VAGAL MODULATION OF HEART RATE IN THE NEURONAL NITRIC OXIDE SYNTHASE KNOCKOUT MOUSE *IN-VITRO*

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The role of nitric oxide (NO) synthesized by neuronal NO-synthase (nNOS) within cardiac parasympathetic neurones in the vagal control of pacemaking currents is controversial. We investigated the vagal regulation of heart rate in isolated spontaneously beating atrial/right vagal preparations from wild-type (WT) mice and mice with a nNOS mutation (nNOS-/-). nNOS was immmunohistologically localized within intrinsic neurones innervating the sino-atrial node region of the right atrium (n=4 WT mice). Baseline HR was significantly higher in the nNOS-/- (361±7 bpm; n=39) compared to the WT (322±6 bpm; n=67; $P<0.01$) atria. During vagal stimulation (3Hz, 10V, 30s) the rate of decline in HR was significantly slowed in the nNOS-/- (time to 50% of maximum vagal heart rate response; TT50% = 7.30±0.38 s; n=39) versus the WT atria (TT50% = 5.93±0.28 s; n=28; $P<0.01$). Similarly, in WT atria the NOS inhibitor L-NMMA (100μM; n=8) significantly increased the TT50% for the vagal HR response from 6.51±0.55 s to 7.44±0.56 , an effect that was reversed to 6.63±0.53 s with L-Arginine (1mM; ANOVA; $P<0.01$). Bypassing endogenous NO production with the NO donor sodium nitroprusside (SNP; 10mM) significantly enhanced the magnitude of the vagal HR response (3Hz) in both WT (control = 44±6 bpm; SNP = 60±8 bpm; n=10) and nNOS-/- atria (control = 35±6 bpm; SNP = 47±8 bpm; n=7; $P<0.05$). The downstream intracellular pathways were therefore intact in the nNOS-/- atria. In conclusion, these findings indicate that NO synthesized by nNOS modulates the HR response to cardiac parasympathetic nerve stimulation.