

Effect of Ethanol on Cell Proliferation of Renal Proximal Tubule Cells and Related Signal Pathways

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Background: It has been reported that ethanol affects the cell growth and cell proliferation in a variety of cell types. Although ethanol has been reported to inhibit cell proliferation, it is not yet cleared effect of ethanol on cell proliferation of renal proximal tubule cells. Thus the effect of ethanol on [3H]-thymidine incorporation and its related signal pathway were examined in the primary cultured rabbit renal proximal tubule cells (PTCs).

Methods: PTCs were grown in D-MEM/F-12 (5 mM glucose) supplemented with three growth supplements (5 µg/ml insulin, 5 µg/ml transferrin, and 50 nM hydrocortisone). In this experiments, PTCs were exposed to ethanol for 48 hr and [3H]-thymidine incorporation, arachidonic acid (AA) release, prostaglandin E2 (PGE2) assay, and Western blotting were performed.

Results: When PTCs were incubated with different concentration of ethanol (50-300 mM) for various time (24-72 hr), [3H]-thymidine incorporation was inhibited in time- and dose- dependent manner. Ethanol-induced inhibition of cell proliferation was significantly blocked by H-7 or bisindolylmaleimide I (protein kinase C inhibitors). Also that was blocked by PD 98059, a p44/42 mitogen activated protein kinase (MAPK) inhibitor, but not by SB 203580, p38 MAPK inhibitor. Ethanol-induced inhibition of cell proliferation was also blocked by AACOCF3, HELSS, and OPC [phospholipase A2 (PLA2) inhibitors], suggesting the role of arachidonic acid (AA). However, the inhibition of cell proliferation by ethanol exposure was not affected by U73122 or neomycin [phospholipase C (PLC) inhibitors]. Indeed, ethanol increased AA release and PGE2 production. In addition, ethanol increased the PKC activity and phosphorylation of p44/42 MAPK. On the other hand, ethanol-induced inhibition of cell proliferation was significantly prevented by EGF in a concentration dependent manner.

Conclusion: Ethanol inhibited cell proliferation via PKC, PLA2, p44/42 MAPK pathway in primary cultured renal proximal tubule cells and EGF protected ethanol-induced inhibition of cell proliferation.