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KATP channels openers are capable of brain mitochondria KATP channel opening on nanomolar scale independent of MgATPase activity

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In CNS mitochondrial KATP channel (mKATP channel) is a promising target for the protection of neurons under metabolic stress conditions. While it is generally assumed that pharmacological mKATP channels openers (KCOs) require MgATPase activity for mKATP channel opening, literary data regarding this issue are controversial. Thus, we studied the effect of most used KCOs, diazoxide and pinacidil, on mKATP channel activity in isolated brain mitochondria in the absence and the presence of MgATP. Using light scattering technique, we obtained strong evidence that MgATP complex is dispensable for mKATP channel activation by KCOs and established high sensitivity of brain mKATP channel to these openers with full activation at <0.5 μM of KCOs. Neither Mg^{2+}, nor ATP alone affected the channels affinity to the drugs, but MgATP shifted it to conventional micromolar concentrations. To assure full channel activation, it was specifically blocked by MgATP with consequent activation by KCOs in micromolar range. The blocking of the activated channel by glibenclamide and 5-hydroxydecanoate gave the same estimate of maximal channel activity proving KCOs' ability to elicit full activation on nanomolar scale without MgATP. Based on our experiments we came to the following conclusions: 1) native KATP channels of brain mitochondria are highly sensitive to diazoxide and pinacidil, which open KATP channel independent of MgATPase activity on nanomolar concentration scale; 2) neither Mg^{2+}, nor ATP alone affected the mKATP channels affinity to KATP channels openers, but the presence of MgATP shifted it to much higher micromolar concentrations of the drugs; 3) native brain mKATP channel might comprise the sites with high affinity to diazoxide and pinacidil screened by the binding of MgATP. Obtained results indicate novel common features in the mechanism of native mKATP channel activation by pharmacological openers that would help bring new insight into understanding of mKATP channel properties.

Speaker Biography

Olga V Akopova has completed her PhD in 1997 and a Doctor of Sciences Degree in Biochemistry in 2016. Now she is a principal investigator at Circulation department of AA Bogomoletz Institute of Physiology, Ukraine. Research interests: mitochondrial potassium transport; the impact of K^+ transport on mitochondrial bioenergetics and metabolism; mKATP channels, their properties and cell-specific functions. She published a number of well cited research works devoted to the study of bioenergetic and functional effects of mKATP channel opening in brain and liver mitochondria. At present her interest is focused on the study of pharmacological properties of mKATP channels and their interactions with physiological ligands. She is the author of about 35 research works indexed in MEDLINE and Scopus databases.

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