Mechanism of antineoplastic activity of lonidamine.

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Abstract: Lonidamine (LND) was initially introduced as an antispermatogenic agent. It was later found to have anticancer activity sensitizing tumors to chemo-, radio-, and photodynamic-therapy and hyperthermia. Although the mechanism of action remained unclear, LND treatment has been known to target metabolic pathways in cancer cells. It has been reported to alter the bioenergetics of tumor cells by inhibiting glycolysis and mitochondrial respiration, while indirect evidence suggested that it also inhibited l-lactic acid efflux from cells mediated by members of the proton-linked monocarboxylate transporter (MCT) family and also pyruvate uptake into the mitochondria by the mitochondrial pyruvate carrier (MPC). Recent studies have demonstrated that LND potently inhibits MPC activity in isolated rat liver mitochondria (K_i 2.5μM) and cooperatively inhibits l-lactate transport by MCT1, MCT2 and MCT4 expressed in Xenopus laevis oocytes with $K_{0.5}$ and Hill coefficient values of 36-40μM and 1.65-1.85, respectively. In rat heart mitochondria LND inhibited the MPC with similar potency and uncoupled oxidation of pyruvate was inhibited more effectively (IC_{50}~7μM) than other substrates including glutamate (IC_{50}~20μM). LND inhibits the succinate-ubiquinone reductase activity of respiratory Complex II without fully blocking succinate dehydrogenase activity. LND also induces cellular reactive oxygen species through Complex II and has been reported to promote cell death by suppression of the pentose phosphate pathway, which resulted in inhibition of NADPH and glutathione generation. **We conclude that MPC inhibition is the most sensitive anti-tumour target for LND, with additional inhibitory effects on MCT-mediated l-lactic acid efflux, Complex II and glutamine/glutamate oxidation.** PMID: 27497601