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Researchers uncover clues to how existing heart drugs work

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Some of the most commonly prescribed drugs for the treatment of heart failure are beta-blockers and nitrates, which help to relax blood vessels and decrease the heart's workload. The drugs were thought to produce those effects through distinct molecular pathways, but according to a new study led by scientists at Temple University School of Medicine, both types of drugs may help the failing heart by counteracting the effects of an enzyme known as GRK2. The findings suggest that new drugs aimed specifically at GRK2, which can trigger the death of heart cells, could protect the heart from progressive disease.

The study, which appears online October 29 in the journal *Science Signaling*, describes a previously uncharacterized interaction between GRK2 and an enzyme called endothelial nitric oxide synthase (eNOS), in which the two enzymes attempt to block one another's activity, with different outcomes on heart function.

"When eNOS is activated, GRK2 is inhibited, and good things happen [to the heart]," explained senior investigator Walter J. Koch, PhD, Professor and Chair of the Department of Pharmacology at Temple's School of Medicine and Director of the Center for Translational Medicine. In heart disease, however, the balance is flipped—GRK2 is activated and eNOS is inhibited, which results in heart cell death and a loss in contractile function.

At the center of the GRK2 and eNOS interaction is nitric oxide (NO), the production of which is controlled by eNOS. Nitric Oxide protects the

heart from damage caused by ischemia, or blocked blood flow to heart tissue. Exactly how it exerts its cardioprotective effects, however, has been a mystery.

To determine whether cardioprotection by NO was linked to GRK2 inhibition, Koch and colleagues conducted a series of experiments in mice. The most pivotal of those experiments involved the development of a novel "knock-in" mouse model in which a point mutation was introduced in GRK2 to prevent NO from binding (a process called nitrosylation). The mutation rendered the mice resistant to nitrosylation by eNOS and dramatically increased the extent of heart injury. In addition, drugs that normally donate NO to help protect the heart were ineffective in the mice, indicating that NO binding to GRK2 is central to the ability of NO donor drugs to protect the heart from ischemic injury.

The therapeutic implications of the findings are far-reaching. They suggest, for example, that NO donor drugs, which carry and then release NO in targeted tissues, could be important in the treatment of heart failure. Currently, however, few NO donor drugs are available for clinical use. The results also indicate that existing heart failure therapies, including beta-blockers and nitrates, which have long been thought to benefit the heart primarily through vasodilation (widening of blood vessels, a process controlled by NO), might exert their most significant effects in part by blocking GRK2 activity—a previously unknown mechanism.

According to Jonathan S. Stamler, MD, a collaborator on the study and Professor of Medicine and Director of the Institute for Transformative Molecular Medicine at Case Western Reserve University, "Neither [beta-blockers nor nitrates] in their current form are ideal." Better would be agents that are capable of increasing NO bioavailability or inhibiting GRK2 directly.

"GRK2 inhibitors may have very real therapeutic benefits, especially in the context of heart failure and ischemic heart disease," Stamler said. βARKct, which Koch's laboratory has been developing as a tool for gene therapy, is one such example.

The research marks another important contribution in cardiovascular research by scientists at Temple's Center for Translational Medicine. "Novel therapeutics for heart disease are needed," Koch said "We plan to continue to look for compounds that can inhibit GRK2."

Provided by Temple University