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Specific biology of neuroendocrine tumors: Peptide receptors as molecular targets

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Neuroendocrine tumors (NET) are characterized by a high overexpression of many different peptide hormone receptors. These receptors represent important molecular targets for imaging and therapy, using either radiolabeled or cold peptide analogs. The clinically best established example is somatostatin receptor targeting. A relatively new application is glucagon-like peptide 1 (GLP-1) receptor-targeted imaging of insulinomas, which is highly sensitive. A potential future candidate for peptide receptor targeting is the gastric inhibitory peptide (GIP) receptor. It was recently found to exhibit a very wide expression in NET and may be a particularly suitable target in somatostatin and GLP-1 receptor negative tumors. With increasing use of peptide receptor targeting, reliable morphologic in vitro tools to assess peptide receptors in tissues are mandatory, such as in vitro receptor autoradiography or thoroughly established immunohistochemical procedures.

Introduction

Neuroendocrine tumors (NET) are very heterogeneous with respect to site of origin, hormonal symptoms and metastatic behavior. But they exhibit a common, quite unique biologic feature: They show a high overexpression of specific peptide hormone receptors (Table 1). These receptors, very diverse and large in number, belong to the class of G protein-coupled membrane receptors. They are bound by small peptides, usually less than fourty amino acids long. Physiologically, they regulate many

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different functions in the central and peripheral nervous system, gastrointestinal tract and endocrine system. In tumors, they control mainly hormone secretion and cell proliferation.

Tumoral peptide receptors represent important molecular targets for clinical applications. There are principally two different ways of peptide receptor targeting of NET. The first is based on the peptide effects on tumor cells mediated by the peptide receptors. Cold, long-acting peptide analogs are applied to interfere with these effects. The second approach makes use of the high number of peptide receptors on the tumor cells, irrespective of the peptide effects. Peptide analogs coupled with a radioisotope are administered which specifically bind to the tumoral receptors. This leads to an accumulation of radioactivity in the tumor area, which can be used for tumor imaging or radiation therapy (peptide receptor radionuclide therapy, PRRT).

While the clinical side of peptide receptor targeting of NET will be discussed in detail elsewhere in this issue, the present chapter focuses on basic biological and translational aspects. It will provide an overview on the clinically most important receptors, namely somatostatin and GLP-1 receptors, and on a newly characterized, promising receptor in this field, the gastric inhibitory peptide (GIP) receptor.

Biological and methodological background of peptide receptor targeting of NET

For a peptide receptor to be suitable for in vivo targeting of NET, four important requirements have to be fulfilled, which are in part interrelated and which will be outlined below.

First, the peptide receptor biology has to be characterized in humans. This focuses mainly on expression analyses. Peptide receptors have to be identified and quantified in human tumors as well as in normal tissues. Indeed, a high over-expression of a peptide receptor in tumors in terms of incidence and density is an important prerequisite for successful clinical applications. Equally important is a low receptor expression in non-neoplastic background tissues. Only a high tumor-to-background ratio of peptide receptor levels will allow recognizing a tumor by peptide receptor imaging [1]. It also predicts a

Table 1
Peptide receptors for NET targeting.

	Somatostatin receptors	GLP-1 receptor	GIP receptor
Receptor subtypes	sst1, sst2A, sst3, sst4, sst5	None	None
Physiological receptor distribution	Pancreatic islets, disseminated endocrine system of the gastrointestinal tract, myenteric plexus, adrenal gland, thyroid gland, pituitary gland, kidney, prostate, lymphatic tissues, brain	Pancreatic acini and islets, duodenal Brunner's glands, myenteric plexus, posterior pituitary gland, meninges, breast, lung, kidney	Pancreatic islets, gall bladder (rare), lymph nodes (rare), lung (rare)
Physiological peptide actions	Inhibition of hormone secretion, proliferation and angiogenesis	Stimulation of glucose-dependent insulin secretion	Stimulation of glucose-dependent insulin secretion
Receptor distribution in NET	Ileal NET, functioning and non-functioning pancreatic NET, medullary thyroid carcinoma, bronchopulmonary NET, small cell lung cancer (SCLC), pheochromocytoma, paraganglioma, pituitary adenoma	Insulinoma, pheochromocytoma, paraganglioma (rare), medullary thyroid carcinoma (rare)	Ileal NET, functioning and non-functioning pancreatic NET, bronchopulmonary NET
Peptide actions in NET	Inhibition of hormone secretion, proliferation and angiogenesis	Stimulation of insulin secretion and proliferation	Stimulation of insulin secretion and proliferation
In vitro receptor identification	In vitro receptor autoradiography (^{125}I-Tyr^{3}-octreotide, ^{125}I-LTT-SS-28; immunohistochemistry for sst2A (UMB-2); immunohistochemistry for sst1 (UMB-7), sst3 (UMB-5), sst5 (UMB-4)?	In vitro receptor autoradiography (^{125}I-GLP-1(7–36)amide); immunohistochemistry (3F52)?	In vitro receptor autoradiography ([^{125}I-Tyr^{10}]-GIP(1–30))
Clinical applications	Imaging of NET (OctreoScan; ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA–TOC; ^{68}Ga-NODAGA-JR11?). PRRT (^{177}Lu-DOTA-TATE, ^{90}Y-DOTA-TOC; ^{177}Lu-DOTA-JR11?).	Imaging of insulinoma (^{111}In-DOTA-exendin-4 SPECT/CT, ^{111}In-DTPA-exendin-4 SPECT/CT, ^{68}Ga-DOTA-exendin-4 PET/CT)	None