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С Response to applied noradrenaline higher in the SHR NO donor, SNP, does not alter the response to noradrenaline in the WKY Early hypertension is associated with tachycardia, high cardiac output (Julius et al. 1991), 140 elevated plasma catecholamines (Esler et al. 1977) and decreased parasympathetic tone Wasł 2 120 hange in HR (bpm) Ad.eGFF 0.7 05 (Julius et al 1971). 100 Change in HR (200 bpm) WKY Contro Change in H (200 bpm) 0.3 80 0.1 60 Functionally, enhanced sympathetic activity may be due to reduced bioavailability of nitric WKY SN 40 ΰ oxide (NO) or guanylate cyclase (GC) since neuronal nitric oxide synthase (NOS-1) SHR (n=12) WKY (n=9) 20 Ad.nNOS 30 s Change in HR (200 bpm) activation of the NO-cGMP pathway decreases central sympathetic activity (Li et al. 2002), 0.1uN 0.3uM 0.5uM п the peripheral pre-synaptic release of noradrenaline (NA) (Schwarz et al. 1995) and the Noradrenaline SNP reduces the response to noradrenaline in the SHR to the WKY level 160 heart rate (HR) response to sympathetic nerve stimulation (SNS) (Choate and Paterson в 140 NO donor, SNP, reduces response to noradrenaline in the SHR Response to applied noradrenaline lower with Ad.nNOS 1999). Ê 120 0.5 0.7 100 SHR Contro Ĥ Ĥ eGFP Control(ECso -6.01) Change in H (200 bpm) 0.3 80 (mqd) Ē AIMS nNOS Control(EC. 0 1 8 60 SHR SNP Is the enhanced sympathetic response during hypertension brought about 땊 5 40 Ξ. by impaired NO-cGMP signalling ? 30 s ge 20 Can adenoviral gene transfer of NOS-1 provide a potential strategy for f Con SNP Con SN Con SNP Con SNF Con SNP SHR Con SNP WK) 0.1uM 0.3uM 0.5uM targeting sympathetic overactivity in hypertension ? GC expression down in SHR atria, nNOS, eNOS unchanged. -6.5 -6.0 -5.5 Is there a pre-synaptic component? log [Noradrenaline] WKY in HR Ad.nNOS Ad.eGFP Change i (100 b (atria) In-vitro rat atrial preparation and Western Blotting β-GC (77 kD nNOS (160 kD) 3 Hz 1 Hz 30s The heart rate (HR) response to β -adrenergic activation was examined in isolated rat •GFP (27 kD) Sympathetic Nerve Stimulation SHR WKY Heart rate response to sympathetic nerve α,-GC ß.-GC B-actin (42 kD) atria/stellate ganglion preparations from 16 wk old spontaneously hypertensive rats 800 (SHR, n=15) and normotensive Wistar-Kyoto rats (WKY, n=14). Western blot analysis 600 nNOS & eGFF expression incre for NOS-1 and guanylate cyclase was performed on atria from both groups. 400 in Ad.nNOS & Ad.eGFP treated 8 animals respectivel 200 В ā New findings: In-vivo neuronal nitric oxide synthase adenoviral gene transfer in a Atria Atria (Ad.nNOS-treated) (Ad.eGFP-treated) • The enhanced adrenergic response in the SHR is related to impaired NO-cGMP signalling. normotensive guinea pig • The small down-regulation of sGC is not consistent with the hypothesis that the major REFERENCES impairment resides at the level of guanylate cyclase and may occur further downstream. REFERENCES Cholate and Paterson. (1999). Journal of the Autonomic Nervous System, 75:100-108. Ester et al. (1977). New England Journal of Medicine, 296:405-411. Julius et al. (1997). J. Hypertension, 977-64. Julius et al. (1997). J. Hypertension, 977-64. Julius et al. (1997). J. Hypertension, 977-64. Under general anaesthesia, 2 groups of guinea pigs (n=16 per group) were injected with • Upregulation of NOS-1 using adenoviral gene transfer may be a useful strategy to compensate Ad.nNOS or Ad.eGFP adenovirus (5x109-5x1010 virus particles/uL) directly into the atrial for the enhanced post-synaptic adrenergic overactivity during the early stages of hypertension. wall. A period of 3-5 days was given for viral incubation in-vivo and following this, all in-ACKNOWLEDGEMENTS

vitro procedures in A were repeated.