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МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

MECHANISM(S) OF MODULATION OF Cd^{2+}-INDUCED CYTOTOXCITY BY PAXILLINE AND NS1619/NS004: AN INVOLVEMENT OF Ca^{2+}-ACTIVATED BIG-CONDUCTANCE POTASSIUM CHANNEL AND/OR RESPIRATORY CHAIN OF MITOCHONDRIA?

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The aim of the present study was to investigate molecular mechanisms of modulating action of effectors of Ca^{2+}-activated big-conductance potassium channel (BK(Ca)) against toxicity and cell death evoked by heavy metal ions, cadmium (Cd^{2+}). Experiments were conducted on two cell types (AS-30D, PC12) and isolated liver mitochondria of rat. Previously we observed that cytotoxic effects of Cd^{2+} decreased in the presence of paxilline - BK(Ca) blocker and enhanced in the presence of NS1619 or NS004 – BK(Ca) openers. In this work we have shown that both BK(Ca) activators under test induce apoptosis of AS-30D cells which is sensitive to paxilline. In the simultaneous presence of Cd^{2+} and NS1619 or NS004 in the incubation medium the apoptosis of AS-30D cells increased and paxilline had no influence on it. As recently obtained by us, paxilline does not induce apoptosis per se as well as does not affect the Cd^{2+}-induced apoptosis of AS-30D cells. At the same time, paxilline produced transient decrease of maximal, i.e. completely uncoupled, respiration of AS-30D cells, and enlarged the intracellular production of reactive oxygen species, ROS. Besides, paxilline partially inhibited Cd^{2+}-induced necrosis both of AS-30D and PC12 cells. Moreover, paxilline temporally depressed maximal respiration rate of PC12 cells as well and decreased their ROS production in the presence of Cd^{2+} (Belyaeva, Sokolova, 2020). Using PC12 cells, in the present work we have shown that NS1619 and NS004 do not change significantly the Cd^{2+}-induced ROS generation. Interestingly, maximal decrease of the Cd^{2+}-enhanced ROS formation was observed when PC12 cells were incubated with paxilline in the presence of NS1619 or NS004. The both BK(Ca) openers enhanced harmful effects of Cd^{2+} on respiration and membrane permeability of isolated rat liver mitochondria in incubation media of different ion content.

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