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Poster presentation

Nitroxyl, the novel redox sibling of NO, suppresses cerebrovascular NADPH oxidase

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Background

Nitroxyl (HNO), the reduced and protonated congener of nitric oxide (NO), is emerging as a novel entity with distinct pharmacology and therapeutic advantages over NO• [1]. Importantly, HNO has vasoprotective actions with the potential to serve as an antioxidant. Here we explored the ability of HNO to modulate cerebrovascular NADPH oxidase activity, a major source of superoxide ($\cdot O_2^-$) in the vasculature.

Materials and methods

Intracranial (pooled middle cerebral and basilar) and extracranial (carotid) cerebral arteries from male C57BL/6J mice were treated with angiotensin II (10 nM) acutely (30 min) and chronically (24 h), respectively, in the absence and presence of the HNO donor, Angeli's salt (AS). NADPH (100 μM)-stimulated $\cdot O_2^-$ production was then measured using lucigenin (5 μM)-enhanced chemiluminescence.

Results

AS (1 μM) did not scavenge $\cdot O_2^-$ generated in a cell free xanthine (100 μM)/xanthine oxidase (0.05 U/ml) activity assay (control: 447.9 ± 90.8; AS 507.1 ± 113.3 counts, n = 4). In contrast, acute and chronic treatment with AS (0.01–1 μM) caused a concentration-dependent decrease in NADPH oxidase-derived $\cdot O_2^-$ production by intracranial and extracranial cerebral arteries, respectively (carotid 0.59 ± 0.05; AS 0.1 μM 0.33 ± 0.08; AS 1 μM 0.16 ± 0.03 10^3 counts/s/mg, $P < 0.05$, n = 8). The effects of AS were reversed by the HNO scavenger, L-cysteine (3 mM) but unchanged in the presence of the NO• scavenger carboxy-PTIO (200 μM) and sGC inhibitor, ODQ (10 μM).

Conclusion

HNO suppresses vascular NADPH-oxidase activity both acutely and chronically, possibly via a cGMP-independent mechanism. Such antioxidant actions of HNO may confer therapeutic advantages in the treatment of cerebrovascular disorders.

References

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