ABSTRACT

STUDY OF RENAL BIOELIMINATION OF XENOBIOTICS AT THE CELLULAR LEVEL II.

Synthetic somatostatin analogues labeled with suitable metal radionuclides are used in nuclear medicine for scintigraphy. Recently, they are also used for targeting radiotherapy in some types of malignant tumors with higher expression of somatostatin receptors. Their therapeutical use is restricted due to a potential radiotoxic effects on kidneys. This is a consequence of accumulation of those radiopeptides in the renal tubular cells. The reason of this cumulation is the reabsorption of radiopeptides in renal tubules. The mechanism of accumulation has not been expained so far. The aim of this work was to study the accumulation of an experimental receptor specific derivate of somatostatin, DOTA-NOC (DOTA-1-Nal^3-oktreotid) labeled with indium-111 (^{111}In-DOTA-NOC). The experiments were mainly focused on a study of the mechanism of renal uptake and on possibilities how to modify an unfavourable accumulation of the studied radiopeptide in the renal cells. Freshly isolated renal rat cells, which we obtained by the collagenase method, were used as an experimental model. Verification of the viability of renal cells was made by trypan blue exclusion test. The preparates of renal cells showed viability approximately 90% and therefore they could have been used for the given type of experiment. Albumin is a substrate and an inhibitor of megalin endocytic transport system. It increased moderately the accumulation of radiopeptide instead of the expected inhibition of the uptake. Surprisingly, probenecid, which inbibits transporters for organic anions, decreased the accumulation of radiopeptide markedly. Similarly, an inhibitor of peptide membrane transporter, ampicilin, lowered the accumulation of ^{111}In-DOTA-NOC in the renal cells significantly. The discovered results could mean that can be mediated by both transporters for organic anions as well as transporters for oligopeptides. However, it is necessary to eliminate a possibility that the concentration we have used, are not potentionally cytotoxic. This can lead to declining the cumulation rate of radioactivity as a consequence of decreasing the number of active cells in preparates. The expected participation of megalin endocytic system was not proved in our experiments.