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Review

The locus coeruleus and central chemosensitivity☆

Luciane H. Gargaglioni[a], Lynn K. Hartzler[b], Robert W. Putnam[c,*]

[a] Department of Animal Morphology and Physiology, FCAVJ-UNESP-São Paulo State University, Jaboticabal, Brazil
[b] Department of Biological Sciences, Wright State University, Dayton, OH 45435, USA
[c] Department of Neuroscience, Cell Biology and Physiology, Wright State University, Dayton, OH 45435, USA

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ABSTRACT

The locus coeruleus (LC) lies in the dorsal pons and supplies noradrenergic (NA) input to many regions of the brain, including respiratory control areas. The LC may provide tonic input for basal respiratory drive and is involved in central chemosensitivity since focal acidosis of the region stimulates ventilation and ablation reduces CO_2-induced increased ventilation. The output of LC is modulated by both serotonergic and glutamatergic inputs. A large percentage of LC neurons are intrinsically activated by hypercapnia. This percentage and the magnitude of their response are highest in young neonates and decrease dramatically after postnatal day P10. The cellular bases for intrinsic chemosensitivity of LC neurons are comprised of multiple factors, primary among them being reduced extracellular and intracellular pH, which inhibit inwardly rectifying and voltage-gated K^+ channels, and activate L-type Ca^{2+} channels. Activation of K_{Ca} channels in LC neurons may limit their ultimate response to hypercapnia. Finally, the LC mediates central chemosensitivity and contains pH-sensitive neurons in amphibians, suggesting that the LC has a long-standing phylogenetic role in respiratory control.

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1. Introduction

Locus coeruleus (LC) is a well-delineated cluster of noradrenergic neurons located bilaterally adjacent to the fourth ventricle in the pontine region of the brainstem (Dahlström and Fuxe, 1964). It is estimated that ~50% of all the noradrenergic projections in the central nervous system originate in the LC which are directed toward the forebrain, cerebellum, brainstem and spinal cord (Aston-Jones et al., 1995; Berridge and Waterhouse, 2003). The LC exhibits arousal-state-dependent activity and it is considered a major wakefulness promoting nucleus with activation of the LC resulting in an increase in EEG and signs of alertness (Samuels and Szabadi, 2008).

The LC is implicated in the control of many homeostatic functions including maintenance of attention, motivation, arousal states (Svensson and Thorén, 1979; Bhaskaran and Freed, 1988), sleep (Aston-Jones and Bloom, 1981), circadian regulation of arousal and performance (Aston-Jones et al., 2001), cognitive behaviors (for review see Sara, 2009), fever response (Almeida et al., 2004), control of breathing (Oyamada et al., 1998; Fabris et al., 1999; Hilaire et al., 2004; Putnam et al., 2004; Viemari et al., 2004, Biancardi et al., 2008; de Souza Moreno et al., 2010), and cardiovascular function (Sved and Felsten, 1987). This nucleus is involved in some pathophysiological states as well, such as panic disorder (Charney et al., 1990; Kaplan, 1992; Sullivan et al., 1999; Bailey et al., 2003; Griez and Schruers, 2003) and Rett syndrome (RTT) (Taneja et al., 2009).

Regarding the regulation of breathing, LC neurons have been shown to be involved in the central respiratory network (Coates et al., 1993; Oyamada et al., 1998; Biancardi et al., 2008). Further, CO_2/H^+ sensitive neurons have been identified in the LC (Elam et al., 1981; Pineda and Aghajanian, 1997; Filosa et al., 2002). In fact, LC neurons have been extensively studied with respect to the bases for and mechanisms of chemosensitive signaling (Putnam et al., 2004).

In this review, we will discuss the evidence for involvement of LC in basal respiratory drive as well as central chemosensitivity. We will further consider studies of the basis for cellular CO_2/H^+ sensitivity in chemosensitive LC neurons. Finally, we will examine evidence that shows LC neurons play a role in the control of breathing in amphibians as well as in mammals.

2. LC neurons and basal respiratory drive

In mammals there are some studies demonstrating that LC neurons display a respiratory-related activity, i.e., they have direct access to information about the timing of the respiratory output from the medullary respiratory centers (Oyamada et al., 1998, 1999; Andrzejewski et al., 2001). Electrical and chemical stimulation applied to the LC attenuates the inspiratory inhibition caused

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* Corresponding author at: Department of Neuroscience, Cell Biology and Physiology, Wright State University Boonshoft School of Medicine, 3640 Colonel Glenn Highway, Dayton, OH 45435, USA. Tel.: +1 937 775 2288; fax: +1 937 775 3391.
E-mail address: robert.putnam@wright.edu (R.W. Putnam).

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by electrical stimulation at the Bötzinger Complex, suggesting that the LC also plays a role in the modulation of the inspiratory inhibition of Bötzinger Complex stimulation (Wang et al., 2004). LC neurons also exert a tonic inhibitory effect on IX respiratory activity in neonatal rat brainstem-spinal cord preparations via alpha2 adrenergic receptor indicating that LC regulates upper-airway expiratory activity as well (Yamanishi et al., 2008).

The Phox2a gene is responsible for differentiation of catecholaminergic neurons in restricted areas such as LC (Viemari et al., 2004). The inactivation of *Phox2a* leads to the agenesis of the LC proper, but leaves intact all the other noradrenergic centers: the locus subcoeruleus and groups A7, A5, A2, and A1 (Morin et al., 1997; Pattyn et al., 2000). Complete *Phox2a* inactivation produces depression of the central respiratory generator and elimination of LC and sensory afferent neurons (Wrobel et al., 2007). Elimination of the LC in *Phox2a*$^{-/-}$ mutants is linked to a severe decrease in the breathing frequency (Viemari et al., 2004). LC contributes to the adaptation of breathing to physiological needs and according to some studies it provides a tonic excitatory drive that contributes to a normal breathing rate in rats (Guyenet et al., 1993; Jodkowski et al., 1997; Oyamada et al., 1998; Dawid-Milner et al., 2001; Li and Nattie, 2006) and mice (Shirasawa et al., 2000; Hilaire et al., 2004). In this context, Hilaire et al. (2004) demonstrated that LC noradrenergic neurons provide a tonic excitatory stimulus that maintains breathing frequency and are necessary for the development of a normal respiratory rhythm. Recently, Li and Nattie (2006) showed that substantial lesions of brainstem catecholaminergic neurons (including LC) slow breathing frequency during air breathing and that this effect is present in both wakefulness and in NREM sleep. Thus, taken together these data suggest that LC noradrenergic neurons provide a tonic drive to breathe. However, Biancardi et al. (2008) demonstrated that selective lesion of the LC in adult rats using 6-OHDA (a toxin that selectively eliminates catecholaminergic neurons) did not change basal ventilation and breathing frequency (Fig. 1A), suggesting that noradrenergic neurons located in the LC play no role in respiratory control under resting conditions in adults. Further, injection of a potent toxin conjugate, SP-SAP, in the LC of adult rats for killing neurons expressing the neurokinin-1 (NK-1) receptor did not alter adult breathing under basal conditions (Fig. 1B, de Carvalho et al., 2010). In agreement with this notion, LC unilateral cooling in neonatal sheep did not affect breathing in normoxic normocarbic conditions (Moore et al., 1996). The differences between these results and Li and Nattie's study may be due to the fact the elimination of noradrenergic neurons also results in the loss of neurons not located in the LC, since DBH-SAP was injected via the 4th ventricle promoting elimination of other catecholaminergic groups such as A5, A7, C1 and C2. Another possible explanation could be that most of the previous cited studies were performed using anesthetized rats (Guyenet et al., 1993; Jodkowski et al., 1997; Dawid-Milner et al., 2001) or neonatal preparations (Oyamada et al., 1998; Shirasawa et al., 2000; Hilaire et al., 2004) whereas we used unanesthetized and adult animals. Whatever the explanation, in all of our lesion or microinjection studies using animals with manipulations specifically performed in the LC, no difference in basal ventilation has been observed (Biancardi et al., 2008, 2010; de Souza Moreno et al., 2010; de Carvalho et al., 2010).

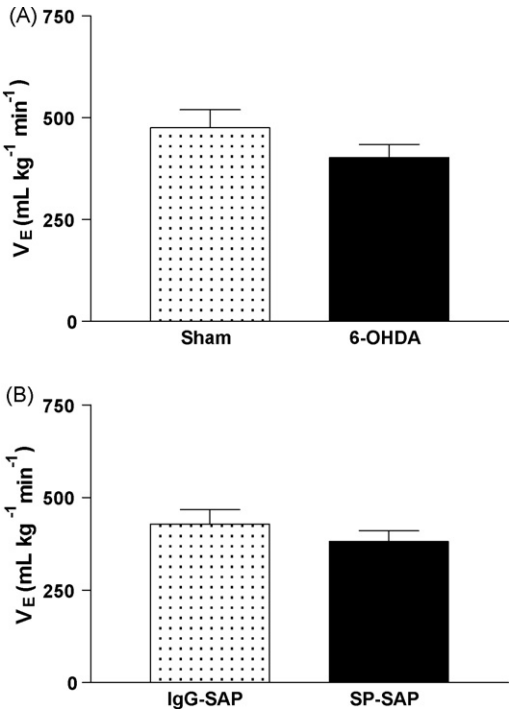

Fig. 1. (A) Minute ventilation (V_E) of the sham ($n = 8$) and 6-OHDA rats ($n = 10$) groups during normocapnia (adapted with permission from Biancardi et al., 2008). (B) Minute ventilation (V_E) of the IgG-SAP rats (control, $n = 9$) and SP-SAP ($n = 8$) groups during normocapnia (adapted with permission from de Carvalho et al., 2010). Values are means ± SEM. There is no difference between groups in both A and B.

3. LC and central chemosensitivity

3.1. Studies in intact animals

3.1.1. Lesion and stimulation studies

Some studies have demonstrated that the c-fos technique can be used to identify neurons involved in the responses elicited by hypercapnia (Haxhiu et al., 1996; Teppema et al., 1997; Berquin et al., 2000). Although neuronal function cannot be inferred from Fos expression, these studies brought new insight into the anatomical distribution of putative intrinsically chemosensitive neurons within chemoreflex pathways (Berquin et al., 2000). In mammals, studies under *in vivo* conditions showed that CO_2 stimulation increases the expression of the c-Fos gene in LC neurons (Haxhiu et al., 1996; Teppema et al., 1997). In addition, extracellular recordings from LC neurons in both neonatal and adult rats showed that they respond to systemic hypercapnia with an increase in spike frequency under *in vivo* conditions (Elam et al., 1981). Elam et al. (1981) demonstrated a dose-dependent increase in firing frequency of LC neurons in response to hypercapnia (3–20% CO_2) under *in vivo* conditions, such that the response at ~7% CO_2 would correspond to a ~25% increase in firing frequency. Additionally, using a brain slice preparation, Stunden et al. (2001) reported a ~44% increase in firing frequency of LC neurons when solution CO_2 was increased from 5 to 10% and Filosa et al. (2002) saw a 93% increase in LC firing rate when solution CO_2 was increased from 5 to 15% CO_2. Thus, the firing response of LC neurons to hypercapnia appears to be dose dependent both in *in vivo* and *in vitro* preparations, although this response also appears to saturate at high levels (between 10 and 20%) of CO_2 (Pineda and Aghajanian, 1997; Ritucci et al., 2005).

One of the first pieces of evidence that demonstrated that LC neurons may function directly as respiratory CO_2/pH chemosensors was reported by Coates et al. (1993). In this study, the authors injected acetazolamide, which produces a small and focal acidosis, into various brainstem sites (Coates et al., 1993). Focal acidification of LC noradrenergic neurons promotes a large increase in phrenic nerve discharge (37%) in cats. The LC neurons are of particular interest in CO_2 challenge since >80% of these neurons are found to be chemosensitive, responding to hypercapnia with an increased firing rate (Pineda and Aghajanian, 1997; Oyamada et al., 1998; Filosa

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