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The nitroxyl anion (HNO) donor, Angeli's salt, does not develop tolerance *in vivo*

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In addition to the free radical form of nitric oxide (NO•), the reduced form of NO (NO^-/HNO) is also produced endogenously, causes vasorelaxation and has therapeutic potential in the treatment of heart failure. Given we have shown previously that, unlike the NO• donor glyceryl trinitrate (GTN), the HNO donor Angeli's salt (AS) does not develop tolerance *in vitro* [1], this study aimed to determine whether AS was also resistant to the development of tolerance *in vivo*. Initial experiments using WKY rats confirmed that infusion with the HNO scavenger, *N*-Acetyl-L-cysteine (6.7 μmol/kg/min) significantly ($P < 0.0001$) attenuated the concentration dependent depressor responses to AS, whilst those to GTN or the additional NO• donor, DEA/NO, were unchanged. Rats were instrumented with arterial and venous catheters and the depressor effects of GTN, AS and DEA/NO were examined in vehicle treated and GTN (10 μg/kg/min), AS (20 μg/kg/min) or DEA/NO (2 μg/kg/min) pre-treated animals (3 day infusion via osmotic mini pump). Following this, aortae were removed and *ex vivo* tolerance to all vasodilators assessed via examining vasorelaxation responses. GTN pre-treatment significantly blunted the depressor response to 50 μg/kg GTN (-9 ± 1 mmHg MAP) compared to vehicle treated rats (-40 ± 2 mmHg MAP; n = 8–9; $P < 0.001$) but did not alter the depressor responses to either AS or DEA/NO. Similarly, *in vitro* relaxation responses to GTN in GTN pre-treated rats showed a significant 6-fold decrease in sensitivity (pEC_{50} = 6.72 ± 0.23; R_{max} = 79.4 ± 3.4%; n = 7) compared with vehicle treated rats (pEC_{50} = 7.51 ± 0.14; R_{max}= 93.4 ± 2.1%; n = 6; $P < 0.05$) yet vasorelaxation to AS and DEA/NO was unchanged. In addition, vasorelaxation to acetylcholine (ACh) was attenuated in GTN pre-treated rats (R_{max} = 54.4 ± 5.4%; n = 6) compared to vehicle treated rats (R_{max} = 77.1 ± 2.3%; n = 5). In contrast, AS was resistant to *in vivo* tolerance development. Thus the depressor response to 200 μg/kg AS (-33 ± 4 mmHg MAP; n = 6–7) was unchanged following AS pre-treatment (-34 ± 3 mmHg MAP). Furthermore AS did not cause cross tolerance to either GTN or DEA/NO *in vivo*. Likewise, there was no change in the *in vitro* relaxation responses to AS in AS pre-treated rats (pEC_{50} = 6.77 ± 0.15; R_{max} = 92.3 ± 1.7%; n = 7) compared with vehicle treated rats (pEC_{50} = 6.77 ± 0.17; R_{max} = 93.0 ± 2.7%; n = 6), nor was there a reduced response to ACh. Like AS, DEA/NO did not develop tolerance either *in vitro* or *in vivo*. In conclusion, the HNO donor AS does not develop tolerance *in vivo*, thus suggesting that HNO donors may represent a novel class of nitrovasodilator for the treatment of cardiovascular disorders, such as heart failure and angina.

References

1. Irvine JC, Favaloro JL, Widdop RE, Kemp-Harper BK: **Nitroxyl anion donor, Angeli's salt, does not develop tolerance in rat isolated aortae.** *Hypertension* 2007, **49**:885-892.