Interaction between group IIA secreted phospholipases A2 and mitochondria

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A. Ivanušec[I,II], J. Šribar[I], M. Zorović[III], M. Živin[III], P. Veranič[IV], I. Križaj[I]

[I]Jozef Stefan Institute, Department of Molecular and Biomedical Sciences, Ljubljana, Slovenia, [II]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, [III]University of Ljubljana, Faculty of Medicine, Institute for Pathophysiology, Ljubljana, Slovenia, [IV]University of Ljubljana, Faculty of Medicine, Institute of Cell Biology, Ljubljana, Slovenia

Group IIA secreted phospholipase A_2 (GIIA) is a mammalian orthologue of ammodytoxin (Atx), a β-neurotoxic GIIA (β-ntxs) from the snake venom. It plays both physiological and pathological roles in mammalian brain. Physiologically, it is involved in regulation of neurotransmission, neuritogenesis and mitochondrial homeostasis, while pathologically, it is implicated in neurodegenerative and cerebrovascular diseases. The action of GIIA in these pathologies is far from being clear on the molecular level. To reveal them, β-ntxs may be very useful as they inflict apparently identical damage to neuronal mitochondria as GIIA. Using Atx, we identified a high affinity $sPLA_2$ membrane receptor in neuronal mitochondria as the subunit II of cytochrome c oxidase (CCOX-II), the essential constituent of the respiratory chain. We have shown in isolated mitochondria as well as on rat brain tissue sections that Atx inhibited the enzymatic activity of CCOX. Interestingly, the observed inhibitory effect of Atx was not dependent on its phospholipase activity, as also the enzymatically inactive mutant of Atx was able to induce it. Using heterologous competition assay, we demonstrated that mammalian GIIA binds to CCOX-II with a 100-fold lower affinity than Atx. Homologous competition assay using ^{125}I-GIIA, however revealed that endogenous $sPLA_2$ primarily targeted another binding protein in mitochondria, which is lighter than CCOX-II. Taken together, our results suggest the explanation of the mechanism by which β-ntxs hinder production of ATP in the poisoned nerve ending and open an important direction of study to advance the understanding of the involvement of the mammalian GIIA in mitochondrial function and dysfunction.