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Structure, function and clinical relevance of the cardiac conduction system, including the atrioventricular ring and outflow tract tissues

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ABSTRACT

It is now over 100 years since the discovery of the cardiac conduction system, consisting of three main parts, the sinus node, the atrioventricular node and the His–Purkinje system. The system is vital for the initiation and co-ordination of the heartbeat. Over the last decade, immense strides have been made in our understanding of the cardiac conduction system and these recent developments are reviewed here. It has been shown that the system has a unique embryological origin, distinct from that of the working myocardium, and is more extensive than originally thought with additional structures: atrioventricular rings, a third node (so called retroaortic node) and pulmonary and aortic sleeves. It has been shown that the expression of ion channels, intracellular Ca^{2+}-handling proteins and gap junction channels in the system is specialised (different from that in the ordinary working myocardium), but appropriate to explain the functioning of the system, although there is continued debate concerning the ionic basis of pacemaking. We are beginning to understand the mechanisms (fibrosis and remodelling of ion channels and related proteins) responsible for dysfunction of the system (bradycardia, heart block and bundle branch block) associated with atrial fibrillation and heart failure and even athletic training. Equally, we are beginning to appreciate how naturally occurring mutations in ion channels cause congenital cardiac conduction system dysfunction. Finally, current therapies, the status of a new therapeutic strategy (use of a specific heart rate lowering drug) and a potential new therapeutic strategy (biopacemaking) are reviewed.

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1. Introduction

The cardiac conduction system consists of the sinus (or sinuatrial or sinoatrial) node, the atrioventricular (AV) conduction axis (including the AV node), its right and left bundle branches, and the terminal Purkinje network. All of these structures, made up of specialised cardiac myocytes, have unique anatomical, molecular and functional properties that permit them to work collectively as the electrical system of the heart. The system has been the subject of extensive studies since its elucidation in the first decade of the 20th century. Recent advances in technologies have aided our further understanding of this specialised system of the heart. In particular, other myocytes with comparable properties, such as the AV ring tissue and myocytes in the ventricular outflow tracts, especially the right ventricular outflow tract, have attracted notice because of their arrhythmogenic properties. A common feature of the different tissues of the cardiac conduction system is the ability to show pacemaking and Fig. 1 shows the perhaps surprising widespread distribution of tissues with pacemaking potentiality in the heart. Our aim in this review is to describe our current understanding of the expanded concept of the cardiac conduction system, in terms of anatomy, function and clinical relevance. So-called channelopathies related to the cardiac conduction system are also discussed.

2. Embryonic development

2.1. Cardiac conduction system in relation to working myocardium

The heart initially forms as a midline tube ventral to the foregut at the stage of embryonic folding. Its cells are derived from visceral mesoderm, with the cells forming a linear primary heart tube containing the primordium for little more than the left ventricle, or even less (Cai et al., 2003; Aanhaanen et al., 2009). Ongoing development depends on the addition of cells to the primary tube from the heart-forming areas at both the venous and arterial poles (Fig. 2A). At this early undifferentiated stage, the walls of the heart tube are made up of so-called 'primary myocardium' (Moorman & Christoffels, 2003). The myocytes of this myocardium have a phenotype that includes slow growth, slow contraction, slow conduction and the ability to depolarize spontaneously (Moorman & Christoffels, 2003). As the new material is added at the venous and arterial poles (Kelly & Buckingham, 2002), the tube itself undergoes looping. Subsequent to looping, the primordiums of the eventual atrial and ventricular chambers balloon from the cavity of the primary tube, with the right and left atrial appendages ballooning in parallel from the atrial component of the tube, and the apical ventricular components ballooning in series from the inlet and outlet parts of the ventricular loop (Fig. 2B). The myocytes making up these new parts together make up the chamber myocardium (Moorman & Christoffels, 2003). Chamber myocardium is distinct from primary myocardium in a number of ways, including the possession of gap junctions made up of connexin40 (Cx40) and connexin43 (Cx43), which permit rapid conduction, along with rapid rates of cell division. There is also formation of pectinate muscles and trabeculations in the newly forming chamber components of the atria and the ventricles, respectively. Already at this early stage, however, while it is still possible to distinguish the areas of primary and chamber myocardium, and while there is muscular continuity throughout the developing heart, it is possible to record a relatively normal electrocardiogram (ECG). The tracing incorporates a period of AV delay, even though at this stage it is not possible to recognise any of the components of the definitive cardiac conduction system. The areas of the tube made up of primary as opposed to chamber myocardium are also different in that blocks of cushion mesenchyme are formed within their lumens that will ultimately form the valves of the heart, and set the scene for separation of the systemic and pulmonary pathways of the circulation. It is also within these components of the primary tube that the remodelling takes place to allow correct alignment of the separating atrial and ventricular chambers and the systemic and pulmonary outflow tracts. Parts of this primary myocardium also retain their initial embryonic phenotype so as to form the cardiac nodes and AV conduction axis (Fig. 2C; Davis et al., 2001; Rentschler et al., 2001; Hoogaars et al., 2004), with some of the ventricular trabeculations being incorporated to form the rapidly conducting Purkinje network. These changes are achieved by so-called 'patterning', or regional expression of developmental gene programmes (Christoffels et al., 2004), with the other parts of the initial primary myocardium becoming transformed into chamber myocardium. Development of the cardiac conduction system is controlled by transcription factors and for an excellent review of this fast developing field see Christoffels et al. (2010).

2.2. Atrioventricular ring tissue

As described above, only a small part of the primary myocardium eventually develops into nodal tissues, retaining the characteristics of automaticity, and failing to be converted into working myocardium. It is now well established that the expression of the transcriptional inhibitor Tbx3 is responsible for this fundamental process (Hoogaars et al., 2007). Ectopic expression of Tbx3 in the atrial chambers has been shown to result in the formation of functional ectopic nodes exhibiting pacemaker activity. The expression of Tbx3, however, marks not only the normal cardiac conduction system, but also the so-called AV ring tissues (Anderson et al., 1974a, 1974b; Yanni et al., 2009a). The areas of the primary heart tube such as the AV canal, the interventricular ring and the ventricular outflow tract can be considered as supportive of this concept, albeit that the "rings" do not appear as new entities, but rather are part of the initial primary heart tube, becoming evident as "rings" only subsequent to the formation of the chamber myocardium. In particular, part of the embryonic AV canal persists in the definitive heart within the atrial vestibules as the specialised AV rings that surround the orifices of the tricuspid and mitral valves, with the ring tissues originating from the dorsal aspect of the AV node, and crossing over the bundle of His to join so as to form a ventral retroaortic node (Yanni et al., 2009a).

2.3. Right ventricular outflow tract

The initial common outflow tract is exclusively composed of the primary myocardium of the linear heart tube, and is entirely supported by the right ventricle. The distal portion of this common outflow tract is remodelled by further addition of cells from the visceral mesenchyme to form the intrapericardial arterial trunks. At this stage, the more proximal parts retain their muscular walls, with the pulmonary and aortic valves, along with their sinuses, developing within a muscular sleeve. The most proximal part of the common outflow tract will form the right ventricular outflow tract and the aortic vestibule, with the proximal cushions themselves fusing and muscularising to form the dorsal part of the infundibulum, this part also fusing with the crest of the muscular ventricular septum so as to commit the aorta to the left ventricle. As development progresses, the proximal right ventricular outflow tract largely differentiates into working right ventricular myocardium (Rana et al., 2007), with the more distal parts that initially surrounded the developing arterial valves disappearing by apoptosis (Barbosky et al, 2006). It has been suggested that not all myocytes in the right ventricular outflow tract differentiate into working ventricular myocytes and some myocytes retain their initial nodal-like phenotype (Yanni et al., 2009a; Boukens et al., 2009; Monfredi et al., 2010a, 2010b).

3. Cardiac conduction system: anatomy, function and clinical relevance

3.1. Sinus node

In health, the sinus node is the pacemaker of the mammalian heart. Even more than 100 years after its first description by Keith &