

ABSTRACTS FOR ORAL PRESENTATION, SESSION 1, HRC2014

ACUTE AND CHRONIC WITHDRAWAL OF DORSAL VAGAL PREGANGLIONIC ACTIVITY IN THE CENTRAL NERVOUS SYSTEM PREDISPOSES TO VENTRICULAR ARRHYTHMIA

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Introduction: Electrical stimulation of the vagus nerve has been shown to protect against ventricular tachyarrhythmia (VT). The exact mechanism of this effect is unknown and it also remains unclear whether acute or chronic withdrawal of tonic vagal efferent activity to the heart predisposes the heart to VT. To investigate this, we acutely silenced the vagal preganglionic neurones in the dorsal motor nucleus of the vagus nerve (DVMN) in a rat model using a pharmogenetic approach, and we used the triple-synuclein-null mice as a model of autonomic dysfunction associated with chronic reduction of vagal tone.

Methods: In 12 male Sprague-Dawley rats (380-420g), lentiviral vectors were used to

Methods: In 12 male Sprague-Dawley rats (380-420g), lentiviral vectors were used to transduce DVMN neurones to express an inhibitory Gi-protein-coupled Drosophila allatostatin receptor (AlstR) or green fluorescent protein as a control. Application of a natural ligand of AlstR - an insect peptide allatostatin (5 μl) produces selective and rapid silencing of targeted neurones. To investigate the role of age-dependent autonomic dysfunction, 7 young (2-3 months) and 8 old (12-16 months) wild type (WT) and triple-synuclein-null (TKO) mice were studied. The animals underwent programmed electrical stimulation of the right ventricle under urethane anaesthesia (1.3g/kg) to obtain ventricular effective refractory period (VERP). Ventricular tachycardia (VT) inducibility by burst pacing was also assessed in the acute rat models.

Results: Acute inhibition of the DVMN vagal preganglionic neurones in rats resulted in shortening of the VERP (32.6 \pm 0.8 vs 41.5 \pm 0.5 ms; p = 0.002) and lowered VT threshold on burst pacing (21.7 \pm 4.2 vs 44.4 \pm 8.9 Hz; p = 0.043). Young TKO mice showed no difference in VERP (37.0 \pm 5.2 vs 37.0 \pm 3.1 ms). However, development of autonomic dysfunction in older TKO mice was associated with a reduction in VERP (30.6 \pm 2.3 vs 43.4 \pm 2.3 ms; p = 0.003). In old WT animals, systemic administration of methylatropine (2mg/kg) minicked the pro-arrhythmic phenotype of synuclein deficiency with significant VERP shortening (31.0 \pm 2.6 vs 43.4 \pm 2.3 ms; p = 0.004). Conclusion: This study demonstrates that both acute and chronic decrease in activity of a dis-

Conclusion: This study demonstrates that both acute and chronic decrease in activity of a distinct population of vagal preganglionic neurones in the DVMN predisposes the heart to ventricular arrhythmia by reduction of the effective refractory period. CNS disorders associated with autonomic dysfunction (mimicked here by synuclein deficiency) and decreased DVMN activity may lead to pro-arrhythmic phenotype.