Diagnostic imaging of dopamine receptors in pituitary adenomas

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Abstract

Dopamine D2 receptor scintigraphy of pituitary adenomas is feasible by single-photon emission computed tomography using ¹²³I-S-(–)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide (¹²³I-IBZM) and ¹²³I-epidepride. ¹²³I-epidepride is generally superior to ¹²³I-IBZM for the visualization of D2 receptors on pituitary macroadenomas. However, ¹²³I-IBZM and ¹²³I-epidepride scintigraphy are generally not useful to predict the response to dopaminergic treatment in pituitary tumour patients. These techniques might allow discrimination of non-functioning pituitary macroadenomas from other non-tumour pathologies in the sellar region. Dopamine D2 receptors on pituitary tumours can also be studied using positron emission tomography with ¹¹C-N-raclopride and ¹¹C-N-methylspiperone.

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Introduction

Pituitary adenomas are subclassified according to hormonal hypersecretion into clinically functioning and clinically non-functioning. Among the hormone products secreted are: prolactin (PRL), growth hormone (GH), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), gonadotrophins (luteinizing hormone and follicle-stimulating hormone) or glycoprotein hormone subunits.

In the field of nuclear medicine, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) techniques have become available for the study of dopamine D2 and D3 receptors and somatostatin receptor subtype expression. For a review on the latter, see reference (1).

Dopamine D2 receptors

The expression of functionally active dopamine D2 receptors has been demonstrated in PRL-, GH-, ACTH-, TSH-secreting and clinically non-functioning pituitary tumours (2–11). The presence of high numbers of high-

affinity D2 receptors on prolactinomas, some GH-, TSH- and ACTH-secreting tumours is the pharmacological basis for therapy with dopamine receptor agonist drugs, like the ergot-derived substances bromocriptine, pergolide and cabergoline and the nonergot dopamine agonist quinagolide (7).

Dopamine D2 receptor SPECT

Several centres, including our own, have shown that D2 receptor scintigraphy of pituitary adenomas is feasible by SPECT using ¹²³I-S-(–)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide (¹²³I-IBZM; 12–15). In a patient with a metastatic malignant macroprolactinoma, ¹²³I-IBZM SPECT failed to visualize the primary tumour, whereas the uptake in a metastasis was lower than that observed for the striatum. A partial response of this metastatic tumour to quinagolide could be demonstrated *in vivo* and *in vitro* (16). In another patient with a mixed TSH/ α -SU/PRL-secreting pituitary macroadenoma, SPECT with ¹²³I-IBZM and ¹¹¹In-DTPA-pentetreotide both visualized the tumour (17). An acute *in vivo* response of the tumour to octreotide and bromocriptine could be demonstrated. However, long-term combined treatment did not result in tumour regression or a decrease in circulating hormone levels (17). Thus, the demonstration of receptors *in vivo* in these patients did not positively predict the outcome of medical therapy with these two receptor agonists.

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We have performed scintigraphy using ^{123}I -IBZM in a series of 37 patients with pituitary tumours (5 patients with PRL-secreting macroadenomas, 2 patients with PRL-secreting microadenomas, 17 patients with clinically non-functioning pituitary adenomas (NFPAs), 12 patients with GH-secreting adenomas and 1 patient with a TSH-secreting macroadenoma; (15)). SPECT showed significant uptake of ^{123}I -IBZM in the pituitary region in three out of five macroprolactinoma patients. These results correlated closely with the response of plasma PRL levels to quinagolide. In two scan-positive prolactinoma patients, repeated SPECTs during therapy with quinagolide showed a reduction in the pituitary uptake of ^{123}I -IBZM. Pituitary SPECT was negative in the two microprolactinoma patients who responded to quinagolide administration. In 4 out of 17 patients with NFPA, significant uptake of the radioligand in the pituitary region was observed. In two out of three scan-positive NFPA patients, who were treated with quinagolide, shrinkage of the pituitary tumours was observed. Treatment with quinagolide resulted in stabilization of tumour growth in the other scan-positive patients. Four out of seventeen patients with NFPA and a negative SPECT were treated with quinagolide. Tumour growth was observed in one patient and tumour size did not change in the other three patients. The pituitary region of none of the 12 acromegaly patients showed significant uptake of ^{123}I -IBZM (15).

Panza and co-workers have performed pituitary scintigraphy with ^{123}I -IBZM in two patients with mixed GH/PRL-secreting pituitary tumours and acromegaly (18). One patient showed high pituitary uptake of ^{123}I -IBZM and >80% GH suppression was observed after a single dose of bromocriptine. Combined therapy with bromocriptine and octreotide also resulted in significant tumour regression. Another patient had negative ^{123}I -IBZM scintigraphy and in this patient, there was no GH response to a single bromocriptine dose. In this patient, combined octreotide and bromocriptine therapy also resulted in tumour regression (18).

Ferone and co-workers have performed pituitary scintigraphy with ^{123}I -IBZM in four patients with mixed GH/PRL-secreting pituitary tumours and acromegaly (19). One patient showed high pituitary uptake of ^{123}I -IBZM. In this patient, cabergoline therapy failed to normalize pathologically elevated GH levels. Another patient only showed slight pituitary uptake of ^{123}I -IBZM. In this patient quinagolide reduced, but did not normalize, pathologically elevated GH levels. In two other patients, ^{123}I -IBZM scintigraphy was negative and neither cabergoline nor quinagolide therapy was effective (19).

These studies demonstrate that the sensitivity of ^{123}I -IBZM SPECT for imaging pituitary adenomas is rather poor, which presumably results from the relatively low target:background ratio of ^{123}I -IBZM binding (12–15).

These studies also show that the clinical usefulness of ^{123}I -IBZM scintigraphy for predicting the clinical

efficacy of dopamine agonists in patients with NFPAs or acromegaly is limited.

Consequently, investigators have been actively testing SPECT radiopharmaceuticals for the D2 receptor which show higher receptor affinity. Another substituted benzamide derivative, epidepride, ^{123}I -(S)-N-[(1-ethyl-2-pyrrolidiny) methyl]-5-iodo-2, 3-dimethoxybenzamide (^{123}I -epidepride) has shown to provide high target-to-background uptake and hence high image quality (20–22). Subsequent D2 receptor scintigraphic studies were performed using ^{123}I -epidepride (20, 21). Pirker and co-workers have reported a high sensitivity of ^{123}I -epidepride SPECT for demonstrating dopamine receptors on pituitary tumours (23). We have compared pituitary SPECT after ^{123}I -epidepride and ^{123}I -IBZM in NFPAs in the same 15 patients. Four dopamine agonist-sensitive macroprolactinomas were used as positive controls (24). In parallel with studies demonstrating a much greater relative striatal uptake of ^{123}I -epidepride than of ^{123}I -IBZM (25), we have also observed a much higher uptake of ^{123}I -epidepride in NFPAs and macroprolactinomas than of ^{123}I -IBZM (24). All four macroprolactinomas showed pituitary uptake of ^{123}I -epidepride, but pituitary uptake of ^{123}I -IBZM was only demonstrated in one of these tumours (24). The pituitary region of 9 out of 15 NFPA patients showed significant uptake of ^{123}I -epidepride, but the uptake of ^{123}I -IBZM was only shown in 6 out of 15 patients (24). Therefore, we concluded that ^{123}I -epidepride is superior to ^{123}I -IBZM for the visualization of D2 receptors on pituitary macroadenomas, and that therefore ^{123}I -epidepride should be the radioligand of choice for D2 receptor SPECT studies in pituitary tumour patients (24).

We have subsequently studied the correlation between the results of ^{123}I -epidepride scintigraphy and the radiological response to dopamine agonists in 18 NFPAs (26). Patients were treated with either cabergoline (1–2 mg/week) or quinagolide (150–300 µg/day) for a mean period of 89.7 months (range: 34–187 months). Pituitary uptake of ^{123}I -epidepride varied from slight uptake, classified as grade 0, to very high, classified as grade 3. Grade 0 uptake was found in four patients; grade 1 in three patients; grade 2 in ten patients and grade 3 uptake in one patient. NFPA stabilization or shrinkage with dopamine agonist therapy showed no significant difference between grades 0, 1 and 2 tumours (mean tumour stabilization or shrinkage: 31, 30 and 36% respectively) (26). We concluded that ^{123}I -epidepride scintigraphy is not useful to predict the response to long-term dopaminergic treatment in NFPA patients (26). However, when we considered a decrease in tumour size ranging from 0 to 20% as tumour stabilization and >20% decrease in tumour size as true shrinkage, one out of four NFPAs with grade 1 uptake, two out of three NFPAs with grade 1 uptake and eight out of ten NFPAs with grade 2 uptake showed tumour shrinkage (26).

As with ^{123}I -IBZM scintigraphy, the clinical usefulness of ^{123}I -epidepride scintigraphy for predicting the clinical

Figure 1 Preoperative ^{123}I -IBZM coronal SPECT (left) and ^{123}I -epidepride coronal SPECT (right) images of the head of a 64-year-old man with a clinically non-functioning pituitary macroadenoma, showing intense (grade 3) uptake of the radioligand in the pituitary tumour.

efficacy of dopamine agonists in selected patients with NFPA is therefore limited.

Discrimination of NFPA from other pathologies in the sellar region is generally not difficult when modern MRI protocols are applied. ^{123}I -epidepride scintigraphy, however, might still be useful in specific situations – for discrimination of scar tissue from NFPA recurrence or residual NFPA, or for the differential diagnosis between pituitary tumours and metastases (Fig. 1) for example.

PET

Muhr and co-workers and Bergström and co-workers have performed PET studies with ^{11}C -labelled dopamine D2 antagonists such as ^{11}C -N-raclopride and ^{11}C -N-methylspiperone for *in vivo* measurement of D2 receptors in prolactinomas and GH-secreting pituitary adenomas (27–30). They have demonstrated higher dopamine receptor binding in patients responsive to dopamine agonists than in therapy-resistant patients (27–30). In a patient with a malignant prolactinoma, presenting with multiple intracranial metastases, these techniques clearly visualized the primary tumour as well as a number of metastases. Bromocriptine treatment resulted in tumour regression, a decrease in circulating PRL levels and a decrease in ^{11}C -N-labelled dopamine antagonist binding as determined *in vivo* by PET (31).

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