ACTIVATION OF K_{ATP} CHANNELS AND NO-CGMP PATHWAY DECREASE THE HEART RATE RESPONSE TO SYMPATHETIC NERVE STIMULATION IN-VITRO

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Activation of ATP-sensitive K^+ channels (K_{ATP}) (Oe et al. *Card. Res.*43:125-134, 1999) and the NO-cGMP pathway (Schwarz et al. *Circ. Res.*77:841-8, 1995) have both been implicated in reducing norepinephrine (NE) release during cardiac sympathetic nerve stimulation (SNS). Our aim was to test whether these pathways could interact and modulate cardiac excitability during SNS. The effect of inhibitors and activators of K_{ATP} channels and the NO-cGMP pathway on the heart rate (HR) response to cardiac SNS in the isolated guinea pig double atrial/right stellate ganglion preparation was studied (n=35). The K_{ATP} channel activator, diazoxide (DZ:100μM, n=6) or *in-vitro* hypoxia (0% O_2 / 5% CO_2, n=6) significantly attenuated the HR response to SNS; an effect that was reversed by the K_{ATP} channel inhibitor, glibenclamide (GLIB: 30μM). GLIB (n=6) on its own enhanced the HR response to SNS. Bath applied NE (0.1-0.7μM, n=6) did not affect the HR response to DZ, although an increased response to GLIB was observed at 0.3 and 0.5μM NE. The NOS inhibitor, L-NA (100μM, n=6) significantly increased the HR response to SNS in the presence of DZ. This effect was reversed with excess L-arginine (1mM). Conversely, sodium nitroprusside (20μM) significantly attenuated the HR response to SNS. Addition of GLIB (30μM, n=10) could still enhance the response to SNS. Similar results were seen with 8 Br-cGMP (0.5mM, n=12). Taken together, our results are consistent with the hypothesis that the NO-cGMP pathway and K_{ATP} channels act in a complementary fashion to regulate the HR response to cardiac SNS via a pre-synaptic modulation of NE release.