**INTRODUCTION**

Myocardial ischemia is an intermediate stage in coronary artery disease during which the heart tissue is starved of oxygen and nutrients. Eventually, the affected heart tissue can suffer massive cell death, occasionally leading to a heart attack when blood flow is completely blocked.

In normal condition, in heart, FFA is preferred substrate (70%FFA and 30% glucose & lactate), because the β-oxidation of 1 mol palmitate results in more ATP than glucose (129 versus 38 ATP per 1 mol), but consumes also more oxygen. During ischemia, glucose levels are rapidly depleted and FFAs accumulate. Increased levels of FFAs depress myocardial contractility, inhibit glycolytic flux, accumulate as myocyte toxic metabolites cause membrane damage and arrhythmias, and increase myocardial oxygen consumption without increasing myocardial work.

GIK: Recently it has been shown that necrosis following experimental myocardial ischemia can be reduced by GIK. At 1970, it was found that GIK causes membrane damage and arrhythmias, and increase myocardial oxygen consumption without increasing myocardial work. GIK is effective in preventing necrosis of the ischemic myocardium. The mechanism by which GIK prevents myocardial ischemia-reperfusion injury is not completely understood. Several mechanisms have been proposed to explain the beneficial effect of GIK in the treatment of ischemia-reperfusion injury, which include: (1) stabilization of the cell membrane, (2) reduction of calcium overload, (3) inhibition of free radical formation, and (4) induction of anti-inflammatory and anti-apoptotic mechanisms.

**OBJECTIVES**

1. Study the current status of GIK use in ACS.
2. Define the GIK-induced main pathway of cardiac protection.
3. Determination of benefits of GIK in acute myocardial ischemia

**METHODOLOGY**

This project has been made as a scientific review using original articles found in PubMed and other scientific articles used have been picked up considering their abstract, conclusions, concetration into the objective, date of publication and quality, as well as if they had been referred in previous articles read. Thus, approximately 70 publications have been read, although 50 have been finally used in the project writing.

**GLUCOSE & POTASSIUM PATHWAY**

Heart metabolism and pathway provided by GIK

Left: Adverse metabolic pathways and consequences. Right: Beneficial glucose-related metabolic changes. TCA: The Citric Acid cycle; ETC: Electron Transport Chain

**INSULIN SIGNALING**

IR (human INSR)

Insulin-induced changes activate a phosphorylation activity (active site position 1155). It is not to General receptors, but it is only in the phosphorylation pathway present in the pathological concentration of insulin (100-500pM). The hyperglycemia may be the type 1 diabetes under physiological concentration.

IRS (IR and IRS2) have a PTB domain at their N terminus which binds specifically to phosphorylated insulin receptor IR. In the absence of insulin, IRS contain recognizably tyrosine motifs for IR such as IRS1, IRS3 and IRS6. Phosphorylated IRS are able to bind specifically to IRS1 domains of proteins.

PI3K (human PIK3)

PI3K (especially class Ia) is a heterodimeric lipid kinase composed of a 85kDa catalytic subunit and one 85kDa regulatory subunit. The p85 subunit contains SH2 domain that is responsible for recognition of phosphorylated YXXM motif. The accumulation of its products PIP3,PIP2 in membrane recruits subsequent effectors like PKD1, PI3K, Akt, etc.

PKD1 (human PDK1)

PKD1 (Phosphatidylinositol-4-phosphate 3-kinase) gene, has two domains: a catalytic domain (Apo-205) and the PI domain. The PI domain is responsible for phosphatidylinositol lipid binding capacity. In response to insulin, PKD1 is recruited and then activated by phosphorylation on Tyr-5, Tyr-231 and Tyr-176 by IR. Insulin stimulates PKD1 production when autophosphorylates itself on Thr-242.

**AKT DOWNSTREAM EFFECTS**

**CONCLUSION**

Multiple complementary mechanisms may contribute to GIK-related myocardial protection.

1. The shift of the myocardial metabolism from LCGAs to glucose oxidation during reperfusion, which is more oxygen efficient and prevents the production of toxic LCGA metabolites.
2. Activated PKD/Akt leads to several protective mechanisms: PKD/Akt phosphorylates, sequencers, and/or inactivates several pro-apoptotic proteins including BAD and Bax, and caspase-9.
3. PKD1 also phosphorylates and activates eNOS, inducing protection most likely via NO- and cGMP-dependent mechanisms.
4. The PKD/Akt/eNOS/gSOD pathway is also supposed to be protective by promoting, among others, the post-ischemic synthesis of contractile proteins.
5. Maintenance of cardiac pH and glucose levels, by affording the necessary substrate for ATP formation.
6. Full metabolic monitoring needs to be performed to definitively prove the beneficial effect of GIK infusion. Although the cardioprotective properties of glucose-insulin- potassium (GIK) remain controversial, in part because of the different contexts, doses, and protocols of GIK used in different studies, there is a growing consensus supporting the utility of GIK in cardiac surgery and emergency.

**Keywords**

GIK= Recently it has been shown that necrosis following experimental myocardial ischemia can be reduced by GIK. At 1970, it was established as a possible treatment. Although there are many things remain unknown, now a day the GIK clinical uses are having positive effects in some specific cases.

**Key words**

AC/Nuclear coronary syndromes, FFA=free fatty acid, MI=myocardial infarction, PAR=Parra et al., 2014. SIE=sodium mustard, GIK: GIK (Glucose-insulin-potassium)...

**REFERENCES**

**Glucose & Potassium Pathway**

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