Nitroxyl (HNO) as a vasoprotective signalling molecule

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Nitroxyl (HNO), the reduced and protonated congener of nitric oxide (NO·), is rapidly emerging as a novel entity with distinct pharmacology and therapeutic advantages over NO· (Bullen *et al.* 2011). Unlike NO•, HNO interacts directly with thiols to increase myocardial contractility, elevates plasma levels of calcitonin gene-related peptide and is resistant to scavenging by superoxide ($\cdot O_2^-$). Whilst these unique properties of HNO confer potential in the treatment of heart failure, our studies have also highlighted vasoprotective actions of HNO. The vasoprotective actions of HNO were studied in models of hypertension and atherosclerosis. Our studies have shown that like NO·, HNO donors serve as potent vasorelaxants (including human arteries; Andrews *et al.*, 2015), and inhibit platelet aggregation, mediating these effects predominantly *via* sGC activation and an elevation in cGMP. In contrast to NO·, HNO donors are resistant to scavenging by $\cdot O_2^-$ and vascular tolerance development and target distinct vascular signaling pathways. Indeed we have shown that the vasoprotective (vasorelaxant, anti-aggregatory) actions of HNO are sustained in the setting of hypertension (SHR rat) and atherosclerosis (ApoE-/- mouse), where endogenous NO· bioavailability is reduced. Furthermore, HNO rapidly suppresses vascular $\cdot O_2^-$ generation from Nox2-NADPH oxidase, *via* a cGMP-independent action, and limits vascular dysfunction (Miller *et al.*, 2013). In conclusion, HNO donors offer considerable advantages over traditional NO· donors due to their preserved bioavailability in oxidative stress, lack of tolerance and favourable vasoprotective properties and may provide innovative pharmacotherapy for the treatment of vascular disease.

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