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Glycyrrhizin and some analogues induce growth of primary cultured adult rat hepatocytes via epidermal growth factor receptors.

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We investigated the effects of glycyrrhizin (GL-1) and some analogues on DNA synthesis and proliferation in serum-free primary cultures of adult rat hepatocytes. The hepatocytes underwent DNA synthesis and proliferation in response to GL-1 and some analogues. The effects of these agents occurred in a time- and dose-dependent manner. The proliferative potency as judged by half-maximal effective concentrations was in the following order: 18-β-*H*-glycyrrhetinic acid (GL-3; 4.5×10^{-9} M)<18-β-*H*-glycyrrhizin (GL-1; 4.4×10^{-8} M)<18-β-*H*-glycyrrhetinic acid (GL-6; 6.0×10^{-8} M). The analogue 18-β-*H*-glycyrrhetinic acid 3-O-β-D-monoglucuronide (GL-5; 1.0×10^{-7} M) weakly stimulated hepatocyte DNA synthesis and proliferation, whereas 18-β-*H*-glycyrrhizin (GL-4) and 18-β-*H*-glycyrrhetinic acid 3-O-β-D-monoglucuronide (GL-2) did not. The growth-promoting effects of GL-1, GL-3, and GL-6 were significantly inhibited at higher initial plating densities (7.0×10^4 and 10×10^4 cells/cm^2). A monoclonal antibody against epidermal growth factor (EGF) receptor (1-100 ng/ml), but not that against EGF (1-100 ng/ml), dose-dependently inhibited glycyrrhizin- and analogue-induced hepatocyte DNA synthesis and proliferation. Specific inhibitors of growth-related signal transducers, such as genistein, PD98059 and rapamycin, completely blocked glycyrrhizin- and analogue-induced hepatocyte DNA synthesis and proliferation. Treatment of hepatocytes with GL-1, -3, and -6 rapidly stimulated tyrosine phosphorylation of the EGF receptor and p42 MAP kinase, which were inhibited by genistein and PD98059, respectively. These results suggest that

glycyrrhizin and some analogues are primary hepatocyte mitogens that bind to EGF receptors, and subsequently stimulate the receptor tyrosine kinase/mitogen-activated protein kinase pathway to induce hepatocyte DNA synthesis and proliferation.