Investigation of insulin/IGF-1 signal in Zucker Fatty Rat

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[purpose] The involvement of insulin/IGF-1 signals in spinal ligament cells and leptin signals was investigated under hyperleptinemia and hyperinsulinemia using Zucker Fatty Rat (fa/fa) that had mutation of the leptin receptor gene (fa) and Monosodium Glutamate-treated rats that presented obesity by destroying the hypothalamic ventromedial nucleus. [Methods] The following rats were used: (1) fa/fa rats (ZFR group), (2) monosodium glutamate-treated Fa/Fa rats (MSG group), and Fa/Fa rats (Control group). Each group consisted of 20 male rats aged 10 months. Thoracotomy was performed under general anesthesia, and blood was collected. Fasting blood glucose, insulin, IGF-1, and leptin were measured. The thoracic vertebrae were excised and made with Paraffin, H.E. staining and Immunohistological staining of insulin receptors, IGF-1 receptors, and IRS-1 and -2 (insulin receptor substrate) was performed using the LSAB method, moreover the amount of the protein was quantified by the Western Blot Hybridization. [Results] The ZFR and MSG groups developed hyperleptinemia and hyperinsulinemia. On histological staining, bulging of the cartilage endplate, destruction of the anulus fibrosus accompanied by an increase in the number of chondrocyte-like cells at the enthesis site, and hyperplasia of fibrocartilage were significant in the ZFR group. IRS-1-positive cells significantly increased and the appearance of the IRS-1 protein was eminent in the cartilage nous endplate and the enthesis region in the ZFR group, but IRS-2-positive cells slightly decreased in the ZFR group compared to those in the MSG and Control groups. [Discussion] Insulin/IGF signals and leptin signals in spinal ligament cells were investigated in ZFR. IRS-1-positive cells significantly increased in the hyperplastic chondrocyte-like cell region, suggesting that IRS-1-mediated signaling for cell proliferation was enhanced.

Glycyrrhizin and its metabolite suppress Smad3-stimulated collagen gene expression and hepatic fibrosis in mice

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Glycyrrhizin has been widely used for the treatment of chronic hepatitis C. It decreases the serum aminotransferase levels and suppresses progression of hepatic fibrosis as well as subsequent occurrence of hepatocellular carcinoma. It is not known, however, whether the inhibitory action of glycyrrhizin on hepatic fibrosis merely represents the secondary effect of its cytoprotective and anti-inflammatory activities, or it has direct anti-fibrotic effects. This study was aimed to determine whether glycyrrhizin directly suppresses progression of hepatic fibrosis and, if so, to study the underlying molecular mechanisms by using transgenic collagen promoter reporter mice and cultured activated hepatic stellate cells. Administration of glycyrrhizin or its metabolite, glycyrrhetic acid, significantly suppressed activation of collagen promoter and progression of hepatic fibrosis induced by repeated carbon tetrachloride injections. This was achieved without affecting the serum aminotransferase levels or activation of hepatic stellate cells. In cultured activated hepatic stellate cells, glycyrrhizin, inhibited type I collagen synthesis mostly at the level of gene transcription. Immunofluorescence study revealed that this effect of glycyrrhetic acid was exerted, at least in part, by suppressing nuclear accumulation of Smad3. Although glycyrrhetic acid rapidly phosphorylated extracellular signal-regulated kinase and p38 mitogen-activated protein kinase, its inhibitory effect on collagen gene transcription was independent of activation of those mitogen-activated protein kinase pathways. Altogether, these results provide molecular basis for anti-fibrotic effects and clinical usefulness of glycyrrhizin and its metabolite.