Scientists unlock potential heart attack drug without side effects

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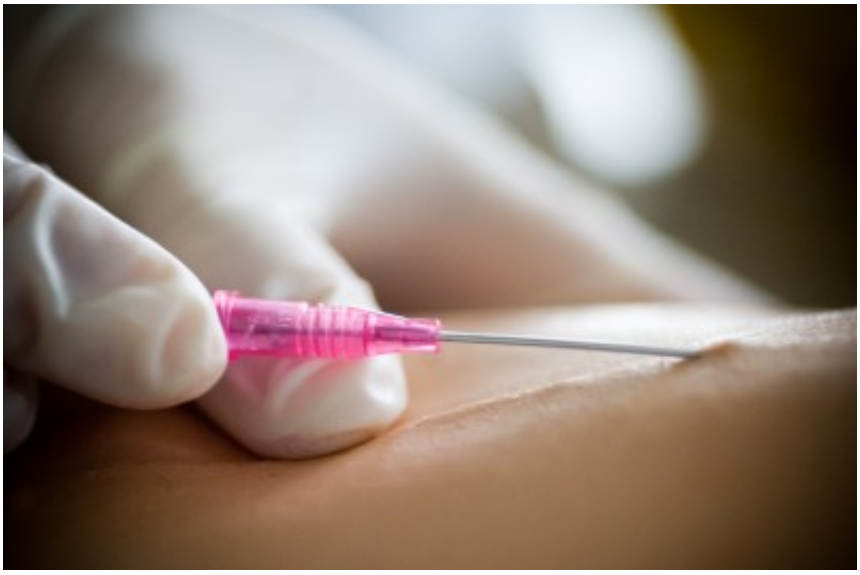

(Medical Xpress)—Melbourne scientists are a step closer to creating a new drug to stop a heart attack in its tracks and reduce the damage caused, without any side effects.

The Monash University research, published today in the journal, *Proceedings of the National Academy of Sciences* (*PNAS*), offers new hope to thousands of people who experience heart attacks and heart failure – one of the major causes of death worldwide.

Professors Arthur Christopoulos and Peter Scammells from the Monash Institute of Pharmaceutical Sciences (MIPS) led a team of scientists combining molecular pharmacology and medicinal chemistry to reveal new insights into a specific protein belonging to the family of G protein-coupled receptors (GPCRs). After successfully combining two molecules, they are a step closer to creating a brand new class of drug that is more targeted and could possess minimal side effects.

GPCRs play a role in virtually every biological process and most diseases, including, cardiovascular disease, obesity and diabetes, neuropsychiatric disorder, inflammation and cancer. Almost half of all current medications available use GPCRs to achieve their therapeutic effect.

Current GPCR drugs work either by fully activating or completely blocking receptors, treating the protein like a simple "on-off" switch. This new research discovered alternative recognition sites on GPCRs that can be targeted by drugs to fine-tune the behavior of the protein, basically converting the "on-off" switch into a "dimmer switch".

Professor Christopoulos said it was this insight that enabled the new breakthrough.

"When a heart attack strikes, heart cells die because of a lack of oxygen and nutrients. But even more damage is caused when the blood rushes back to the heart cells due to the release of inflammatory chemicals and damaging free radicals," Professor Christopoulos said.

Currently, drugs to minimise damage to the heart activate the adenosine A1 receptor, a GPCR found in the heart. However, a major issue in activating the A1 receptor also slows down the heart, and too much activation can stop the heart.

"Correct dosage has been a serious challenge in clinical trials for A1 receptor drugs. The consequences are serious; a dosage that is too high can stop the heart from beating. Too low, and the drug fails to prevent cell damage. Getting this balance right has been a big problem," Professor Scammells said.

Professor Christopoulos said the Monash study focused on finding new ways to activate the protein, to achieve the beneficial effects (protection) without the side effects (slowing the heart).

"We turned to our knowledge of alternative recognition sites on the A1 receptor and specifically designed a new class of molecule that contained two active components linked together, one binding to the main site on the receptor for activation, and another binding to the alternative site for fine-tuning of the activity. Our "dimmer switch" strategy worked, resulting in a molecule that protected heart cells but did not affect heart rate at all – at least in our animal models," Professor Christopoulos said.

"The beauty of this protein is that if you activate it effectively, you minimise the heart attack and protect the heart cells, and that's something that's never been done before."

The findings will inform the next phase of the research to develop a new drug that could potentially be made available for use by clinicians and emergency paramedics.

More information: Separation of on-target efficacy from adverse effects through rational design of a bitopic adenosine receptor agonist, www.pnas.org/cgi/doi/10.1073/pnas.1320962111

Provided by Monash University