Autonomic Neuroscience: Basic and Clinical xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Cardiac vagal preganglionic neurones: An update

Alexander V. Gourine *, Asif Machhada, Stefan Trapp, K. Michael Spyer

Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, Physiology and Pharmacology, University College London, London WC1E 6BT, UK

ARTICLE INFO

Article history:
Received 6 May 2016
Accepted 17 June 2016
Available online xxxx

Keywords:
Atrioventricular conductance
Contractility
Excitability
Left ventricle
Parasympathetic
Vagal preganglionic neurones

ABSTRACT

The autonomic nervous system controls the heart by dynamic recruitment and withdrawal of cardiac parasympathetic and sympathetic activities. These activities are generated by groups of sympathoexcitatory and vagal preganglionic neurones residing in a close proximity to each other within well-defined structures of the brainstem. This short essay provides a general overview and an update on the latest developments in our understanding of the central nervous origins and functional significance of cardiac vagal tone. Significant experimental evidence suggests that distinct groups of cardiac vagal preganglionic neurones with different patterns of activity control nodal tissue (controlling the heart rate and atrioventricular conductance) and the ventricular myocardium (modulating its contractility and excitability).

Contents

1. Brainstem nuclei harbouring cardiac vagal preganglionic neurones

Neuronal tracing studies conducted in rats (Izzo et al., 1993; Nosaka et al., 1979, 1982; Stuesse, 1982; Cheng and Powley, 2000; Sampaio et al., 2014), cats (Sugimoto et al., 1979; Ciriello and Calaresu, 1980, 1982; Geis and Wurster, 1980b; Kalia and Mesulam, 1980; Bennett et al., 1981; Geis et al., 1981; Miura and Okada, 1981; Jones et al., 1995; Ford et al., 1990), dogs (Bennett et al., 1981; Hopkins and Armour, 1982, 1984; Plecha et al., 1988) and pigs (Hopkins et al., 1984, 1997) identified cardiac vagal preganglionic neurones (cVPNs) primarily residing within the brainstem nucleus ambiguus (NA) and the dorsal vagal motor nucleus (DVMN) (Fig. 1). Studies on the ontogenesis of the brainstem vagal system in metamorphosing amphibians undergoing anatomical and physiological changes during the transition from water- to air breathing indicate that the DVMN is the primary vagal nucleus. During metamorphosis, rapidly developing cardiorespiratory interactions initiate ventral migration of a subset of DVMN neurones giving rise to a compact formation of the NA which acquires respiratory modulation of activity from the neighbouring respiratory network (Burggren, 1995; Burggren and Infantino, 1994; Smatresk, 1994). The intermediate zone between DVMN and NA is a likely remnant of the migrating population post nuclear division (Jones, 2001; Taylor et al., 1999). The parasympathetic nervous system develops first in the evolution of vertebrates with the sympathetic division appearing relatively late (cardiac sympathetic innervation is not present in elasmobranch fish) (Jones, 2001; Taylor et al., 1999). Therefore, the DVMN is probably the most (evolutionary) ancient CNS structure which harbours autonomic neurones in vertebrates.

* Corresponding author at: Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London WC1E 6BT, UK.
E-mail address: a.gourine@ucl.ac.uk (A.V. Gourine).

http://dx.doi.org/10.1016/j.autneu.2016.06.003
1566-0702/

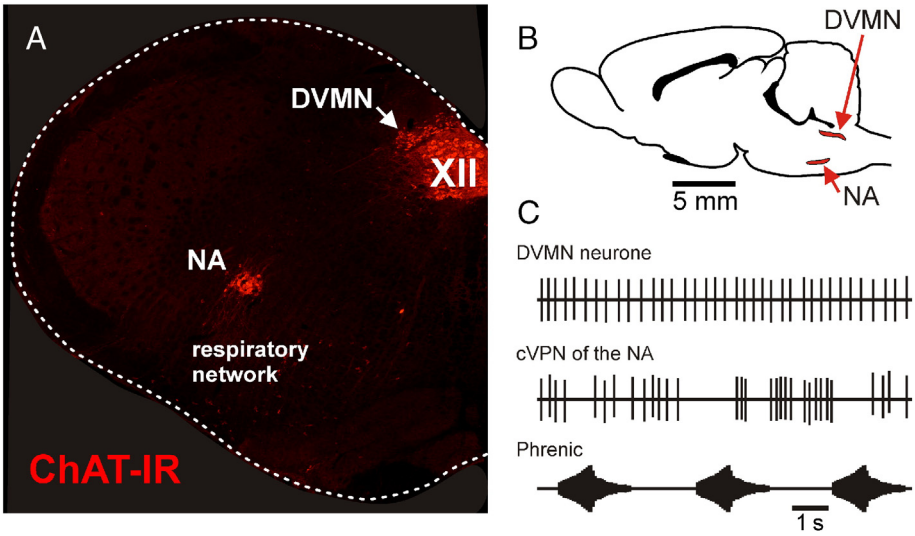

Fig. 1. Vagal preganglionic neurones. *A*, photomicrograph of the coronal section of the rat brainstem illustrating a representative example of the brainstem distribution of choline acetyltransferase (ChAT)-positive vagal preganglionic neurones of the dorsal motor nucleus of the vagus nerve (DVMN) and the nucleus ambiguus (NA). Neurones of the NA are located in a close proximity to the brainstem respiratory rhythm and pattern generating circuits. XII, hypoglossal motor nucleus (also ChAT-positive); *B*, schematic drawing of the rat brain in a sagittal projection illustrating CNS location and rostro-caudal extent of the DVMN and NA; *C*, schematic illustration drawn from representative electrophysiological recordings of the discharge patterns exhibited by the DVMN (Trapp S, unpublished) and NA (Gilbey et al., 1984) neurones plotted in relation to the activity of the phrenic nerve.

2. Vagal innervation of the heart

Vagal efferent fibres are well-known to innervate the nodal tissue and the atria controlling the heart rate, atrioventricular conductance and the strength of atrial contraction (for a review, see (Coote, 2013). The very existence and the functional role of vagal innervation of the cardiac ventricles has been repeatedly questioned, despite clear anatomical evidence showing rich cholinergic innervation of epicardial and endocardial ventricular surfaces in human (Kent et al., 1974; Pauza et al., 2000), pig (Crick et al., 1999; Ulphani et al., 2010) and rat hearts (Zang et al., 2005; Mastitskaya et al., 2012). Evidence for significant parasympathetic innervation of the cardiac ventricles were also obtained in experimental studies conducted in cats and dogs where the release of acetylcholine within the ventricular myocardium was recorded during electrical stimulation of the vagus nerve (Eliakim et al., 1961; Akiyama et al., 1994; Akiyama and Yamazaki, 2001).

3. Cardiac vagal preganglionic neurones of the nucleus ambiguus

cVPNs of the NA have rhythmic, respiratory-related patterns of discharge (Fig. 1) with B fibre axons innervating the nodal tissue (McAllen and Spyer, 1976, McAllen and Spyer, 1978a; Ciriello and Calaresu, 1982). cVPNs have been visualized following retrograde transport of horseradish peroxidase or viral tracers from the cardiac vagal branches or the fat pads that surround the myocardium and contain the post-ganglionic neurones that directly innervate the heart. The morphology of cVPNs is unspectacular as they resemble other motoneurones. These cells have unindented nuclei and their cytoplasm is rich in organelles and in ultrastructural studies are seen to have many synaptic connections on their dendrites (Izzo et al., 1993). The richest afferent input to the NA comes from the nucleus tractus solitarius (NTS) although it also receives inputs from other areas of the brain. There are also indications in some species that there are cVPNs with C fibre axons in the NA (Jordan and Spyer, 1986).

Electrophysiological studies have shown that these VPNs that have an effect on heart rate are localized in the ventrolateral part of the nucleus although some may be distributed more widely (McAllen and Spyer, 1976, 1978b). These represent a subpopulation of the NA neurones that form the cardiac and pulmonary branches of the vagus. In their electrophysiological description of cVPNs, McAllen & Spyer (McAllen and Spyer, 1976, 1978b) demonstrated that under anaesthesia, NA neurones are either silent or have a very low resting discharge rate. However, their discharge at rest, or when facilitated by application of glutamate, is rhythmic. Two major rhythms dominate: the first is correlated with the arterial pulse and is dependent on inputs from the arterial baroreceptors; the second is related to the central respiratory rhythm (Gilbey et al., 1984). The cardiac rhythm is driven by glutamatergic projections from the NTS and is abolished by glutamate receptor antagonists. Powerful baroreceptor modulation and respiratory-related activity distinguishes cVPNs of the NA from the cardiac projecting neurones of the DVMN which are unaffected by these inputs.

Activation of the arterial chemoreceptors triggers a powerful and complex effect on the NA neurones. The direct effect of chemoreceptor activation is to excite cVPNs if a brief stimulus is delivered during expiration. However, the same stimulus delivered during inspiration is ineffective. This resulted in a considerable controversy in regard of the underlying mechanism for the apparent respiratory gating of the chemoreceptor reflex (Daly, 1997). The answer lies in the second key rhythm displayed by the cVPNs of the NA. Whilst synaptic inputs from the arterial baroreceptors largely control the excitability of these neurones, their rhythmic pattern of respiratory-related discharge reflects powerful excitatory and inhibitory inputs from the neighbouring central respiratory oscillator. cVPNs receive an excitatory input during post-inspiration and a powerful inhibitory input during inspiration (Gilbey et al., 1984). These respiratory-related changes in cVPN excitability provide a plausible explanation of an apparent 'gating' of other excitatory and inhibitory inputs, including inputs from the peripheral chemoreceptors.

This respiratory patterning of cVPNs discharge and changing sensitivity to other afferent inputs it imposes is of a major physiological significance. It ensures that cardiac output is tightly linked to the respiratory minute volume (Spyer, 1994). Suppression of the respiratory activity as in the diving reflex removes the inspiratory inhibitory input to the cVPNs inducing cardiac slowing. The accompanying fall in the arterial PO_2 in the induced breath-holding will activate the arterial chemoreceptors which exert their excitatory effect on cVPNs producing further bradycardia. Conversely, high respiratory drive as in exercise leads to an enhanced inhibition of cVPNs and increases heart rate. Any enhancement of the post-inspiratory state, with meditation and yoga for example, will act to lower the heart rate by enhancing cVPNs

Please cite this article as: Gourine, A.V., et al., Cardiac vagal preganglionic neurones: An update, Auton. Neurosci. (2016), http://dx.doi.org/10.1016/j.autneu.2016.06.003