Review

Chemosensory pathways in the brainstem controlling cardiorespiratory activity

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Cardiorespiratory activity is controlled by a network of neurons located within the lower brainstem. The basic rhythm of breathing is generated by neuronal circuits within the medullary pre-Bötzinger complex, modulated by pontine and other inputs from cell groups within the medulla oblongata and then transmitted to bulbospinal pre-motor neurons that relay the respiratory pattern to cranial and spinal motor neurons controlling respiratory muscles. Cardiovascular sympathetic and vagal activities have characteristic discharges that are patterned by respiratory activity. This patterning ensures ventilation–perfusion matching for optimal respiratory gas exchange within the lungs. Peripheral arterial chemoreceptors and central respiratory chemoreceptors are crucial for the maintenance of cardiorespiratory homeostasis. Inputs from these receptors ensure adaptive changes in the respiratory and cardiovascular motor outputs in various environmental and physiological conditions. Many of the connections in the reflex pathway that mediates the peripheral arterial chemoreceptor input have been established. The nucleus tractus solitarii, the ventral respiratory network, pre-sympathetic circuitry and vagal pre-ganglionic neurons at the level of the medulla oblongata are integral components, although supramedullary structures also play a role in patterning autonomic outflows according to behavioural requirements. These medullary structures mediate cardiorespiratory reflexes that are initiated by the carotid and aortic bodies in response to acute changes in PO₂, PCO₂ and pH in the arterial blood. The level of arterial PCO₂ is the primary factor in determining respiratory drive and although there is a significant role of the arterial chemoreceptors, the principal sensor is located either at or in close proximity to the ventral surface of the medulla. The cellular and molecular mechanisms of central chemosensitivity as well as the neural basis for the integration of central and peripheral chemosensory inputs within the medulla remain challenging issues, but ones that have some emerging answers.

Keywords: chemosensitivity; hypercapnia; hypoxia; medulla oblongata; sympathetic; vagus

1. INTRODUCTION

The cardiorespiratory system has evolved to serve its main function of delivering sufficient amounts of oxygen to and removing excess carbon dioxide (CO₂) from all tissues of the body (Taylor et al. 1999). Water-breathing animals have to exert efforts to extract enough oxygen from the water, while CO₂ can simply diffuse out of the body. In contrast, in air-breathing animals, systemic hypoxia is rarely a major problem but removing CO₂ is a main task since production varies greatly from tissue to tissue and excretion is dependent on vascular flow through the organs. There is significant experimental evidence indicating that the mammalian central nervous circuitry that generates respiratory activity is silent in the absence of CO₂ and requires CO₂ to operate (see Phillipson et al. 1981).

The cardiorespiratory neuronal circuitry has to be fully operational before birth and must generate adequate motor output to the respiratory muscles, heart and different vascular beds to ensure survival and adaptation of the organism in variable environmental and physiological conditions. It continues to develop after birth, but elements of foetal and neonatal functions are retained as ‘safety factors’ that can be used in pathophysiological circumstances (for discussion see Richter & Spyer 2001). Respiratory and cardiovascular rhythms are regulated synergistically to ensure adequate ventilation–perfusion matching within the lungs to maintain optimal respiratory gas exchange. Respiratory sinus arrhythmia—the increase in heart rate during inspiration owing to a rhythmic partial withdrawal of the inhibitory vagal tone—represents a classical example of this precise cardiorespiratory coupling. Anatomically, both cardiac vagal pre-ganglionic and pre-sympathetic neuronal circuitries are located in the ventrolateral regions of the medulla oblongata, either within or in close proximity to the respiratory network (figure 1). The evidence of central cardiorespiratory integration can be seen even at the level of individual brainstem neurons (Gilbey et al. 1984; Haselton & Guyenet 1989). For example, cardiac vagal pre-ganglionic neurons of the nucleus

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ambiguously receive powerful inhibitory inputs during inspiration as well as excitatory inputs during post-inspiration (figure 2); these rhythmic changes in their activity partly underlie respiratory sinus arrhythmia.

When the organism is challenged by environmental or physiological demands, cardiorespiratory homeostasis is restored and maintained by appropriate changes that occur in both systems. Activation of ‘respiratory afferents’, such as peripheral chemoreceptors of the carotid bodies, has a profound effect on the activity of the cardiovascular system. Similarly, activation of ‘cardiovascular afferents’ modifies central respiratory drive (e.g. increases in arterial blood pressure reduce respiratory activity following activation of the arterial baroreceptors).

In this short review, we discuss how cardiorespiratory activities are generated, and how these activities are maintained and controlled by the inputs from both peripheral and central chemoreceptors.

2. GENERATION OF THE RESPIRATORY AND CARDIOVASCULAR ACTIVITIES

(a) Respiratory circuitry

Neurophysiological data indicate that the central nervous system (CNS) respiratory neuronal circuitry oscillates in a three-phase respiratory pattern (Richter & Spyer 2001). These three phases are defined as inspiration, post-inspiration (passive expiration) and expiration (active expiration). From a motor control perspective, these phases represent successive activation of different respiratory muscles.

The neuronal circuits responsible for the generation and shaping of the three-phase respiratory pattern, as well as transmitting this pattern to the motoneurons controlling respiratory and resistance muscles, are located in the lower brainstem. This circuitry is located bilaterally, particularly in the dorsal respiratory group and ventral respiratory column (VRC) of the medulla oblongata as well as in the dorsolateral pons (figure 1) (Bianchi et al. 1995; Richter & Spyer 2001; Feldman et al. 2003; Feldman & Del Negro 2006; Smith et al. 2007). The VRC is essential and sufficient to generate the respiratory rhythm and can be divided into several functional compartments, including those from the rostral to the caudal: overlapping retrorubral Bötzinger complex, pre-Bötzinger complex (preBötC) and rostral and caudal ventral respiratory groups (figure 1). Lesioning of the preBötC has identified it as a principal kernel, or ‘neuromodulator of respiratory rhythm generation, containing neuronal circuits that produce basic inspiratory activity (Feldman et al. 2003; Feldman & Del Negro 2006). The rhythm generated by an intact brainstem remains in conditions where the individual key ion channels for pacemaker activity are blocked, suggesting that basic inspiratory activity is generated by neuronal networks exhibiting oscillatory behaviour through chemical and electrical synaptic interactions (Paton et al. 2006; Smith et al. 2007).

Recent evidence suggests that RTN/pFRG may also contribute to the generation of the respiratory rhythm—it produces an expiratory rhythm according to Feldman & Del Negro (2006), but pre-inspiratory activity on the basis of observations of Onimaru & Homma (2003). Therefore, the functional role of this more rostral oscillator is still a subject of debate. The other functional compartments of the VRC and pontine respiratory groups are involved in shaping the basic rhythm (produced by preBötC), generating the respiratory pattern and relaying this pattern to cranial and spinal respiratory motor neurons (Smith et al. 2007). Neuronal interactions within the dorsolateral pontine parabrachial and Kölliker–Fuse nuclei (pontine respiratory group, referred as ‘pneumotaxic centre’ in the older literature) provide input to the VRC and play a role in reflex regulation and shaping of the respiratory activity patterns (Smith et al. 2007).

(b) Sympathetic circuitry

Regional vascular resistance and heart rate are controlled by sympathetic vasomotor and cardiac neural activity, which is produced by the sympathetic preganglionic neurons in the spinal cord. Excitatory drive from supraspinal regions within the brainstem and the hypothalamus determines the activity of spinal preganglionic neurones (Spyer 1994; Guyenet et al. 1996; Dampney et al. 2003). These regions include the rostral ventrolateral medulla (RVLM, figure 1), rostral ventromedial and midline medulla, the A5 cell group of the pons and the paraventricular hypothalamic nucleus (Cechetto & Saper 1990; Spyer 1994; Guyenet et al. 1996; Dampney et al. 2003; Madden & Sved 2003). The neuronal circuits of the RVLM appear to be the most important in generating sympathetic vasomotor tone. In anaesthetized experimental animals, acute bilateral inactivation of RVLM circuitry leads to a marked fall in arterial pressure with sympathetic activity falling to levels observed after transection of the spinal cord or during ganglionic blockade (Ross et al. 1984; Horiuichi & Dampney 1998; Dampney et al. 2003). Sympathoexcitatory RVLM neurones, referred to here as ‘pre-sympathetic’ neurones, provide monosynaptic projections to the spinal sympathetic pre-ganglionic neurones, and their discharge is very similar to that of the latter (Spyer 1994; Sun 1996; Dampney et al. 2000). This RVLM pre-sympathetic circuitry is embedded within the VRC respiratory network (figure 1). Not surprisingly, rhythmic respiratory modulation of sympathetic activity is usually present and can be recorded from the majority of RVLM pre-sympathetic neurones (Haselton & Guyenet 1989), spinal sympathetic pre-ganglionic neurones (Gilbey et al. 1986) and sympathetic nerves (Adrian et al. 1932; Habler et al. 1994; Gilbey 2007; Simms et al. 2009).

(c) Vagal circuitry controlling the heart

The vagus nerve is responsible for the heart’s major chronotropic regulation. Cardiac vagal pre-ganglionic motoneurones are found in two medullary locations—in the dorsal vagal motor nucleus and within and near the nucleus ambiguus of the ventrolateral medulla oblongata (figure 1) (Spyer 1994; Jones 2001). The latter population appears to be of major importance as rhythmic respiratory-related changes in their discharge underlie respiratory sinus arrhythmia. Detailed
analysis of the firing pattern of cardiac vagal motoneurons revealed that they fire during post-inspiration, with a variable discharge in expiration, but are inhibited during inspiration (figure 2) (McAllen & Spyer 1978; Gilbey et al. 1984; Spyer 2002). Inspiratory inhibition of cardiac vagal motoneurons ensures that any stimulus that enhances inspiration actively increases heart rate (by vagal withdrawal), while inputs, peripheral or central, that suppress ventilation or prolong expiration lower heart rate via cardiac vagal activation. Populations of cardiac vagal motoneurons are located within and/or adjacent to VRC respiratory network as well as RVLM pre-sympathetic circuitry (figure 1). In fact, their discharge is similar to a class of medullary respiratory neurons—the post-inhibitory neurons—that are an integral component of the respiratory pattern-generating network. This synaptic coupling ensures that any feed-forward modification of the respiratory activity can induce an immediate adjustment of cardiac output.

3. PERIPHERAL CHEMOSENSORY INPUTS
Activity of brainstem cardiorespiratory circuitry is controlled by inputs originating from higher centres of the brain as well as from various peripheral afferents, including cardiovascular and respiratory chemo- and mechano-sensors, proprioceptors in muscles, tendons and joints, skin thermoreceptors and others. Chemosensory inputs are probably of primary importance, as the respiratory circuitry, at least in mammals, does not appear to be active in the absence of CO₂.

Hypoxia fails to stimulate breathing in experimental animals, in which the peripheral chemoreceptors are denervated. This indicates that they are the primary functional respiratory oxygen-sensitive organs (Heymans & Neil 1958; Daly 1997). Peripheral chemoreceptors are localised within the carotid bodies of all mammalian species and to a varying degree in the aortic arch (i.e. present in man and cat, but not in rabbit, rat or mouse; Daly 1997). Carotid chemoreceptors are also sensitive to changes in PCO₂ and pH in arterial blood. However, their contribution to the overall ventilatory CO₂ sensitivity has been
somehow undeservedly neglected, largely owing to the well-known fact that strong ventilatory responses to CO₂ are usually preserved in animals with denervated peripheral chemoreceptors (see, Heeringa et al. 1979). Recent evidence suggests that the carotid chemoreceptors contribute about one-third of the overall response to CO₂ challenge and play an even more significant role in controlling arterial PCO₂ during eupneic breathing (Forster et al. 2008).

In adult mammals, the specialized neurosecretory glomus cells of the carotid body are the primary peripheral oxygen, CO₂ and pH respiratory chemosensors. While the nature of O₂-sensitive mechanism(s) is still a subject of debate (Kemp 2006; Kumar 2007), it appears that CO₂ is sensed via a proxy of pH changes that are detected by the acid-sensitive K⁺ channels of the tandem P-domain potassium channel family expressed by the glomus cells (Trapp et al. 2008). When stimulated, glomus cells release excitatory mediator(s) such as ATP and acetylcholine to activate afferent fibres of the carotid sinus nerve (Rong et al. 2003; Nurse 2005). Chemosensory information is then relayed to the brain via the glossopharyngeal (from the carotid bodies) and vagus (from the aortic bodies) nerves and is processed by neuronal circuitry in the dorsal medullary nucleus of the solitary tract (NTS; see Jordan & Spyer 1986, for a detailed review).

4. INTEGRATION WITHIN THE NUCLEUS OF THE SOLITARY TRACT

The majority of cardiovascular and respiratory afferent information is transmitted to the NTS via the vagus and glossopharyngeal nerves and subsequently processed and integrated by NTS neuronal circuits (figure 2). For the purpose of this review, we shall focus primarily on the organization of the arterial chemoreceptor reflex inputs.

The NTS is located in the dorsomedial medulla and is divided into several distinct subnuclei. In the cat, chemoreceptor afferent fibres appear to terminate preferentially in the commissural NTS at the level of, and behind, the obex with a significant input into the ventrolateral subnucleus (Donoghue et al. 1984). Neurons in these regions have been shown to receive both a monosynaptic excitatory input on sinus nerve stimulation and are excited by natural peripheral chemoreceptor stimulation (Spyer 1990; Mifflin 1992; Paton et al. 2001). There is an ordered distribution of the sites of termination of these afferents, but the subnuclei themselves are not clearly organized in functional domains, although some specialization has been inferred from the pattern of innervation of the NTS from the vagus and glossopharyngeal nerves and their branches (Loewy 1990). The wide distribution of the dendrites of many NTS neurons (including those activated by peripheral chemoreceptors; Paton et al. 2001) extends beyond a single subnucleus, and so the localization of perikarya may yield little specific information about the potential functional role of any subnuclei. However, it is clear that the medial, dorsomedial and commissural subnuclei are particularly strongly innervated by chemoreceptor afferents (cat, Jordan & Spyer 1986; Mifflin 1992, 1993; rat, Paton et al. 2001). One of the two main groups of medullary respiratory neurons is located in the ventrolateral subnucleus of the NTS, a region that does appear to receive a significant innervation by chemoreceptor afferents. A limited number of ‘chemoreceptor’ second-order neurons have been identified physiologically and labelled intracellularly. These were all located either within or close to the commissural subnucleus (Paton et al. 2001).

Detailed electrophysiological studies indicated that chemoreceptor and baroreceptor afferents are synaptically linked to different populations of NTS neurons, although there is evidence of convergence onto something of the order of 40 per cent of NTS neurons investigated (Mifflin 1992, 1993; Paton 1998; Silva-Carvalho et al. 1998). It is likely that the neurons that are excited by both chemoreceptor and baroreceptor inputs exert a synaptic influence on cardiac vagal activity (Paton et al. 2001). However, there is a tendency for a convergence of chemosensitive inputs from various end organs within the NTS and equivalent convergence of mechano-receptor afferent inputs onto a separate group of NTS neurons (Paton 1998; Silva-Carvalho et al. 1998). This implies that the nucleus is not coded by the nature of the input, but rather by the efferent connections of the nucleus. This concept has been recently implied for the arterial baroreceptor reflex (Simms et al. 2007) and may be demonstrated by further consideration of the chemoreceptor control of inspiratory activity.

Chemoreceptor reflex inputs enhance central inspiratory drive (figure 2), and there are numerous data illustrating the action of this excitatory input on medullary inspiratory neurons. While these afferents exert an excitatory effect on second-order NTS neurons, the inspiratory neurons of the NTS are not directly excited and indeed appear to receive a disynaptic inhibitory input (Lipski et al. 1977). They are, however, excited indirectly by the evoked increases in inspiratory activity, which is a result of actions of the input within the ventrolateral medulla over a polysynaptic pathway (see Spyer 2009 for discussion). The RTN/pFRG receives a powerful excitatory input from the NTS on peripheral chemoreceptor stimulation and provides an excitatory input to the rhythm generating circuitry in the preBoëTć (figure 2) (Guyenet 2008).

The effects of peripheral chemoreceptor activation on respiratory outputs are well documented, and there is evidence in the rat that expiratory activity may also be enhanced by such stimuli (Eldridge 1978). Considerable advances have been made by studying the synaptic mechanisms underlying brief peripheral chemoreceptor stimulation (and other stimuli) at different times in the respiratory cycle. This is illustrated by considering the effects of peripheral chemoreceptor as well as baroreceptor inputs on the activities of cardiac vagal pre-ganglionic neurons. Both evoke a bradycardia by activation of these neurons, only if the stimuli are delivered during the post-inspiratory or expiratory phases of the respiratory cycle (see Spyer 1994; Daly 1997, for detailed

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reviews). An equivalent stimulus during inspiration is ineffective. As indicated earlier, there is evidence of a limited degree of convergence of these two inputs within the NTS. While the baroreceptor input is known to inhibit inspiratory activity, peripheral chemoreceptor inputs powerfully stimulate inspiration as described earlier, so that their excitatory input to cardiac vagal neurons is simultaneously gated by hyperpolarization of these neurons during inspiration (Gilbey et al. 1984). Hence, baroreceptor activation typically evokes a vagal bradycardia, but peripheral chemoreceptor inputs have the effect of inducing a tachycardia through vagal inhibition and a concurrent sympathetic activation unless respiration is inhibited (by superior laryngeal nerve stimulation or lung inflation as examples; Daly 1997).

5. CENTRAL CHEMOSENSITIVITY

CO₂ provides the major tonic drive to breathe. Even a small increase in arterial PCO₂ evokes robust increases in respiratory activity (in humans 1 mm Hg increase in arterial PCO₂ may lead to a 2 litre min⁻¹ increase in lung ventilation). As mentioned earlier, the contribution of the peripheral chemoreceptors is significant; however, CO₂-evoked respiratory response is mediated predominantly by the actions of CO₂ at the chemoreceptors located within the lower brainstem.

The primary central CO₂ chemosensors are believed to be located near the ventral surface of the medulla oblongata (Loeschcke 1982; Guyenet 2008), although other regions of the brainstem such as the preBoëC, the medullary raphe nuclei, the NTS and the locus coeruleus have been proposed to contain functional chemosensitive structures (Nattie 1999; Putnam et al. 2004). This idea of a ‘distributed’ central chemosensitivity is supported by the evidence that in conscious states, lesions of glutamatergic neurons in the RTN/pFRG, serotonergic neurons of the medullary raphe, locus ceruleus noradrenergic neurons or NK-1 receptor expressing cells in the ventral medulla reduce (albeit to a different degree) the ventilatory responses to CO₂ (Nattie & Li 2009). The existence of functional respiratory chemosensors in several brainstem sites has value in ensuring redundancy and stability within the system. All these brainstem chemosensitive structures have been shown to be located either within or are interconnected with medullary

Figure 3. CO₂ induces ATP release from the classical chemosensitive areas of the ventral surface of the medulla oblongata. (a) Schematic drawing of the ventral aspect of the rat medulla oblongata showing sites that exhibited release of ATP in response to CO₂ (filled circles). No ATP release was detected in locations depicted by open circles. Miniature (125 or 250 μm in diameter) disc ATP biosensors were used to map the sites of CO₂-induced ATP production. (b) Representative raw data illustrating CO₂/H⁺-induced release of ATP from the ventral medullary surface in vitro. CO₂-induced acidification of the incubation media from pH 7.4 to 7.0 evoked ATP release from the most ventral slice of the medulla oblongata, which contained surface chemosensitive areas. (c) Summary data (mean ± s.e.) of peak CO₂/H⁺-induced release of ATP from horizontal slices of the medulla. ATP release occurs predominantly within 400 μm of the ventral surface. Black bar, n = 19; grey bar, n = 19; white bar, n = 8. The ‘net ATP’ trace represents the difference in signal between ATP and null sensors. PNG, integrated phrenic nerve activity (arbitrary units). 7n, relative position of the facial nucleus; XII, hypoglossal nerve roots. Adapted from Gourine et al. (2005).
respiratory circuitry. Although all these structures have been found to contain neurons that are excited by rising levels of PCO2/[H+] in vitro, whether these ‘chemoresponsive’ neurons are functional respiratory chemosensors is not known in most cases. RTN/pFRG glutamatergic neurons fulfil some of the key criteria—they are highly sensitive to changes in pH in vivo and in vitro, have excitatory projections to the respiratory network and their activation triggers increases in respiratory activity (Guyenet 2008). However, it is not yet known whether acute experimental silencing of RTN chemosensitive neurons would result in a severe deficiency in central respiratory chemosensitivity.

If the concept of distributed chemosensitivity is correct, then the existence of several putative chemosensitive structures scattered throughout the lower brainstem would complicate studies of the underlying cellular mechanisms—as these could be quite distinct in chemosensory neurons at different locations (again for the purpose of ensuring the necessary level of redundancy within the system). Regarding the ventral surface of the medulla, we found recently that CO2 chemosensitivity is not known in most cases. RTN/pFRG chemosensors are functionally respiratory circuitry. Although all these structures have been found to contain neurons that are excited by rising levels of PCO2/[H+] in vitro, whether these ‘chemoresponsive’ neurons are functional respiratory chemosensors is not known in most cases. RTN/pFRG glutamatergic neurons fulfil some of the key criteria—they are highly sensitive to changes in pH in vivo and in vitro, have excitatory projections to the respiratory network and their activation triggers increases in respiratory activity (Guyenet 2008). However, it is not yet known whether acute experimental silencing of RTN chemosensitive neurons would result in a severe deficiency in central respiratory chemosensitivity.

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