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Prostaglandin E_2 (EP_1) receptor agonist-induced DNA synthesis and proliferation in primary cultures of adult rat hepatocytes: The involvement of transforming growth factor-α.

Mitsutoshi Kimura(木村光利), Sachie Osumi(大澄幸恵), and Masahiko Ogihara (荻原政彦)

Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado 350-0295, Japan

We studied the effects of EP receptor subtype agonists on DNA synthesis and proliferation in primary cultures of adult rat hepatocytes to elucidate their mechanisms of action. Maintained in short-term cultures (i.e., 3.5 h) in a serum-free, defined medium, hepatocyte parenchymal cells underwent DNA synthesis and proliferation in the presence of sulprostone (10^{-6} M), prostaglandin E_2 (PGE_2; 10^{-6} M), and 17-phenyl-trinor-prostaglandin E_2 (17-pt-PGE_2; 10^{-9} M) in a time- and dose-dependent manner. PGE_2 was less potent than 17-pt-PGE_2 in stimulating hepatocyte mitogenesis. Sulprostone (10^{-6} M) and 11-deoxy-PGE_1 (10^{-6} M) showed weak and no significant stimulation, respectively, for hepatocyte mitogenesis. These effects of PGE_2, 17-pt-PGE_2, and sulprostone were abolished by treatment with a specific EP_1 receptor antagonist, SC-51322 or phospholipase C (PLC) inhibitor, U-73122. The effects of these EP_1 receptor agonists were potentiated by ionomycin, and blocked by verapamil. Hepatocyte mitogenesis was almost completely blocked by specific inhibitors of growth-related signal transducers, such as genistein, wortmannin, PD98059, and rapamycin. A monoclonal antibody against transforming growth factor-α (TGF-α) dose-dependently inhibited the PGE_2- and 17-pt-PGE_2-induced hepatocyte mitogenesis. Hepatocyte levels of TGF-α in response to the EP_1 receptor agonists was decreased from 550 pg/mg protein to 100 pg/mg protein within 10 min. The reduction in cellular TGF-α levels was blocked by SC-51322, U-73122, somatostatin, and verapamil, and potentiated by ionomycin. The specific inhibitors of growth-related signal transducers did not affect the hepatocyte TGF-α levels induced by the EP_1 receptor agonists. These results

suggest that the proliferative mechanisms of action of EP_1 receptor agonists is mediated through an increase in the autocrine secretion of TGF-α, which is dependent on the EP_1 receptor/Gq/PLC/Ca^{2+} system. The locally secreted TGF-α, in turn, acts as a complete mitogen rather than incomplete for the primary cultured hepatocytes.