Charles University in Prague, Faculty of Pharmacy in Hradec Kralove

Department: Department of Pharmacology and Toxicology

Candidate: Mgr. Jana Kanokova

Supervisor: Doc. PharmDr. Frantisek Trejtnar, CSc.

Title of rigorous thesis: Study of renal transport mechanisms of radiolabeled antibodies

Utilization of monoclonal antibodies belongs to one of the important strategies in the treatment of oncological diseases. This treatment has a great advantage in precise focusing on the target structure with minimal damage to surrounding non-target tissue. The antibodies against the receptor for epidermal growth factor (EGFR) expressed in higher rate by variety of tumor types represent one of the important group. Nowadays oncology utilizes both unconjugated antibodies, and the ones conjugated with other effector components, e.g. cytostatic agents, radionuclides, toxins. One of the important limits for the antibodies conjugated with radionuclides appears to be their potential accumulation in kidneys with subsequent radiotoxic damage to the kidney tissue. The aim of this experimental study was to investigate the accumulation of three ^{131}I–labeled anti-EGFR antibodies - panitumumab, cetuximab and nimotuzumab using a kidney model in vitro, and compare it with renal uptake of the natural peptide ligand EGFR which was labeled in the same manner (^{131}I-EGF). Isolated rat kidney cells obtained by the collagenase perfusion method were used as an experimental in vitro model. Incubation under standard and lowered temperature (37 °C vs. 4 °C) was realized in order to assess the nature of the transport. The results of accumulation studies showed that for all three investigated antibodies labeled with ^{131}I, the uptake in rat kidney cells was comparable. In comparison to the peptide ^{131}I-EGF, the rate of accumulation of the labeled antibodies was much lower. The low incubation temperature did not lead to a significant decrease of accumulation, suggesting an insignificant contribution of active transport mechanisms to renal uptake. This result also confirms absence of a significant dependence of the uptake in the kidney cells on incubation time. The results obtained in vitro indicate low potential of studied iodine-131 labeled monoclonal antibodies for renal accumulation as well as passive nature of their renal uptake.