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EFFECT OF PROLYL 4-HYDROXYLASE INHIBITOR HOE 077 AND ITS DERIVATIVES ON THE COLLAGEN SYNTHESIS IN HSC-T6 CELLS

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The abnormal accumulation of collagen is progressive and often results in impairment of liver function, i.e. liver cirrhosis. Collagen synthesis requires several posttranslational events. Prolyl 4-hydroxylase is the key enzyme in collagen synthesis that catalyzes the hydroxylation of peptide-bound proline residues to 4-hydroxyproline. A competitive inhibitor of prolyl 4-hydroxylase, HOE 077 {pyridine-2,4-dicarboxylic-di (2-methoxyethyl) amide} was reduced the hepatic fibrosis by not only inhibiting collagen synthesis but also preventing the activation of rat hepatic stellate cells. In this work, we studied effects of HOE 077 and its metabolites, pyridine 2,4-dicarboxylic acid and mys-yl-3 (pyridine 2,4-diethyl carboxylate) on the collagen synthesis in HSC-T6 cell, which is fully activated rat hepatic stellate cell line. All three compounds showed weak cytotoxicity (EC₅₀= 306-468 μ g/mL). Hydroxyproline content in cells was reduced about 25, 10, and 15% by 100 μ g/mL of HOE 077, pyridine 2,4-dicarboxylic acid and mys-yl-3, respectively. The mRNA level of Timp 1 and prolyl 4-hydroxylase α and β subunit was decreased by treatment of HOE 077 or its derivatives, however the mRNA level of procollagen 2 α (I) was not changed. HOE 077 seemed not effectively to inhibit the collagen synthesis in HSC-T6 cells compared to the previously reported data, in vivo system or quiescent hepatic stellate cells. This result may suggest that HOE 077 is only inhibiting collagen synthesis in fully activated stellate cells. Thus, we are studying their effects on the cell proliferation and cell cycle in HSC-T6 cells.

Keyword : hepatic fibrosis, HOE 077, HSC-T6 cell, collagen