3-BROMOPYRUVATE: POSSIBLE SITES OF ACTION ON HEPG2 CELLS.

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3-Bromopyruvate has been suggested 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 leading to a decreased rate of ATP synthesis. Hexokinase isoform type II was considered to be the main target of this drug action leading to cell death. We confirmed that 3-Bromopyruvate decreases the viability of human hepatoma cells HepG2 and this effect is time and concentration dependent. The sensitivity of different Hexokinase isoforms (I, IV and II from HepG2 mitochondrial fraction) to 3-Bromopyruvate is different. The type IV isoform activity is more sensitive (IC_{50} = 350 μM) than types I and II that presents only 20 % of inhibition with 5 mM of 3-Bromopyruvate. Low concentrations of 3-Bromopyruvate had no effect on HexokinaseII activity. On the other hand, mitochondrial state 3 respiration sustained by succinate oxidation is inhibited by 50 % with 100 μM of 3-Bromopyruvate. The mitochondrial membrane potential is decreased in the same conditions suggesting a blockage of electron transfer chain. The respiration induced by TMPD/ascorbate is not affected by 3-Bromopyruvate indicating that the inhibition of respiration occurs at the level of complex II-III. The HepG2 dehydrogenases are also sensitive to 3-Bromopyruvate inhibition. We propose that 3-Bromopyruvate have an anti-proliferative action by reducing the respiration and disturbing the redox state of HepG2 cells.