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UW Grant-in-Aid:

“The Obligatory Role of Kir6.1 in Exercise-Induced Reperfusion Recovery”

Ischemic heart disease has been a leading cause of morbidity and mortality in the United States. Early and prompt restoration of coronary blood flow is extremely important for the survival of myocardium at risk. However, following percutaneous coronary intervention for acute myocardial infarction, often there exists a no-reflow or slow-reflow phenomenon which is a serious clinical complication and strong independent predictor of mortality. Therefore, developing effective strategies to achieve prompt reperfusion of the ischemic myocardium is critical for successful reperfusion therapy. Exercise has been recognized as an effective and practical intervention to protect the ischemic heart. However, the underlying mechanisms for exercise-induced cardioprotection against myocardial ischemia and reperfusion injury have been scarce.

Since opening of the ATP-dependent K+ channels on coronary vascular smooth muscle cells (VSMC sarc-KATP) hyperpolarizes membrane potential and relaxes vascular tone, in the current proposal we hypothesize that exercise up-regulates VSMC sarc-KATP channel, improves blood perfusion following ischemia, and protects the heart from ischemia/reperfusion injury. To test this novel hypothesis, we design experiments to determine: 1) whether exercise up-regulates Kir6.1 (the pore-forming subunit of VSMC sarc-KATP) and improves blood reperfusion following ischemia; and 2) the obligatory role of Kir6.1 in exercise-induced cardioprotection. To achieve these goals, we will exercise the mice and transfect the exercised mice with a dominant negative gene Kir6.1AAA to determine whether blood reperfusion following ischemia is delayed and the exercise-induced protection is abrogated. This new exercise-induced mechanism may serve as a potential therapeutic target to protect the ischemic heart from reperfusion injury.