

Adrenergic control mechanisms of heart rate - down to a T?

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Each heart beat originates from complex molecular processes which result in the generation of a spontaneous action potential that triggers an electrical cascade to the rest of the heart, converted into co-ordinated mechanical action to allow effective function as a pump. The sinoatrial nodal pacemakers cells (SANCs) at the right atrium contain ion channels and transporters which interact to mediate a diastolic depolarisation bringing the resting membrane potential above a threshold leading to excitation and firing of the pacemaker action potential. Many of these components reside on the cellular surface membrane of SANCs (through which flow their respective currents) including L-type Ca^{2+} channels (I_{CaL}), T-type Ca^{2+} channels (I_{CaT}), delayed rectifier K^+ channels (I_{K}), $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) (I_{NCX}) and the hyperpolarization-activated, funny channels (I_{f}). For a long time, these have been regarded as the primary electrogenic processes that generate the pacemaker beats and in the setting of this 'membrane' clock (M-clock), many would regard the funny current, I_{f} , to be the dominant current that determines the intrinsic beating rate. More recently, experimental data have emerged that support the role of *intracellular* processes which are involved with Ca^{2+} cycling at the sarcoplasmic reticulum (SR) that generate Ca^{2+} oscillations, with the introduction of the concept of an intracellular " Ca^{2+} clock". These oscillations come from rhythmic local Ca^{2+} release from the SR through ryanodine receptors (RyRs). There has been much debate as to the relative importance of the M- and Ca^{2+} -clocks in pacemaker function and which one dominates. A current view is that both membrane and intracellular mechanisms are coupled to each other and act dynamically and synergistically to effect normal pacemaker function (Lakatta et al. 2010). Like many aspects of normal bodily function, heart rate is under tight control from the 2 branches (sympathetic and parasympathetic) of the autonomic nervous system. Abnormal autonomic control is a hallmark of many disease conditions and thus a clear understanding of autonomic modulation mechanisms is important as these may present as therapeutic targets for the pathologic states. Sympathetic activity modulates changes via the actions on adrenergic receptors by catecholamines primarily released from nerve terminals as well as those circulating in the blood. The overall effect of adrenergic activation in the heart is one of cardiac stimulation with increased heart rate, conduction velocity, contractility and relaxation.

In a recent issue of The Journal of Physiology, Li et al.(2018) presented data from transgenic murine studies to explore the role of T-type Ca^{2+} channels(TTCCs) in heart rate modulation by adrenergic activation with isoproterenol(Iso). TTCCs are voltage-gated Ca^{2+} channels with very small conductance and rapid decay rates, hence termed 'transient'. They are activated at potentials around -70 mV, hence capable of participating in the diastolic depolarisation that generates pacemaker action potentials. Of the 3 TTCCs(Cav3.1, Cav3.2 and Cav3.3) that exist in mammals, Cav3.1 and Cav3.2 are the major channels in the heart and Cav3.1 has been shown to be the predominant TTCC in adult mouse SANCs. Li et al.(2018) showed that upregulation of the gene that encodes the α_1 subunit, α_{1G} , of Cav3.1 increased the sensitivity of the acceleration of heart rate and atrioventricular conduction by adrenergic stimulation whereas a reduced sensitivity was seen in α_{1G} knockout(KO) mice. Congruous results were shown in ECGs in *in vivo* and *ex vivo* (Langendorff-perfused hearts) experiments and also for spontaneous beating rates in isolated SANCs. Patch clamp experiments demonstrated the absence of I_{CaT} in α_{1G} KO SANCs whereas I_{CaT} was augmented in α_{1G} overexpression with evidence of upregulation with Iso in both wild type and α_{1G} overexpressed SANCs. I_{CaL} was shown to be reduced in α_{1G} overexpressed SANCs which was interpreted as compensatory changes with a resultant lack of a significantly increased spontaneous beating rates in α_{1G} overexpressed hearts and SANCs. Furthermore, low dose Iso increased heart rates in control mice and more so in α_{1G} overexpressed hearts but not in KO mice. These results support the notion that enhanced Cav3.1 activity plays a role in heart rate regulation by adrenergic stimulation and led the authors to propose that TTCCs may be potential treatment target for slowing heart rate.

There is a clinical need for better pharmacological strategies targeted at controlling heart rate. Drug therapies are often ineffective in conditions such as inappropriate sinus tachycardia(IST) and postural orthostatic tachycardia syndrome(POTS) which occur typically in young patients with structurally normal hearts. In heart failure where a heightened adrenergic state is present, and as such beta-blockers have become established effective treatment counterintuitive to initial caution regarding negative inotropic properties, separate targeted treatment to reduce heart rate with the I_f blocking drug, ivabradine, has also been shown to be of benefit. Targeting TTCCs seems appealing based on the above study especially if reduced adrenergic sensitivity of heart rate could be achieved without

causing significant baseline bradycardia. Drug development could pose challenges - not only considering potential dangers of ion channel modification drugs in abnormal hearts (Ng 2017) and proarrhythmic effects of seemingly pure drugs on other ion channels (Melgari et al. 2015). Mibefradil is a selective TTCC antagonist previously developed for the treatment of hypertension and angina but was withdrawn from the market worldwide due to serious interactions with many drugs related to off-target effects on their metabolism (Po and Zhang 1998). Adrenergic activation is often involved in conditions like IST and POTS. Moving beyond beta-blockers to specific targeted therapy requires detailed understanding of the relevant intricate mechanisms and more importantly, carefully conducted studies that verify the safety and efficacy of pharmacological agents which modulate them.

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