K_v as a target for nitroxyl anion (NO^-)-mediated vasodilatation

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Traditionally the vascular effects of nitric oxide (NO) have been attributed to the free radical form of NO ($NO^•$) yet the reduced form of NO (NO^-) is also produced endogenously and vasodilates both large conduit and small resistance-like arteries (Irvine *et al.*, 2003). Interestingly, $NO^•$ and NO^- have been shown to have distinct mechanisms of action in the cardiovascular system, particularly in the heart (Paolocci *et al.*, 2003). This study aimed to determine if the vasorelaxant effects of NO^- differed to those of $NO^•$ in rat small mesenteric resistance arteries. Male Sprague-Dawley rats were killed *via* CO_2 sedation and cervical dislocation. Mesenteric arteries (~350μm diameter) were isolated, mounted in small vessel myographs and isometric force and intracellular membrane potential measured simultaneously. Cumulative concentration-response curves to $NO^•$ (NO gas), the NO^- donor, Angeli's salt and the NO-independent soluble guanylate cyclase (sGC) activator, YC-1 were examined. 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, 10μM AS -17.8±4.4 mV, n=4). In contrast, maximal vasorelaxation to $NO^•$ (pEC_{50}=6.82±0.39, 92.1±1.3%) was achieved before a small hyperpolarisation response was observed at 1μM $NO^•$ (-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 (3mM) and virtually abolished by the sGC inhibitor, ODQ (10μM; $P<0.05$, n=4). In contrast, ODQ only decreased the sensitivity of $NO^•$-mediated vasorelaxation approximately 10-fold ($P<0.05$, n=4) and failed to affect $NO^•$-mediated hyperpolarisation. The K_v channel inhibitor, 4-aminopyridine (1mM) caused a 4-fold ($P<0.05$, n=4) decrease in sensitivity to Angeli's salt and abolished the hyperpolarisation response ($P<0.05$). Glibenclamide (K_{ATP} channel inhibitor) and charybdotoxin (BK_{Ca}/IK_{Ca} channel inhibitor) were without effect. YC-1 also induced smooth muscle hyperpolarisation (10μM YC-1 -43.0±6.3 mV, n=3) which was attenuated by 4-aminopyridine (10μM YC-1 -23.5±2.3 mV, $P<0.05$, n=3). In conclusion, in rat small mesenteric arteries, NO^- mediates relaxation in part *via* cGMP-dependent activation of K_v channels. In contrast, $NO^•$-mediated vasorelaxation occurs independently of vascular smooth muscle hyperpolarisation and in part *via* cGMP-independent pathways. Thus, the redox siblings $NO^•$ and NO^- have distinct mechanisms of vasorelaxation in resistance-like arteries.

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