Thiol antioxidant reversal of pyrrolidine dithiocarbamate-induced reciprocal regulation of AP-1 and NF-κB.

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Abstract

Pyrrolidine dithiocarbamate (PDTC) has been shown to have unique reciprocal activities in activating AP-1 and inhibiting NF-KB, two oxidative stress-sensitive transcription factors. The opposing effects of PDTC on these two transcription factors have been attributed to its thiol antioxidant properties. In the present study, PDTC activation of AP-1, like its inhibition of NF-KB, in bovine cerebral endothelial cells (BCECs) was zinc-dependent, consistent with the contention that PDTC acts as a zinc ionophore and the apparent reciprocal actions of PDTC are mediated by zinc. Unlike PDTC, other thiols and non-thiol antioxidants did not activate AP-1 on their own. Thiol, but not non-thiol, antioxidants reversed PDTC actions on AP-1 and NF-KB. PDTC reduced the intracellular glutathione content, and depletion of the cellular glutathione store by buthionine sulfoximine (BSO) further augmented PDTC actions on AP-1 and NF-KB. N-acetyl-cysteine (NAC), a thiol antioxidant, reversed PDTC actions even after irreversible depletion of the cellular glutathione store by BSO. These findings together suggest that thiol antioxidant reversal of PDTC actions on AP-1 and NF-KB is independent of their established roles in scavenging oxygen free radicals or repleting the cellular glutathione content. The results in the present and earlier studies suggest that thiol antioxidants are likely to act as metal chelators that buffer zinc mediation of the reciprocal actions of PDTC on AP-1 and NF-KB.