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### Aerosolized 3-bromopyruvate inhibits lung tumorigenesis without causing liver toxicity.

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#### Abstract

3-Bromopyruvate, an alkylating agent and a well-known inhibitor of energy metabolism, has been proposed as a specific anticancer agent. However, the chemopreventive effect of 3-bromopyruvate in lung tumorigenesis has not been tested. In this study, we investigated the chemopreventive activity of 3-bromopyruvate in a mouse lung tumor model. Benzo(a)pyrene was used to induce lung tumors, and 3-bromopyruvate was administered by oral gavage to female A/J mice. We found that 3-bromopyruvate significantly decreased tumor multiplicity and tumor load by 58% and 83%, respectively, at a dose of 20 mg/kg body weight by gavage. Due to the known liver toxicity of 3-bromopyruvate in animal models given large doses of 3-bromopyruvate, confirmed in this study, we decided to test the chemopreventive activity of aerosolized 3-bromopyruvate in the same lung tumor model. As expected, aerosolized 3-bromopyruvate similarly significantly decreased tumor multiplicity and tumor load by 49% and 80%, respectively, at a dose of 10 mg/mL by inhalation. Interestingly, the efficacy of aerosolized 3-bromopyruvate did not accompany any liver toxicity indicating that it is a safer route of administering this compound. Treatment with 3-bromopyruvate increased immunohistochemical staining for cleaved caspase-3, suggesting that the lung tumor inhibitory effects of 3-bromopyruvate were through induction of apoptosis. 3-Bromopyruvate also dissociated hexokinase II from mitochondria, reduced hexokinase activity, and blocked energy metabolism in cancer cells, finally triggered cancer cell death and induced apoptosis through caspase-3, and PARP in human lung cancer cell line. The ability of 3-bromopyruvate to inhibit mouse lung tumorigenesis, in part through induction of apoptosis, merits further investigation of this compound as a chemopreventive agent for human lung cancer.

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