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Review

The effects of baroreceptor stimulation on central respiratory drive: A review☆

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ABSTRACT

The neural systems that control breathing and the circulation are located in adjacent longitudinal columns in the ventrolateral medulla. They have much in common, in terms of their structure, function, and evolution. In the most part, both systems are affected by the same sensory modalities and receive input from many of the same higher centres. Indeed, such is the parallel organisation of the two systems that stimuli that alter the behaviour of the one almost invariably influence the other.

It is well-known that rhythmic respiratory inputs exert powerful effects on parasympathetic and sympathetic outputs. However, the question of whether cardiovascular inputs exert any influence on respiratory rhythmogenesis is more contentious. Here, we review the effects of baroreceptor activation, classically considered a 'cardiovascular' stimulus, on respiratory drive. We show that, although subtle, baroreceptor inputs evoke reproducible prolongation of expiration in a range of preparations. The consequences of this reflex are discussed with regard to cardiorespiratory coordination.

1. Introduction

Although the influences that the respiratory system exert on cardiovascular output have been known of for over 100 years, evidence that the cardiovascular system can influence the respiratory system has largely been ignored. This review will examine the evidence for cardiovascular modulation of respiratory activity.

Medullary networks that coordinate the respiratory and cardiovascular systems are highly conserved across the vertebrate subphylum and have much in common with each other (Taylor et al., 1999). Located in the rostral medulla immediately caudal to the facial nucleus, the neurons that control these two crucial homeostatic functions lie in adjacent overlapping longitudinal columns (reviewed by Alheid and McCrimmon, 2008; Guyenet, 2006; Taylor et al., 1999). In phylogenetically ancient species such as cyclostome fish (e.g. lamprey), the sympathetic ganglia closely resemble clusters of chromaffin cells, and receive no obvious input from spinal sympathetic preganglionic neurons (see Gibbins, 1994; Taylor et al., 2009); in these species central cardiovascular control seems predominantly orchestrated by parasympathetic cranial outputs, perhaps involving communication between vagus and sympathetic ganglia. Similarly, respiratory motor output is entirely subserved by cranial motoneurons, which control the propulsion of water through the gills. Even at this relatively low level of evolutionary sophistication, autonomic reflexes such as the chemoreceptor (see Randall, 1982) and baroreceptor (Lutz and Wyman, 1932) reflexes are well-developed, and there is strong evidence of cardiorespiratory integration (Taylor et al., 2006, 2009). As fish evolved, the level of organisation of the sympathetic nervous system rapidly increased. Elasmobranch fish (e.g. sharks) have recognisable chains of sympathetic ganglia under neurogenic control (Opdyke et al., 1983), presumably via spinal preganglionic neurons (Gibbins, 1994). As dedicated lung-breathing emerged, the respiratory system also became supplemented by bulbospinal pathways: the relative importance of the muscles innervated by cranial motoneurons becomes overshadowed by the predominant role that trunk musculature, and later the diaphragm, took in powering ventilation.

Information pertaining to the internal (e.g. pH, blood oxygen) or external (e.g. skin temperature, noxious inputs) environments, and input from higher centres (e.g. arousal, sleep) all have strong coordinating influences on both respiratory and cardiovascular control systems. Indeed, it is difficult to think of a naturalistic stimulus that selectively influences either. The sensory modalities that particularly influence baseline respiratory outflow in the mammal are pH (and hence CO_2) and, to a lesser degree, blood oxygen. It is interesting to note that oxygen-sensing is predominant over pH in determining respiratory drive in lower (aquatic) vertebrates. This is likely related to the high variability of oxygen concentration in water compared to air (Burleson, 2009). Both modalities potently activate sympathetic output. Blockade of central respiratory rhythm does not alter the maximal sympathetic responses to hypoxia (Koshiya and Guyenet, 1996), so it seems likely that sympathetic premotor neurons receive direct chemosen-

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sory input, in addition to excitatory and inhibitory drive secondary to enhanced respiratory activity. Blood oxygen and pressure sensation are subserved by vagal afferents in the gills in lower vertebrates (Burleson, 2009), and their evolutionary derivatives in mammals – the chemoreceptors and baroreceptors of the carotid sinus and aortic arch (Burleson, 2009; Sundin et al., 2007).

In addition to similarities in structure and evolution, both the respiratory and cardiovascular systems share some strikingly similar functional attributes. For example, both exhibit a basal level of activity that is intrinsically rhythmic. The phasic nature of respiration is one of its more obvious features, but the bursting of nerves related to cardiovascular function is less straightforward and merits further consideration. The irregular bursting of sympathetic nerves results from multiple overlaid rhythms of different frequencies that are out of phase from one other. It is thought that the different frequency components of sympathetic nerve activity reflect inputs from a variety of different sources; one of the most obvious components is a strong respiratory modulation. This feature of cardiovascular control was first proposed in the 1860s, but respiratory-modulated sympathetic nerve activity was not recorded until 60 years later (Adrian et al., 1932; reviewed by Habler et al., 1994). The degree of respiratory modulation is dependent on the strength of respiratory drive (Haselton and Guyenet, 1989), the tissue innervated by the nerve (Habler et al., 1999), and the species of animal and anaesthetic used. Repeated exposure to hypoxia can enhance the strength of respiratory-sympathetic coupling (Dick et al., 2007), suggested as one of the mechanisms that may underlie the pathophysiology of obstructive sleep apnoea. The same mechanism is also suggested to underlie the hypertensive phenotype of the spontaneously hypertensive rat (Simms et al., 2009).

Overlaid upon relatively slow rhythms related to central respiratory drive, many sympathetic outputs oscillate at the same frequency as heart rate. The degree of pulse-modulation of nerve activity depends on the blood pressure of the animal and the barosensitivity of the nerve. When isolated from respiratory and baroreceptor-mediated inputs, sympathetic nerve activity continues to occur in bursts. This continued bursting reflects some degree of central cardiovascular coordination; it seems likely that the bursting effect is caused by the synchronous recruitment of postganglionic nerve fibres, which in humans generally fire one action potential per burst, rather than a high level of activity in a restricted number of individual fibres (Macefield and Elam, 2003; Macefield et al., 2002). The frequencies at which bursting occurs in 'free-running' sympathetic nerve activity is species- and tissue-dependent. In rat, vasomotor nerves (Allen et al., 1993; Kocsis and Gyimesi-Pelczer, 2004) and barosensitive sympathetic premotor neurons (Tseng et al., 2009; McMullan, unpublished observation) show a broad band of activity up to around 10 Hz, whereas temperature-related sympathetic nerve activity (e.g. tail and brown fat) exhibit a narrow peak in power between 0.4 and 1.2 Hz (Gilbey, 2007; Huang and Gilbey, 2005; Morrison, 1999). Similar properties of sympathetic nerves have been reported in other species (Barman et al., 1992; Barman and Kenney, 2007; Kocsis and Gyimesi-Pelczer, 2004).

2. Evidence of barorespiratory effects

In contrast to the many studies that have demonstrated a clear effect of central respiratory drive on sympathetic nerve activity, the effect of baroreceptor or central sympathetic inputs on respiratory activity is still highly controversial. Although the effects of changes in carotid sinus pressure on respiration were first described in the 1930s (Heymans and Bouckaert, 1930 (see Fig. 1); Schmidt, 1932), many investigators still consider the baroreflex a purely cardiovascular stimulus. This is perhaps based on the lack of any

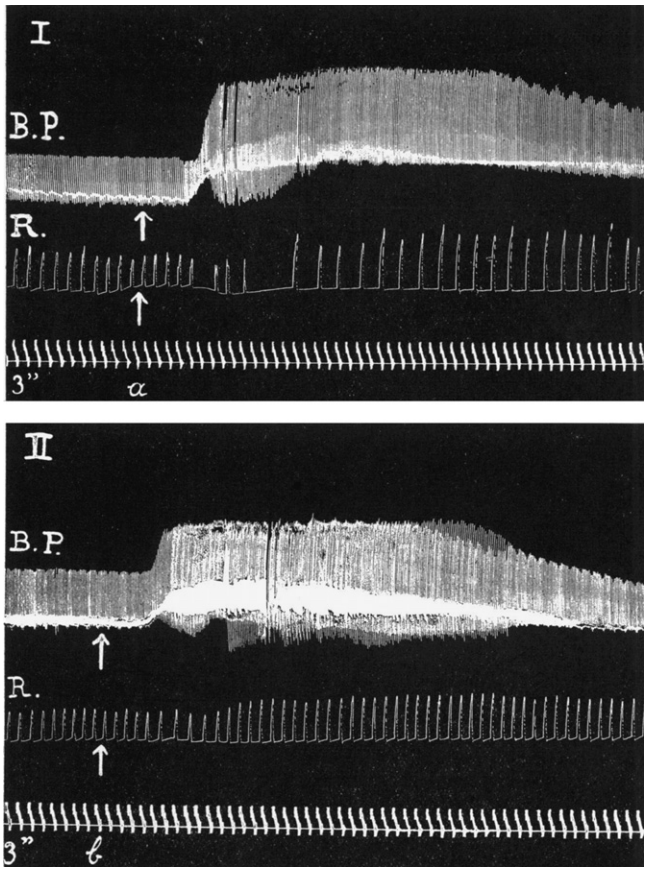

Fig. 1. Increases in blood pressure evoked by intravenous adrenaline suppress ventilation. Blood pressure (BP) and respiratory (R) responses to intravenous injection of 0.2 mg adrenaline (arrow) in a chloralose-anaesthetised dog before (Plate I) and after (Plate II) section of the carotid sinus nerves. Reproduced with permission from Heymans and Bouckaert (1930).

obvious physiological advantage to barorespiratory interactions in the species most commonly studied, or perhaps the segregation by academe of these overlapping fields into 'cardiovascular' and 'respiratory' disciplines. However, such thinking represents a teleological error, and ignores a wide range of experimental evidence to the contrary.

Many experimental approaches have demonstrated a considerable sensitivity of the central respiratory generator to baroreceptor inputs. Suppression of respiration by prolongation of expiratory duration (T_E) is common in the overwhelming majority of studies, albeit with differences in the magnitude of effects and the extent to which inspiratory duration (T_I) and depth of ventilation are affected. Baroreceptor activation prolongs T_I and generally has no effect on phrenic nerve amplitude in the rat (Baekey et al., 2008; Jung et al., 1995; McMullan et al., 2009), but reduces T_I (Maass-Moreno and Katona, 1989) and inspiratory depth in the cat (Biscoe and Sampson, 1970; Grunstein et al., 1975; Maass-Moreno and Katona, 1989). A different pattern again is found in the dog; extension of T_I, sometimes accompanied by an *increase* in inspiratory depth (Brunner et al., 1982; Heistad et al., 1975; Heymans and Bouckaert, 1930 (see Fig. 1); Maass-Moreno and Katona, 1989).

2.1. Naturalistic baroreceptor stimulation

It is well known that acute reductions in blood pressure, for example during haemorrhage, rapidly increase ventilation, which has been suggested to be baroreceptor mediated (Clement et al., 1981; Heistad et al., 1975; Miserocchi and Quinn, 1980). How-