OP-767 Substantial reduction of the activity retention in the kidneys of radiohybrid-based minigastrin analogues by modifying the charge distribution within the linker section [Abstract]

N. Holzleitner, T. Günther, S. Fischer, R. Beck, Constantin Lapa, H. Wester

Angaben zur Veröffentlichung / Publication details:

Holzleitner, N., T. Günther, S. Fischer, R. Beck, Constantin Lapa, and H. Wester. 2023. "OP-767 Substantial reduction of the activity retention in the kidneys of radiohybrid-based minigastrin analogues by modifying the charge distribution within the linker section [Abstract]." *European Journal of Nuclear Medicine and Molecular Imaging* 50 (Supplement 1): S343. https://doi.org/10.1007/s00259-023-06333-x.

OP-767

Substantial Reduction of the Activity Retention in the Kidneys of Radiohybrid-Based Minigastrin Analogues by Modifying the Charge Distribution Within the Linker Section

N. Holzleitner[1], *T. Günther*[1], *S. Fischer*[1], *R. Beck*[1], *C. Lapa*[2], *H. Wester*[1];
[1]*Technical University Munich, Munich, GERMANY,*
[2]*University of Augsburg, Augsburg, GERMANY.*

Aim/Introduction: In order to reduce elevated activity retention in the kidneys of previous radiohybrid-based minigastrin analogues, such as [^{177}Lu]Lu-DOTA-rhCCK-18 ([^{177}Lu]Lu-DOTA-D-Dap(SiFA)-(D-γ-Glu)$_8$-Ala-Tyr-Gly-Trp-Asp-Nle-Phe-NH$_2$), we substituted the negatively charged poly-D-γ-glutamate chain by polyethylene glycol moieties of various length ((PEG)$_{4-11}$). We further evaluated the influence of a different charge distribution in proximity to the silicon-based fluoride acceptor (SiFA) moiety on CCK-2R affinity, lipophilicity and biodistribution properties by insertion of different SiFA building blocks (SiFA and SiFAlin) as well as a D-γ-glutamate moiety next to the D-Dap(SiFA/SiFAlin) unit. ***Materials and Methods:*** ^{177}Lu-labelling was performed at 90°C within 15 min (1.0 M NaOAc buffer, pH=5.5, 0.1 M sodium ascorbate). CCK-2R affinity (IC$_{50}$, n=3) was evaluated on AR42J cells. Lipophilicity (expressed as n-octanol/PBS distribution coefficient; logD$_{7.4}$) was determined. Biodistribution studies (n=4) were carried out at 24 h post-injection in AR42J tumour-bearing CB17-SCID mice. ***Results:*** Synthesis via solid-phase peptide synthesis yielded 4-8% RP-HPLC-purified labelling precursor. 177Lu-labelling proceeded in high radiochemical yields and purities of >95% and molar activities of 30-40 GBq/µmol. CCK-2R affinities of most compounds evaluated were found to be in a range of 8-20 nM, which resulted in slightly increased or comparable IC$_{50}$ values to [^{nat}Lu]Lu-DOTA-rhCCK-18 and [^{nat}Lu]Lu-DOTA-PP-F11N (IC$_{50}$: 4.7±0.6 and 12.8±2.8 nM), respectively. Lipophilicity was noticeably decreased for compounds containing a D-γ-glutamate moiety next to the D-Dap(SiFA) unit as compared to their counterparts lacking the additional negative charge. Combining the highest CCK-2R affinity and lipophilicity of all compounds investigated, [$^{177/nat}$Lu]Lu-DOTA-rhCCK-70 (DOTA-D-Dap(SiFA)-D-γ-Glu-(PEG)$_7$-D-γ-Glu-(PEG)$_3$-Trp-(N-Me)Nle-Asp-1-Nal-NH$_2$; IC$_{50}$: 12.6±2.0 nM; logD$_{7.4}$: −1.67±0.08) and [$^{177/nat}$Lu]Lu-DOTA-rhCCK-91 (DOTA-D-Dap(SiFAlin)-D-γ-Glu-(PEG)$_4$-D-γ-Glu-(PEG)$_3$-Trp-(N-Me)Nle-Asp-1-Nal-NH$_2$; IC$_{50}$: 8.6±0.7 nM; logD$_{7.4}$: −1.66±0.07) were further evaluated in vivo. Biodistribution data at 24 h post-injection for both [^{177}Lu]Lu-DOTA-rhCCK-70 and [^{177}Lu]Lu-DOTA-rhCCK-91 showed substantially decreased activity levels in the kidneys (8.4±0.8 and 6.6±0.5 %ID/g, respectively), when compared to [$^{177/nat}$Lu]Lu-DOTA-rhCCK-18 (134±18 %ID/g). However, activity levels in the tumour were found to be decreased as well (12.0±0.8 and 7.5±1.0 versus 25.4±4.7 %ID/g, respectively). In comparison to [^{177}Lu]Lu-DOTA-PP-F11N (tumour: 1.9±0.8 %ID/g, kidney: 3.0±0.5 %ID/g) activity levels in the tumour at 24 h post-injection were observed to be much higher for both compounds investigated, resulting in favourable tumour to kidney ratios (1.45±0.12 and 1.13±0.12 versus 0.62±0.30). ***Conclusion:*** In this study we could successfully demonstrate a reduction of activity accumulation in the kidneys by a reduction of negative charges in the linker section of radiohybrid-based minigastrin analogues, while maintaining a good tumour uptake, which led to more favourable tumour/kidney ratios in vivo compared to the references [^{177}Lu]Lu-DOTA-PP-F11N and [^{177}Lu]Lu-DOTA-rhCCK-18.