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264. Gamma-glutamyldehydroalanylglycine is an electrophilic metabolite of glutathione

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Gamma-Glutamyldehydroalanylglycine (EdAG) is a dethiolated, electrophilic metabolite of glutathione (GSH) derived from the Phase II conjugation of GSH with busulfan catalyzed by glutathione S-transferase (GST), specifically isoform

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A1-1. Electrophilic substrates of GST, such as ethacrynic acid and 1-chloro-2,4-dinitrobenzene, have been shown to be irreversible inhibitors of glutathione transferase activity at high concentrations in vitro. EdAG at high concentration (10 mM) was found to be an irreversible inhibitor of human GSTA1-1, and at lower concentrations showed noncompetitive inhibition (Ki = 11 μM). Conversion of GSH to EdAG represents a loss of thiol-related redox properties and the gain of a dehydroalanine group with the potential to scavenge ROS. EdAG competed with DMPO for hydroxyl radical generated in the Fenton reaction in a concentration-dependent manner. The results suggest a stabilized carbon-based captodative radical intermediate in the reaction of EdAG with hydroxyl radical. In support of a captodative mechanism was the identification of a dimerized gamma-glutamylserylglycine as a product in the reaction of hydroxyl radical with EdAG. In summary, it was determined here that EdAG can inhibit GSTA1-1 and also scavenge hydroxyl radical in vitro through a proposed captodative mechanism. The results indicate that the chemical instability of a busulfan metabolite results in the conversion of GSH into EdAG, a reactive compound that is a Michael acceptor and free radical scavenger. The biological implications of EdAG reactivity may have an impact on GSH biochemistry, cellular free radical reactivity, and busulfan toxicology.

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