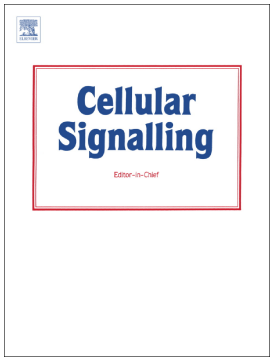

Endothelin-1 promotes hypertrophic remodelling of cardiac myocytes by activating sustained signalling and transcription downstream of endothelin type A receptors

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Endothelin-1 promotes hypertrophic remodelling of cardiac myocytes by activating sustained signalling and transcription downstream of endothelin type A receptors

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Abstract

G-protein coupled receptor (GPCR) mediated activation of the MAPK signalling cascade is a key pathway in the induction of hypertrophic remodelling of the heart – a response to pathological cues including hypertension and myocardial infarction. While levels of pro-hypertrophic hormone agonists of GPCRs increase during periods of greater workload to enhance cardiac output, hypertrophy does not necessarily result. Here we investigated the relationship between the duration of exposure to the pro-hypertrophic GPCR agonist endothelin-1 (ET-1) and the induction of hypertrophic remodelling in neonatal rat ventricular myocytes (NRVM) and in the adult rat heart *in vivo*. Notably, a 15 minute pulse of ET-1 was sufficient to induce markers of hypertrophy that were present when measured at 24 hours *in vivo* and 48 hours *in vitro*. The persistence of ET-1 action was insensitive to ET type A receptor (ET_A receptor) antagonism with BQ123. The extended effects of ET-1 were dependent upon sustained MAPK signalling and involved persistent transcription. Inhibitors of endocytosis however conferred sensitivity upon the hypertrophic response to BQ123, suggesting that endocytosis of ET_A receptors following ligand binding preserves their active state by protection against antagonist. Contrastingly, α_1 adrenergic-induced hypertrophic responses required the continued presence of agonist and were sensitive to antagonist. These studies shed new light on strategies to pharmacologically intervene in the action of different pro-hypertrophic mediators.

Keywords: Endothelin-1, Cardiac hypertrophy, Signalling, MAPK, GPCRs.

Abbreviations:

actinomycin D, Act D; angiotensin II, Ang II; atrial natriuretic factor, ANF; brain natriuretic factor; BNP; calcineurin, CN; cardiovascular disease, CVD; cytosine b-D-arabinofuranoside; ara-C; disintegrations per minute, DPM; dominant negative β-Arrestin-1, DN β-Arr1; dual specificity phosphatase-6, DUSP6; endothelin-