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Inhibition of nitric oxide synthesis by methylene blue

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Abstract

Methylene blue appears to inhibit nitric oxide-stimulated soluble guanylyl cyclase and has been widely used for inhibition of cGMP-mediated processes. We report here that endothelium-dependent relaxation of isolated blood vessels and NO synthase-dependent cGMP formation in cultured endothelial cells were both markedly more sensitive to inhibition by methylene blue than effects induced by direct activation of soluble guanylyl cyclase. These discrepancies were also observed when superoxide dismutase (SOD) was present to protect NO from inactivation by superoxide anion. Subsequent experiments showed that formation of L-citrulline by purified NO synthase was completely inhibited by 30 microM methylene blue (IC50 = 5.3 and 9.2 microM in the absence and presence of SOD, respectively), whereas guanylyl cyclase stimulated by S-nitrosoglutathione was far less sensitive to the drug (50% inhibition at approximately 60 microM, and maximal inhibition of 72% at 1 mM methylene blue). Experimental evidence indicated that oxidation of NADPH, tetrahydrobiopterin or reduced flavins does not account for the inhibitory effects of methylene blue. Our data suggest that methylene blue acts as a direct inhibitor of NO synthase and is a much less specific and potent inhibitor of guanylyl cyclase than hitherto assumed.

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