Lonidamine Induces Intracellular Tumor Acidification and ATP Depletion in Human Melanoma, Breast, Prostate and Ovarian Cancer Xenografts

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We demonstrate here using noninvasive NMR techniques that the effects of lonidamine (LND, 100 mg/kg in tris-glycine buffer [1], i.p.) are similar for a number of xenograft models of human cancer including DB-1 melanoma (previously reported) [2], HCC1806 breast cancer (ER, PR, HER2 triple negative), BT-474 breast cancer (triple receptor positive), LNCaP prostate cancer, and A2870 ovarian cancer. Each of these tumors exhibits a rapid decrease in intracellular pH to 6.4±0.2, a small decrease in extracellular pH to 6.8±0.1, a concomitant monotonic decrease in nucleoside triphosphate, increase in inorganic phosphate and increase in lactate over a 2–3 hr period. Since mitochondrial respiration is reduced so is the rate of oxygen consumption resulting in tumor oxygenation. These effects of LND are discussed in terms of its mechanism of action as an inhibitor of both monocarboxylic acid transporters and the putative mitochondrial pyruvate carrier. No effect of LND was noted in normal tissues including liver, brain or muscle. Because of the induced specific acute tumor acidification, ATP depletion and inhibition of oxygen consumption rate, LND has been shown to be a potent sensitizer of response to hyperthermia [3] and ionizing radiation as well as to N-mustards and anthracyclines. These results suggest that LND could play a critical role in the management of a number of prevalent forms of human cancer. (Supported in part by NIH grants R01-CA129544 and R01-CA172820.)

References:

