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Review

Characterization of the intrinsic cardiac nervous system

Emily Wake, Kieran Brack Dr *

Department of Cardiovascular Sciences, Cardiology Group, Glenfield Hospital, Groby Road, University of Leicester, LE3 9QP, United Kingdom
Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, United Kingdom

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ABSTRACT

Heart disease is the number one cause of mortality in the developed world and it is well recognised that neural mechanisms are important in pathology. As well as peripheral autonomic nerves, there is a rich intrinsic innervation of the heart that includes cardiac ganglia, collectively termed ganglionic plexuses (GP). Understanding the role that the intrinsic cardiac nervous system (ICNS) play in controlling cardiac function and how it interacts with information between central command centers and its integration with sensory information from the myocardium could prove crucial for prophylactic and corrective treatments of heart disease. This article in the timely and important special issue on central and peripheral nervous control of the heart in Autonomic Neuroscience; Basic and Clinical will focus on the anatomical and physiological characteristics that define the ICNS.

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* Corresponding author at: Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester LE3 9QP, United Kingdom.
E-mail address: keb18@le.ac.uk (K. Brack).

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The heart is supplied and controlled by centrally derived sympathetic and parasympathetic nerves. The classical augmenting influence of sympathetic inputs is accepted as dogma, but the inhibitory influence of the cervical vagus, in particular on ventricular function and electrophysiology is still passionately debated. Traditionally, autonomic control of the heart has focused on centrally derived extrinsic signals or the investigation of electrical stimulation of peripheral nerves. However, neurocardiac control is more complex owing to the existence of an extensive network of intrinsic cardiac neurons i.e. the intrinsic cardiac nervous system (ICNS) that has been collectively called the hearts '*little brain*' (Randall et al., 1996; Ardell, 2004). These neurons can be characterised broadly speaking by 1) their anatomical / topographical layout, 2) their chemical phenotype and 3) their functional influences on the heart. This review will characterise the ICNS in each of these components.

1. Anatomy of the intrinsic cardiac nervous system

Historically, methylene blue was used to visualize neurons from organs but it is often unstable following routine chemical fixation (Müller, 1990) so cannot reliably be used to characterize the ICNS of the heart. The most popular, cost effective, and reliable method used to identify nerves and their cell bodies was initially described by Karnovsky and Roots (1964) at various levels of the rat and guinea pig gastrointestinal tract, the rat ovary and guinea pig striated muscle i.e. the histochemical stain for acetylcholinesterase (AChE). This method allows a distinct and permanent signal that has permitted a more complete picture of the intrinsic cardiac nervous system to be developed from a wide range of mammalian species including mice, rat, guinea pig, rabbit, cat, dog, sheep, pig and humans.

AChE histology results in a dark brown stain and is considered a pan-neuronal marker so indiscriminately stains all cell bodies and nerve fibres. The ICNS comprises of collections of neuronal somata and connecting nerve fibres known as ganglionic plexuses (GPs). (See Fig. 1) Somata are typically between 15 and 30/20–45 μm (Rysevaite et al., 2011a; Leger et al., 1999) on the short and long axis respectively and occur as individual entities, gathered into ganglia containing anywhere between 2 and 1500 neurons, or grouped into 'clusters' with a number of smaller groups of cell bodies in close vicinity. The majority (≈90%) of somata reside on supra-ventricular tissues, lying flat on the epicardial surface but can also occur within fat pads outside the heart hilum. Ganglia are primarily found on the dorsal atrial surface, around the base of aorta / pulmonary artery, dorsal and ventral to the pulmonary veins and on the anterior ventricular surface (Table 1).

The number of cardiac ganglia is species dependent ranging from 19 in the mouse (Rysevaite et al., 2011a) to over 800 in humans (Pauza et al., 2000; Armour, 1997; Singh et al., 1996) (Table 2). In general, GPs in the hearts of smaller mammals such as mice and rats (Batulevicius et al., 2003; Rysevaite et al., 2011a) are comparatively similar to that of larger mammals including sheep (Saburkina et al., 2010) and pigs (Batulevicius et al., 2008). There is however a reduced density of innervation by cell bodies in smaller mammals compared to larger mammals, where cardiac neuronal innervation is more numerous and more liberally distributed across the hilum of the heart.

Ganglia from small mammals appear to be discretely located, but become progressively scattered and profusely distributed in larger mammals. Fields of ganglionated plexuses have been generalised into 5–7 regions (dependent on species), which importantly take into account the nervous supply and projections to different effector sites (Table 2). These regions are the right dorsal atrial (DRA), ventral right atrial (VRA), left dorsal (LD), ventral left atrial (VLA), middle dorsal (MD), right coronary (RC) and left coronary (LC) plexuses (Table 3). GPs in all of these regions have been demonstrated in the rabbit (Saburkina et al., 2014), dog (Yuan et al., 1994), sheep (Saburkina et al., 2010) and human (Pauza et al., 2000).

1.1. Extrinsic innervation into and cardiac innervation from ganglia

Evidence from the guinea pig (Batulevicius et al., 2005) and rabbit (Saburkina et al., 2014) suggests that ganglia are heterogeneously innervated by bilateral autonomic inputs but confirmation from neuronal tracing studies in experimental species is very much needed. In larger mammalian species such as sheep, pigs and dogs, extrinsic mediastinal nerves access the heart at multiple sites via arterial and venous routes. As is seen in many experimental mammalian species, extrinsic cardiac nerves access the heart arterially, around the roots of the pulmonary artery (PA) and aortic root (Ao) and at the venous portion of the heart hilum around the roots of the pulmonary veins (PVs) and superior vena cava (SVC) (Batulevicius et al., 2008; Saburkina et al., 2010; Pauza et al., 2002a,b, Richardson et al., 2003; Batulevicius et al., 2003).

Intrinsic cardiac nerves extend epicardially from GPs on the heart to innervate the atria, interatrial septum and the ventricles (Pauza et al., 2000; Saburkina et al., 2014). Two subplexus routes extend from the arterial region of the hilum between the pulmonary trunk (PT) and the aorta (Ao), to effector sites on the left and right ventricles: the left (LC) and right coronary (RC) subplexuses respectively. Another five subplexuses originate from the venous region on the heart hilum around the PVs. In general, 1) the dorsal right atrial subplexus originates from either the right caudal vein (RCV) or the superior vena cava branching out to supply the sinoatrial node (SAN) and the dorsal region of the right atrium. 2) The middle dorsal (MD) subplexus branching from amongst the pulmonary veins in the direction of the dorsal coronary groove with neuronal connections with 3) the left dorsal subplexus, terminating on dorsal left atrial and ventricular regions. Two ventral subplexuses also exist with the sparse nerves of 4) the ventral left atrial subplexus, beginning ventrally to the left PV and joining ganglia on the ventral left atrial region and finally, connecting the ventral right atrium to the ventro-medial region around the superior vena cava, 5) the right ventral subplexus. These defined routes noted in the rabbit are comparatively similar to those previously identified in several other mammalian species demonstrating a common trait for heterogeneous neurocardiac control by the ICNS. For a cross species illustration of the generalised GP layout and innervation route see Fig. 2.

1.2. Ventricular innervation

In contrast to the data regarding cardiac innervation of the atria, that of the ventricles still remains relatively unknown and more importantly widely underappreciated. Mammalian ventricles were historically believed to be devoid of ganglia and any innervation from the ICNS until Gagliardi et al. (1988) described ganglia present on human ventricular myocardium at locations ventral to the coronary groove and around the region of the conus arteriosus (CA). These findings have since been replicated in humans (Pauza et al., 2000), sheep (Saburkina et al., 2010), dog (Yuan et al., 1994), cat (Johnson et al., 2004) and rabbit (Pauziene et al., 2016; Saburkina et al., 2014). An illustration of ventricular ganglia in the rabbit is shown in Fig. 3. Unlike larger species where ventricular ganglia are clearly evident, smaller species appear to lack the presence of such ganglia. Ventricles are now known to be innervated by ganglia located adjacent to the aortic root and the root of the pulmonary trunk as well as at the cranial aspect of the ventral interventricular groove and a smaller ganglia at the region of the left atrioventricular sulcus (Armour, 1997; Pauza et al., 2000). In the rabbit, the pattern of innervation originates as described previously via the accessing mediastinal nerves entering arterially around the Ao and PT or venously around the roots of the PVs on the heart hilum. The numbers of ganglia present around the region of the CA varies dramatically between hearts, ranging from 11 to 220 (Pauziene et al., 2016).

In smaller animals, such as rats and mice, ventricular nerve supply originates entirely from the atria, with the ventral surface of the ventricles being principally supplied by the subplexus route originating from the right ventral atrial region (Batulevicius et al., 2003). This is in stark