A-769662 potentiates the effect of other AMP-activated protein kinase activators on cardiac glucose uptake

Aurélie Timmermans (1), Audrey Ginion (1), Carole De Meester (1), Kei Sakamoto (2), Jean-Louis Vanoverschelde (1), Sandrine Horman (1), Christophe Beauloye (1), Luc Bertrand (1)
(1) Université catholique de Louvain, IREC-CARD, Bruxelles, Belgique – (2) Nestlé Institute of Health Sciences SA, Head of Diabetes, Lausanne, Suisse

**Purpose:** The AMP-activated protein kinase (AMPK) regulates metabolic homeostasis and plays a protective role in the ischemic and diabetic hearts. The A-769662 compound, which directly binds and activates AMPK, has recently been characterized. Here, we studied the impact of A-769662 on cardiac AMPK signaling and glucose uptake which is known to participate in the protective action of AMPK.

**Methods:** Insulin and/or A-769662 were used to stimulate adult cardiomyocytes. The effect of A-769662 on the action of other AMPK activators has been also tested. Glucose uptake was measured by the dehydrogenation rate of glucose. The effect of A-769662 on the action of other AMPK activators has been characterized. Here, we studied the impact of A-769662 on cardiac AMPK signaling and glucose uptake which is known to participate in the protective action of AMPK.

**Results:** Glucose uptake was increased by both insulin and oligomycin. In the presence of insulin, oligomycin leads to an overstimulation of glucose uptake that correlated with an Akt overphosphorylation. In contrast, A-769662 had no insulin sensitizing effects. Indeed, A-769662 promoted AMPK phosphorylation but did not stimulate glucose uptake and did not induce an overphosphorylation of Akt or an overstimulation of glucose uptake in the presence of insulin. Otherwise, A-769662 potentiates the effects of other AMPK activators. We showed an overphosphorylation of AMPK and of its downstream targets, when A-769662 was added to oligomycin or hypoxia. This potentiation effect was accompanied by an overstimulation of glucose uptake and by a decrease in cell mortality and ROS production.

**Conclusions:** A-769662, by itself, is unable to stimulate glucose uptake or to increase insulin sensitivity. However, its ability of potentiating the action on other AMPK activators makes it a potentially useful participant in the protective role of AMPK in the heart.