MedicalXpress

Researchers identify new target for common heart condition

January 8 2013

Researchers have found new evidence that metabolic stress can increase the onset of atrial arrhythmias, such as atrial fibrillation (AF), a common heart condition that causes an irregular and often abnormally fast heart rate. The findings may pave the way for the development of new therapies for the condition which can be expected to affect almost one in four of the UK population at some point in their lifetime.

The British Heart Foundation (BHF) study, led by University of Bristol scientists and published in *Circulation: Arrhythmia and Electrophysiology*, found that metabolic stress—a condition induced by insufficient oxygen supply to the heart (e.g. following blockage of a coronary artery)—caused marked changes in the electrical activity of the heart's atria (the upper chambers of the heart).

While it has been recognised for many years that metabolic stress causes ventricular arrhythmias—abnormal heart rhythms that originate in the two lower chambers of the heart (the ventricles) and which form the basis to heart attacks—it is the first time it has been demonstrated for arrhythmias in the atria.

The research team led by Dr Andrew James from the University's School of Physiology and Pharmacology together with Professor Saadeh Suleiman in the School of Clinical Sciences, examined the contribution of a particular kind of protein underlying the electrical activity of the atria during metabolic stress.

These proteins, known as KATP channels enable cells to respond to changes in metabolism. ATP (adenosine triphosphate) is a small molecule that represents the 'energy currency' for cell metabolism and when ATP levels inside cells fall, KATP channels are activated. For example, KATP channels in the pancreas are involved in the regulation of insulin secretion and drugs targeting these channels are used to treat type 2 diabetes mellitus.

Dr Andrew James, the study's lead author, said: "It is well-established that KATP channels in the ventricles of the heart can become activated following metabolic stress caused by blockage of a coronary artery. In principle, their activation could protect the heart muscle cells against metabolic stress-induced damage. On the other hand, the activation of ventricular KATP channels can contribute to disturbances in the electrical activity of the heart known as arrhythmias.

"Arrhythmias in the ventricles can be very dangerous, leading to ventricular fibrillation and death. Atrial arrhythmias, such as atrial fibrillation (AF), are not usually immediately fatal but they are very common and a major cause of stroke. Notably, KATP channels are also found in the atria but, in contrast to the ventricles, their role in atrial arrhythmias remains unknown."

The findings show that metabolic stress caused marked changes in the electrical activity of the atrium consistent with the activation of KATP channels. Electrical stimulation was applied to try to evoke atrial arrhythmia. It was possible to induce atrial arrhythmia during, but not before, metabolic stress.

Importantly, blockade of KATP channels with drugs used to treat patients with type 2 diabetes (glibenclamide and tolbutamide), completely reversed the effects of metabolic stress on the electrical activity of the atrium and prevented the induction of atrial arrhythmia.

The anti-diabetic drugs were without effect in the absence of metabolic stress.

The findings represent a 'proof-of-principle' (the stage at which any new drug must undergo before full-scale clinical trials can begin) that atrial KATP channels can be activated by metabolic stress and facilitate atrial arrhythmias. Thus, atrial KATP channels may represent a target for drugs for the treatment of atrial arrhythmias, such as atrial fibrillation.

However, Dr James added: "Further studies are required and a key point to address will be whether differences exist between the properties of atrial, ventricular and pancreatic KATP channels that might be exploited to produce an atrial-selective drug. Perhaps these channels might be useful as targets to treat atrial arrhythmias."

Professor Jeremy Pearson, Associate Medical Director at the BHF, commented: "Atrial fibrillation is a very common irregular heart rhythm which greatly increases the risk of stroke. This study brings us closer to understanding how it develops, in particular in people whose hearts are under greater pressure due to the effects of a previous history of heart disease. It's vital that we continue to improve our understanding of this condition so we can find new treatments for patients in the future."

More information: The BHF-funded study, entitled 'Activation of Glibenclamide-Sensitive KATP Channels during β-Adrenergically-Induced Metabolic Stress Produces a Substrate for Atrial Tachyarrhythmia' is published online in the journal *Circulation: Arrhythmia and Electrophysiology*.

Provided by University of Bristol