Signalling Requirements for ET-1-Induced Hypertrophy

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Cardiac hypertrophy occurs as a response to enhanced cardiac workload and is characterised by an increase in cardiomyocyte size and distinct changes in gene expression without an increase in proliferation. Complex signalling mechanisms have been implicated in the generation of hypertrophic response, including those activated by Endothelin-1 (ET-1), which binds to its receptor (ETAR) signalling downstream to stimulate Ca2+, MAPK and PKC pathways.

We hypothesise that a transient ET-1 signal is sufficient to upregulate the hypertrophic gene programme and that the hypertrophic phenotype is maintained in the absence of ET-1.

Stimulation of neonatal rat ventricular cardiac myocytes for 15 minutes with ET-1 was sufficient to upregulate expression of the hypertrophic associated genes ANF and BNP, when measured 24 hours later. Nascent ANF transcripts were also detected 24 hours after the 15 min ET-1 incubation, whereas inhibition of RNA polymerase II with actinomycin D applied 15 min after ET-1 attenuated hypertrophic gene transcription. Inhibition of Ca2+ and MAPK pathways with 2-APB (IP3R inhibitor) and PD184352 (MEK Inhibitor) 15 minutes after ET-1 application also suppressed the induction of gene transcription.

These data show that transient exposure to ET-1 is sufficient to induce hypertrophic remodelling of cardiomyocytes. Moreover, these data indicate that the persistent effect of ET-1 upon hypertrophic gene transcription is via sustained activation of its downstream signalling mediators and not through a permanent effect on the genome.