CHARLES UNIVERSITY
FACULTY OF PHARMACY

TRANSPORT AND ACCUMULATION OF RECEPTOR-SPECIFIC PEPTIDES IN RENAL CELLS

Hradec Králové 2007 **Mgr. Marie Vaňková**

ABSTRACT OF RIGOROUS THESIS

The work was aimed at the usage of the method of freshly isolated renal rat cells for studying of the accumulation of selected radiolabeled receptor-specific somatostatin analogues. For this purpose a comparison of accumulation of two peptides from the above-mentioned group - ^{111}In-DOTA-octreotate and ^{125}I-Gluc-octreotate with several model substances (^{99m}Tc-MAG_3, sucrose, methylglucose) was performed. The type of transport mechanism to the renal cells and the megalin/cubilin transport system's participation were also explored. Isolated rat kidney cells were obtained using *in situ* kidney perfusion with a medium containing collagenase with following digestion of cellular preparation by collagenase. After the isolation, a separation to two fractions was performed with the using centrifugation in a density gradient. Cell viability was tested by trypan blue. The accumulation ratio of the model substances with an active or passive influx into renal cells was compared with accumulation parameters of the studied radiopeptides. To explore type of the transport mechanism into the cells, accumulation studies were also performed at low temperature inhibiting energetically dependent transport mechanisms. Megalin participation in the influx of the radiopeptides was explored by competitors of this system such as albumin and gentamicine. A method for routine testing of drug renal transport mechanisms using the isolated rat renal cells was developed and a separation into two size-distinct cells' fraction was introduced. Nevertheless, there was no distinct diferences in the accumulation of model substances or radiopeptides in two cell fractions as was assumed. The accumulation rate of octreotates in renal cells was comparable with high active-transported model substances. The uptake was significantly decreased at low temperature. Abumin also lowered accumulation. ^{125}I-Gluc-octreotate accumulation rate in kidney cells was approximately three times higher then that of ^{111}In-DOTA-octreotate. ^{111}In-DOTA-octreotate and ^{125}I-Gluc-octreotate are accumulated in isolated rat kidney cells thanks to the mechanism which at least partly comprises an active transport system. The inhibition influence of albumin on the uptake may be a sign of partition of the megalin/cubilin system. Structural changes in the octreotate molecule result in significant changes in the accumulation rate.