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Inhibition of aldose reductase in human erythrocytes by vitamin C.

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Ascorbic acid, or vitamin C, has been reported to lower erythrocyte sorbitol concentrations, and present studies were performed to determine the mechanism of this effect. Incubation of erythrocytes with increasing concentrations of glucose (5-40 mM) progressively increased erythrocyte sorbitol contents, reflecting increased flux through aldose reductase. At extracellular concentrations of 90 microM, both ascorbic acid and its oxidized form, dehydroascorbate, decreased intracellular sorbitol by 25 and 45%, respectively. This inhibition was not dependent on the extracellular glucose concentration, or on erythrocyte contents of free NADPH or GSH. To test for a direct effect of ascorbate on aldose reductase, erythrocyte hemolysates were prepared and supplemented with 100 microM NADPH. Hemolysates reduced glucose to sorbitol in a dose-dependent manner that was inhibited with a K_i of 120 microM by the aldose reductase inhibitor tetramethylene glutaric acid. Above 100 microM, ascorbic acid also lowered hemolysate sorbitol generation by about 30%. Studies with ascorbic acid derivatives showed that the reducing capacity of ascorbic acid was not required for inhibition of sorbitol production from glucose in erythrocyte hemolysates. **These results show that high, but physiologic, concentrations of ascorbic acid can directly inhibit erythrocyte aldose reductase, and provide a rationale for the use of oral vitamin C supplements in diabetes.**