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Lipoic acid protects efficiently only against a specific form of peroxynitrite-induced damage.

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Abstract

The ability of the sulfur-containing compounds glutathione (GSH), glutathione disulphide (GSSG), S-methylglutathione (GSMe), lipoic acid (LA), and dihydrolipoic acid (DHLA) to protect against hypochlorous acid (HOCl)-mediated damage and peroxynitrite (ONOOH)-induced damage has been compared. Protective activity was assessed in competition assays by monitoring several detectors, i.e. dihydrorhodamine-123 (DHR-123) oxidation, alpha(1)-antiproteinase (alpha(1)-AP) inactivation, and glutathione S-transferase P1-1 (GST-P1-1) inactivation. In addition, nitration of tyrosine was measured to assess protection of the sulfur-containing compounds against ONOOH. For protection against HOCl, the efficacy of the antioxidant was controlled by the ratio of the reaction rates of the antioxidant and the detector molecule with the oxidant. The rank order of the activity of the antioxidants (GSH > DHLA approximately LA approximately GSMe > GSSG) appeared to be independent of the detector used. However, the rank order of the antioxidants against ONOOH-induced damage is strongly dependent on the detector. LA was 40 times less active than GSH in the inhibition of ONOOH-induced DHR-123 oxidation, whereas LA was 20 times more active than GSH in preventing the inhibition of GST-P1-1 by ONOOH. This points to different molecular mechanisms of ONOOH damage to DHR-123 compared with ONOOH damage to GST-P1-1. LA is a poor antioxidant in protecting against the form of ONOOH damage involved in DHR-123 oxidation. In the form of ONOOH toxicity involved in GST-P1-1 inhibition, LA is the most potent sulfur-containing antioxidant in our series. It is proposed that an intermediate product in which both sulfur atoms of LA have reacted is involved in the reaction of ONOOH with LA. The high potency of LA to protect GST-P1-1 against ONOOH might be of therapeutic interest.

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