ABSTRACT

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Title of Thesis: Study on renal accumulation of receptor-specific radiopeptides

Radiolabeled peptides targeted to cholecystokinin/gastrin receptors are promising compounds for radiodiagnostics and radiotherapy of some malignancies. Shorter chain derivates of gastrin called minigastrins are particularly interesting. The use of these agents is limited by their nephrotoxicity caused by accumulation of the radiopeptides in the kidney. The aim of the study was to investigate accumulation rate and renal uptake mechanisms of new receptor specific peptides from the group of gastrin analogs using in vitro models. The investigation was aimed at a comparison of the renal uptake of DOTA-minigastrin 48 (DOTA-MG48) and DOTA-minigastin 11 (DOTA-MG11), both labeled with indium-111. In addition, a potential influence of the radiolabel on the renal accumulation was also investigated using DOTA-MG11 labeled with indium-111 or with lutecium-177. A comparison of the renal accumulation of the radiolabeled minigastrins with compounds from another group of receptor specific radiopeptides - somatostatin analogs such as ^{111}In-DOTA-NOC and ^{111}In-DOTA-TATE was also carried out. To determine contribution of active transport mechanisms to the renal accumulation of the radiopeptides, accumulation studies were performed under conditions when energy-dependent processes were inhibited. A potential influence of cell models on the renal accumulation was also evaluated. For quantitative assessment, the renal uptake of the minigastrins was compared with accumulation of substances well-known for considerable renal uptake such as ^{99m}Tc-mercaptoacetyltriglycin (^{99m}Tc -MAG3) and ^{99m}Tc-dimercaptosuccinate (^{99m}Tc-DMSA). As the experimental cell models were used isolated rat renal cells obtained by the perfusion collagenase method from the native tissue and renal porcine cell line LLC-PK1 The results demonstrated that ^{111}In-DOTA-MG48 was accumulated in the renal cells with a lower intensity than ^{111}In-DOTA-MG11. Both minigastrins were transported into the renal cells probably by passive transport, since a participation of active mechanisms was not provable. ^{111}In-DOTA-MG11 accumulation in the isolated rat renal cells was higher than that of ^{177}Lu-DOTA-MG11, but not significantly. While ^{111}In-DOTA-MG11 was accumulated in the cells in a similar or lower

rate than the investigated somatostatin derivatives, ^{111}In-DOTA-MG48 was captured in the cells in a far-lower rate. In comparison with ^{99m}Tc-MAG3 and ^{99m}Tc-DMSA, the accumulation of both minigastrins was significantly lower. The results demonstrate that the studied ^{111}In-DOTA-MG48 shows relatively low accumulation in renal cells. From that point of view it could be a promising compound for further investigations aimed at perspective development of a new radiopharmaceutical.