Impaired cardiac adrenergic and NO-cGMP signalling in the spontaneously hypertensive rat

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Introduction

Early hypertension is associated with tachycardia, high cardiac output (Julius et al. 1991), elevated plasma catecholamines (Esler et al. 1977) and decreased parasympathetic tone (Julius et al 1971).

Functionally, enhanced sympathetic activity may be due to reduced bioavailability of nitric oxide (NO) or guanylate cyclase (GC) since neuronal nitric oxide synthase (NOS-1) activation of the NO-cGMP pathway decreases central sympathetic activity (Li et al. 2002), the peripheral pre-synaptic release of noradrenaline (NA) (Schwarz et al. 1995) and the heart rate (HR) response to sympathetic nerve stimulation (SNS) (Choate and Paterson 1999).

AIMS

Is the enhanced sympathetic response during hypertension brought about by impaired NO-cGMP signalling ?

Can adenoviral gene transfer of NOS-1 provide a potential strategy for targeting sympathetic overactivity in hypertension ?

Methods

A

***In-vitro* rat atrial preparation and Western Blotting**

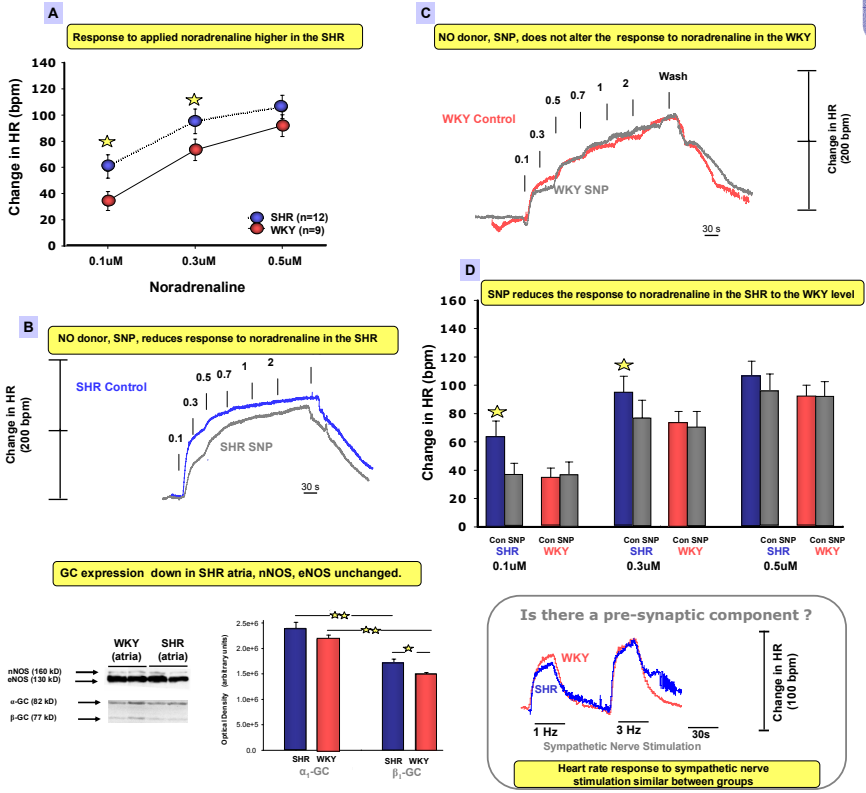
The heart rate (HR) response to β-adrenergic activation was examined in isolated rat atria/stellate ganglion preparations from 16 wk old spontaneously hypertensive rats (SHR, n=15) and normotensive Wistar-Kyoto rats (WKY, n=14). Western blot analysis for NOS-1 and guanylate cyclase was performed on atria from both groups.

B

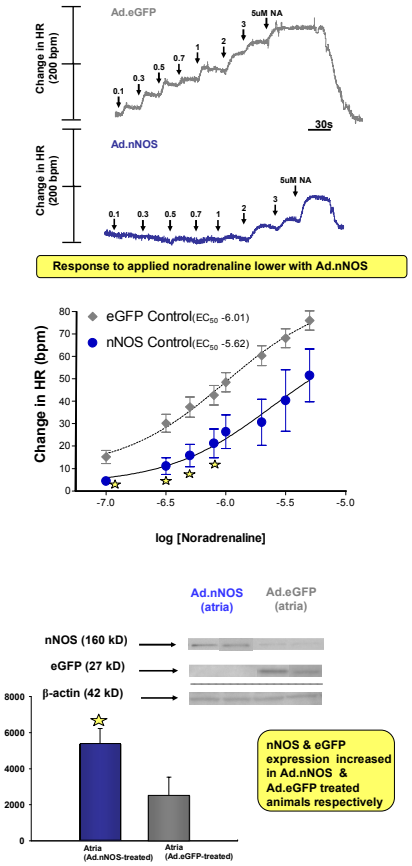
***In-vivo* neuronal nitric oxide synthase adenoviral gene transfer in a normotensive guinea pig**

Under general anaesthesia, 2 groups of guinea pigs (n=16 per group) were injected with Ad.nNOS or Ad.eGFP adenovirus ($5x10^9$-$5x10^{10}$ virus particles/μL) directly into the atrial wall. A period of 3-5 days was given for viral incubation *in-vivo* and following this, all *in-vitro* procedures in A were repeated.

Results A: *In-vitro* phenotype in SHR &WKY



Results B: *In-vitro* phenotype following gene transfer



Conclusion

New findings:

- **The enhanced adrenergic response in the SHR is related to impaired NO-cGMP signalling.**
- **The small down-regulation of sGC is not consistent with the hypothesis that the major impairment resides at the level of guanylate cyclase and may occur further downstream.**
- **Upregulation of NOS-1 using adenoviral gene transfer may be a useful strategy to compensate for the enhanced post-synaptic adrenergic overactivity during the early stages of hypertension.**

References

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