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Dopamine D2 Receptor Imaging in Pituitary Adenomas Using Iodine-123-Epidepride and SPECT

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Epidepride is a novel benzamide derivative with high affinity for D2 receptors. Epidepride, in its ^{123}I-labeled form, can be used for SPECT imaging of striatal and extrastriatal dopamine D2 receptors. The present study evaluated the usefulness of epidepride and SPECT for in vivo imaging of dopamine receptors in pituitary adenomas. **Methods:** SPECT imaging was performed in 19 patients with pituitary adenomas (among them 9 patients had prolactinoma, 4 acromegaly, 4 clinically nonfunctioning pituitary adenoma, 1 Cushing's disease and 1 Nelson's syndrome) and 7 control subjects 180 min after intravenous bolus injection of 3.9 ± 1.1 mCi [^{123}I]epidepride. The ratio target/cerebellum minus 1, reflecting specific/nonspecific binding was used as semiquantitative measure of D2 receptor binding. **Results:** Eight of nine prolactinoma patients demonstrated specific binding within the adenoma. The adenoma/cerebellum ratio 3 hr p.i. showed a wide variation with values from 2.5–33. In three prolactinomas, binding was higher than in the striatum. Specific binding within the lower range of prolactinomas (adenoma/cerebellum ratios 2 and 4.8) could be demonstrated in two of four GH-secreting adenomas. All four nonfunctioning tumors showed specific binding. The adenoma/cerebellum ratio was within the lower range of prolactinomas (5.2–7.5) in three of these patients but extremely high in one (52.3). No specific tracer uptake could be demonstrated in patients with Cushing's disease or Nelson's syndrome. The striatum/cerebellum ratio 3 hr p.i. in pituitary adenoma patients was not significantly different from control subjects (17.3 ± 5.5 versus 17.8 ± 6.6; patients versus control subjects). **Conclusion:** Epidepride appears to be an excellent ligand for in vivo imaging of dopamine D2 receptors in pituitary adenomas. Epidepride SPECT could serve as a predictor for response to dopamine agonist treatment.

Key Words: dopamine; D2 receptors; epidepride; SPECT; pituitary adenomas

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Pituitary adenomas are relatively common, amounting to about 5%-10% of all intracranial tumors. The majority of pituitary adenomas is characterized by hormonal secretion. Therefore, these tumors result in well-known clinical syndromes such as acromegaly or Cushing's disease. About 30% of pituitary adenomas secrete either none or a relatively low amount of hormone, or a hormone that does not produce a recognizable clinical syndrome. The latter adenomas are referred to as "clinically nonfunctioning" pituitary adenomas (*1*).

Membrane binding studies have identified dopamine receptors in normal anterior pituitary (*2–4*) as well as in prolactinomas (*2–6*), GH-secreting pituitary adenomas (*2,5,7,8*) and clinically nonfunctioning pituitary adenomas (*4,5,8*). The dopamine receptors in the normal anterior pituitary and in pituitary adenomas are of D2 subtype (*9*). The presence of dopamine receptors in pituitary adenomas is the pharmacological basis for the treatment of these tumors with dopamine agonists. Ergot-derived substances like bromocriptine, lisuride and cabergoline and recently the nonergot dopamine agonist quinagolide (CV 205–502) are widely used for the medical treatment of prolactinomas and occasionally tried in GH-secreting adenomas.

Bromocriptine treatment leads to a clear-cut reduction of tumor size in about 60% of prolactinomas and to a reduction or normalization of prolactin (PRL) secretion in most but not all prolactinoma patients (*6,10*). In acromegaly, dopamine agonist treatment lowers plasma GH levels in 50% of patients, but normalization of plasma IGF-I, which may be a more appropriate measure of clinical efficacy, is achieved only in 10% of patients. A reduction of tumor size is observed only in a minority of patients (*11*). However, symptomatic improvement is observed in a large percentage of acromegalic patients during dopamine agonist treatment, even though GH levels are not adequately suppressed (*11*). Until recently, medical treatment played a minor role in clinically nonfunctioning pituitary adenomas, but decreased tumor size, as reported by Kwekkeboom et al. (*12*), necessitated medical treatment for several patients undergoing dopamine agonist treatment.

Dopamine agonist sensitive and resistant adenoma patients are clinically indistinguishable. No reliable laboratory test is known that may predict response to dopaminergic treatment (*6,11*). Using membrane binding techniques it was shown in prolactinomas that the density of D2 receptors is markedly reduced in bromocriptine resistant adenomas as compared to dopamine agonist sensitive adenomas (*6*).

Muhr et al. (*13,14*) and Bergström et al. (*15*) who pioneered PET imaging of pituitary adenomas used ^{11}C-labeled raclopride

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and N-methylspiperone for measurement of D2 receptor density in pituitary adenomas. They reported on higher dopamine receptor binding in patients responsive to dopamine agonist treatment than in nonresponsive patients. More recently, it was shown by Assies et al. (*16*), Verhoeff et al. (*17*) and our group (*18*) that D2-receptor imaging in pituitary adenomas is also possible with SPECT using [^{123}I]IBZM. But, we also found that the sensitivity of IBZM-SPECT for imaging pituitary adenomas, presumably due to the relatively low target-to-background ratio of IBZM binding, is poor.

Recently, the substituted benzamide epidepride, (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dimethoxybenzamide has been developed (*19–21*). This ligand predominantly labels dopamine D2 receptors with an affinity of about 30 p*M* in striatal and cortical tissue of postmortem human brain (*19,22*). A part of striatal epidepride binding was shown to be due to D3 receptors (*23*) and a low percentage of cortical binding is represented by adrenergic two receptors (*19,21,24,25*). It has been suggested that this compound might be useful for studying striatal and extrastriatal dopamine D2 receptors (*26–29*).

The aim of the present study was to demonstrate if in vivo imaging of D2 receptors in pituitary adenomas is possible using [^{123}I]epidepride and SPECT.

MATERIALS AND METHODS

Subjects

Nineteen patients with pituitary adenomas (7 women, 12 men, aged 18–75 yr, mean age 46.9 yr) and 7 control subjects (2 women, 5 men, aged 19–54 yr, mean age 35.6 yr) were examined. The patient group consisted of nine patients with prolactinoma, four patients with acromegaly, four patients with clinically nonfunctioning pituitary adenoma, one patient with Cushing's disease and one patient with Nelson's syndrome. Table 1 shows clinical data of the examined patients including their response to dopaminergic treatment.

MRI was performed in all patients and demonstrated a macroadenoma in 18 of 19 patients. A possible tumor residue of an indeterminate volume (millimeter) was visible in only one patient (Patient 10). In 13 patients (Patients 1–3,5–7,9,11,13,14,16–18), the pituitary adenoma was removed surgically after the SPECT study. Four of those patients (Patients 3,7,11,17) already were operated through a subfrontal or trans-sphenoidal route and suffered from tumor recurrence at the time of the SPECT study. In all of these 13 patients the diagnosis was confirmed by immunohistochemistry. The six remaining patients (Patients 4,8,10,12,15,19) had undergone subfrontal or transsphenoidal surgery before the SPECT study and conventional histopathological examination confirmed the diagnosis of pituitary adenoma.

One patient (Patient 3) had radiation therapy of his adenoma after two subfrontal operations more than 30 yr before the SPECT study. Eight of the patients (Patients 4–8,10–12) received dopamine agonist treatment before the SPECT study. In six of these patients (Patients 4,6,8,10–12) dopaminergic treatment was stopped at least 4 mo before the SPECT study. In two patients (Patients 5,7) bromocriptine was discontinued for at least 36 hr before the SPECT study. Four patients (Patients 1–3,9) started bromocriptine after the SPECT study.

Dopaminergic treatment led to a marked reduction of plasma PRL in all prolactinoma patients and in two of the three treated acromegalic patients. At the time of diagnosis, Patient 5 with plasma prolactin received 945 ng/ml of bromocriptine up to 7.5 mg a day for 1 mo, which led to a >25% reduction of tumor size and normalization of plasma PRL before the SPECT study. Surgery was performed six days after the SPECT study. Immunohistochemistry demonstrated marked fibrosis of the tumor with only some damaged cells left expressing PRL. Patient 9, who was treated daily with 10 mg bromocriptine after the SPECT study responded with a moderate (<25%) reduction of tumor size.

Data Acquisition and Analysis

SPECT studies were performed using a triple-head rotating scintillation camera with a transaxial resolution of 9 mm FWHM. Camera heads were equipped with medium energy collimators. Synthesis of [^{123}I]epidepride was described in detail earlier (*29*).

Iodine-123-epidepride (3.9 ± 1.1 mCi) was injected intravenously as a single bolus. To determine the optimal time for data collection, dynamic studies with 4–15 scans were performed in four control subjects. To study the kinetics of tracer accumulation in pituitary adenomas, dynamic studies with 2–6 scans were performed in eight patients. Because specific binding in the striatum (striatum-cerebellum; cpm/mCi × kg body weight) showed a maximum between 2–4 hr postinjection (p.i.), the time between 180 and 200 min p.i. was used as standard acquisition time for further studies. The rotation time was 20 min for all data acquisitions starting up to 12 hr p.i. and 40 min for acquisitions starting more than 12 hr p.i., respectively. For each scan, a total of 180 frames was collected in a step and shoot mode; 3.5-mm-thick cross sections oriented parallel to the canthomeatal plane were reconstructed by filtered backprojection (Butterworth filter) in 128 × 128 matrices. Attenuation correction was performed assuming uniform attenuation within an ellipse drawn around the head contour (attenuation coefficient = 0.120/cm).

For data analysis, irregular regions of interest (ROIs) were manually drawn in areas corresponding to the left and right striatum, both cerebellar hemispheres and the area of the adenoma, in accordance to their location on the MR scan.

Counts in striatal regions were calculated in several consecutive 3.5-mm-thick axial slices and the highest value for each striatum was taken to avoid tilting errors. The two striatal regions were pooled together and the average counts/pixel were calculated. Counts in the adenoma region were calculated in all slices on which the adenoma was visible. Average counts/pixel of the slice with the highest value were taken for analysis. ROIs were drawn in both cerebellar hemispheres. Values of both cerebellar ROIs in three consecutive axial slices were pooled together, and the average cerebellar counts were calculated. The cerebellum was assumed to represent nonspecific bound and free radioactivity.

Data were analyzed as the average regional radioactivity normalized to injected dose and body mass, decay corrected for the time of injection (cpm/pixel/mCi × kg body mass). Additionally, a ratio was calculated between average counting rates in different regions and the cerebellum. This ratio minus 1 represents specific/nonspecific binding at a given time point. The study was approved by the local ethical committee and informed consent was obtained from every subject examined.

Statistical Analysis

Specific binding, calculated by subtraction of striatal minus cerebellar counting rates and striatum/cerebellum ratios minus 1, obtained 3 hr p.i. were used for statistical analysis. Differences between groups were evaluated with two-tailed Student's t-test. Results are expressed as mean ± s.d.

RESULTS

Kinetic Studies

Striatal uptake occurred with peak values at about 3 hr p.i. and a slow decline thereafter. Because of the more rapid washout of cerebellar activity, as compared to binding in the striatum and in adenoma, striatum/cerebellum and adenoma/cerebellum ratios steadily increased with time. The individual

TABLE 1
Clinical Data

Patient no.	Sex	Age (yr)	Yr of pituitary tumor*	Plasma PRL (ng/ml) at the time of the SPECT study	Plasma GH (ng/ml) at the time of the SPECT study	Dopaminergic treatment (maximal daily dose) Before SPECT study	Dopaminergic treatment (maximal daily dose) After SPECT study	Response to dopaminergic treatment
Prolactinoma								
1	M	18	<1	767		–	2.5 mg Bromocriptine	Reduction of PRL
2	M	52	<1	417		–	2.5 mg Bromocriptine	Reduction of PRL
3	M	65	24	5811		–	3.25 mg Bromocriptine	Reduction of PRL
4	F	50	22	389		0.06 mg Lisuride	0.06 mg Lisuride	Reduction of PRL
5	M	50	<1	11		7.5 mg Bromocriptine	7.5 mg Bromocriptine	Normalization of PRL, >25% reduction of tumor size
6	F	35	2	314		Bromocriptine†	1.25 mg Cabergoline‡	Reduction of PRL
7	M	33	11	1077		40 mg Bromocriptine	40 mg Bromocriptine	Reduction of PRL
8	M	39	10	198		Bromocriptine§	–	Reduction of PRL
9	M	60	<1	847			10 mg Bromocriptine	Reduction of PRL, <25% reduction of tumor size
Acromegaly								
10	M	41	7	7	45.0	5 mg Bromocriptine	–	Reduction of GH
11	F	46	13	4	50.8	30 mg Bromocriptine	–	Reduction of GH
12	F	61	21	1	4.7	20 mg Bromocriptine	–	No reduction of GH
13	F	50	5	12	10.7	–	–	
Nonfunctioning pituitary adenoma								
14	F	35	1	42		–	–	
15	F	75	6	53		–	–	
16	M	35	1	20		–	–	
17	M	58	19	6		–	–	
Cushing's disease								
18	F	45	2	26		–	–	
Nelson's syndrome								
19	F	43	15	140		–	–	

*Duration in years since diagnosis of pituitary tumor.
†Two years before SPECT study, not tolerated.
‡Once weekly.
§Ten years before SPECT study, daily dose unknown.

variation of striatum/cerebellum binding ratios was smaller than the variation of specific striatal binding normalized to injected dose and body mass.

Figure 1 shows the time course of epidepride binding in four prolactinomas (two tumors in Patient 3), one GH-secreting and one nonfunctioning pituitary adenoma. Kinetic data obtained in prolactinoma patients show a maximum of binding in the area of the adenoma about 3 hr p.i. Prolactinomas with relatively lower binding demonstrated no significant increase of epidepride binding between 2 and 3 hr p.i., whereas specific binding markedly increased during this time in one prolactinoma with extremely high binding. Specific binding in the adenoma was still visible and amounted to 32%–58% of maximal binding 20 hr p.i. in prolactinomas.

Epidepride binding reached a maximum 1 hr p.i. and remained relatively stable up to 4 hr p.i. in a GH-secreting adenoma. Binding within this adenoma was no more visible 20 hr p.i. Specific binding in a clinically nonfunctioning pituitary adenoma showed a moderate decrease between 2 and 3 hr p.i.

Specific Binding within the Adenoma

Figure 2 shows the adenoma/cerebellum ratios 3 hr p.i. of [^{123}I]epidepride. Table 2 additionally gives specific binding in the adenoma and the MRI findings of the patients examined.

Eight of nine prolactinoma patients showed specific binding within the area of the adenoma. The adenoma/cerebellum ratio, 3 hr p.i. showed a wide variation with values from 2.5 to 33. In three prolactinomas, binding was higher than in the striatum. One prolactinoma patient (Patient 3, Fig. 3) had two areas of marked extrastriatal epidepride binding. One focus corresponded to an intrasellar adenoma, a second more frontal and left area of specific binding was due to an extra-axial frontobasal tumor, which was removed surgically after the SPECT study. Histopathological examination confirmed the diagnosis of prolactinoma. No clear-cut specific binding in the area of the adenoma could be demonstrated in one prolactinoma patient (Patient 5), who demonstrated a marked (>25%) tumor size reduction after bromocriptine treatment before the SPECT study.

Specific binding in the adenoma could be demonstrated in two of four GH-secreting adenomas. The adenoma/cerebellum ratio (2 and 4.8) was within the lower range of prolactinoma patients. One acromegalic patient, without specific binding, only demonstrated questionable tumor residue on MRI.

All four patients with clinically nonfunctioning pituitary adenomas had specific binding within the adenoma. In three of these, the adenoma/cerebellum ratio was within the lower range

of prolactinomas (5.2–7.5). One nonfunctioning adenoma showed extremely high binding, with an adenoma/cerebellum ratio of 52.3. MRI revealed a large intra- and suprasellar tumor mass of about 30 × 30 × 50 mm. No specific binding, in the area of the adenoma, was found in the patient with Cushing's disease or in the patient with Nelson's syndrome.

Specific Binding within the Striatum

Epidepride showed highest binding in the striatum in control subjects and in the majority of patients. The striatum/cerebellum ratio 3 hr p.i. in pituitary adenoma patients as a group was not significantly different from control subjects (17.3 ± 5.5, range 11.3–24.7 versus 17.8 ± 6.6, range 8.1–31.7; $p = 0.87$; patients versus control subjects). One patient (Patient 3) who had undergone subfrontal tumor removal twice and subsequent radiotherapy more than 30 yr before the SPECT study showed striatal binding below the range of control subjects (striatum/cerebellum ratio 8.1).

Although the individual variation of specific binding in striatum (normalized to injected dose and body mass) was bigger than the variation of striatum/cerebellum ratios, no significant group differences were seen (172.1 ± 47.7, range 93–297 versus 148.5 ± 20.5, range 120–181 cpm/mCi × kg; $p = 0.12$; patients versus control subjects).

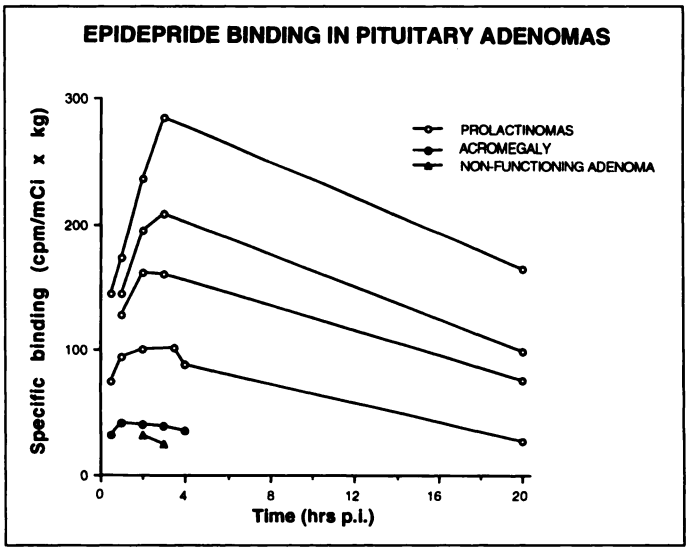

FIGURE 1. Time course of specific binding (adenoma minus cerebellum) of [^{123}I]epidepride in four prolactinomas, in a GH-secreting adenoma and in a clinically nonfunctioning pituitary adenoma.

DISCUSSION

Recent reports demonstrate that epidepride, a novel substituted benzamide derivative with high affinity for D2 receptors, can be used for studying striatal and extrastriatal dopamine D2 receptors in humans (*26,29,30*). The present study has evaluated the usefulness of [^{123}I]epidepride and SPECT for in vivo imaging of dopamine receptors in pituitary adenomas.

Previous studies by others and by our group have shown that dopamine D2 receptor imaging in PRL secreting pituitary adenomas, which are known to contain D2 receptors in high density, is possible with SPECT using [^{123}I]IBZM (*16–18*). However, we found that the sensitivity of IBZM-SPECT for imaging pituitary adenomas, presumably due to the relatively low target to background ratio of IBZM binding, is poor. Assies et al. (*16*) and Verhoeff et al. (*17*) only reported on successful imaging in one intracranial prolactinoma metastasis and one TSH-PRL secreting pituitary adenoma, respectively. In our series of 15 patients, including five patients with macroprolactinoma, specific IBZM binding could only be demonstrated in one prolactinoma patient. Recently, Scillitani et al. (*30*) could visualize one of two macroprolactinomas with IBZM and SPECT.

In the present series, we could visualize eight of nine prolactinomas, two of four GH-secreting adenomas and four of four clinically nonfunctioning pituitary adenomas with SPECT using [^{123}I]epidepride as a ligand. A wide variation of specific binding with higher binding in the adenoma than in the striatum in some patients was found in prolactinomas. This is consistent with in vitro findings and PET studies showing a wide variation of dopamine D2 receptor density in prolactinomas (*6,14*). Using membrane binding techniques, Pellegrini et al. (*6*) demonstrated that the density of D2 receptors is markedly reduced in bromocriptine-resistant prolactinomas as compared to dopamine agonist sensitive prolactinomas. The fact that all of our prolactinomas responded well to dopaminergic drugs is in accordance with the positive receptor studies in these patients.

No specific binding in the area of the adenoma could be demonstrated in one prolactinoma. This patient showed a >25% tumor size reduction and a normalization of plasma PRL after only 1 mo of bromocriptine before the SPECT study. Transsphenoidal surgery was performed 6 days after the SPECT study. Immunohistochemistry demonstrated marked fibrosis of the tumor with only some damaged cells left expressing PRL. Fibrosis and reduction of lactotroph cell size, sometimes even tumor cell damage, are well-known morphological effects of dopamine agonist treatment in prolactinomas (*31*). The immunohistochemical finding of marked fibrosis and a low amount of PRL expressing cells could explain the negative SPECT study in this patient.

Low-specific binding in the area of the adenoma could be demonstrated in two of four patients with acromegaly. This is in accordance with the in vitro finding of lower or in some cases even undetectable D2 receptor density in GH-secreting adenomas (*2,5,7,8*). One of the two acromegalic patients with a positive epidepride SPECT study had responded well to dopaminergic treatment about 10 yr before the SPECT study, the other never has been treated with dopamine agonists. Visualization of the adenoma failed in two patients with a GH-secreting adenoma. One of these patients, who had been operated on three times and who showed good response to dopamine agonist treatment, did not show a clear-cut tumor residue on MRI at the time of the SPECT study. The other acromegalic patient with a negative SPECT study had not responded to dopaminergic treatment before the SPECT study and bromocriptine was therefore withdrawn after the study.

Interestingly, all four clinically nonfunctioning pituitary adenoma patients were visualized with [^{123}I]epidepride SPECT. One of these patients showed an extremely high binding within the adenoma, which may be due in part to the large intra- and suprasellar extension of this tumor. Binding within the lower range of prolactinomas was found in the three other nonfunctioning adenomas. This is consistent with in vitro findings of low D2 receptor densities in all (*4*) or in a part and lack of D2 receptors in another part of clinically nonfunctioning adenomas (*5,8*) and low D2 receptor binding in PET studies using [^{11}C]N-methylspiperone and -raclopride (*14*). Like Muhr et al. (*13*), we found some overlap between D2 receptor binding in prolactinomas and clinically nonfunctioning pituitary adenomas.

No specific epidepride binding in the adenoma could be demonstrated in the patient with Cushing's disease or Nelson's

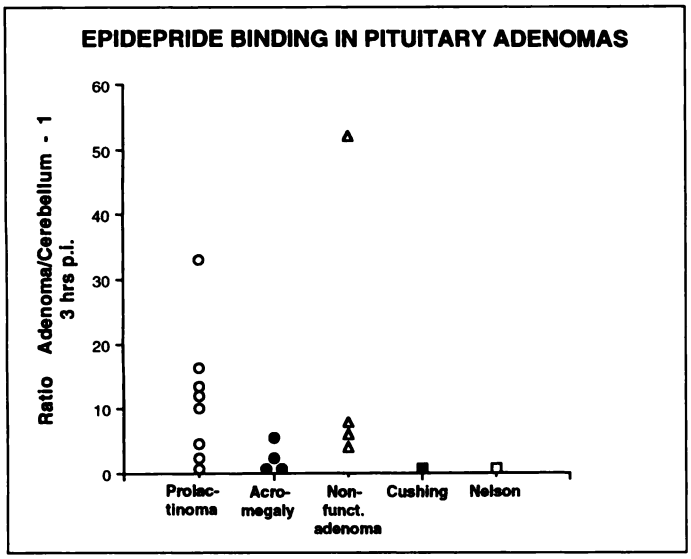

FIGURE 2. Adenoma/cerebellum ratios minus 1 at 3 hr p.i. of [^{123}I]epidepride in 17 patients with pituitary adenomas. Ratios of intrasellar and frontal tumor parts of Patient 3 (10.0; 13.0) are given separately. Values of Patients 1 (21.3) and 8 (4.5) are not included because data acquisition started 210 min p.i. in these patients.

syndrome. By using membrane binding techniques, Cronin et al. (*2*) found no D2 receptor binding in two ACTH-secreting adenomas. Thus, a lack of dopamine D2 receptors may explain the lack of response of these tumor types to dopamine agonist treatment.

MRI is the technique of choice for the diagnosis of tumors in the sella region due to its excellent spatial resolution. Differential diagnosis of these lesions is readily made by plasma hormone evaluations in the case of endocrine active adenomas. However, discrimination of clinically nonfunctioning pituitary adenomas from other tumors in the sella region, like meningioma, may be difficult. A positive D2 receptor SPECT study could indicate a pituitary adenoma. Epidepride SPECT, therefore, might be able to assist in the differential diagnosis of tumors in the sella region.

More importantly, SPECT using epidepride could serve as a predictor for response to dopamine agonist treatment in pituitary adenomas. As resistance to dopamine agonists is seen only in a minority of prolactinomas, dopaminergic treatment may be tried in any case in these patients. However, in GH-secreting and clinically nonfunctioning pituitary adenomas, which show a less favorable response to dopamine agonists, an in vivo assessment of D2 receptor density could help to identify the group of patients, which may respond to dopaminergic treatment. Our finding of a positive epidepride scan in a patient responding to dopaminergic treatment and a negative scan in a patient resistant to this treatment in the group of GH-secreting macroadenomas is in accordance with this assumption. The positive D2 receptor SPECT studies would suggest susceptibility for dopamine agonist treatment in clinically nonfunctioning adenomas. Further studies will have to clarify if epidepride SPECT might be a sufficiently reliable indicator of response to dopamine agonist treatment in pituitary adenomas.

Our kinetic data show a maximum of tracer uptake and

TABLE 2
Neuroradiologic and SPECT Findings

Patient no.	Tumor extension on MRI at time of SPECT study*	Specific binding within adenoma	Ratio adenoma/ cerebellum-1	Adenoma binding 3 hr p.i. (cpm/mCi × kg)
Prolactinoma				
1	Macroadenoma	+	[21.3]†	[102]†
2	Macroadenoma + r > 1 PSE	+	16.3	285
3	Macroadenoma + r PSE + frontobasal‡	+	10.0/13.0§	160/208§
4	Macroadenoma + r PSE	+	4.5	48
5	Macroadenoma + SSE	−		
6	Macroadenoma	+	2.5	27
7	Macroadenoma + r + 1 PSE	+	12.0	59
8	Macroadenoma	+	[4.5]¶	[52]¶
9	Macroadenoma + 1 PSE	+	33.0	377
Acromegaly				
10	questionable left parasellar tumor residue	−		
11	Macroadenoma + r PSE	+	2.0	39
12	r Macroadenoma + r PSE	−		
13	Macroadenoma + r PSE	+	4.8	31
Nonfunctioning pituitary adenoma				
14	Macroadenoma + 1 PSE	+	5.2	25
15	Macroadenoma	+	7.5	85
16	Macroadenoma + SSE + PSE	+	52.3	264
17	Macroadenoma + 1 > r PSE + SSE	+	6.0	42
Cushing's disease				
18	Macroadenoma	−		
Nelson's syndrome				
19	Macroadenoma + 1 PSA	−		

*Macroadenoma: intrasellar adenoma with diameter > 10 mm, SSE: suprasellar extension, PSE: parasellar extension, l: left, r: right.
†Data acquisition starting 209 min p.i.
‡Intrasellar adenoma with right parasellar extension and second extra-axial frontobasal adenoma.
§Values of intrasellar adenoma/frontobasal adenoma.
¶Data acquisition starting 212 min p.i.

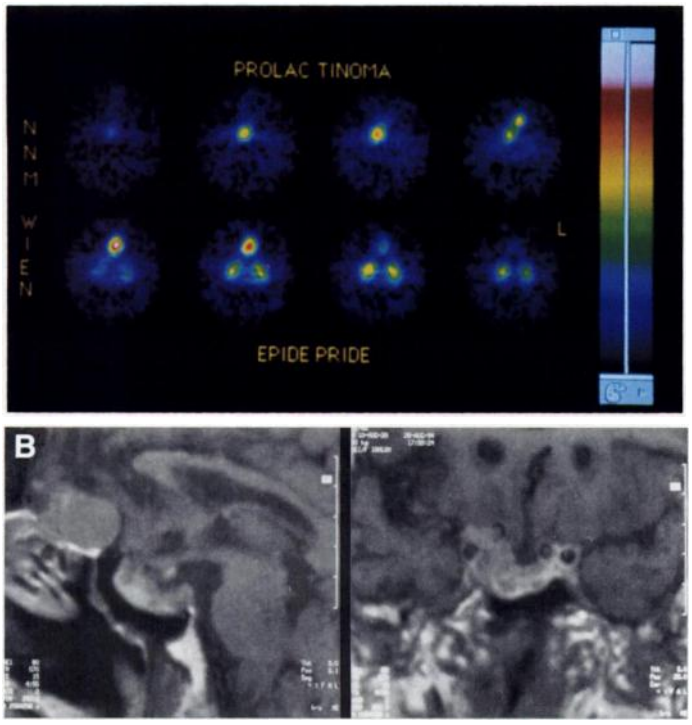

FIGURE 3. Iodine-123-epidepride SPECT 3 hr p.i in prolactinoma Patient 3. Specific binding in the lower and more central focus (top row) corresponded to an intrasellar adenoma, binding in a second, more frontal and left focus (upper right and three lower left slices) was due to a frontobasal tumor extending from the anterior skull base to the falx. Four bottom slices display striatal binding (A). Corresponding sagittal MRI image (left) showing an enlarged sella with the intrasellar adenoma and the frontobasal tumor and coronal MRI image (right) displaying the intrasellar tumor and its parasellar extension (B).

specific binding about 3 hr after injection in striatum and in prolactinomas and a slow decline thereafter. Binding in a GH-secreting adenoma and in a clinical nonfunctioning adenoma peaked earlier but remained relatively stable for up to 3 hr p.i. The earlier maximum of binding in the latter adenomas, which are known to contain D2 receptors in lower densities, could be explained by the general principle that peak uptake will occur earlier in areas with fewer binding sites when tracer uptake is limited by delivery to target sites (*32*). Because of the different kinetics in different tumor types the adenoma/cerebellum ratio may not accurately reflect the binding potential. Equilibrium of tracer binding may be reached later than 3 hr p.i. in prolactinomas with high D2-receptor density and reached earlier than 3 hr p.i. in GH-secreting or nonfunctioning adenomas. Thus, binding in these adenomas may be underestimated in both, pituitary adenomas with high and pituitary adenomas with low D2-receptor binding calculating a ratio adenoma/cerebellum 3 hr p.i.

A marked interindividual variation of specific epidepride binding in striatum was found in patients and control subjects. The individual variation of striatum/cerebellum binding ratios was smaller but still considerable with a range of 8.1 to 31.7 in patients and 11.3 to 24.7 in control subjects. The use of various cortical reference regions (data not shown) did not result in a smaller variation of striatum/reference region ratios. Striatal epidepride binding in pituitary adenoma patients as a group was not significantly different from control subjects. Only one patient, who had undergone subfrontal tumor removal twice and subsequently radiotherapy more than 30 yr before the SPECT study showed striatal binding below the range of control subjects.

The wide variation of striatum/cerebellum ratios may complicate separation of different patient groups with basal ganglia disorders. However, in pituitary adenomas visualization of the adenoma and determination of high- or low-specific binding may be sufficient for diagnostic purposes and for predicting response to dopaminergic treatment.

CONCLUSION

Epidepride appears to be an excellent ligand for in vivo imaging of dopamine D2 receptors in pituitary adenomas. Epidepride SPECT could serve as a predictor for response to dopamine agonist treatment.

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Reduced Coronary Flow Reserve in Familial Hypercholesterolemia

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Familial hypercholesterolemia (FH) presents the highest risk for coronary artery disease (CAD) among patients with hyperlipidemia. Therefore, early detection of coronary arterial atherosclerosis is important for the treatment of FH patients. The aim of this study was to detect early coronary arterial abnormalities that may relate to future atherosclerosis in asymptomatic FH patients by measuring coronary flow reserve (CFR) using PET and ^{13}N-ammonia. **Methods:** Twenty-five patients with FH (14 men, 11 women) without a history of myocardial ischemia and 14 control subjects (9 men, 5 women) were studied. Total serum cholesterol (mmole/liter) was 5.33 ± 0.66 in control subjects and 7.90 ± 0.77 in FH patients ($p < 0.01$ versus control subjects). **Results:** Myocardial blood flow (MBF) at rest and during dipyridamole loading was measured using PET, and CFR was calculated. MBF (ml/min/100 g weight heart) at rest in the FH group (79.0 ± 20.0) was comparable to that in control subjects (70.0 ± 17.0). However, MBF during dipyridamole loading was significantly lower in FH patients (163.0 ± 67.0) than in control subjects (286.0 ± 120.0, $p < 0.01$). CFR in FH patients (2.09 ± 0.62) was also significantly lower than that in control subjects (4.13 ± 1.38, $p < 0.01$). CFR showed a gender-specific variance in FH patients (1.85 ± 0.40 in men versus 2.55 ± 0.74 in women $p < 0.05$) but not in control subjects. Significant inverse correlations between CFR and the total plasma cholesterol level as well as plasma LDL cholesterol were observed. **Conclusion:** The CFR was reduced in patients with FH. This abnormality was more prominent in men than in women patients. Noninvasive assessment of CFR by ^{13}N-ammonia PET was useful to detect early abnormalities of the coronary arteries in asymptomatic patients with FH.

Key Words: familial hypercholesterolemia; myocardial blood flow; coronary flow reserve; PET; dipyridamole.

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Familial hypercholesterolemia (FH) is dominantly an inherited disease caused by mutation of low-density lipoprotein (LDL) receptor genes (*1*). The most important clinical characteristics of FH is the high incidence of coronary artery disease (CAD), increased mortality by CAD and reduced longevity with gender-specific variance (*2–9*). Therefore, early detection of abnormal coronary arteriosclerosis or abnormal coronary flow dynamics in FH patients is important in the management of this disease.

The inverse relationship between the severity of coronary stenosis and coronary flow reserve (CFR), as demonstrated by Gould et al. (*10*), showed that CFR decreases even in coronary arteries with 40%–50% stenoses. Furthermore, reduced CFR in hyperlipidemic patients without evidence of myocardial ischemia has been recently demonstrated (*11*). This suggests that a decrease in CFR should occur even in FH patients who have no evidence of myocardial ischemia. However, little is known about whether CFR is reduced in FH patients. Moreover, it has not been well-understood whether a decrease in CFR occurs with gender-specific variance in asymptomatic patients with FH or with any hyperlipidemia.

The aim of this study was to determine, by using PET and ^{13}N-ammonia, whether CFR decreases in asymptomatic FH patients, and, if so, to find out whether the reduced flow reserve is related to serum cholesterol level and to investigate a possible gender-specific variance in CFR.

MATERIALS AND METHODS

Subjects

Twenty-five patients with FH but no history of ischemic heart disease (14 men, 11 women) and 14 control subjects (9 men, 5 women) were studied. The diagnosis of FH, proposed by Mabuchi et al. (*3*) was made according to the following criteria: primary hypercholesterolemic patients with a total cholesterol >6.71 mmole/liter (260 mg/dl) and LDL cholesterol >4.64 mmole/liter (180 mg/dl) and an Achilles tendon thickness of >10 mm, or (b) primary hypercholesterolemic patients with a total cholesterol >6.71 mmole/liter (260 mg/dl) and LDL cholesterol >4.64 mmole/liter (180 mg/dl) with a family history of hypercholesterolemia in a first-degree relative. All patients with FH were asymptomatic and had not taken lipid lowering agents. Fourteen normo-lipidemic, normo-glycemic asymptomatic subjects without a history of heart disease were selected as control subjects. In all study subjects, resting ECG was normal. Symptom-limited treadmill testing was performed on 17 patients with FH and all normal subjects. We did not include those patients with typical chest pain or abnormal ECG indicating myocardial ischemia in this study.

Coronary angiography was performed in only five patients with FH, and all of them had normal coronary arteries. Table 1 summarizes the general characteristics of our study subjects. There were no significant differences in age, sex, body weight, height, body mass index (BMI), blood pressure or fasting plasma glucose concentration between the two groups. Gender-specific variance was not observed in either control subjects or patients with FH with the exception of height. Before participation, the nature of the study was explained to all subjects according to the study protocol which was approved by the local Ethics Committee.

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