Scientific Poster

Targeting the GLP-1 receptor on pancreatic β-cells: Signaling and radiopharmaceutical application

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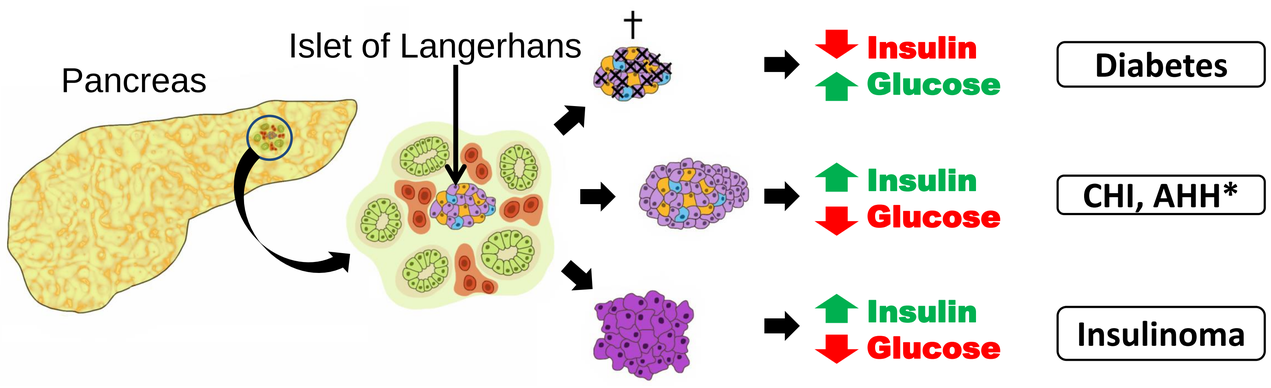
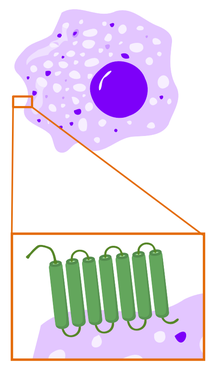
Pancreatic β-cells and the Glucagon-like peptide-1 receptor (GLP-1R)





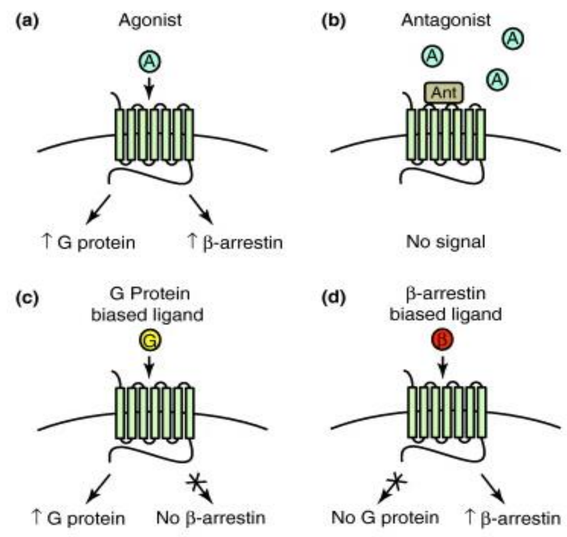
β-cell
- produces and secretes insulin after food intake → control of glucose metabolism
- expresses the GLP-1 receptor

GLP-1R
- G-protein coupled receptor (GPCR)
- endogenous ligand GLP-1 has very short biological halflife of ~2min → more stable analogues used clinically, e.g exendin-4

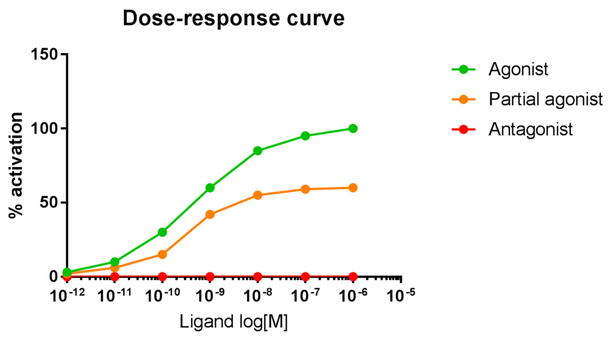
The islets of Langerhans in context. The different consequences of β-cell dysfunctions are illustrated on the right. β-cell death leads to diabetes mellitus, whereas Congenital Hyperinsulinism (CHI) and Adult Hyperinsulinemic Hypoglycemia (AHH) are caused by hyperplasias of the β-cells. Insulinomas also lead to hyperinsulinism. The majority of islet cells are insulin-producing β-cells, expressing GLP-1R.

Investigating GLP-1R signaling

Ligand-receptor interactions

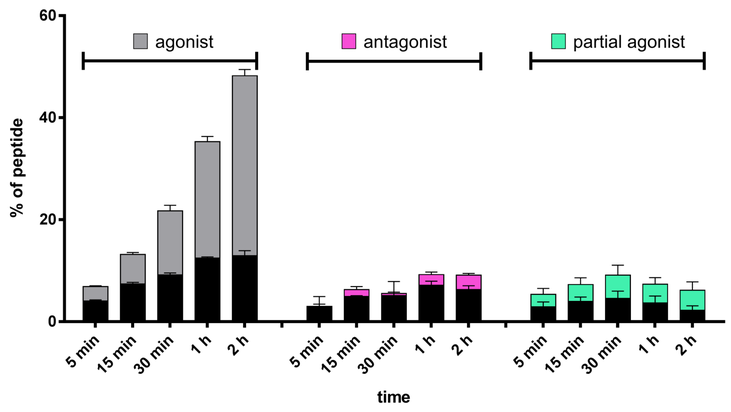


Adapted from Whalen E. et al (2010), Trends Mol Med, 17(3), 126-139

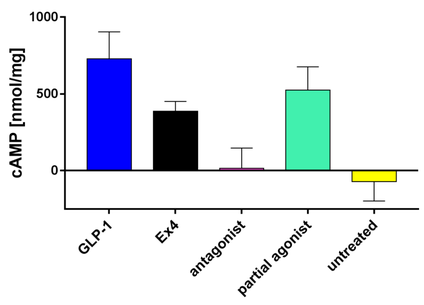


Ligands may interact differently with a GPCR, giving rise to agonism, antagonism, biased agonism and partial agonism. Ligand-GPCR interactions are frequently exploited clinically.

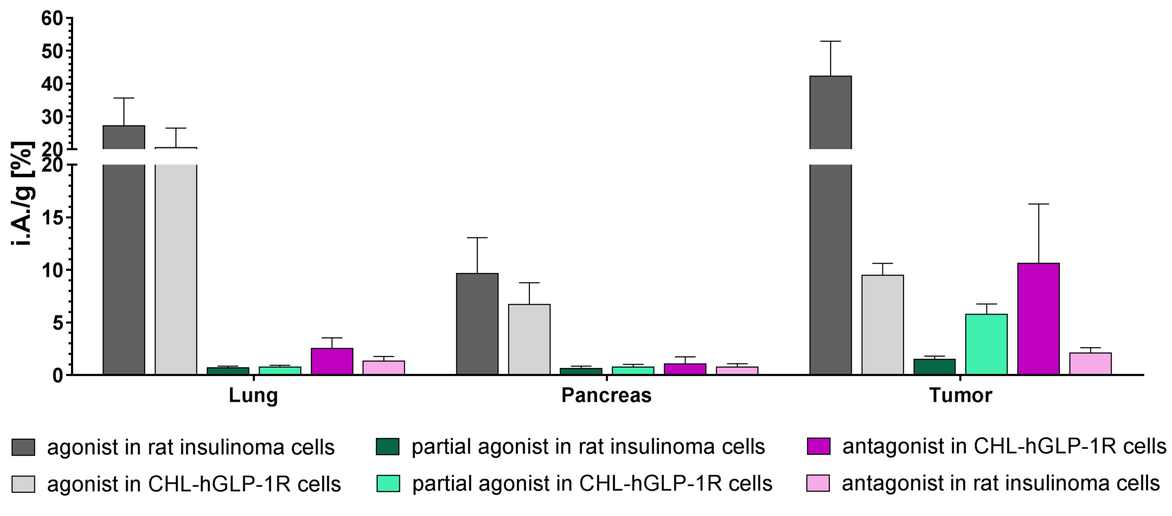
In vivo and *in vitro* effects of ligand-receptor interaction



Peptide	IC_{50}
agonist	21.1 ± 1.7 nM
antagonist	18.4 ± 5.9 nM
partial agonist	24.8 ± 5.0 nM



Above: GLP-1R mediated cell internalization (*left*) shows little uptake in antagonist and partial agonist, but it is not due to loss of receptor affinity, as asserted by IC_{50} determination (*top right*). The partial agonist elicits similar cAMP second messenger stimulating properties as the known agonists (*bottom right*).
Below: Biodistribution study with indium-111 labeled peptides in mice with tumors derived from two different GLP-1R positive cell lines. While the agonist and the antagonist preferentially accumulate in tumors of rat insulinoma origin, the biased agonist accumulates more strongly in tumors expressing the human receptor. Thus, similar *in vitro* results may mask divergent physiological behavior.



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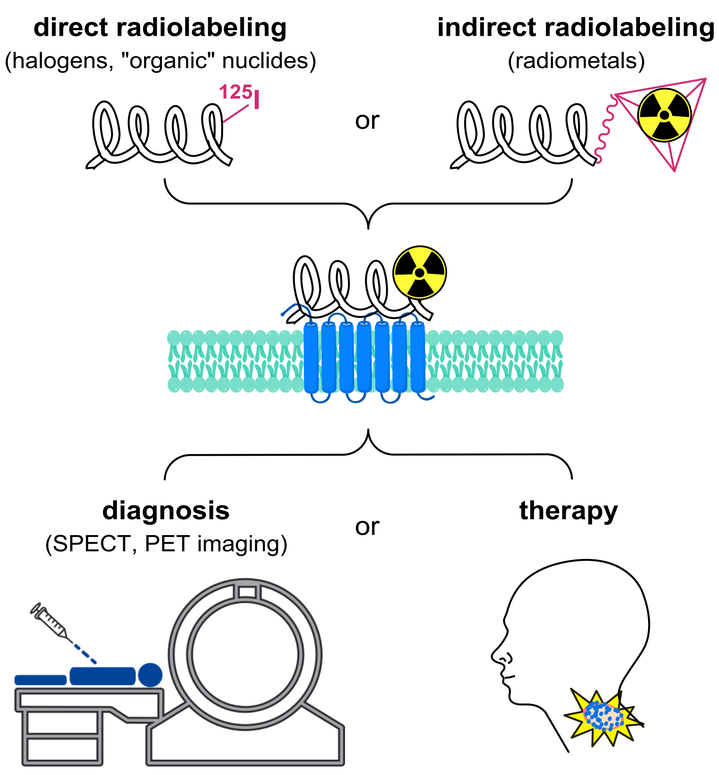
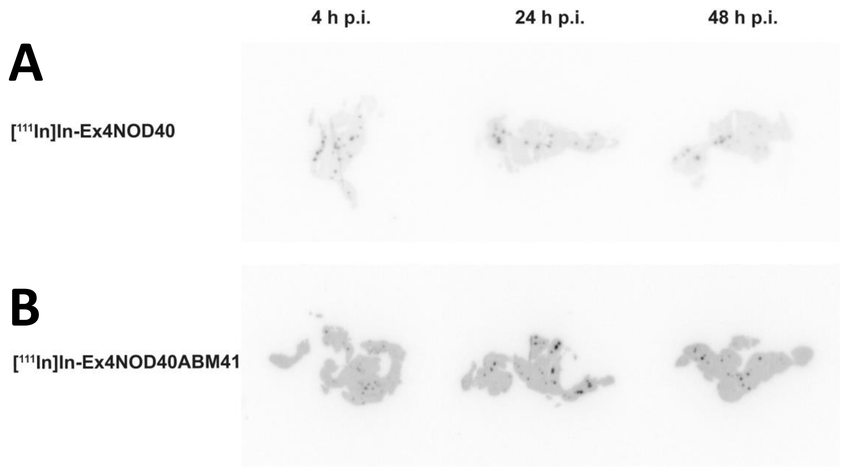
GLP-1R for the diagnostic imaging of β-cell derived pathologies

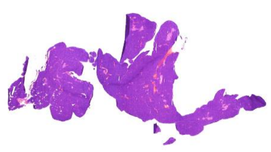
Principles and applications of nuclear medicine



Direct radiolabeling is performed if the radionuclide can be integrated in the peptide's structure during an organic chemistry reaction.
Indirect radiolabeling with radiometals requires a chelator to be conjugated to the peptide to coordinate the nuclide.
The choice of nuclide, together with the pharmacokinetics of the peptide and the identity of the target, determines its use as a tracer for diagnostic purposes or as a drug for radiotherapy.

In vivo evaluation of a modified exendin-4-based radiotracer





Above: HE-stained section of the pancreas. Islets appear in bright pink.
Left: Autoradiographies of the pancreas.
(A) Unmodified peptide
(B) modified peptide.

Right: Preclinical SPECT/CT scans of mice carrying GLP-1R positive tumors in both shoulders.
(A) Mouse injected with non-modified lead peptide [111In]In-Ex4NOD40 with low tumor-to-kidney ratio and therefore less favorable imaging quality, and (B) mouse injected with the modified [111In]In-Ex4NOD40ABM41 peptide with high tumor-to-kidney ratio (B). Both SPECT images were adjusted to show the kidneys with the same intensity for comparison,