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Activation of Mitogen Activated Protein Kinases by Medium Change in Primary Cultured Rat Hepatocytes: Role of Mechanical and Redox Stress

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Mechanical stress is known to induce signaling cascades, including mitogen-activated protein kinase (MAPK) pathways. Although mechanical stress has been implicated in hepatic cirrhosis and liver regeneration following hepatectomy, the signaling pathway(s) that may be activated in hepatocytes in response to mechanical stress has not been determined. Using primary cultured rat hepatocytes to examine cellular signaling in response to mechanical stress associated with medium change, we observed that the phosphorylation status of extracellular signal-regulated kinase 1/2 (ERK1/2), Jun N-terminal kinase and p38 MAPK, but not Akt, was altered. MAPK activation, especially ERK1/2, was rapidly increased within 5 min, followed by a subsequent decrease to below basal levels between 30 min and 1 h following medium change. MAPK/ERK kinase (MEK1/2) phosphorylation followed the same pattern. The phosphorylation of Raf-1 in response to medium change was also consisted with Raf-1 serving as an upstream regulator of MEK1/2-ERK1/2 signaling. Phosphorylation of ERK1/2 was increased by shear stress alone, suggesting that mechanical stress may be primarily responsible for ERK1/2 activation in response to medium change. Medium change produced a marked decline in oxidized glutathione levels, but not total glutathione, and the antioxidant N-acetyl-L-cysteine completely prevented the subsequent decrease in ERK1/2 phosphorylation, suggesting a role for oxidative stress in maintaining basal ERK1/2 phosphorylation in cultured hepatocytes. These data suggest that medium change results in immediate activation of the MAPK signaling pathway due to mechanical stress, followed by a subsequent inactivation of MAPK signaling due to a reduction in oxidative stress levels. These processes may be associated with alteration of hepatic hemodynamic circulation observed in hepatic diseases and in liver transplantation.

Keyword : MAPK, Mechanical Stress, Oxidative Stress, Primary Cultured Rat Hepatocytes