P4

DIFFERENTIAL SIGNALLING THROUGH P90 RIBOSOMAL S6 KINASES (RSKS) TO CARDIOMYOCYTE GENE EXPRESSION BY ENDOTHELIN-1 VERSUS α-ADRENERGIC AGONISTS

doi:10.1136/heartjnl-2012-303148a.9

E Amirak,* P H Sugden, A Clerk. *Institute for Cardiovascular and Metabolic Research, University of Reading, Whiteknights, Reading, RG6 6UB*

Endothelin or α1-adrenergic receptor agonists (eg, A61603) promote cardiomyocyte hypertrophy. Both signal through extracellular signal-regulated kinases1/2 (ERKs) to induce changes in gene expression. However, although there is overlap, the transcriptomic responses are not identical. ERKs phosphorylate transcription factors and activate p90 ribosomal S6 kinases (RSKs) that phosphorylate (different) transcription factors. Inhibition of RSKs with BID1870 inhibits ~51% of RNAs upregulated by endothelin in cardiomyocytes. Thus, a major part of the ERK signal to gene expression is via RSKs. We investigated activation profiles and subcellular localisation of ERKs/RSKs in cardiomyocytes to determine if there are differences in degree of activation or isoform selectivity in the response to endothelin versus A61603. Endothelin increased phosphorylated (activated) ERKs in cytosolic and nuclear protein-enriched (NPE) fractions within 30 s (maximal: 2–3 min) with no difference in activation profiles. ERK phosphorylation induced by A61603 was less and was delayed. The NPE fraction contained ~25% of total ERKs, but there was no net change in distribution following stimulation with either agonist. Endothelin promoted phosphorylation of RSKs within 1 min. The NPE fraction contained ~8% of total RSKs in control cells but, on stimulation, this increased to 34% with endothelin or 18% with A61603, indicating that activation is associated with nuclear translocation. Endothelin increased RSK1 and RSK2 isoform content in the NPE fraction whereas A61603 only increased RSK2 content. The greater degree of activation of ERKs/RSKs by endothelin may account for a greater overall transcriptomic response, but differential activation of RSKs may lead to different profiles.