

**Impaired cardiac vagal activation and down regulation of atrial guanylate cyclase in the spontaneously hypertensive rat.**

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Hypertension is associated with reduced cardiac vagal tone and an impairment of the nitric oxide/guanylate cyclase pathway in the vasculature. Our aim was to examine whether this pathway is impaired in the spontaneously hypertensive rat (SHR) during cardiac vagal activation, since it has been shown to facilitate vagal neurotransmission. We studied the heart rate response to cholinergic activation in isolated rat double atrial/ right vagus preparations (at 37°C) from age matched spontaneously hypertensive rats (n=20) and normotensive Wistar-Kyoto rats (n=26). The bradycardia in response to vagal nerve stimulation in SHRs was significantly attenuated compared to WKYs (3 Hz WKY  $28 \pm 2$  bpm, SHR  $19 \pm 2$ ; 5 Hz WKY  $40 \pm 3$ , SHR  $29 \pm 3$ ; 7 Hz WKY  $53 \pm 4$ , SHR  $38 \pm 5$ ;  $p < 0.05$ ). In contrast, the effect of bath applied carbamylcholine (100-500 nmol/L) was slightly enhanced in SHRs compared to WKY rats. The NO donor, sodium nitroprusside (20  $\mu$ mol/L) augmented the vagal response in WKY, but not SHR rats at 10 Hz stimulation, suggesting an impairment of the pre-synaptic NO-cGMP pathway in the SHR. Western blot analysis for guanylate cyclase showed a reduction in expression of the  $\alpha 1$  subunit in the atria and the aorta of the SHR. In conclusion, the decreased heart rate response to vagal nerve stimulation in the SHR and the associated down regulation of atrial guanylate cyclase is consistent with the hypothesis that impairment of the NO-cGMP pathway may underlie cardiac vagal dysfunction in hypertension.