Danson, E.J.F., Mohan, R.M., Garland, T. and Paterson, D.J. NO-cGMP pathway enhances the heart rate response to peripheral vagal nerve stimulation in exercise trained mice *Circulation* 104(17):S833,2001 .

The NO-cGMP pathway has been implicated in the cholinergic regulation of heart rate (HR). We investigated whether the enhanced cardiac vagal tone brought about by exercise training was NO dependent. Isolated atria with intact right vagal innervation were taken from male mice that had been selectively bred for increased wheel-running following 20 weeks of voluntary running (+EX, n=8). Ventricle:Body weight ratios were +EX:6.60$\pm$0.58mg/g versus –EX: 3.97$\pm$0.34mg/g ($P<0.001$) at 20 weeks. The negative chronotropic responses to right vagal nerve stimulation (VNS, 3-5Hz) and bath-applied carbamylcholine (CCh, 0.01-100[micro]mol/L) were measured in +EX and –EX atria. In +EX atria, spontaneous beating rates were significantly lower than those in –EX atria (325$\pm$16 vs. 379$\pm$6 beats per minute, $P<0.01$), and the HR responses to VNS were significantly greater in +EX atria ($P<0.01$). However, there was no difference between the HR response to CCh in +EX and –EX atria, suggesting that the differences observed during VNS resulted from a presynaptic adaptation. Inhibition of neuronal nitric oxide synthase (nNOS) with vinyl-L-nio-hydrochloride (L-VNIO, 100[micro]mol/L) significantly attenuated the HR response to VNS in both +EX and –EX atria ($P<0.01$), but it had a significantly greater effect in +EX atria ($P<0.05$). Moreover, L-VNIO abolished the significant difference between the control HR responses to VNS in +EX and –EX atria, suggesting that this difference may have been related to an exercise-dependent up-regulation of nNOS in +EX atria. Effects of L-VNIO were reversed by L-arginine (1mmol/L). Inhibition of soluble guanylyl cyclase with ODQ (10[micro]mol/L), had a similar effect to L-VNIO in all atria. Enhancing the bioavailability of NO-cGMP with sodium nitroprusside (10[micro]mol/L) or the cGMP analogue 8-Br-cGMP (0.5mmol/L) increased the HR responses to VNS, but not to CCh, to the same extent in both +EX and –EX atria. These results show that exercise training enhances the HR response to peripheral vagal nerve stimulation by a NO-cGMP dependent presynaptic mechanism that probably facilitates acetylcholine release.