International Journal of Cardiology 288 (2019) 119–120

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Cardioprotection by PEDF: A novel form of GLUT4 membrane translocation to reduce myocardial ischemic injury☆

Attila Kiss *, Bruno K. Podesser

Ludwig Boltzmann Cluster for Cardiovascular Research at the Center for Biomedical Research, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Article history:
Received 12 April 2019
Accepted 16 April 2019
Available online 29 April 2019

Despite the significant improvements in medical therapy, acute ST-elevation myocardial infarction is still the major contributor to mortality and morbidity worldwide. Although, timely reperfusion of the occluded coronary artery is necessary for salvage of cardiac cells and functional recovery of the heart, reperfusion of the jeopardized myocardium results in a cascade of harmful events, referred as reperfusion-injury [1]. Of importance, reperfusion-injury itself contributes to the enlargement of myocardial infarction leading to adverse left ventricle remodelling and subsequently to progressive heart failure. Targeted increase in glucose metabolism in cardiomyocytes upon myocardial ischemia is considered to be an effective therapeutic concept to reduce myocardial infarct size and cardiomyocytes apoptosis [2]. Accordingly, previous studies have shown that an increase in glucose uptake and metabolism by ischemic myocardium may protect cardiomyocytes from irreversible damage [2,3]. Mechanistically, recruitment of glucose transport proteins, namely GLUT4 and GLUT1 is the cellular mechanism by which the myocardium increases glucose transport for subsequent metabolism in setting of myocardial ischemia. The mechanosensitive signalling pathways, which trigger glucose transport proteins translocation, have been extensively investigated both during hypoxia *in vitro* and during myocardial ischemia *in vivo*. In addition, numerous experiments demonstrate that AMP-activated protein kinase (AMPK) plays a dominant role in GLUT4 translocation in cardiomyocytes [4]. Nevertheless, AMPK dysregulation has been demonstrated in various cardiovascular diseases [5], whereby AMPK-independent regulation of GLUT4 translocation in cardiomyocytes will provide novel insight into myocardial protection with a potential therapeutic use.

In the featured study by Yuan Y et al. in this issue of *International Journal of Cardiology*, GLUT4 translocation to the plasma membrane and increase in glucose metabolism was induced by Pigment Epithelium-Derived Factor (PEDF) [6]. PEDF is a glycoprotein that belongs to the superfamily of serine protease inhibitors and is produced from a variety of tissues, including vascular cells, inflammatory cells, and adipocytes. Compared to the vehicle treated animals, PEDF adenovirus-mediated gene delivery directly into the hearts was associated with a marked reduction in infarct size, fibrosis and subsequent improvement in cardiac function and viability. Based on the cardioprotective effects of PEDF, the authors further investigated the potential underlying mechanisms in cardiomyocytes under hypoxic condition. Accordingly, PI3K/AKT pathway in cardiomyocytes was identified as a major node of action for GLUT4 translocation to the plasma membrane. This report is interesting because the improvement in glucose metabolism and subsequent cardiac viability are not likely due to activation of AMPK, since the authors conclude that PEDF did not increase the expression levels of phosphorylated AMPK. Moreover, the authors demonstrated that PEDF decreased the expression of p-AMPK and AMPK in cardiomyocytes that were subjected to hypoxia. First, although important, this observation was not discussed in detail in the manuscript. AMPK serves as a protein kinase in several metabolic pathways of the heart including cellular energy sensoring. Therefore, it is tempting to speculate if reduced AMPK levels by PEDF lead to reduced energy charge and glucose metabolism in cardiomyocytes and subsequently induce cardioprotection during hypoxia. Second, because this phenomenon was only observed in isolated cardiomyocytes during hypoxia, it would have been interesting to see whether AMPK levels were comparable in ischemic cardiac tissue following PEDF adenovirus-mediated gene delivery.

Also from a clinical point of view, these findings are relevant as novel therapeutic strategy for the treatment of ST-elevation myocardial infarction. Nevertheless, the PEDF administration by intra-myocardial viral transfection has obvious limitation. What could be the clinical implications of PEDF in particular and serine protease inhibitors? Besides interventional cardiology, cardiac surgery could benefit. Cardiopulmonary bypass and subsequent cardioplegic arrest remain the most popular myocardial protection technique in open heart surgery. Cardioplegic

☆ This editorial refers to 'PEDF increases GLUT4-mediated glucose uptake in rat ischemic myocardium *via* PI3K/AKT pathway in a PEDFR-dependent manner', by Yuan Y et al., 283:136–143.

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.02.035.

* Corresponding author at: Ludwig Boltzmann Cluster for Cardiovascular Research at the Center for Biomedical Research, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.

E-mail address: attila.kiss@meduniwien.ac.at (A. Kiss).

https://doi.org/10.1016/j.ijcard.2019.04.045

arrest renders the heart globally ischemic and, upon reperfusion, triggers myocardial injury [7]. In addition, in cardiac surgery, the number of elderly and multimorbid patients has dramatically increased over the last 20 years, and is associated with elevated perioperative mortality [8]. Therefore, constant efforts to improve intraoperative myocardial protection are essential to optimize postoperative outcome. Current concepts of myocardial protection during cardiopulmonary bypass relay on depolarization, using high concentrations of potassium to arrest the heart in diastole. The net-effect of all this is a reduction of myocardial oxygen consumption that allows safe operations on the arrested heart for a limited time period. So far serine protease inhibitors such as aprotinin have been used only because of their known effect to reduce intraoperative blood loss [9]. However, aprotinin is produced from bovine tissue and has the potential of allergic reactions. Therefore its use has dramatically declined during recent years. Since some recently newly developed serine protease inhibitors have some potential benefit on myocardial function during cardiac surgery, it is tempting to speculate if target interventions on glucose metabolism by PEDF may improve cardiac function in patients undergoing cardiac surgery.

In conclusion, the manuscript by Yuan et al. [6] provides further evidence for the cardioprotective effects of PEDF on the ischemic myocardium *via* a mechanism mediated by the membrane translocation of GLUT4 in cardiomyocytes. This highlights the importance of PEDF as a potential therapeutic approach to reduce myocardial infarct size and improve cardiac function in patients with ST-elevation myocardial infarction or patients undergoing cardiac surgery, respectively.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] D.J. Hausenloy, D.M. Yellon, Myocardial ischemia-reperfusion injury: a neglected therapeutic target, J. Clin. Invest. 123 (2013) 92–100.
[2] L.H. Young, R.R. Russell, R. Yin, M.J. Caplan, J. Ren, R. Bergeron, G.I. Shulman, A.J. Sinusas, Regulation of myocardial glucose uptake and transport during ischemia and energetic stress, Am. J. Cardiol. 83 (1999) 25–30.
[3] R. Ramasamy, Y.C. Hwang, J. Whang, S.R. Bergmann, Protection of ischemic hearts by high glucose is mediated, in part, by GLUT-4, Am. J. Physiol. Heart Circ. Physiol. 281 (2017) H290–H297.
[4] S.C. Bairwa, N. Parajuli, J.R.B. Dyck, The role of AMPK in cardiomyocyte health and survival, Biochim. Biophys. Acta Mol. basis Dis. 1862 (2016) 2199–2210.
[5] M. Arad, C.E. Seidman, J.G. Seidman, AMP-activated protein kinase in the heart, Circ. Res. 100 (2007) 474–488.
[6] Y. Yuan, X. Liu, H. Miao, B. Huang, Z. Liu, J. Chen, X. Quan, L. Zhu, H. Dong, Z. Zhang, PEDF increases GLUT4-mediated glucose uptake in rat ischemic myocardium via PI3K/AKT pathway in a PEDFR-dependent manner, Int. J. Cardiol. 283 (2019) 136–143.
[7] D.J. Chambers, H.B. Fallouh, Cardioplegia and cardiac surgery: pharmacological arrest and cardioprotection during global ischemia and reperfusion, Pharmacol. Ther. 127 (2010) 41–52.
[8] B.K. Podesser, The ageing population - a challenge for cardiovascular surgery, in: B.K. Podesser, D.J. Chambers (Eds.), New Solutions for the Heart - An Update in Advanced Perioperative Protection, Springer, 2011 , (ISBN 978-3-211-85547).
[9] G. Szabó, G. Veres, T. Radovits, H. Haider, N. Krieger, S. Bährle, C. Miesel-Gröschel, S. Niklisch, M. Karck, A. van de Locht, Effects of novel synthetic serine protease inhibitors on postoperative blood loss, coagulation parameters, and vascular relaxation after cardiac surgery, J. Thorac. Cardiovasc. Surg. 139 (2010) 181–188.