NO-cGMP PATHWAY FACILITATES VAGAL NEUROTRANSMISSION AND BRADYCARDIA

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The mechanism by which the NO-cGMP dependent pathway augments the magnitude of vagal induced-bradycardia is not established. We tested the hypothesis that NO facilitates acetylcholine release by phosphorylation of pre-synaptic calcium channels. Atrial/right vagus nerve preparations were dissected from adult guinea pigs and placed in an organ bath containing Tyrode solution at 37°C. Heart rate (HR) was triggered from contraction and right atrial acetylcholine release was measured by radioactively labeling cholinergic transmitter stores. The NO donor sodium nitroprusside (SNP, 10 μM, n=7) augmented the HR response to vagal nerve stimulation (VNS), but not carbamylcholine (100 nM, n=8), and increased the release of 3H-acetylcholine to field stimulation (n=4). No effect of SNP was observed on either the release of ^{3}H-acetylcholine (n=4) or the HR response to VNS (n=5) in the presence of the guanylyl cyclase inhibitor ODQ (10 μM). SNP was unable to increase the vagal bradycardia at any stimulation frequency after inhibition of cGMP inhibited phosphodiesterase (PDE) 3 with milrinone (1 μM, n=7). SNP was still able to augment the vagal bradycardia in the presence of the protein kinase (PK) G inhibitor KT5823 (1 μM, n=6) but not after inhibition of PKA with H-89 (0.5 μM, n=5). SNP still augmented vagal bradycardia after inhibition of P-type calcium channels with ω-agatoxin (50 nM, n=5) but had no effect after inhibition of N-type calcium channels with ω-conotoxin (100 nM, n=6). These results suggest that NO acts via a cGMP-PDE3 dependent pathway to increase cAMP dependent PKA phosphorylation of pre-synaptic N-type calcium channels. This pathway can augment vagal bradycardia by increasing pre-synaptic calcium influx and vesicular release of acetylcholine.

Figure 1A

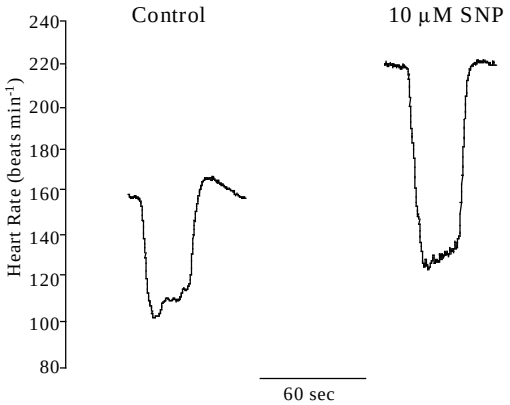

Figure 1B