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Preserved exercise capacity in experimental heart failure by selective optogenetic recruitment of c-fibre vagal motor fibres

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Introduction: Vagus nerve stimulation (VNS) has been shown to reduce the extent of myocardial infarction (MI) and slow the progression of myocardial remodelling and dysfunction in animal models of chronic heart failure. The precise mechanisms underlying the beneficial effect of VNS in heart failure are poorly understood. Vagus is a complex nerve containing both sensory and motor fibres, which conduct impulses from and to the majority of internal organs. It remains unclear whether the potential benefit of VNS in heart failure is due to the recruitment of afferent (sensory) or efferent (motor) vagal fibres by the stimuli delivered via implantable stimulators. Here we targeted vagal preganglionic neurones of the dorsal motor nucleus of the vagus nerve (DVMN) to express light-sensitive optogenetic actuators and determined the effect of selective optical stimulation of vagal C-fibre efferent fibres on exercise capacity in a rat model of MI-induced heart failure

Methods and results: Experiments were performed in accordance with the EU legislature and the UK Scientific Procedures Act 1986 and associated guidelines. In male Sprague-Dawley rats, DVMN neurones were targeted using viral vectors to express either the light sensitive protein - Channelrhodopsin variant ChIEF, or control transgene (eGFP). Four weeks later, animals underwent permanent left anterior descending (LAD) coronary artery ligation or sham surgery. Blue light stimulation (445 nm, 10 ms pulses, 15 Hz) of the transduced neurones via a pre-implanted optrode was performed under mild sedation (1% isoflurane) for 15 min every 48 h for 4 weeks commencing 2 days after the surgery. Exercise capacity was determined using a single lane treadmill. Rats were selected for their compliance after a three-day recruitment protocol and randomized. The experimental protocol involved starting speeds of 20–30 cm/s over 5 min after 15 min acclimatisation. Speeds were then raised in increments of 5 cm/s every 5 min until the defined point of exhaustion. The calculated work (Joules, J) was used as an index of exercise capacity. It was found that the development of post-MI left ventricular dysfunction in rats is associated with a marked reduction in exercise capacity (28±3 vs 56±8 J in sham-operated rats expressing eGFP; p=0.04, ANOVA). Optogenetic stimulation of vagal C-fibre efferents expressing ChIEF significantly enhanced exercise capacity in sham-operated animals (105±11 vs 56±8 J in sham-operated rats expressing eGFP; p=0.001, ANOVA) and preserved exercise capacity in animals with left ventricular dysfunction (56±4 vs 28±3 J in post-MI rats expressing eGFP; p=0.02; ANOVA).

Conclusion: Selective optogenetic recruitment of vagal C-fibre efferents is sufficient to preserve exercise capacity in the pathophysiological context of heart failure developing after a myocardial infarction.