Recycling $K_{\text{ATP}}$ channels for cardioprotection

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THE DISCOVERY AND CHARACTERIZATION OF preconditioning (PC) in the late 1980s has proven to be the most important advancement in the pursuit to identify viable strategies to limit infarct size following myocardial ischemia-reperfusion injury. Ischemic PC (IPC) is a unique, paradoxical phenomenon whereby one or several short intermittent periods of ischemia protects tissue against the injury caused by a subsequent sustained ischemic insult (10). IPC was first described in the canine heart but has now been observed in all species from mice to man and has been observed in other organ systems besides the heart (6). More importantly, IPC has proven to be the only intervention besides reperfusion that has consistently been shown to reduce infarct size. Despite the clear cardioprotective effects of IPC reported in experimental studies, a major drawback to its clinical use is that it is unknown when patients will experience a myocardial infarction. As such, the concept of IPC has been adapted to include more feasible strategies, such as peri- and postconditioning. More recently, it was also demonstrated that the short repetitious ischemic episodes in remote organs could also bring the same beneficial effects as IPC to the ischemic heart (remote ischemic conditioning) (4). Extensive work into the mechanisms of PC has led to the discovery of a variety of cardioprotective signaling pathways. These include the activation of G protein-coupled receptors, tyrosine kinase pathways, protein kinase C, and nitric oxide (12). More importantly, during the course of these investigations, researchers found that exposing the heart to various drugs before myocardial ischemia-reperfusion injury mimicked the protective effects of IPC. This phenomenon is known as pharmacological PC (PPC) (9). Some of the compounds that have been reported to have PPC effects include volatile anesthetics, adenosine, opioids, bradykinin, and nitric oxide (NO) donors (3). The feasibility of these conditioning strategies allows clinicians to initiate their use before or in concert with standard reperfusion therapy (i.e., coronary artery bypass graft and percutaneous coronary intervention) (5).

The ATP-sensitive potassium ($K_{\text{ATP}}$) channel has been shown to play a prominent role in mediating the cardioprotective effects of IPC (12). First discovered in cardiac muscle, $K_{\text{ATP}}$ channels are now known to exist in other tissues such as pancreatic β-cells, skeletal muscle, smooth muscle cells, and brain (11). $K_{\text{ATP}}$ channels located on the sarcolemma (surface $K_{\text{ATP}}$) play an important role in glucose metabolism in the cell by membrane hyperpolarization. $K_{\text{ATP}}$ channels are composed of two types of subunits: four inwardly rectifying potassium channels $K_r6$ ($K_r6.1$, $K_r6.2$) and four sulfonylurea receptors (SUR1, SUR2A, SUR2B). $K_r6$ subunits form the pore of the channel and are capable of opening and closing to regulate ion flow. SUR receptors are a high-affinity receptor sensitive to [ATP/ADP] that facilitates the opening/closing of the $K_r6$ subunits. The variation of the combination of its subunits stipulates its electrophysiological character and sensitivity for drugs. $K_{\text{ATP}}$ channel mainly exists with the combination of SUR2A and Kir6.2 in mouse cardiomyocyte (13). The activation of surface $K_{\text{ATP}}$ channels induces the release of $K^+$ ions into the extracellular space and subsequently causes cell membrane hyperpolarization, shortening of the action potential, and reduced $Ca^{2+}$ influx through L-type $Ca^{2+}$ channels. Thus its activation acts to maintain intracellular homeostasis in various pathophysiological conditions. A role for surface $K_{\text{ATP}}$ channels in mediating the cardioprotective actions of IPC is centered on the experimental evidence that SUR antagonists block the effects of IPC, whereas the $K_{\text{ATP}}$ channel openers like cromakalin, bimakalim, or pinacidil could mimic the protective effects of IPC (1, 2, 12). More importantly, clinical studies revealed the protective effect of the $K_{\text{ATP}}$ channel opener nicorandil against both stable angina (7) and acute coronary syndrome (8).

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Yang and colleagues (15) provide several novel findings regarding surface $K_{\text{ATP}}$ channels and IPC. First, using isolated hearts from inducible cardiac specific Kir6.2 knockout mice, the authors provide novel evidence that Kir6.2-containing $K_{\text{ATP}}$ channels are essential for the infarct-lowering effects of IPC. This provides compelling genetic evidence to support the previously published data that used pharmacological interventions to demonstrate the importance of the surface $K_{\text{ATP}}$ channel in mediating the cardioprotective effects of IPC. Previous studies have focused on the opening of the $K_{\text{ATP}}$ channel as the trigger to induce cardioprotective signaling. However, it has become increasingly evident that membrane channel density is also important. The surface density of ion channels are tightly regulated by endocytosis and recycling (14). $K_{\text{ATP}}$ channels are regulated by this process, but it was not known if this occurred during myocardial ischemia. Here, Yang and colleagues found that ischemia induced the internalization of the surface $K_{\text{ATP}}$ channel by a dynamin-mediated and CaMKII-dependent internalization mechanism. Importantly, IPC prevented the endocytosis. In terms of mechanism, the authors found that the internalization was opposed via an adenosine-protein kinase C signaling cascade. Together, this data suggest that the opening of the $K_{\text{ATP}}$ channel and the maintenance of the surface $K_{\text{ATP}}$ channel density both contribute to the infarct-lowering effects of IPC.

There are some limitations to the current study. First, this study used the Langendorff-perfused heart model, which excludes influences that are closely related to the pathophysiological state of ischemic injury in vivo. As such, additional factors that could influence the endocytosis and recycling of the $K_{\text{ATP}}$ channel were not present. Second, the study solely focused on the effects of IPC to maintain the surface density of...
the $K_{\text{ATP}}$ channel. It would be interesting to know how other conditioning strategies alter the endocytosis and recycling of the channel. In particular, can interventions near or at the time of reperfusion prevent the loss of $K_{\text{ATP}}$ channel surface density? Finally, a comprehensive assessment of $K_{\text{ATP}}$ channel surface density at different periods of reperfusion is needed to fully understand the dynamics and timing of this regulation. In the meantime, the current study has shed first light on a new mechanistic concept regarding the role of $K_{\text{ATP}}$ channel internalization in response to myocardial ischemia and has opened the door to targeting $K_{\text{ATP}}$ channel recycling as a cardioprotective strategy.

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**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

Y.S. and J.W.C. drafted, edited, revised, and approved final version of manuscript.

**REFERENCES**