Poster presentation

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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 μ M)-stimulated \cdot O₂ production was then measured using lucigenin (5 μ M)-enhanced chemiluminescence.

Results

AS (1 μ M) did not scavenge O_2 generated in a cell free xanthine (100 μ M)/xanthine oxidase (0.05 U/ml) activity assay (control: 447.9 \pm 90.8; AS 507.1 \pm 113.3 counts, n = 4). In contrast, acute and chronic treatment with AS (0.01–1 μ M) caused a concentration-dependent decrease in NADPH oxidase-derived O_2^- production by intracranial and extracranial cerebral arteries, respectively (carotid

 0.59 ± 0.05 ; AS 0.1 μ M 0.33 \pm 0.08; AS 1 μ M 0.16 \pm 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 μ M) and sGC inhibitor, ODQ (10 μ M).

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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