The signal pathway regulated by mitochondrial ATP-sensitive potassium channels might be involved in the mechanism of brain ischemic tolerance

Rui Feng a, Xiao Wang a, Feng Zhang b,c,*

a Department of Neurology, The Third Hospital of Hebei Medical University, Shijiazhuang, PR China
b Department of Rehabilitation Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang, PR China
c The Key Laboratory of Orthopedic Biomechanics of Hebei Province, The Third Hospital of Hebei Medical University, Shijiazhuang, PR China

Received 21 January 2014; received in revised form 8 July 2015; accepted 9 July 2015

Transient ischemic attack results in tolerance to a subsequent severe brain ischemic attack, which is known as brain ischemic tolerance (BIT). In other words, preconditioning intervention leads to ischemic tolerance. The preconditioning intervention methods include ischemia, oxidative stress, and drug resistance to oxidative phosphorylation. Because of safety considerations, these methods are only used in animal experiment studies, and are not for human studies. Therefore, the current researchers are trying to explore safe preconditioning methods. Our previous review indicated that treadmill training was a promising method to promote the tolerance to ischemic stroke.1 What is more, the underlying mechanism of exercise preconditioning was still unclear.

Many intracellular signaling pathways participate in ischemic preconditioning. It was reported that exercise training before ischemia could influence the glutamic acid system and reduce brain damage after cerebral ischemia occurs.2 However, the upstream pathways involved in the mechanism of exercise preconditioning require further exploration.

ATP-sensitive potassium channels (KATP) include sarcKATP (plasmalemma K ATP) and mitoKATP (mitochondrial inner membrane KATP). It was reported that sarcKATP did not participate in neuroprotective effect against ischemic stroke,3 while related research indicated that mitoKATP channels participate in the process of BIT. This type of channel is situated in the inner mitochondrial membrane, regulating mitochondrial function. There were several times more mitoKATP channels in brain tissue than in liver or heart, indicating the important role of such channel in the central nervous system. The mitoKATP channels played an important role in the process of preconditioning as both triggers and end effectors in acute and delayed neuroprotection.4 By contrast, the antioxidants and mitochondrial ATP-sensitive potassium (mitoKATP) blockers could cancel out the protective effect of preconditioning.5 Therefore, we speculate that exercise preconditioning could induce BIT through mitoKATP.

As for the downstream pathway of mitoKATP, Tsukamoto et al6 reported that mitoKATP could activate protein kinase C (PKC) to induce cardiac ischemic tolerance.6 PKC represents a family of second messengers that rely on serine/threonine kinases. A study showed that ischemic preconditioning...
upregulated brain mitochondrial sirtuin 1 protein levels, which was mediated by PKC. Therefore, we speculate that exercise preconditioning could induce BIT through mitoK\textsubscript{ATP}–PKC.

Moreover, a previous study indicated that activation of PKC (phosphorylation) reduced glutamate transporter (GLT)-1 expression in cell surface. GLT-1 is mainly distributed in the glial cells, playing a key role in the process of the heavy intake of glutamate. Sun et al. reported that the mitoK\textsubscript{ATP} agonist strengthened the function of glutamate transporter uptake of glutamate by reducing the phosphorylation level of PKC. Therefore, we speculate that exercise preconditioning could induce BIT through mitoK\textsubscript{ATP}–PKC–GLT-1.

In summary, based on the above mentioned literature, we hypothesize that exercise preconditioning could induce BIT through mitoK\textsubscript{ATP}–PKC–GLT-1, strengthening glutamate uptake function by the glial cells, and alleviating brain damage after stroke.

Acknowledgments

The present study was supported by the National Natural Science Foundation of China (No. 81201512).

References


