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Transforming growth factor-β_1 inhibits the growth of primary adult rat hepatocyte cultures by increasing cAMP levels

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We investigated the mechanisms of transforming growth factor-β_1 (TGF-β_1) inhibition of transforming growth factor-α (TGF-α)-induced DNA synthesis and proliferation in primary cultures of adult rat hepatocytes. TGF-α (1.0 ng/ml) produced a 4.2-fold elevation of DNA synthesis during 3 h of culture and a 1.2-fold increase in nucleus number (proliferation) during 4 h of culture. TGF-β_1 dose dependently inhibited the TGF-α-induced hepatocyte DNA synthesis and proliferation: half-maximal inhibition occurred at a TGF-β_1- concentration of 0.08 ng/ml. The inhibitory effects of 1.0 ng/ml TGF-β_1 were almost completely reversed by adenylate cyclase inhibitors, 2, 4-dideoxyadenosine (10^{-6} M) and somatostatin (3×10^{-7} M), or by a specific inhibitor of protein kinase A, H-89 (N-[2-(p-bromocinnamylamino) ethyl]-5-isoquinolinesulfonamide dihydrochloride; 10^{-7} M). In addition, while TGF-α did not affect the basal cellular cAMP levels, TGF-β_1 was found to produce dose-dependent increases in cellular cAMP levels. The cAMP-elevating effects of TGF-β_1 were also reversed by 2, 4-dideoxyadenosine (10^{-6} M), and somatostatin (3×10^{-7} M), but not by H-89 (10^{-7} M). The present results suggest that the specific mechanisms involved in the growth inhibitory effect of TGF-β_1 on TGF-α-induced hepatocyte DNA synthesis and proliferation are via the stimulation of adenylate cyclase, which increases intracellular cAMP and subsequently activates protein kinase A.