Somatostatin receptor scintigraphy with $[^{111}\text{In-DTPA-D-Phe}^{1}]$- and $[^{123}\text{Tyr}^{3}]$-octreotide: the Rotterdam experience with more than 1000 patients

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Abstract. Various tumours, classically specified as either neuroendocrine or non-neuroendocrine, contain high numbers of somatostatin receptors, which enable in vivo localization of the primary tumour and its metastases by scintigraphy with the radiolabelled somatostatin analogue octreotide. In addition granulomas and autoimmune processes can be visualized because of local accumulation of somatostatin receptor-positive activated mononuclear leucocytes. In many instances a positive scintigram predicts a favourable response to treatment with octreotide. It is tempting to speculate that octreotide labelled with an appropriate radionuclide might be used in cancer therapy. The successful application of radiolabelled octreotide in scintigraphy indicates the possible usefulness of other radiolabelled peptides, either native peptides or derivatives of these, in, for example, nuclear oncology. The small size of these peptides, e.g. bombesin and substance P, is of the utmost importance for a relatively fast blood clearance, thus leading to low background radioactivity. In this way peptides are powerful alternatives to (fragments of) monoclonal antibodies, the application of which to scintigraphic localization of specific cell surface antigen-bearing tumours is plagued by slow blood clearance and, hence, high background levels.

Key words: Somatostatin – Octreotide – Tumour targeting – Receptor imaging – Apudoma – Lymphoma

Introduction

Somatostatin and somatostatin receptors

Somatostatin is a peptide hormone consisting of 14 amino acids (SS-14). It is present in the hypothalamus, the cerebral cortex, the brain stem, the gastrointestinal tract and the pancreas. Somatostatin receptors have been identified on many cells of neuroendocrine origin, including the somatotroph cells of the anterior pituitary, the thyroid C cells and the pancreatic islet cells [1, 2]. Also cells not known as classically neuroendocrine, such as lymphocytes [3], may possess these receptors (Fig. 1).

The information with regard to the interaction of somatostatin analogues with the reported somatostatin receptors is rather confusing. At the moment three subtypes of human somatostatin receptors have been cloned [4, 5], while another type has been identified in rat pituitary and brain [6, 7]. Somatostatin receptors are structurally related integral membrane glycoproteins. The human tissue distribution of cloned somatostatin receptors known so far is as follows: type I – stomach and jejunum; type II – brain, kidney and pancreatic islets; type III – pancreatic islets. On the basis of chemical characteristics the rat somatostatin receptor (type IV) is probably different from these human subtypes. The somatostatin analogue octreotide inhibits somatostatin binding to receptor type II in the low nanomolar range, in contrast to much higher values for types I and III. Conflicting results have been described for the effect of octreotide on somatostatin binding to type IV receptors, both sensitivity and non-sensitivity to octreotide having been reported [6, 7]. An explanation might be the existence of two type IV receptors with different affinities for octreotide. Among other things the reported differences in intracellular effector systems between type II and type IV receptors point to the existence of these two receptor subpopulations [8]. For in-
anterior pituitary gland
• adenomas (GH, TSH)

I pancreatic islet cells
• pheochromocytoma
• adrenal medulla
• islet cell tumors
• neuroblastoma
ganglioneuroma
paraganglia

GI endocrine cells
• carcinoids
• endocrine tumors of small cell lung cancer
• neuroendocrine and/or intermediate cell carcinomas

endocrine cells in miscellaneous sites
• neuroendocrine tumors of any origin, endometrium, breast, kidney, lungs, pancreas, sinuses, salivary glands
• paragangliomas

leptomeninges
• meningiomas
• well-differentiated glioma-derived tumors

glia cells
• medulloblastoma
• glioblastoma

ependymoblastoma

neuroendocrine cells with somatostatin receptors

Fig. 1. Tumours and diseases with neuroendocrine cells and/or activated leucocytes with increased density of somatostatin receptors, which can be visualized with 

\[ ^{111} \text{In-DTPA-} \delta \text{Phe}^{1} \text{octreotide scintigraphy [11] } \]

stance, in contrast to type II (and type I), type IV (and type III) mediates its effects via inhibition of adenylyl cyclase activity. Since the effects of octreotide in human tissues seem to be related – at least in the pituitary and meningiomas – to inhibition of adenylyl cyclase activity [9], it is probable that a type IV-like somatostatin receptor also exists in man, which, in addition to the type II receptor, can be visualized with 

\[ ^{125} \text{I-Tyr}^{3} \text{octreotide autoradiography and octreotide scintigraphy.} \]

Somatostatin effects in vitro and in vivo

In the central nervous system somatostatin acts as a neurotransmitter, whereas its hormonal activities include the inhibition of the release (physiological and tumorous) of growth hormone, insulin, glucagon and gastrin [10]. Other actions are (a) an antiproliferative effect on tumours, as has been found for instance in cultured breast cancer cell lines, in numerous animal tumour models and in neuroendocrine tumours in man and (b) specific regulation of immune responses (for a review, see [11]). The antiproliferative effect is ascribed to (a) inhibition of growth via induction of somatostatin receptors, (b) inhibition of the release of hormones and growth factors such as growth hormone and insulin-like growth factor I (IGF-I), (c) inhibition of angiogenesis and (d) modulation of immunological activity.

Distribution of somatostatin receptors in disease states

Besides in normal tissue, somatostatin receptors have been demonstrated in most neuroendocrine tumours, many of which are derived from cells belonging to the amine precursor uptake and decarboxylation (APUD) system [12, 13]. These neuroendocrine tumours contain secretory granules [14]. Recently, somatostatin receptors have also been identified in tumours of the central nervous system (CNS) [15, 16], breast [17], lung [18] and lymphoid tissue [19, 20]. Tables 1–3 show the incidence of somatostatin receptors in various tumours and diseases.

The affinity of somatostatin for its receptor on tumours and lymphomas is in the low nanomolar range. In general, neuroendocrine tumours, lymphomas and activated leucocytes have an increased density of somatostatin receptors, which enables their visualization with radiolabelled somatostatin (analogues).

Table 1. Incidence of somatostatin receptors in neuroendocrine tumours: results of 

\[ ^{111} \text{In-DTPA-} \delta \text{Phe}^{1} \text{octreotide scintigraphy, as compared to in vitro somatostatin receptor autoradiography. In vivo and in vitro data are from different patient groups} \]

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>In vivo scintigraphy</th>
<th>In vitro receptor status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH-producing pituitary tumour</td>
<td>7/10</td>
<td>70%</td>
</tr>
<tr>
<td>TSH-producing pituitary tumour</td>
<td>2/2</td>
<td>100%</td>
</tr>
<tr>
<td>Non-functioning pituitary tumour</td>
<td>12/16</td>
<td>75%</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>12/12</td>
<td>100%</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>14/23</td>
<td>61%</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>Unclassified APUDoma</td>
<td>16/18</td>
<td>89%</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>33/33</td>
<td>100%</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>20/28</td>
<td>71%</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>8/9</td>
<td>89%</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>12/14</td>
<td>86%</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>69/72</td>
<td>96%</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>34/34</td>
<td>100%</td>
</tr>
</tbody>
</table>

In 1987 we introduced the somatostatin analogue 

\[ ^{125} \text{I-Tyr}^{3} \text{octreotide and} \]

\[ ^{111} \text{In-DTPA-} \delta \text{Phe}^{1} \text{octreotide} \]

In 1987 we introduced the somatostatin analogue \[\text{Tyr}^{3}\text{octreotide labelled with iodine-123 for the localization of primary and metastatic somatostatin receptor-rich tu-}