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The nitroxyl anion (NO): a novel regulator of sGC and vascular tone

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Background

Traditionally the vascular effects of nitric oxide (NO) have been attributed to the free radical form of NO ($NO^{\bullet}$) yet the reduced form of NO (NO^{-}) is also produced endogenously and vasodilates both large conduit and small resistance-like arteries. Interestingly, $NO^{\bullet}$ and NO^{-} have been shown to have distinct mechanisms of action in the cardiovascular system, particularly in the heart. This study aimed to determine if the vasorelaxant effects of NO^{-} differed to those of $NO^{\bullet}$ in rat small mesenteric resistance arteries.

Materials and Methods

Mesenteric arteries (~350 μm diameter) were obtained from male Sprague-Dawley rats, mounted in small vessel myographs and isometric force and intracellular membrane potential measured simultaneously. Vessels were precontracted to ~50% of maximum (determined by K^{+}(124 mM)) with methoxamine. Cumulative concentration-response curves to $NO^{\bullet}$ (NO gas), the NO^{-} donor, Angeli's salt and the NO-independent soluble guanylate cyclase (sGC) activator, YC-1 were examined.

Results

Vasorelaxation to Angeli's salt (pEC_{50} = 7.02 ± 0.67 -log M; R_{max} = 96.0 ± 2.2%, n = 4) was accompanied by simultaneous vascular smooth muscle cell hyperpolarisation (pEC_{50} = 6.82 ± 0.32, 10 μM AS -17.8 ± 4.4 mV, n = 4). In contrast, maximal vasorelaxation to $NO^{\bullet}$ (pEC_{50} = 6.82 ± 0.39, 92.1 ± 1.3%) was achieved before a small hyperpolarization response was observed at 1 μM $NO^{\bullet}$ (-4.9 ± 2.3 mV, n = 5). Both relaxation and hyperpolarisation responses to Angeli's salt were significantly attenuated ($P < 0.05$, n = 5) by the NO^{-} scavenger, L-cysteine (3 mM) and abolished by the sGC inhibitor, ODQ (10 μM; $P < 0.05$, n = 4). The K_V channel inhibitor, 4-aminopyridine (1 mM) caused a 4-fold ($P < 0.05$, n = 4) decrease in sensitivity to Angeli's salt and abolished the hyperpolarisation response ($P < 0.05$). In contrast glibenclamide (K_{ATP} channel inhibitor) and charybdotoxin (BK_{Ca}/IK_{Ca} channel inhibitor) were without effect. YC-1 also induced vasorelaxation and hyperpolarisation in rat small mesenteric arteries.

Conclusion

In conclusion, in rat small mesenteric arteries, NO^{-} mediates relaxation in part via cGMP-dependent activation of K_V channels. In contrast, $NO^{\bullet}$-mediated vasorelaxation occurs independently of vascular smooth muscle hyperpolarisation. Thus, the redox siblings $NO^{\bullet}$ and NO^{-} have distinct mechanisms of vasorelaxation in resistance-like arteries.