Will be the insulin a possible treatment for a acute myocardial ischemia?

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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 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.

OBJECTIVES

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

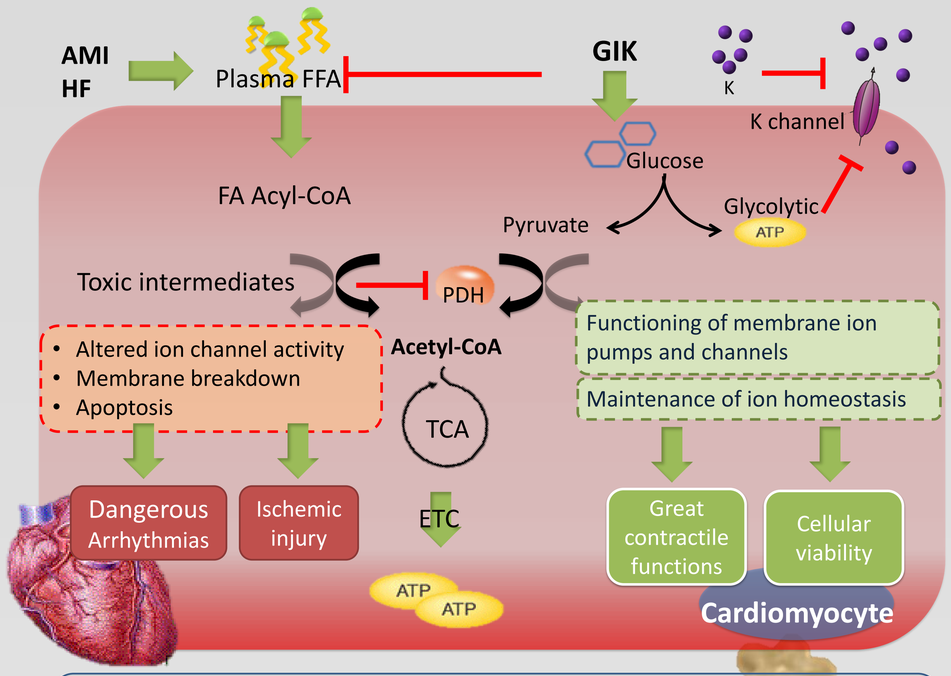
METHODOLOGY

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, concretion 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.

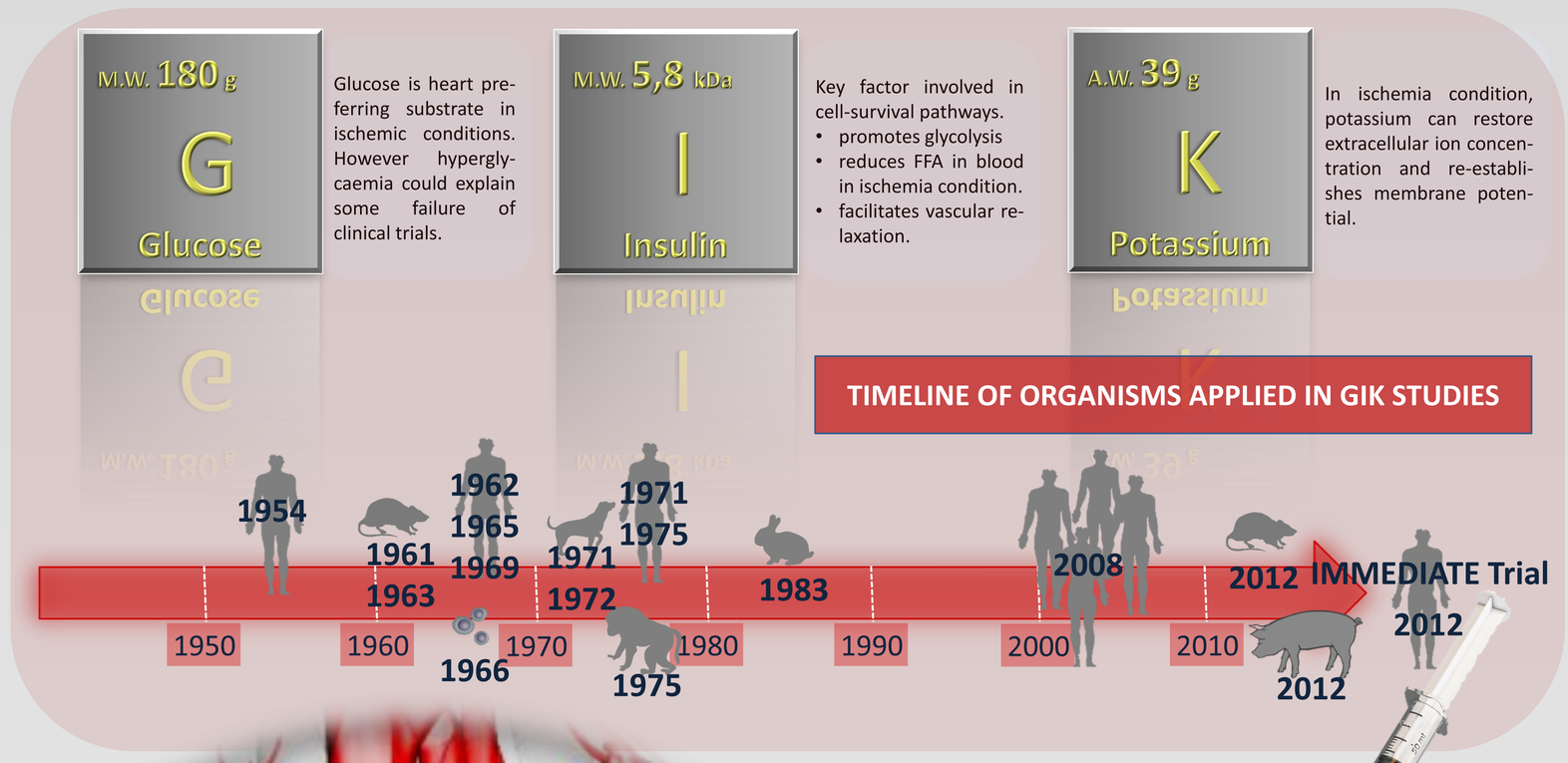
KEY-WORDS

ACS=acute coronary syndromes, FFA=free fatty acid, MI=myocardial infarction,	AMI=acute myocardial infarction, Insulin, IR=insulin receptor tyrosine kinase,	IRS= insulin receptor substrate, PI3K=phosphatidylinositol 3-kinase, PI(3,4,5)P3=phosphatidylinositol 3,4,5-trisphosphate,	PDK1= Phosphoinositide-dependent kinase 1, PKB/Akt= Protein kinase B, GIK=glucose-insulin-potassium.

GLUCOSE & POTASSIUM PATHWAY



Heart metabolism and pathway provided by GIK
Left, Adverse metabolic paths 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 its phosphorylation activity (active site position 1159); it could form with IGFR as a hybrid receptor, IR is selectively under physiological concentration of insulin (100-500pm). The hybrid receptor could be activated under supraphysiological concentration.

IRS

IRS-proteins (IRS1 and IRS2) have a PTB domain at their N-terminus which binds specifically to phosphorylated NPXY-motif of IR. The C terminus are poorly conserved, however contain recognizable tyrosine motifs for IR such as YMXM, YVNI and YIDL. Phosphorylated-IRS are able to bind specifically to SH2 domains of proteins.

PI3K (human PIK3C)

PI3K (especially class IA) is a heterodimeric lipid kinase composed by a p110 catalytic subunit and one p85 regulatory subunit. The p85 subunit contains SH2 domain that isresponsible for recognition of phosphorylated YXXM motif. The accumulation of its products PI3,4,5P3 in membrane recruits subsequent effectors like PDK1, PKB/AKT, etc.

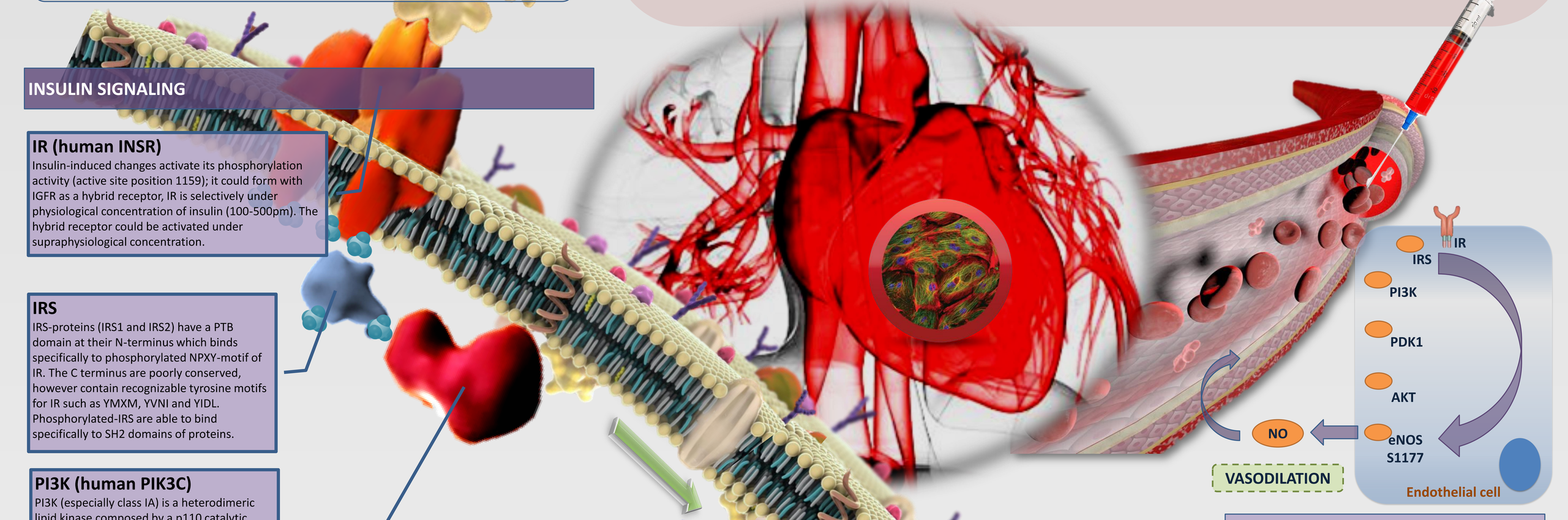
PDK1 (human PDPK1)

A Serine/Threonine kinase. PDK1 has two domains: a catalytic domain (Asp-205) and the PH domain. The PH domain is responsible for the phosphatidylinositol lipids-binding capacity.
In response to insulin, PDK1 is recruited and then activated by phosphorylation on Tyr-9, Tyr-373 and Tyr-376 by IR. Its full activation produced when autophosphorylates itself on Ser-241.

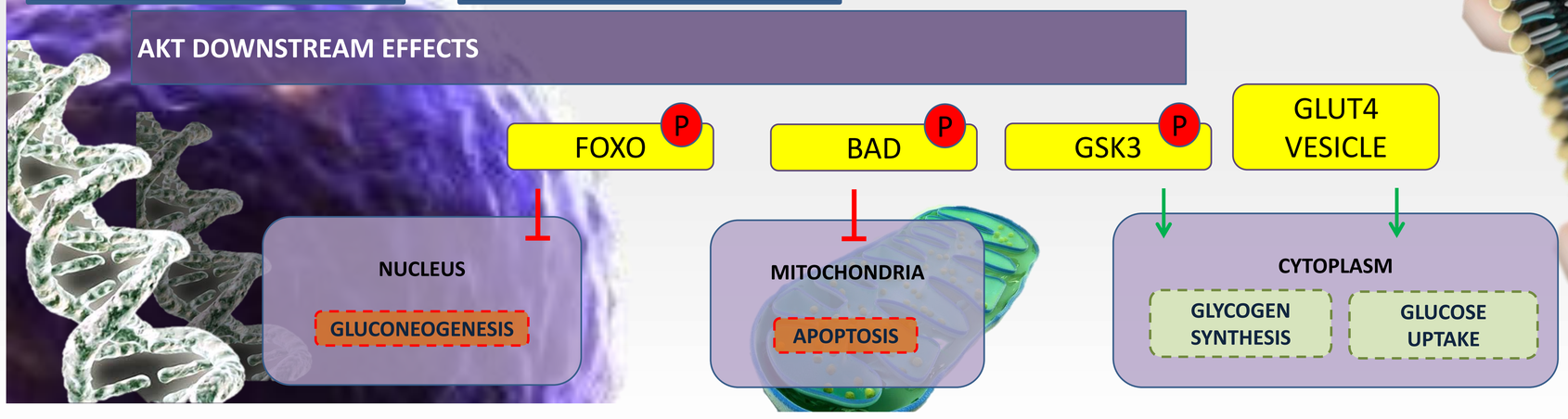
PKB/AKT

It is also a serine/thereonine-protein kinase. AKT2 isoform is mainly involved in the glucose metabolism. AKT2 isoform has got 3 domains: a PH domain that gives it the lipid-binding ability, a protein kinase domain (active site at Asp-275) and a C-terminal AGC-kinase domain.

AKT2 requires phosphorylation on Thr-309 and Ser-474 for its full activity. After its activation, AKT2 phosphorylates a set of effectors



AKT DOWNSTREAM EFFECTS



VASCULAR PROTECTION

In endothelial cells, The insulin-signaling pathway in vascular endothelium that regulates activation of eNOS employing a phosphorylation-dependent mechanism.

CONCLUSION

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

1. The shift of the myocardial metabolism from LCFAs to glucose oxidation during reperfusion, which is more oxygen efficient and prevents the production of toxic LCFA intermediates.
2. Activated PKB/Akt leads to several protective mechanisms. PKB/Akt phosphorylates, sequesters, and/or inactivates several pro-apoptotic proteins including BAD, BAX, and caspase-9.
3. PKB/Akt also phosphorylates and activates eNOS, inducing protection most likely via the NO-dependent.
4. The PKB/Akt/mTOR/ p70S6K is also supposed to be protective by promoting, among others, the post-ischaemic synthesis of contractile proteins.
5. Maintenance of cardiac pH and glucose levels, by affording the necessary substrate for ATP formation.

But full metabolic monitoring needs to be performed to definitively prove the beneficial effect of GIK infusion. Although the cardio-protective properties of glucose-insulin-potassium (GIK) remain controversial, in part because of the different contexts, doses, timing, and protocol of GIK used in different studies, there is a growing consensus supporting the utility of GIK in cardiac surgery and emergency.

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