## Novel nitric oxide mimetics in the treatment of vascular dysfunction

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The therapeutic utility of the nitric oxide (NO) signalling pathway has long been recognised with nitrovasodilators employed in the treatment of cardiovascular disorders such as angina, hypertension, stroke and heart failure for over 100 years. The clinical efficacy of traditional NO donors however, has been limited due to susceptibility to tolerance development, decreased effectiveness under oxidative stress and cytotoxic effects. Excitingly, nitroxyl (HNO) donors and NO-independent soluble guanylyl cyclase (sGC) activators are rapidly emerging as novel pharmacological agents with therapeutic advantages over traditional NO donors in cardiovascular disease (Irvine *et al.*, 2008, Stasch *et al.*, 2006). Our studies have highlighted vasoprotective actions of these novel NO mimetics (Bullen *et al.*, 2011). Thus like NO, HNO donors and sGC activators (*i.e.* BAY 58-2667) serve as potent vasorelaxants (including human arteries), inhibit platelet aggregation and suppress vascular superoxide generation. However, in contrast to NO, these novel NO mimetics are resistant to scavenging by superoxide and vascular tolerance development and BAY 58-2667 preferentially targets the oxidized/heme-free form of sGC which predominates in disease. As such, the efficacy of HNO donors and sGC activators may be preserved under conditions of oxidative stress. Indeed we have shown that the vasoprotective (vasorelaxant, anti-aggregatory) actions of HNO are sustained, and those to BAY 58-2667 enhanced, in the setting of hypertension (spontaneously hypertensive rat) and hypercholesterolemia (apolipoprotein E-deficient mice). In conclusion, HNO donors and NO-independent sGC activators offer considerable advantages over traditional NO donors due to their preserved bioavailability in oxidative stress, lack of tolerance development and favourable vasoprotective properties and may provide innovative pharmacotherapy for the treatment of vascular disease.

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