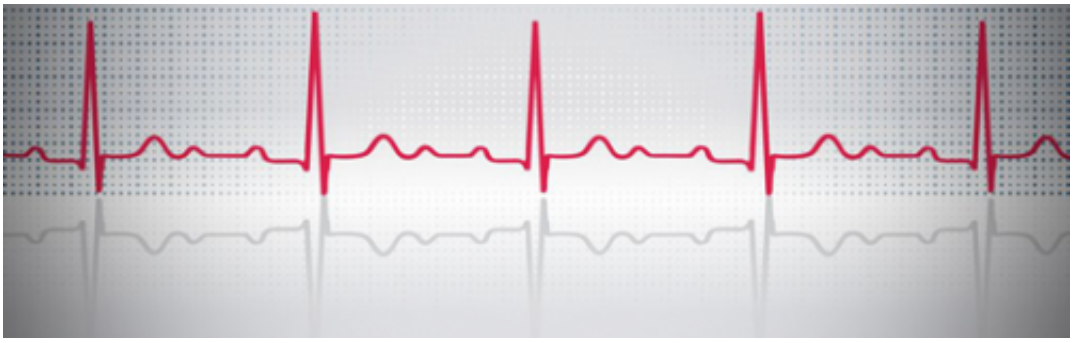
The heart's metronome

November 12 2013



Credit: sukok1 / Fotolia

A specific cell population is responsible for ensuring that our heartbeat remains regular. Researchers from Ludwig-Maximilians-Universitaet (LMU) in Munich have now elucidated the mode of action of one of the crucial components of the heart's intrinsic pacemaker.

The heart possesses a pacemaker of its very own. Specialized pacemaker cells in the so-called sinoatrial node in the left ventricle of the heart control its rate of contraction and relaxation by orchestrating a recurring sequence of electrical signals. Specific proteins known as HCN channels, which are located in the surface membranes of pacemaker cells, play a central role in the generation and transmission of these signals. These proteins function as pores for the passage of electrically charged atoms (ions) across the cell membrane. Because the pore diameter can be regulated, the channels can control the flow of ions across the membrane, and thus determine the difference in electrical potential

between the inner and outer surfaces of the cell. Cyclical changes in this parameter give rise to autonomously generated, rhythmic electrical impulses that dictate heartbeat and cardiac rhythmicity.

HCN channels are found primarily in the heart and in the brain, and come in four subtypes, HCN1-4. HCN4 is responsible for about 80% of the total ion current that passes through HCN channels in the sinoatrial node. The other 20% is carried by HCN1 and HCN2. "But while the functions of HCN2 and HCN4 in the sinoatrial node have been extensively studied, the impact of HCN1 on heart rate has so far remained unknown," says Professor Christian Wahl-Schott of the Department of Pharmacy at LMU, who has now closed this gap in our knowledge of the heart's intrinsic pacemaker.

Wahl-Schott and his team and also researchers from Professor Martin Biel's group, tackled the problem by using a mouse strain in which the HCN1 channels in the cells of the sino-atrial node are defective. With the aid of this new experimental model, they were able to demonstrate, for the first time, that HCN1 is involved not in generating the electrical impulse but also in its propagation within the node. Defects in HCN1 function compromise the normal operation of the pacemaker. This results in bradycardia – a pathological reduction in heart rate – and increases the incidence of arrhythmias. As a consequence, overall cardiac output is significantly reduced. "We were also able to confirm these effects in vivo by means of telemetric electrocardiography," Wahl-Schott adds.

Defects in cells of the sino-atrial node are associated with sudden cardiac arrest, and more than half of all implantations of artificial pacemakers worldwide are carried out on patients who suffer from such conditions. But the new findings regarding the role of HCN1 in the regulation of heart function are actually of clinical interest for two reasons. On the one hand, this channel subtype offers a promising target

for drugs designed to normalize heartbeat frequency. However, HCN1 is also found in nerve cells in the brain, where it likewise acts to control rates of neural firing. This explains why HCN1 blockers are under consideration for use in the treatment of epilepsy, chronic pain and depression. "In light of our results, the potential effects of HCN1 blockers on cardiac function should be carefully assessed before such agents are used in other contexts," Wahl-Schott warns.

More information: circ.ahajournals.org/content/e …
.113.003712.abstract

Provided by Ludwig Maximilian University of Munich