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Stimulation of DNA synthesis and proliferation by prostaglandins in primary cultures of adult rat hepatocytes.

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We studied the effects of several prostaglandins on DNA synthesis and proliferation in serum-free primary cultures of adult rat hepatocytes. Maintained in short-term cultures (i.e., 3.5 h), the hepatocyte parenchymal cells synthesized DNA and proliferated in the presence of various prostaglandins in a dose-dependent manner. The half-maximal effective concentrations (ED_{50}) of prostaglandin $F_{2\alpha}$, prostaglandin E_1, prostaglandin E_2, and prostaglandin I_2 for proliferation were estimated to be $1.7x10^{-9}$ M, $2.3x10^{-8}$ M, $2.7x10^{-8}$ M, and $3.3x10^{-9}$ M, respectively. Prostaglandin E_2 and prostaglandin I_2 produced greater maximal responses than did either prostaglandin E_1 or prostaglandin $F_{2\alpha}$. The cells responded only weakly to prostaglandin D_2. The stimulatory effects of 10^{-6} M prostaglandin E_1 and 10^{-6} M prostaglandin E_2 on hepatocyte DNA synthesis and proliferation were inhibited by a specific antagonist of the EP_1 receptor, SC-51322 (8-Chlorodibenz[b, f][1, 4]oxazepine-10(11H)carboxylic acid, 2-[3-[(2-furanylmethyl)-thio]-1-oxopropyl]hydrazide): 10^{-6} M). Specific inhibitors of signal transducing elements (e.g., U-73122 (1-[6-[17β-3-Methoxyestra-1, 3, 5(10)-trien-17-yl]amino] hexyl)-1H-pyrrol-2, 5-dione: 10^{-6} M), 10^{-6} M verapamil, $5x10^{-6}$ M genistein)

almost completely blocked the growth-promoting effects of the prostaglandins. These results suggest that prostaglandins stimulate hepatocyte DNA synthesis and proliferation by their own receptors and exert their effects through both phospholipase C/$Ca^{2+}$and receptor tyrosine kinase pathways.