N-terminal sugar conjugation and C-terminal Thr-for-Thr(ol) exchange in radioiodinated Tyr3-octreotide: effect on cellular ligand trafficking in vitro and tumor accumulation in vivo.

Abstract:
For effective targeting of somatostatin receptor (sst) expressing tumors by radiolabeled octreotide analogues, high ligand uptake into sst-positive cells is mandatory. To optimize it, two modifications have been introduced into [(125)I]Tyr(3)-octreotide [(125)I]TOC): C-terminal Thr-for-Thr(ol) exchange (leading to Tyr(3)-octreotate (TOCA)) and N-terminal derivatization with different carbohydrates. Both have significant impact on radioligand uptake into sst(2)-expressing cells in vitro and in vivo. Glucose conjugation via Amadori reaction by itself led to improved tumor uptake of [(123)I]Gluc-TOC in vivo, which is based on an enhancement of peptide internalization despite a reduction in receptor affinity. In the case of the doubly modified analogues [(123)I]Gluc-TOCA, [(123)I]Gluc-S-TOCA, and [(123)I]Gal-S-TOCA, a cumulative effect of both structural modifications was observed, leading up to a 5-fold increased uptake of these compounds in sst-expressing tumors compared to [(125)I]TOC. Thus, glycosylation with small carbohydrates was found to be a suitable tool to enhance receptor-mediated uptake of radiolabeled octreotide analogues into sst-positive malignancies, leading to tracers with excellent characteristics for in vivo sst-imaging applications.

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