PET as a Tool in the Clinical Evaluation of Pituitary Adenomas

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Positron emission tomography (PET) was used in over 400 examinations in patients with pituitary adenoma. It was demonstrated that PET with carbon-11-methionine can give valuable complementary information in the diagnosis of this tumor due to PET's ability to adequately depict viable tumor tissue in contrast to fibrosis, cysts and necrosis. Furthermore, PET with dopamine D2 receptor ligands can characterize the degree of receptor binding and thus give information as to the prerequisites for dopamine agonist treatment. Most important is the very high sensitivity given by PET with carbon-11-methionine in the evaluation of treatment effects. It is concluded that when properly used PET can be fully justified in the clinical handling of patients with pituitary adenomas and other intracranial tumors.

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Pituitary adenoma is a relatively common tumor, originating from the pituitary gland. This tumor type is of great interest to basic researchers and endocrinologists as a model for hormone secreting and hormone-dependent tumors. The inaccessibility of the tumor has prompted elaborate indirect studies using serum hormone levels as indicators of tumor type, response to medication, etc. Although in many cases these hormone determinations will adequately reflect the tumor conditions, we see several cases where a full understanding of the tumor characteristics cannot be reached from hormonal and clinical evaluations. A histologic classification will in most cases necessitate a full surgical procedure to obtain a tissue sample.

For several years we have been interested in the clinical aspects of pituitary adenoma and have used PET for the in vivo characterization of biochemical and functional aspects of this tumor (*1–8*). This work has been highly integrated into clinical practice and PET has been used as a very important complement to other techniques, such as hormonal evaluations, clinical examinations, radiologic studies, etc., and has been used to guide decisions on type of treatment. In this presentation, we wish to summarize our experiences in over 400 PET studies in patients with pituitary adenomas.

For a proper understanding of how these patients are handled, it is necessary to have some background information on the specifics of the normal pituitary gland and pituitary adenomas. The pituitary consists of six different intermingled cell types, five of which are characterized by secretion of specific hormones: growth hormone (GH), adrenocorticothropic hormone (ACTH), luteinizing hormone (LH) and follicle stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin (PRL). The sixth cell type, follicle stellate cell, is not known to have hormone secretion but probably fulfills a role similar to glia in the brain: nutritional support and phagocytosis.

Pituitary adenomas might originate from any of these hormone-secreting cells. The tumor cells usually retain most of the properties of the cell of origin, i.e., with respect to hypersecretion of the specific hormone. Furthermore, the adenoma cells often retain the regulatory system of the cell of origin. Thus, prolactinoma cells in most cases retain the inhibitory regulation through dopamine D2 receptors and GH-secreting tumors can be stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin through interaction with the respective receptor system.

The clinical manifestation of these slowly growing tumors usually includes hormone disturbances due to hypersecretion of a hormone or interference with the function of the normal pituitary gland. When the tumors grow large, the pressure on the chiasm can lead to severe visual impairment. In these instances, immediate intervention is often necessary to prevent irreversible damage to the optic nerves.

The most common type of pituitary adenoma, the prolactinoma, can in most instances be treated well with bromocriptine or another dopamine D2 agonist (*9,10*). Some of the GH-secreting adenomas can be treated with bromocriptine or somatostatin analog, but the most common treatment is surgery. Radiation therapy frequently is used but often has the disadvantage of a very slow onset of therapeutic effect, up to several years.

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MATERIALS AND METHODS

Patients with pituitary adenomas were referred to the neurologic department and evaluated clinically and hormonally. All patients were examined with CT and MRI before and at regular intervals during medical treatment. The diagnoses in most cases were verified by surgery or fine needle puncture and included immunocytochemistry.

The PET studies were performed as dynamic examination sequences with 15–20 scans obtained during 30–50 min after a rapid i.v. bolus injection of the tracer substance. The scanning times were successively increased from 20 sec to 300 sec. The PET unit (Scanditronix PC-384-3B) simultaneously produced three slices with a thickness of about 11 mm and a spatial resolution of 8 mm (*11*). Before the first PET study, a CT examination with an individual head fixation system (*12*) was performed in each patient to select the proper section for PET studies. The same fixation system was then used at each successive PET examination to ensure the same positioning during repeat examinations. The PET tracer substances were synthesized at the Department of Organic Chemistry and the ^{11}C was obtained from a tandem van der Graaf accelerator at the The Svedberg Laboratory.

Regions of interest were selected in the images to represent tumor tissue and normal brain tissue. In these regions of interest, the dynamic accumulation was calculated from the examination sequence. The quantitative analyses were performed in two different ways. The technique of Gjedde (*13*) using methionine and that of Patlak (*14*) using plasma radioactivity as a reference were used to calculate the rate of trapping of methionine in the tumor and normal brain tissue. Alternatively, the tumor-to-brain tissue ratio of radioactivity was plotted against time. This ratio, which became constant about 10 min after injection, was used as a relative measure of amino acid metabolism in the tumor. With dopamine antagonists, the uptake in cerebellum was used as a reference. In all these studies, a repeat study was performed either after blocking of the receptors using a therapeutic dose of haloperidol, or using the inactive enentiomer to separate specific and nonspecific receptor binding.

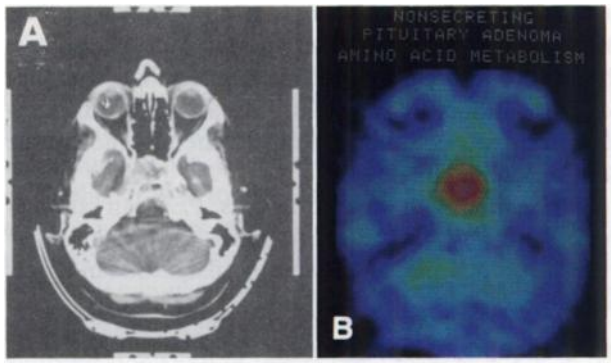

FIGURE 1. Patient with a non-secreting pituitary adenoma, operated several years ago. Now referred again because of clinical symptoms of tumor regrowth. CT demonstrates soft-tissue mass in the sella region (A), but the interpretation is complicated because of previous surgery. PET with ^{11}C-methionine (B) shows high localized accumulation thereby proving the diagnosis of tumor recurrency.

Differential Diagnosis

The differential diagnosis in most cases of hormone-secreting adenomas is readily obtained through hormonal evaluation of serum. With a supra- or parasellar mass with or without only slightly elevated hormone levels, the differential diagnosis includes non-secreting pituitary adenoma, craniopharyngioma, meningioma, neurinoma, chordoma, metastasis, sarcoidosis, and aneurysm. We have shown that PET with ^{11}C-methionine can clearly separate pituitary adenoma from neurinoma: the former always has a tumor-to-brain ratio uptake higher than 2, whereas the latter's ratio is always less than 2. In a few recent studies using ^{11}C-labeled L-deprenyl we have demonstrated that pituitary adenomas have high amounts of monoamine oxidase (MAO-B), whereas meningiomas have low levels of this enzyme (Fig. 2). Chordomas seem to demonstrate a different pattern of glucose-to-methio-

RESULTS

Diagnosis of Pituitary Adenoma

The radiologic evaluation of pituitary adenoma is best performed with MRI because of its excellent spatial resolution and the possibility of sagittal and coronal sections (*15*). In a number of instances, however, PET has made a significant contribution to diagnostic aspects because of its ability to depict viable tumor tissue and its high contrast between tumor tissue and brain tissue (*16–18*). As shown in previously operated adenomas, PET with ^{11}C-methionine can well discriminate active tumor from fibrosis, cysts, bleedings, etc. (Fig. 1). Furthermore, in images taken later than 20 min after the injection of ^{11}C-methionine, the tracer concentration in blood is very low compared with that in tumor tissue. Thus, tumor tissue with its high accumulation of tracer is readily discriminated from parasellar blood pools and aneurysms.

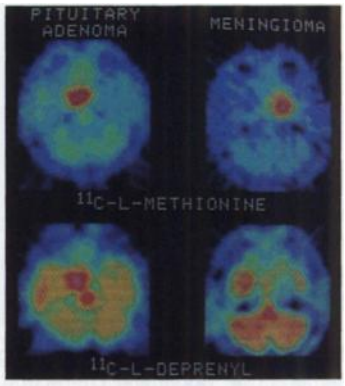

FIGURE 2. Comparison of uptake of ^{11}C-L-methionine (upper images) and ^{11}C-L-deprenyl (lower images) in a patient with a pituitary adenoma (left) and a parasellar meningioma (right). Both tumors show high uptake of methionine but only the pituitary adenoma demonstrate deprenyl binding to monoamineoxidase, MAO-B, thus enabling differential diagnosis.

nine relationship with a higher glucose-to-brain ratio than methionine-to-brain ratio. The pituitary adenomas have higher tumor-to-brain ratio of methionine than with glucose. As mentioned above, aneurysms are readily discriminated from active tumors using ^{11}C-methionine by the lack of uptake in late images.

In conclusion, with selected ligands, PET can complement other diagnostic techniques to add further information leading to a proper differential diagnosis and thus avoid biopsies.

Characterization Prior to Medical Treatment

For the medical, hormonal treatment of pituitary adenomas, in most instances an intact receptor system is a prerequisite for a good therapeutic effect. For example, in the treatment of prolactinomas with bromocriptine, a high amount of dopamine D2 receptors is a necessary prerequisite. In order to facilitate the study of this receptor system, we have used the ^{11}C-labeled dopamine antagonists raclopride (*19*) and N-methylspiperone (*20*). Both these ligands are adequate to use, but raclopride is more specific and offers less problems with labeled metabolites. An example of receptor binding in pituitary adenomas using ^{11}C-raclopride is given in Figure 3 and Figure 4.

For an adequate assessment of specific receptor binding, it is necessary to perform at least two PET studies in pituitary adenomas. The native study is supplemented with a second study in which either the receptors are previously blocked by haloperodol or the second study is performed with an inactive enantiomer. The first study demonstrates total uptake, including both specific and nonspecific binding. The second study only represents nonspecific binding. By subtracting these two studies, the specific binding can be extracted. If the patient is to be treated with dopamine agonist therapy, it is clearly advantageous to conduct the procedure using two different enantiomers to avoid the pharmacologic blocking of the receptors.

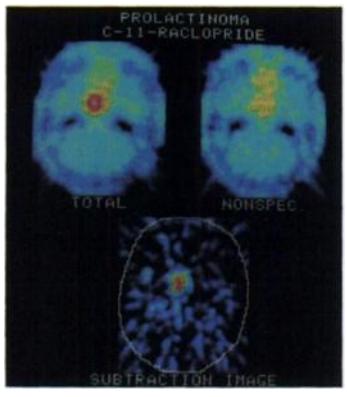

FIGURE 3. Patient with prolactinoma investigated with ^{11}C-raclopride to demonstrate dopamine D2-receptor binding. The native study (upper left) shows an uptake related to the sum of specific and nonspecific binding. A repeat study after the administration of 3 mg of haloperidol, which blocked the D2-receptor binding, gives an image related to nonspecific binding (upper right). The subtraction image (lower) correlates to specific receptor binding.

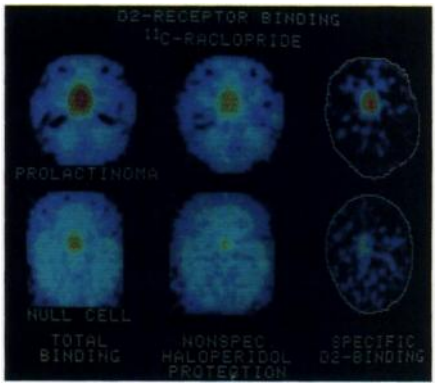

FIGURE 4. Patient with a prolactinoma (upper row) and nonsecreting adenoma (lower row) examined with ^{11}C-raclopride. The prolactinoma demonstrates high-specific dopamine-receptor binding whereas the nonsecreting adenoma shows low D2-binding.

In most prolactinomas, it is not clinically necessary to perform a receptor study, but dopamine agonist treatment can be started based on high serum prolactin levels. In GH-secreting adenomas, the receptor study can be valuable because only about 30% of the adenomas respond to dopamine agonist treatment. The respondents in our experience demonstrate higher dopamine receptor binding than the non-respondents.

We have recently started to evaluate the somatostatin receptors in pituitary adenomas using a ^{11}C-labeled somatostatin analog. The limited number of completed experiments preclude firm conclusions, but it is feasible to assume that such a study will be of importance to select patients for treatment with somatostatin analog. This drug is very expensive, which is another reason why it is important to know whether this treatment can be expected to be effective or not.

Evaluation of Treatment Effects

We believe that the most important aspect of PET in brain tumors is its superior sensitivity in the evaluation of treatment effects, for which we have traditionally used ^{11}C-labeled methionine. In nonsecreting pituitary adenomas, the tumor-to-brain ratio of methionine uptake is about 2.5. With active hormone secretion, this tumor-to-brain ratio increases linearly with serum hormone level, reaching values up to 9.0 in very active prolactinomas. When the prolactinomas are treated with bromocriptine, a very rapid and significant reduction in the methionine uptake is observed (*3*) (Fig. 5). Within a few hours, the methionine uptake in the tumor is already reduced by 40%. Within a few days, an 80% reduction in the metabolism is seen. This reduction in methionine uptake is followed by a significant reduction in serum hormone levels. With continued medication, an antitumoral effect is achieved, which is also observed in CT and MRI with reduction of

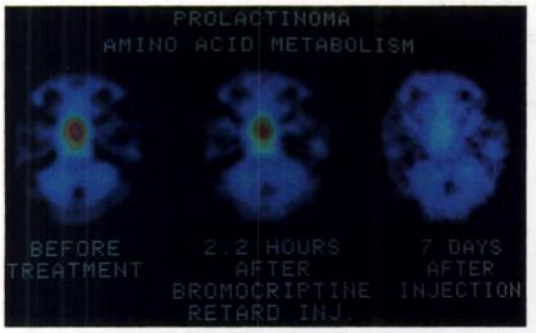

FIGURE 5. Patient with prolactinoma examined with ^{11}C-methionine before and after initiation of bromocriptine treatment. The initially very high metabolism in the tumor is already, within a few hours after start of treatment, markedly reduced. One week after start of treatment the amino acid metabolism is reduced by 80%. Still in this instance no effect on tumor size can be seen with CT or MRI, but 3–6 mo later a tumor size reduction was observed.

tumor size and/or development of cysts and necrosis noted within a few weeks to months. Thus, with PET, the effectiveness of this medication is seen within a few hours or days, whereas with CT and MRI the effect is seen within a few weeks to months. This example relates to treatment of prolactinomas with dopamine agonists, but we have many examples of treatment with medication of other types of pituitary adenomas in which PET with methionine could very rapidly confirm or contradict effects of treatment.

In a previously operated patient with a GH-secreting adenoma, PET revealed lack of effect during the initial attempt with a relatively low dose of somatostatin analog (Fig. 6). When the dose was successively increased to 1200 μg/day, a clear reduction of amino acid metabolism was observed. A PET study demonstrated that the effect of one

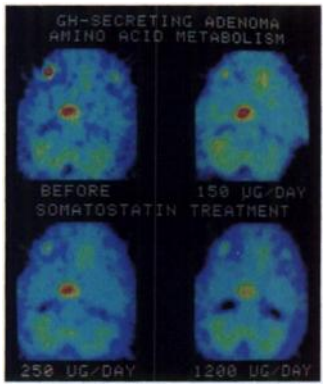

FIGURE 6. A patient with previously operated GH-secreting adenoma evaluated with ^{11}C-methionine. High amino acid metabolism is demonstrated in the recurrent tumor and in the lacrimal gland (upper left). After treatment with a somatostatin analogue (150 μg/day) no effect is seen on the metabolism (upper right). With an increased dose of 250 μg/day (lower left), a minimal effect is observed, and with 1200-μg/day dose, a clear reduction in amino acid metabolism is induced (lower right). Within a few months of treatment, a significant tumor size reduction occurs.

injection of somatostatin analog had a short duration; the metabolism returned to normal within a few hours after the injection. Thus, a more feasible mode of administration of this drug is to use a constant infusion. When the patient was treated with a constant infusion using an infusion pump, a further reduction in the metabolism was observed as compared with the same dose given four times per day. Within a few months after start of treatment, a significant reduction in tumor size was noted.

In a patient with a prolactinoma, an initial good response was observed with marked reduction in amino acid metabolism, reduction of serum prolactin level and, within a few weeks, a clear reduction of tumor size (Fig. 7). During the bromocriptine treatment, however, the tumor suddenly increased significantly in size. MRI and CT demonstrated a solid expanding tumor without signs of necrosis or cysts and only minimal bleeding. Contrast administration showed adequate perfusion. Thus, the radiologic techniques worked in favor of a rapidly growing tumor. A renewed PET with methionine showed almost complete lack of metabolism in the tumor, thus negating the possibility of active growth. Our interpretation was that the medication was effective, but at a certain stage the cellular damage had led to swelling of the cells and thus to an increase in tumor size. With a fine needle trans-spenoidal puncture (*21*), a thick fluid could be removed whereupon the tumor size decreased. With continued medication a significant tumor regression was observed. This example points to one other important factor of using a functional aspect in treatment follow-up. Some treatments may have a good antitumoral effect on the tumor cells, although a decrease in tumor size may not be attained due to other types of cellular effects, such as swelling, development of fibrosis, etc. An example of a prolactinoma that showed regrowth during bromocriptine therapy is presented in Figure 8.

DISCUSSION

In a large number of PET studies of pituitary adenomas, we have demonstrated the great advantages of a biochemical and functional characterization of the tumor conditions. The attainable information can be of great clinical value, enabling a better diagnosis, differential diagnosis, and characterization of the tumor before treatment and, most important, in treatment follow-up. Although PET is a very expensive technique, the specific information that can be gained may have such great impact as to fully justify these costs. In many cases, the hospital time necessary for patient evaluation may be shortened, and expensive and risky surgical procedures may be avoided by an adequate assessment of the effects of medical treatment alternatives. A proper judgment on the effects of medical treatment alternatives allows for more reliable information for continuing or discontinuing such treatment.

The high demand for clinical PET studies in our insti-

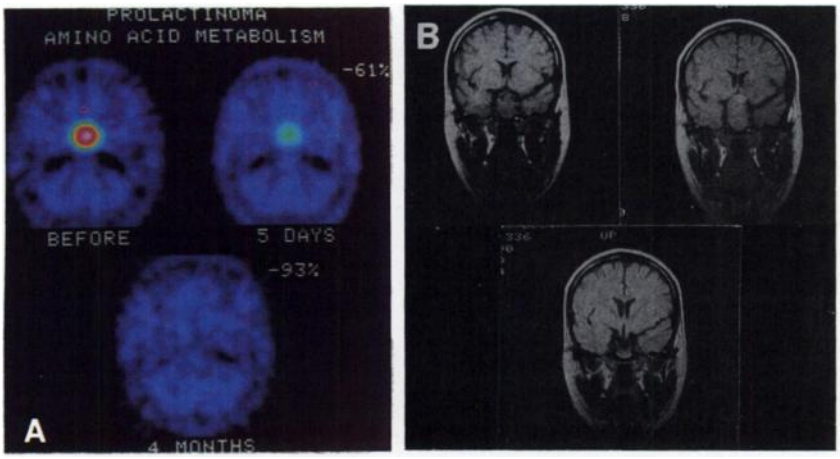

FIGURE 7. (A) A patient with prolactinoma was evaluated with ^{11}C-methionine. The initially very high metabolism in the tumor (upper left) is rapidly reduced when bromocriptine therapy is started (upper right). Within 3 mo, the tumor size is reduced to half its original size and the amino acid metabolism is reduced by 70%. The patient was referred again 1 mo later because of rapid expansion of the tumor, suggesting escape from response to medication. PET demonstrates (lower) lack of metabolism in the tumor thus excluding active tumor growth. (B) MRI performed 2 mo after start of treatment (upper left) showed reduced tumor size, whereas MRI at 4 mo after start of treatment (upper right) demonstrated a rapidly expanding tumor without signs of necrosis but a small bleeding that could not explain the great enlargement of the tumor. A 2-yr follow-up (lower) showed a marked regression of the tumor.

tution has prompted us to structure studies to allow for high throughput with limited personnel. In one 10-hr day, one of the authors (MB), together with one technician, performed 11 PET studies with blood sampling and analysis of the results during scanning. Each synthesis of methionine was divided into smaller batches for 2–3 patients per synthesis. Thus, we believe that PET can be not only a superior research tool, but also a tool for routine clinical investigations in brain tumors.

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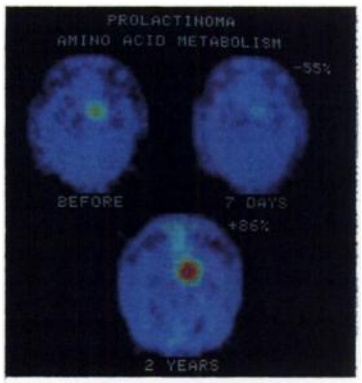

FIGURE 8. A patient with an invasive prolactinoma was examined with ^{11}C-methionine. The high amino acid metabolism (upper left) is markedly reduced 7 days after start of bromocriptine therapy (upper left). Two years after start of treatment the tumor size rapidly increased in spite of increased doses of medication. (Lower panel) PET with methionine demonstrates a highly active tumor. When the medication was changed to another type of dopamine agonist, amino acid metabolism decreased markedly, which was later accompanied by a tumor size reduction.

REFERENCES

1. Bergström M, Muhr C, Ericson K, et al. The normal pituitary examined with positron emission tomography and (C-11-methyl)-L-methionine and (C-11-methyl)-D-methionine. *Neuroradiology* 1987;29:221–225.
2. Bergström M, Muhr C, Lundberg PO, et al. In vivo study of amino acid distribution and metabolism in pituitary adenomas using positron emission tomography with ^{11}C-D-methionine and ^{11}C-L-methionine. *J Comput Assist Tomogr* 1987;11:384–389.
3. Bergström M, Muhr C, Lundberg PO, et al. Rapid decrease in amino acid metabolism in prolactin-secreting pituitary adenomas after bromocriptine treatment—a PET study. *J Comput Assist Tomogr* 1987;11:815–819.
4. Lundberg PO, Muhr C, Bergström K, et al. PET and NMR in diagnosis of pituitary adenomas. In: *PET and NMR: new perspectives in neuroimaging and in clinical neurochemistry.* New York: Alan R Liss Inc; 1986:407–424.
5. Muhr C, Lundberg PO, Antoni G, et al. The uptake of ^{11}C-labeled bromocriptine and methionine in pituitary tumors studied by positron emission tomography (PET). In: Lamberts, Tilders, van der Veen, et al., eds. *Trends in diagnosis and treatment of pituitary adenomas.* Amsterdam: Free University Press; 1984:151–155.
6. Muhr C, Bergström M, Lundberg P-O, et al. Dopamine receptors in pituitary adnomas: PET visualization with C-11-N-methylspiperone. *J Comput Assist Tomogr* 1986;10:175–180.
7. Muhr C, Bergström M, Lundberg PO, et al. Dopamine receptors in pituitary adenomas and effect of bromocriptine treatment — evaluation with PET and MRI. Proceedings from the 14th International Cancer Congress, Budapest, 1986.
8. Muhr C, Bergström M, Lundberg PO, et al. Malignant prolactinoma with multiple intracranial metastases studies with positron emission tomography. *Neurosurgery* 1988;22:374–379.
9. Benker G, Gieshoff B, Freundlieb O, et al. Parenteral bromocriptine in the treatment of hormonally active pituitary tumors. *Clin Endocrinol* 1986;24:505–513.
10. Kordon C, Wandscheer D, Shu C, et al. Neural control of prolactin secretion. In: McLeod RM, Thorner MO, Scapagnini U, eds. *Prolactin. Basic and clinical correlates.* Fidia Research series, vol. I. Padova: Liviana Press; 1985:61–71.
11. Litton J-E, Bergström M, Eriksson L, et al. Performance study of the PC-384 positron camera system for emission tomography of the brain. *J Comput Assist Tomogr* 1983;8:74–87.
12. Bergström M, Boethius J, Eriksson L, Greitz T, Ribbe T, Widen L. Head fixation device for reproducible position alignement in transmission CT and positron emission tomography. *J Comput Assist Tomogr* 1980;5:136–141.
13. Gjedde A. High- and low-affinity transport of D-glucose from blood to brain. *J Neurochem* 1981;36:1463–1471.
14. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood*

Flow Metab 1983;3:1–7.
15. Lundberg PO, Bergström K, Thuomas K-Å, Muhr C, Enoksson P. Magnetic resonance imaging of tumours of the sellar region: evaluation of treatment with bromocriptine retard. *Acta Radiologica* 1986;(suppl 369):310–313.
16. Bergström M, Collins P, Ehrin E, et al. Discrepancies in brain tumor extent as shown by CT and positron emission tomography using Ga-68-EDTA, C-11-glucose and C-11-methionine. *J Comput Assist Tomogr* 1983;7:1062–1066.
17. Ericson K, Lilja A, Bergström M, et al. Positron emission tomography with (methyl-11-C)-L-methionine, 11-C-glucose and 68-Ga-EDTA in the examination of supratentorial tumors. *J Comput Assist Tomogr* 1985;9:683–689.
18. Mosskin M, Ericson K, Hindmarsh T, et al. Positron emission tomography compared with magnetic resonance imaging and computed tomography in supratentorial gliomas using multiple stereotactic biopsies as reference. *Acta Radiol Diagn* 1989;30:225–232.
19. Farde L, Ehrin E, Eriksson L, et al. Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proc Natl Acad Sci* 1985;82:3863–3867.
20. Wagner NH Jr, Burns HD, Dannals RF, et al. Imaging dopamine receptors in the human brain by positron emission tomography. *Science* 1983;221:1264–1266.
21. Lundberg PO, Muhr C, Bergström K, et al. Trans-sphenoidal therapeutic puncture of a cystic pituitary adenoma. *Uppsala Journal of Medical Sciences* 1987;92:59–64.