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Laboratório de Farmacologia e Laboratório de Toxicologia
Faculdade de Farmácia da Universidade do Porto

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CVP1  ALPHA1-ADRENERGIC STIMULATION DECREASES MYOCARDIAL STIFFNESS: A NOVEL PKC MEDIATED-EFFECT

Ana Patrícia Fontes-Sousa1,2, Luisa Lopes-Conceição1, Carmen Brás-Silva1 & Adelino F. Leite-Moreira1 (introduced by Paulo Correia-de-Sá1)
1Departamento de Fisiologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal; 2Endereço actual: Laboratório de Farmacologia e Neurobiologia-UMIB, Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), Universidade do Porto, Porto, Portugal

Alpha1-adrenoceptor (AR) stimulation has an important role in the regulation of mammalian cardiac function under physiological and pathophysiological conditions. Recently, we showed that neurohumoral agents acutely decrease myocardial stiffness, effect that could be altered in heart failure (HF) (Leite-Moreira et al., 2003; Leite-Moreira et al., 2006; Fontes-Sousa et al., 2007; Brás-Silva et al., 2008; Fontes-Sousa et al., 2009). Therefore, the present study was designed to determine the, yet unknown, acute effects of α1-AR stimulation on the diastolic properties of the myocardium in healthy rabbits and in the model of doxorubicin-induced HF. The role of different signalling pathways involved in this effect was also investigated.

New-Zealand white rabbits were treated with doxorubicin via a marginal ear vein by bolus injection (1 mg/kg) twice weekly for 8 weeks to induce HF (DOX-HF) or saline (control). Effects of phenylephrine (PE; 3.10^−7-10^−4M), an α1-AR agonist, were tested in papillary muscles (Krebs-Ringer: 1.8mM CaCl2, 35°C) from the control (n=12) and DOX-HF group (n=8). In the former, the effects of PE were evaluated in the presence of (i) a damaged endocardial endothelium (EE; n=7), or in the presence of (ii) NO synthase inhibitor, N^G-Nitro-L-Arginine (L-NNA; 10^−5 M; n=10), (iii) indomethacin (INDO, cyclooxygenase inhibitor; 10^−5M; n=7), or (iv) PKC inhibitor, chelerythrine (CHE; 10^−5M; n=13); passive length-tension relations were also constructed before and after a single concentration of PE (10^−5M; n=7). Reported parameters include: active tension (AT; mN/mm^2), maximum velocities of tension rise and decline (dT/dt_{max} and dT/dt_{min}, respectively; mN/mm^2/s), passive tension (PT; mN/mm^2) and muscle length (L; L_{max}). Only significant results are given, expressed as % change from baseline.

PE induced positive inotropic and lusitropic effects, with a maximum effect at 10^−5M, promoting an increase of 138.3±22.8% AT, 149.7±26.3% dT/dt_{max}, and 117.4±21.6% dT/dt_{min}. PE also promoted a concentration-dependent increase in resting muscle length up to 1.012±0.002 L/L_{max} at the highest concentration. Correcting muscle length to its initial value resulted in a 28±5% decrease of PT, indicating a significant decrease of muscle stiffness, also evident in the down and rightward shift of the passive length-tension relation. This latter effect was however abolished in the presence of PKC inhibitor. Both systolic and diastolic myocardial effects of PE were maintained in DOX-HF group.

The present study demonstrated that PE promotes a decrease of myocardial stiffness, modulated by the activation of PKC. These findings reinforce the importance of alpha1-adrenergic stimulation in the regulation of myocardial function, including diastolic function, which highlights its role as a potential powerful regulator of cardiac filling. On the other hand, this effect occurs even after EE removal, is independent of NO and prostaglandins release and is preserved in HF, which might have important pathophysiological implications in this syndrome where EE dysfunction occurs.