiratory rhythm generator and more specifically the activity of respiratory pacemaker neurons (Peña et al. 2002; 2004; Ramirez et al., 2004; Doi & Ramirez, 2008; 2010). It has been shown that pacemaker neurons are differentially regulated by several neuromodulators, including serotonin (5-HT) (Peña et al. 2002; Peña & Ramirez, 2004; Viemari & Ramirez, 2006; Tryba et al., 2008). As reported for motoneurons in the spinal cord (Harvey et al., 2006a, b), activity of the persistent sodium current, in the preBötC, is regulated by tonic activation of 5-HT_{2A} receptors (Peña & Ramirez 2002). We reported that type I (or Cd^{2+}-insensitive) pacemaker neurons require endogenous activation of 5-HT_{2A} receptors to maintain bursting activity; whereas type II (or Cd^{2+}-sensitive) pacemaker neurons do not (Peña & Ramirez 2002; Tryba et al. 2006, Table 1). Interestingly, pharmacological blockade of 5-HT_{2A} receptors resemble the actions of riluzole (Peña & Ramirez 2002; Peña et al. 2004; Tryba et al. 2006). Namely, bath application of $5HT_{2A}$ antagonists specifically inhibits type I (or Cd^{2+}-insensitive) pacemaker neurons, eliminates sigh activity and affects eupneic activity without producing apnea (Peña & Ramirez 2002; Tryba et al. 2006). As reported for riluzole, $5HT_{2A}$ antagonists abolished gasping generation in hypoxia and produce apnea in normoxia when they were applied in conjunction with FFA (Tryba et al. 2006). Data suggest that endogenous $5HT_{2A}$ receptor activation is essential for type I pacemaker activity and gasping generation *in vitro* (Peña & Ramirez 2002; Tryba et al. 2006). This finding may have important implications for understanding the failure of autoresuscitation in SIDS since serotonergic abnormalities have been reported in the brainstem of SIDS victims (Ozawa & Takashima 2002; Sridhar et al. 2003; Weese-Mayer et al., 2003; Weese-Mayer et al, 2003; Kinney et al., 2003).

Other neuromodulator that differentially affects pacemaker activity in the PreBötC is substance P (Peña & Ramirez 2004; Ben-Mabrouk & Tryba, 2008). We have shown that substance P produce a generalized PreBötC excitation by activating a TTX-insensitive sodium current, possibly a TRP channel (Crowder et al., 2007; Mironov, 2008; Ben-Mabrouk & Tryba, 2008), in all recorded respiratory neurons. In particular we observed that whereas substance P increased burst frequency of type I (or Cd^{2+}-insensitive) pacemaker neurons, it potently enhanced bursting activity in type II (or Cd^{2+}-sensitive) pacemakers (Peña &

Ramirez 2004), which seems to contribute to the increase in the regularity of the rhythm induced by this neuromodulator (Ben-Mabrouk & Tryba, 2008). A similar effect is observed with noradrenaline. Viemari & Ramirez (2006) have shown that noradrenaline depolarizes most respiratory neurons and increases burst frequency of type I (or Cd^{2+}-insensitive) pacemaker neurons but, as reported for SP, noradrenaline potently enhances bursting activity in type II (or Cd^{2+}-sensitive) pacemaker activity (Viemari & Ramirez 2006). This differential modulation of pacemaker properties might be important to differentially modulate shape and stability of respiratory activity (Peña & Ramirez 2002; 2004; Viemari & Ramirez 2006; Doi & Ramirez, 2008; 2010).

In conclusion we can affirm that the journey to understand the basic mechanisms involved in respiratory rhythm generation is at the beginning. This challenge is complicated by the fact that pacemaker neurons in the PreBötC constitute a highly heterogeneous population regarding its intrinsic properties, sensitivity to oxygen concentration and response to neuromodulators. All these factors must be taken into account if we really want to understand this circuit. It is important never to forget that such diversity is there and that might contribute to respiratory rhythm generation in a state-dependent manner.

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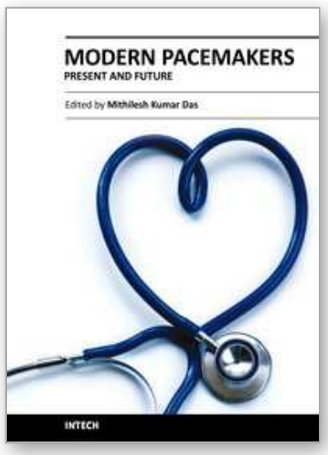
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Modern Pacemakers - Present and Future

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The book focuses upon clinical as well as engineering aspects of modern cardiac pacemakers. Modern pacemaker functions, implant techniques, various complications related to implant and complications during follow-up are covered. The issue of interaction between magnetic resonance imaging and pacemakers are well discussed. Chapters are also included discussing the role of pacemakers in congenital and acquired conduction disease. Apart from pacing for bradycardia, the role of pacemakers in cardiac resynchronization therapy has been an important aspect of management of advanced heart failure. The book provides an excellent overview of implantation techniques as well as benefits and limitations of cardiac resynchronization therapy. Pacemaker follow-up with remote monitoring is getting more and more acceptance in clinical practice; therefore, chapters related to various aspects of remote monitoring are also incorporated in the book. The current aspect of cardiac pacemaker physiology and role of cardiac ion channels, as well as the present and future of biopacemakers are included to glimpse into the future management of conductions system diseases. We have also included chapters regarding gut pacemakers as well as pacemaker mechanisms of neural networks. Therefore, the book covers the entire spectrum of modern pacemaker therapy including implant techniques, device related complications, interactions, limitations, and benefits (including the role of pacing role in heart failure), as well as future prospects of cardiac pacing.

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