HYPOCHLOROUS ACID INHIBITS GLUTATHIONE S-CONJUGATE TRANSPORT

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Hypochlorous acid (HOCl) is a highly reactive oxidant, and it is thought to play an important role in both microbial killing (the bactericidal action of phagocytic cells) and inflammatory tissue injury by neutrophils. The transport of glutathione-S-conjugates is an important element of xenobiotic detoxification, often referred to as detoxification phase III. It apparently plays a significant role in cellular defense under oxidative stress conditions since: (i) it is able to transport glutathione conjugates of lipid peroxidation products; and (ii) it extrudes oxidized glutathione helping to maintain and restore the proper redox state of the cells. The aim of this study was to examine the effect of HOCl on this important cellular transport process in human red blood cells (RBCs). It was found that hypochlorous acid inhibits the active efflux of glutathione S-conjugates, 2,4-dinitrophenyl-S-glutathione ($c_{50\%}=258±24$ µM HOCl) and bimane-S-glutathione ($c_{50\%}=125±16$ µM HOCl) from human erythrocytes, oxidises intracellular glutathione (the ratio $[\text{HOCl}]/[\text{GSH}]_{\text{oxidized}} = 4$) and inhibits basal as well as 2,4-dinitrophenol- and 2,4-dinitrophenyl-S-glutathione-stimulated $\text{Mg}^{2+}$-ATPase activities of erythrocyte membranes. Multidrug resistance-associated protein (MRP1) mediates the active export of glutathione S-conjugates in mammalian cells, including human erythrocytes. A direct impairment of erythrocyte membrane MRP by hypochlorous acid was shown using electrophoresis and immunoblotting ($c_{50\%}=478±36$ µM HOCl). The stoichiometry of the MRP/HOCl reaction was 1:1. These results demonstrate that MRP can be one of the cellular targets for the inflammatory mediator hypochlorous acid.