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Uric Acid Inhibits [3H]-thymidine Incorporation Via PKC, MAPK, cPLA2, NF-kB, and Oxidative Stress Signal Pathways in Primary Cultured Renal Proximal Tubule Cells

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Background : Although hyperuricemia is associated with hypertension, vascular renal disease, and cardiovascular events, the role of uric acid has not been elucidated in renal proximal tubule cells. Thus, the present study was performed to examine the effect of uric acid on [3H]-thymidine incorporation and its related signal pathway in primary cultured rabbit renal proximal tubule cells (PTCs).

Methods : [3H]-thymidine incorporation, [3H]-arachidonic acid (AA) release, western blotting analysis, electrophoresis morbility shift assay (EMSA), and transforming growth factor (TGF)-b 1 assay were performed in the primary cultured renal PTCs.

Results : Uric acid inhibited [3H]-thymidine incorporation in a time- and dose-dependent manner. An inhibitory effect of uric acid on [3H]-thymidine incorporation was predominantly observed after 2 hr treatment with 500 mM uric acid. Uric acid-induced inhibition of [3H]-thymidine incorporation was blocked by bisindolylmaleimide I, staurosporine or H-7 (PKC inhibitors), suggesting a role of PKC. Indeed, uric acid induced a PKC translocation from the cytosolic to membrane fraction. Furthermore, uric acid significantly increased both p38 MAPK and SAPK/JNK activity except for p44/42 MAPK. Uric acid-induced inhibition of [3H]-thymidine incorporation was completely blocked by SB 203580 (p38 MAPK inhibitor) and SP 600125 (SAPK/JNK inhibitor) but not PD 98059 (p44/42 MAPK inhibitor). In addition, uric acid stimulated [3H]-AA release and translocation of cPLA2 from cytosolic fraction to membrane fraction. Uric acid-induced increase of [3H]-AA release and inhibition of [3H]-thymidine incorporation were prevented by AACOCF3 and mepacrine (phospholipase A2 inhibitors). In experiments to examine the relationship between uric acid and NF-kB activation, uric acid increased NF-kB activity, and PDTC or SN 50 (NF-kB inhibitor) prevented uric acid-induced NF-kB activation as well as inhibition of [3H]-thymidine incorporation. On the other hand, uric acid increased TGF-b1 secretion in dose-dependent manner. Uric acid-induced increase of TGF-b1 secretion was blocked by H-7, SB 203580, AACOCF3, SN 50.

Conclusions : These findings suggest that uric acid inhibits renal PTC proliferation via PKC, p38 MAPK, SAPK/JNK, cPLA2, and NF-kB, oxidative stress signaling pathway.