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Review

Characterization of the effects of Ryanodine, TTX, E-4031 and 4-AP on the sinoatrial and atrioventricular nodes

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Abstract

Aims: To characterize the effects of inhibition of Ryanodine receptor (RyR), TTX-sensitive neuronal Na^+ current (i_{Na}), "rapidly activating" delayed rectifier K^+ current (i_{Kr}) and ultrarapid delayed rectifier potassium current (I_{Kur}) on the pacemaker activity of the sinoatrial node (SAN) and the atrioventricular node (AVN) in the mouse.
Methods: The structure of mouse AVN was studied by histology and immunolabelling of Cx43 and hyperpolarization-activated, cyclic nucleotide-binding channels (HCN). The effects of Ryanodine, TTX, E-4031 and 4-AP on pacemaker activities recorded from mouse intact SAN and AVN preparations have been investigated.
Results: Immuno-histological characterization delineated the structure of the AVN showing the similar molecular phenotype of the SAN. The effects of these inhibitors on the cycle length (CL) of the spontaneous pacemaker activity of the SAN and the AVN were characterized. Inhibition of RyR by 0.2 and 2 μM Ryanodine prolonged CL by $42 \pm 12.3\%$ and $64 \pm 18.1\%$ in SAN preparations by $163 \pm 72.3\%$ and $241 \pm 91.2\%$ in AVN preparations. Inhibition of TTX-sensitive i_{Na} by 100 nM TTX prolonged CL by $22 \pm 6.0\%$ in SAN preparations and $53 \pm 13.6\%$ in the AVN preparations. Block of i_{Kr} by E-4031 prolonged CL by $68 \pm 12.5\%$ in SAN preparations and $28 \pm 3.4\%$ in AVN preparations. Inhibition of i_{Kur} by 50 μM 4-AP prolonged CL by $20 \pm 3.4\%$ in SAN preparations and $18 \pm 3.0\%$ in AVN preparations.
Conclusion: Mouse SAN and AVN showed distinct different response to the inhibition of RyR, TTX-sensitive I_{Na}, I_{Kr} and i_{Kur}, which reflects the variation in contribution of these currents to the pacemaker function of the cardiac nodes in the mouse. Our data provide valuable information for developing virtual tissue models of mouse SAN and AVN.

Keywords: Sinoatrial node; Atrioventricular node; Pacemaking; TTX-sensitive neuronal Na^+ current (i_{Na}); "Rapidly activating" delayed rectifier K^+ current (i_{Kr}); Ultrarapid delayed rectifier potassium current (I_{Kur})

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Contents

1. Introduction

There is an effort to build anatomically and biophysically detailed models of different regions of the heart. Such models require knowledge of anatomy, physiology, and molecular and cellular biology of the different regions.

In mammalian heart, each heartbeat is normally initiated from the sinoatrial node (SAN), the primary pacemaker of the heart. The SAN contains special "pacemaker" cells generating the electrical signals that control the pace and rhythm of the heart. The signals travel from the SAN to the AVN. From the AVN, the signals are conducted along pathways and spread into the ventricles, causing them to contract and pump blood into the lungs and throughout the body. The function of the AVN is normally to act as a conduction pathway between the atria and ventricles under physiological condition, but it can also act as a major subsidiary pacemaker, initiating heartbeat by generating the junctional rhythm in the circumstance of failure of the SAN.

Although all parts of cardiac conduction system have the capability of generating rhythmic heartbeat, i.e. the capacity of automaticity, such capacity varies regionally. Thus, the SAN has a highest automaticity; its discharge rate determines the heart rate that is normally within the physiological range (e.g. 60–120 beats/min in human). The automaticity of the AVN is lower than that of the SAN and it generates the junctional rhythm (sub-physiological range) having much slower rate than the sinus rhythm (e.g. <60 beats/min in human). The more down stream of the conduction system (i.e. Purkinje fibres) is, the lower automaticity has. The pacemaking mechanisms for cardiac conduction tissue, the SAN in particular, have been extensively investigated over the past two to three decades and have been largely defined (for reviews, see Irisawa et al., 1993; Boyett et al., 2000; Kleber and Rudy, 2004). The mechanism underlying the regional difference in automaticity within the conduction system, however, has been rarely explored. Recent studies suggest that the diversity in electrophysiology in different regions of the heart (e.g. SAN and AVN) is likely attributed to variable expression of ion channel gene products in different regions of the heart. For example, high-density real-time RT-PCR analysis suggested a specific pattern of ionic channel gene expression associated with pacemaker activity in the mouse heart (Marionneau et al., 2005). Further detailed characterization of the