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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 detergent rate of myocytes. The effect of A-769662 on the action of other AMPK activators makes it a potentially useful participant in the protection of the heart.

Results: 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.

Conclusion: Collectively, our results using low dose of A-769662 suggest a yet to be identified mechanism by which AMPK can regulate cardiac hypertrophy.

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Differential AMP-activated protein kinase (AMPK) activation in platelets, in response to various agonists. Comparison between human and murine platelets

Sophie Lepropre (1), Marie-Blanche Onselæer (1), Cécile Oury (2), Luc Bertrand (1), Jean-Louis Vanoverschelde (1), Christophe Beauloye (1), Sandrine Horman (1)

(1) Université catholique de Louvain, Recherche cardiovasculaire CARB, Woluwe Saint-Lambert, Belgique – (2) Université de Liège, GIGA-Research, Human Genetics Unit, Liège, Belgique

AMPK is activated during platelet aggregation and controls the phosphorylation state of key cytoskeletal targets. CaMKKβ is responsible for thrombin-induced AMPK activation. Substantial differences have been observed between human and murine platelets. This study aims to bring out the differences in AMPK signalling pathway between human and murine platelets. Only ε1 catalytic subunit of AMPK is present in human platelets. Thrombin induces a dramatic AMPKε1 activation and subsequent acetyl-CoA carboxylase (ACC) phosphorylation, while thromboxane A2 (U46619) and collagen exert a marginal effect on both enzymes. ADP has no effect at all. These differences cannot be entirely related to a lower calcium production in response to U46619, collagen and ADP. Indeed, U46619 increases calcium with a similar extent than thrombin while it does not modify ACC phosphorylation. PAR1 but not PAR4-activating peptide reproduces the effect of thrombin on ACC. In addition, inhibition of CaMKKβ/AMPKε1 activation blunts platelet aggregation in response to thrombin and does not affect the response upon stimulation by the other agonists.

Murine platelets express AMPKε1 and AMPKζ2. AMPK can be activated either by thrombin or U46619 or collagen but not by ADP. The absence of AMPKζ2 blocks ACC phosphorylation induced by the three agonists. It mainly inhibits the thrombin-induced platelet aggregation but also significantly reduces aggregation in response to U46619 and collagen. The absence of AMPKζ2 does not affect the increase in ACC phosphorylation, whatever the agonist used.

Conclusion: AMPKε1 is the sole catalytic subunit of AMPK expressed in human platelets and is activated by thrombin through PAR1. Murine platelets contain both catalytic subunits although ε1 plays a predominant role. In mice, thrombin is not the predominant AMPK activator probably because of the difference in the type of PAR expression. Signalling events of mouse platelets can diverge from those of human platelets.