NO-cGMP DEPENDENT PATHWAY AND THE MODULATION OF VAGAL CONTROL OF HEART RATE

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The role of the NO-cGMP dependent pathway in the vagal control of heart rate (HR) is controversial. Double atrial/right vagus nerve preparations were dissected from adult (550-750 g) and young (150-250 g) female guinea pigs and placed in an organ bath containing Tyrode solution at 37 °C. Inhibition of NOS with 100 μM Nω-Nitro-L-Arginine (L-NA) in the adult guinea pig significantly reduced the negative chronotropic response to vagal nerve stimulation (VNS) at 5 Hz (5-10 V, 1 ms duration, 30 s); this effect was reversed with 1mM L-arginine (ΔHR 53$\pm$5 bpm control, 43$\pm$5 bpm.L-NA, 53$\pm$6 bpm L-NA+L-arginine, n=5). This effect was not observed in young guinea pigs (n=6). Western blot analysis of nNOS protein levels in right atria showed less protein in young compared to adult guinea pigs. The guanylyl cyclase inhibitor 10 μM 1H-(1,2,4) oxadiazolo (4,3-a) quinoxalin-1-one (ODQ) significantly reduced the negative chronotropic response to VNS at 5 Hz in adult guinea pigs (65$\pm$3 bpm control, 51$\pm$2 bpm ODQ, n=6). Conversely, 10 μM or 100 μM sodium nitroprusside (SNP) increased the HR response to VNS at 5 Hz (53$\pm$4 bpm control, 66$\pm$5 bpm 10 μM SNP, 55$\pm$4 bpm wash, n=7), although this was not seen in the presence of the phosphodiesterase (PDE) III inhibitor 1 μM milrinone (n=7) or the protein kinase A (PKA) inhibitor 0.5 μM H-89 (n=5). Neither 10 μM SNP (n=8) nor 100 μM L-NA (n=5) significantly changed the HR response to 100 nM carbamylcholine. These results are consistent with the hypothesis that NO facilitates the presynaptic release of acetylcholine in adult guinea pigs via cGMP inhibition of PDE III to raise presynaptic cAMP and increase the activity of PKA.