Sensitivity of Liver Mitochondrial Respiratory Chain to 3-bromopyruvate Depends on Respiratory State

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3-Bromopyruvate (3-BrPA) has been suggested to be used as an anti-tumoral drug based on its anti-proliferative property in hepatoma cells. This effect has been proposed to occur by disturbance of glycolysis having as main target of inhibition a hexokinase type II (HK-II) of tumor cells leading to a decreased rate of ATP synthesis. Nevertheless, 3-BrPA was also described to inhibit respiration in hepatoma cells. Previous works described that 3BrPA inhibits succinate dehydrogenase (SDH) activity reacting with SH groups, but the influence of mitochondrial respiration state is unknown. The aim was to investigate the effect of 3-BrPA on mice liver mitochondria electron transport chain (ETC). 3-BrPA caused inhibition of respiration that was associated with a decrease in the membrane potential (? ? m) with succinate. When the mitochondria are phosphorylating ADP (state 3) the IC50 for 3-BrPA inhibition of oxygen consumption was 100 µM. In state 4 (no ADP phosphorylation) the IC50 was 500 µM. Proton unclouper (FCCP), causing the same level of ? ? m depolarization of state 3 was not able to cause the same inhibition. When the respiration was state 3 like induced by yeast HK reaction, 3-BrPA inhibition was faster than in the absence of HK. The same results were observed using rat brain mitochondria that present HK bound to the outer membranes. The results suggest that mitochondrially bound HK type II found in tumors facilitate the 3-BrPa inhibition in tumors mitochondria.

Key Words: Hexokinase, Succinate Dehydrogenase, 3-Bromopyruvate.

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