Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues

Qi Chen*, Michael Graham Espey, Murali C. Krishna, James B. Mitchell, Christopher P. Corpe, Garry R. Buettner, Emily Shacter, and Mark Levine*, ‡

Author Affiliations

*Molecular and Clinical Nutrition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892; ‡Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892; §Free Radical and Radiation Biology Program, University of Iowa, Iowa City, IA 52242–1101; and †Laboratory of Biochemistry, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892

Communicated by J. E. Rall, National Institutes of Health, Bethesda, MD, August 2, 2005 (received for review June 1, 2005)

Abstract

Human pharmacokinetics data indicate that i.v. ascorbic acid (ascorbate) in pharmacologic concentrations could have an unanticipated role in cancer treatment. Our goals here were to test whether ascorbate killed cancer cells selectively, and if so, to determine mechanisms, using clinically relevant conditions. Cell death in 10 cancer and 4 normal cell types was measured by using 1-h exposures. Normal cells were unaffected by 20 mM ascorbate, whereas 5 cancer lines had EC_{50} values of <4 mM, a concentration easily achievable i.v. Human lymphoma cells were studied in detail because of their sensitivity to ascorbate (EC_{50} of 0.5 mM) and suitability for addressing mechanisms. Extracellular but not intracellular ascorbate mediated cell death, which occurred by apoptosis and pyknosis/necrosis. Cell death was independent of metal chelators and absolutely dependent on H_2O_2 formation. Cell death from H_2O_2 added to cells was identical to that found when H_2O_2 was generated by ascorbate treatment. H_2O_2 generation was dependent on ascorbate concentration, incubation time, and the presence of 0.5–10% serum, and displayed a linear relationship with ascorbate radical formation. Although ascorbate addition to medium generated H_2O_2, ascorbate addition to blood generated no detectable H_2O_2 and only trace detectable ascorbate radical. Taken together, these data indicate that ascorbate at concentrations achieved only by i.v. administration may be a pro-drug for formation of H_2O_2, and that blood can be a delivery system of the pro-drug to tissues. These findings give plausibility to i.v. ascorbic acid in cancer treatment, and have unexpected implications for treatment of infections where H_2O_2 may be beneficial.