Differential reconstitution of mitochondrial respiratory chain activity and plasma redox state by cysteine and ornithine in a model of cancer cachexia.

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Abstract

The mechanism of wasting, as it occurs in malignant diseases and various etiologically unrelated conditions, is still poorly understood. We have, therefore, studied putative cause/effect relationships in a murine model of cancer cachexia, C57BL/6 mice bearing the fibrosarcoma MCA-105. The plasma of these mice showed decreased albumin and increased glutamate levels, which are typically found in practically all catabolic conditions. Skeletal muscles from tumor-bearing mice were found to have an abnormally low mitochondrial respiratory chain activity (mito.RCA) and significantly decreased glutathione (GSH) levels. The decrease in mito.RCA was correlated with an increase in the i.m. GSH disulfide/GSH ratio, the plasma cystine/thiol ratio, and the GSH disulfide/GSH ratio in the bile. This is indicative of a generalized shift in the redox state extending through different body fluids. Treatment of tumor-bearing mice with ornithine, a precursor of the radical scavenger spermine, reversed both the decrease in mito.RCA and the change in the redox state, whereas treatment with cysteine, a GSH precursor, normalized only the redox state. Treatment of normal mice with difluoromethyl-ornithine, a specific inhibitor of ornithine decarboxylase and spermine biosynthesis, inhibited the mito.RCA in the skeletal muscle tissue, thus illustrating the importance of the putrescine/spermine pathway in the maintenance of mito.RCA. Ornithine, cysteine, and N-acetyl-cysteine (NAC) also reconstituted the abnormally low concentrations of the GSH precursor glutamate in the skeletal muscle tissue of tumor-bearing mice. Higher doses, however, enhanced tumor growth and increased the plasma glucose level in normal mice. In the latter, cysteine and NAC also decreased i.m. catalase and GSH peroxidase activities. Taken together, our studies on the effects of ornithine, cysteine, and NAC illuminate some of the mechanistic pathways involved in cachexia and suggest targets for therapeutic intervention.

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