Naphthazarin and methylnaphthazarin cause vascular dysfunction by impairment of endothelium-derived nitric oxide and increased superoxide anion generation

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Abstract

The effects of the naphthoquinone analogue, naphthazarin (Nap), and its derivative, methylnaphthazarin (MetNap), on vascular reactivity were studied using isolated rat aortic rings and human umbilical vein endothelial cells (HUVECs). In this study, we determined vessel tension, nitric oxide (NO) formation, endothelial nitric oxide synthase (eNOS) activity, eNOS protein expression, and superoxide anion (O2*-) generation in an effort to evaluate the effect of Nap and MetNap on the impairment of the NO-mediated pathway. Lower concentrations of Nap (0.01-1 microM) and MetNap (1-10 microM) concentration-dependently enhanced phenylephrine (PE)-induced vasocontraction and abrogated acetylcholine (ACh)-induced vasorelaxation in an endothelium-dependent manner. On HUVECs, both Nap and MetNap concentration-dependently inhibited NO formation induced by A23187, and also partially inhibited nitric oxide synthase (NOS) activity. eNOS protein expression by HUVECs was not affected by treatment with Nap or MetNap, even within 24h. These data suggest that Nap and MetNap might act as inhibitors of nitric oxide synthesis in the endothelium. In addition, Nap and MetNap were also shown to generate O2*- on HUVECs with short-term treatment. We concluded that Nap and MetNap inhibited agonist-induced relaxation and induced vasocontraction in an endothelium-dependent manner, and these effects might have been due to modification of the NO content by inhibition of NOS activity and bioinactivation through O2*- generation.