Reply to “Letter to the editor: ‘Zinc and cardioprotection: the missing link’”

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REPLY: In our recent article (3), we reported that zinc prevents reperfusion injury by targeting the mitochondrial permeability transition pore opening through an inactivation of GSK-3β. The effect of zinc on GSK-3β was mediated by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.

In this issue of the *American Journal of Physiology-Heart and Circulatory Physiology*, Mocanu and Yellon (6) have written to the Editor regarding our report. They mentioned that there is a missing link between zinc and the activation of the PI3K/Akt pathway and proposed that zinc may stimulate the PI3K/Akt pathway by inhibiting regulatory phosphatases.

The PI3K/Akt signaling is modulated by various phosphatases at several levels (1). It is regulated by the protein tyrosine phosphatase (PTPase) family at the level of receptor tyrosine kinase (RTK), lipid phosphatases such as the phosphatase and tensin homolog on chromosome 10 (PTEN) at the level of lipids such as phosphatidylinositol-3',4',5'-trisphosphate (PIP₃), generated by PI3K, and Ser/Thr phosphatases that inactivate Akt by reversing the phosphorylation of Thr308 and Ser73. Since zinc can inhibit PTPase in rat glioma cells (4) and zinc-induced activation of the PI3K/Akt pathway is mediated by Src-dependent stimulation of the epidermal growth factor receptor (7), it is possible that exogenous zinc activates RTK by suppressing PTPase, which in turn leads to the activation of PI3K. However, a recent report stated that zinc-dependent Ca²⁺ rise is not mediated by RTK (5).

It is well known that PTEN negatively regulates the PI3K/Akt signaling pathway. As a lipid and protein phosphatase (PP), PTEN is a member of the PTPase family. Thus PTEN can regulate the PI3K/Akt pathway either by dephosphorylating PIP₃ (lipid) or by acting as a PTPase to stimulate RTK (2). Thus it is likely that the zinc-induced activation of the PI3K/Akt pathway was mediated by the inhibition of PTEN. Zinc induces PTEN protein degradation and the loss of function in human airway epithelial cells (8). This effect of zinc is mediated by an ubiquitin-associated proteolytic process. However, PTEN degradation was prominent after a long period (4 h) of treatment with zinc. Thus it is improbable that the treatment of H9c2 cells with zinc for a short time (20 min) could markedly reduce PTEN protein levels in our study. Therefore, it is more practical to speculate that zinc may rapidly inhibit PTEN activity to activate Akt.

In mammalian cells, the major Ser/Thr phosphatases are PP1, PP2A, and PP2B (2). Although Ser/Thr phosphatases may directly alter Akt activity by dephosphorylating Thr³⁰⁸ and Ser⁷³ residues, little is known about the effect of zinc on these enzymes. Thus it would be intriguing to determine whether zinc activates Akt by altering the activities of Ser/Thr phosphatases.

GRANTS

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REFERENCES


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