Activation of ERK1/2 Akt and S6 Kinase, but not PKC, Prior to Cardiac Hypertrophy in Spontaneously Hypertensive Rats

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Cardiac hypertrophy is the result of stress on the heart due to factors such as hypertension. This results in the enlargement of the myocytes (heart muscle cells), of the ventricles, as they work harder to cope with the increase of blood pressure. Cardiac hypertrophy is a dangerous condition that could lead to an increase risk of cardiac arrhythmia, myocardial infarction (heart attack), and heart failure. Understanding the bio-molecular pathways that regulate cardiac hypertrophy is vital for the development of drugs and therapies that will help prevent and cure this cardiac pathology.

Previous studies report that Akt, extracellular regulated kinase (ERK) 1/2, Protein kinase c (PKC) ε, δ, and δI can regulate cardiac hypertrophy. However, the role of PKCδ and δI in vivo remains controversial. We hypothesized Akt and ERK1/2 activation, but not PKC, occurs in spontaneously hypertensive rat (SHR) hearts before the onset of cardiac hypertrophy. Immunoblots were used to determine total and phosphorylated (p) PKCo, δI, δ, ε, Akt, ERK1/2, PDK1, S6 kinase, and S6 ribosomal protein on cardiac homogenates from 9-10 week old SHR (n=5) and Wistar Kyoto controls (WKY, n=6). No cardiac hypertrophy existed at this age (heart/body weight, SHR 3.99±0.10 vs. WKY 3.95±0.11) in spite of greater mean arterial pressure in SHR (SHR 152±3 vs. WKY 116±3 mmHg, p<0.01), suggesting an early phase of the hypertrophic process. ERK1/2 and Akt were significantly activated in SHR vs. WKY (p-ERK1/2 increased 68%, p-ERK1/2 total ERK1/2 increased 60%, p-Akt increased 54%, p-Akt total Akt increased 69% p<0.01). P-PDK1, an upstream activator of Akt, was unchanged. PKCo, δI, δ, ε, p-PKCo, δI, p-PKCo ε were unchanged, and p-PKCo δ was not detectable. Thr389 phosphorylation on p70 S6 kinase, a key regulator of translational control downstream of Akt, PDK1, and ERK, was increased 40% (p<0.05) in SHR, as was Ser235/236 phosphorylation of S6 protein on the 40S ribosomal subunit (increased 70%, p<0.05). Our data indicate activation of p70 S6 kinase mediated translational machinery in the SHR heart prior to the onset of cardiac hypertrophy is likely due to Akt and ERK1/2 activation, and not PKC. We conclude that PKC may not be required for cardiac hypertrophy in the SHR.