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PET studies with L-[1-^{11}C]tyrosine, L-[methyl-^{11}C]methionine and ^{18}F-fluorodeoxyglucose in prolactinomas in relation to bromocryptine treatment

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Abstract. Aspects of metabolism in prolactinomas were investigated by positron emission tomography using L-[1-^{11}C]tyrosine, L-[methyl-^{11}C]methionine and ^{18}F-fluorodeoxyglucose (^{18}FDG). Using L-[1-^{11}C]tyrosine, four patients were monitored prior to and 18 h after an injection of 50 mg bromocryptine. At 18 h after bromocryptine intervention, L-[1-^{11}C]tyrosine uptake into tumour was reduced with 28% ($P<0.07$). A correlation analysis of the bromocryptine-induced decrease in L-[1-^{11}C]tyrosine uptake and the reduction of serum prolactin levels indicated that the action of bromocryptine on prolactin synthesis and prolactin release is not coupled. In the untreated situation, the four patients were investigated with ^{18}FDG as well, but the prolactinomas could not be visualized. Three untreated patients were studied with L-[methyl-^{11}C]methionine. The tumour-imaging potential of L-[methyl-^{11}C]methionine and L-[1-^{11}C]tyrosine appeared to be nearly equivalent for prolactinomas. Unlike prolactinoma tissue, the salivary glands showed a pronounced preference for L-[1-^{11}C]tyrosine as compared to L-[methyl-^{11}C]methionine. L-[1-^{11}C]tyrosine is a valuable tool to obtain information on the metabolism and treatment of prolactinomas.

Key words: Positron emission tomography – ^{11}C-amino acids – ^{18}F-fluorodeoxyglucose – Prolactinoma – Salivary gland

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Introduction

Positron emission tomography (PET) using ^{11}C-labelled amino acids has prominent clinical applications in the field of oncology. PET measurements of the uptake of these radiopharmaceuticals into tumours have predictive value for the grade of malignancy (Schober et al. 1987; Derlon et al. 1989) and therefore implications for the choice of tumour therapy. After tumour treatment, ^{11}C-labelled amino acids are also suitable metabolic probes to assess the beneficial effects of surgery (Lilja et al. 1989) and radiotherapy (Derlon et al. 1989). The majority of the PET studies to establish these applications have been performed with L-[methyl-^{11}C]methionine (^{11}C-me-met), predominantly in gliomas and astrocytomas.

Ten to twenty percent of all intracranial lesions are prolactin-secreting pituitary tumours (Dollar and Blackwell 1986). These slowly growing prolactinomas cause high serum prolactin levels, which inhibit the production of the sex hormones. Therefore, secondary effects arise such as impaired sexual function and decreased libido. In particular, amenorrhoea and galactorrhoea are encountered in the female prolactinoma patient. Prolactinomas are sensitive to treatment with dopamine agonists. In the last few years, this form of treatment for prolactinomas has become the first line of treatment compared to former conventional therapies such as surgery and radiotherapy (Grossman and Besser 1985).

In comparison to PET studies with malignant gliomas and astrocytomas, disproportionately few PET studies have been performed with prolactinomas. Bergström et al. (1987a) have reported a four-patient study describing the bromocryptine-induced reduction of ^{11}C-me-met uptake into these tumours. This effect could be attributed to the binding of bromocryptine to D_2-receptors. In an earlier study, these D_2-receptors had already been demonstrated with PET using ^{11}C-methylspiperone in two untreated patients with pituitary tumours (Muhr et al. 1986).

Besides protein synthesis, methyl-labelled methionine is involved in other metabolic pathways such as transmethylation, which might lead to accumulation of a variety of non-protein metabolites in tumour tissue (Daemen

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et al. 1991). Therefore, carboxylic-labelled amino acids, such as L-[1-^{11}C]tyrosine (^{11}C-tyr) (Ishiwata et al. 1988) and L-[1-^{11}C]leucine (Keen et al. 1989), appear to be more appropriate compounds for determining the protein-synthesizing activity of tumour tissue. The main metabolite of these amino acids is $^{11}CO_2$, which is cleared from tissue to plasma and rapidly expired from lung into air. Therefore, $^{11}CO_2$ does not contribute substantially to the ^{11}C-radioactivity in the tumour tissue, as measured by PET. In animal studies, ^{11}C-tyr has proven to be a sensitive probe for follow-up of the effects of hyperthermia and radiotherapy on tumours (Daemen et al. 1989a, b). Therefore, ^{11}C-tyr was chosen for this study in order to monitor the effect of bromocryptine intervention on patients with prolactinomas.

To compare ^{11}C-amino acid uptake with carbohydrate metabolism, 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}FDG) was also selected for this study. This compound is widely used in PET as a suitable indicator of glycolytic activity of tumours. Determination of the grade of malignancy of intracranial tumours (Di Chiro 1986) and early discrimination between radiation necrosis and recurrence of tumour after radiotherapy (Patronas et al. 1983) appear to be the major clinical applications of PET using ^{18}FDG in oncology. Until now, ^{18}FDG has not been applied for the investigation of prolactinomas and for possibly validating prolactinoma treatment.

The aim of the present study is:

1. To compare the visualization of prolactinomas with ^{11}C-tyr, ^{11}C-me-met and ^{18}FDG by PET.
2. To assess the effect of a pharmacological intervention with bromocryptine on prolactinomas in terms of ^{11}C-tyr uptake, as measured by PET in relation to alterations in serum prolactin levels.

Materials and methods

Materials. Radiochemically pure L-[1-^{11}C]tyrosine was synthesized with a specific activity >3.7 GBq/μmol (100 Ci/mmol) (Bolster et al. 1986). ^{18}FDG was synthesized, no carrier added, with a radiochemical purity >98% (Hamacher et al. 1986). L-[methyl-^{11}C]methionine was synthesized with a specific activity of >2 GBq/μmol (55 Ci/mmol) and a radiochemical purity of 97% (Comar et al. 1976). Serum prolactin was determined with an immunoradiometric assay (Prolactin Maiaclone, Serono Diagnostics, Woking, UK). Parlodel LA (Sandoz, Basel, Switzerland) was used as the bromocryptine preparation.

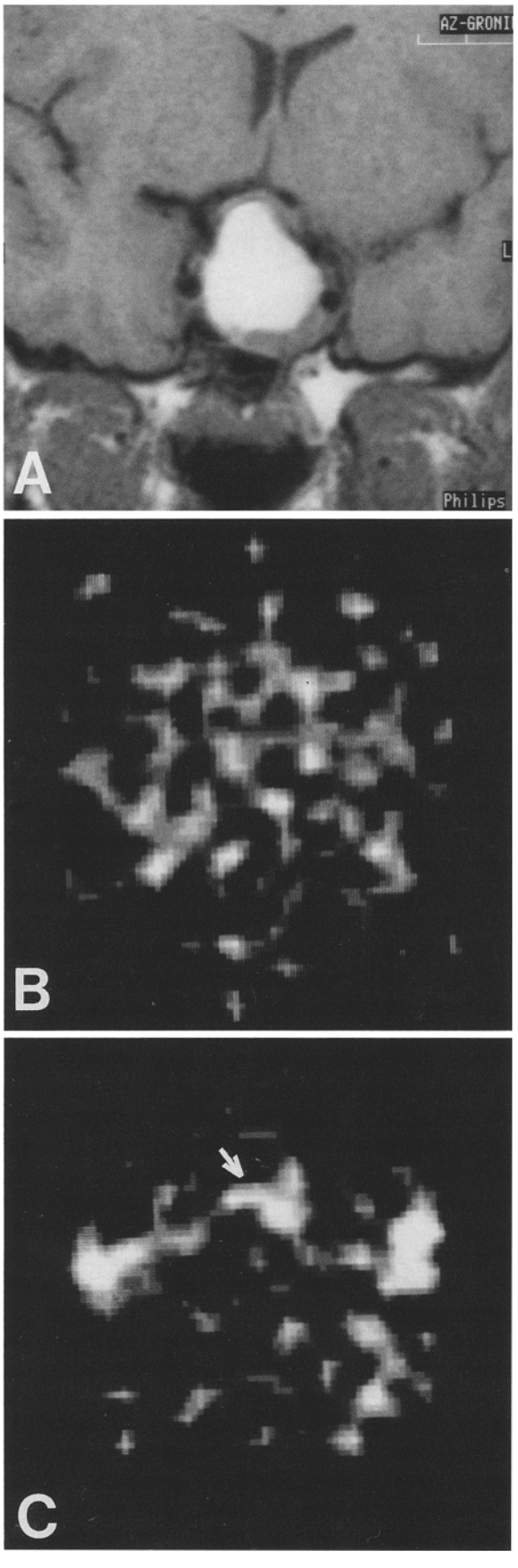
Patients. In seven patients, three women and four men ranging in age from 21 to 57 years, the presence of a prolactinoma was confirmed by the elevated serum prolactin level and MRI. The MRI images were obtained with a Philips Gyroscan S15 (Philips, The Netherlands). The patients had tumours of different sizes; one tumour appeared to be a microprolactinoma (∅ <10 mm), while the other six were macroprolactinomas with suprasellar extensions. Prior to the PET studies, the patients had not been receiving tumour treatment in any form. The patient data are summarized in Table 1.

PET camera. The positron camera used was a double-headed rotating uncollimated camera system (Paans et al. 1985). This imaging apparatus has a spatial resolution of 7.5 mm FWHM and a sensitivity for a point source of 2.7 cps/kBq. The data were acquired in 18 steps of 10° each. The actual data acquisition time for each rotational step was corrected for the physical half-life of the radio-

Table 1. Data on patients with prolactinomas

Patient (sex/age)	Clinical status	MRI findings	Hormone status[a]
1/F/21	Secondary amenorrhoea; galactorrhoea	Intrasellar tumour	Estradiol 0.1
2/F/31	Secondary amenorrhoea; headache	Extension to scull base; displacement of optic chiasm	Estradiol 0.0
3/M/49	Hypogonadism; decreased libido	Tumour invasive into sphenoidsinus; displacement of right carotid artery	Testosterone 5.09
4/M/21	Hypogonadism; arrested puberty; normocytic anaemia	Displacement of optic chiasm and bottom of 3rd ventricle	Testosterone 2.18; substituted thyroid insufficiency
5/M/39	Visual field defects; paralysis of abducent nerve; headache	Giant tumour, invasive into 3rd ventricle; displacement of right carotid artery	Testosterone 7.62
6/M/57	Bitemporal visual field defects	Invasive tumour into sphenoid sinus; displacement of chiasm	Testosterone 1.43; substituted thyroid insufficiency
7/F/22	Secondary amenorrhoea; visual field defects	Suprasellar extensions	Estradiol 0.0; substituted thyroid insufficiency

[a] Normal values: estradiol 0.1–0.2 nmol/l (female); testosterone 18–45 nmol/l (male)



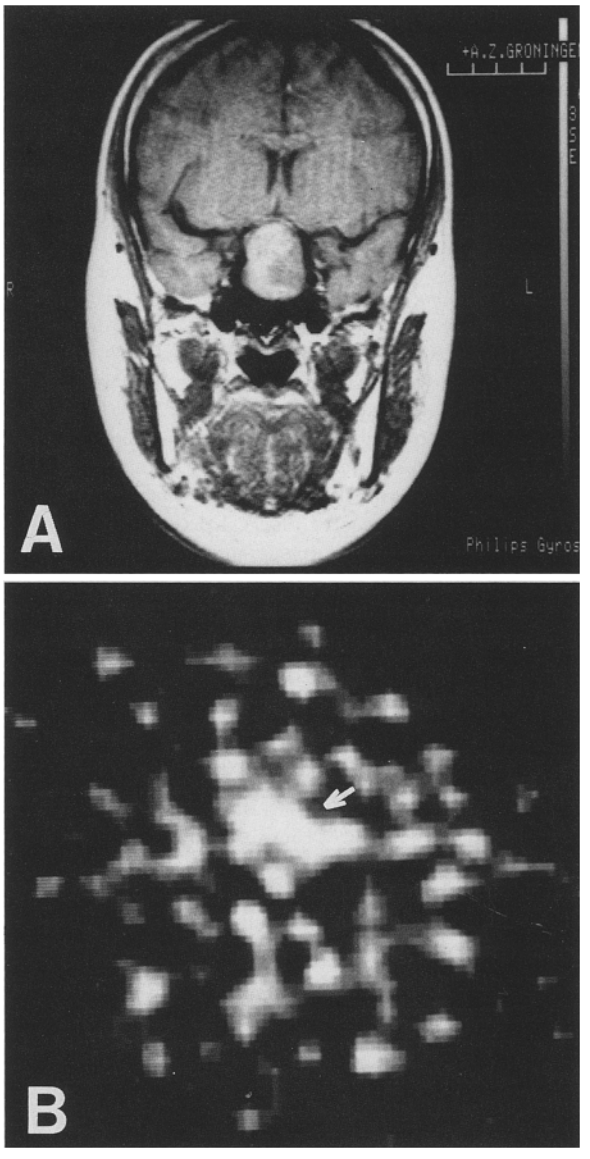


Fig. 1. **A** MRI study (patient 4) with clear visualization of the untreated prolactinoma in a coronal slice. **B** PET study with ^{18}FDG of the same untreated patient in a transaxial slice; tumour could not be visualized. **C** Corresponding PET study using L-[1-^{11}C]tyrosine; position of tumour is indicated by an *arrow*; the *contralateral spots* reflect uptake of ^{11}C-radioactivity into the parotid salivary glands

Fig. 2. **A** MRI study of prolactinoma (patient 7) in a coronal slice. The prolactinoma tissue shows a clear signal heterogeneity. **B** L-[methyl-^{11}C]methionine PET study in a transaxial slice; position of the tumour is indicated by an *arrow*

nuclide used. This procedure results in the same effective data acquisition time for each rotational step. Therefore, the data acquisition time for one static image with ^{11}C- and ^{18}F-activity amounted to 32 and 25 min, respectively. The image was back-projected into a volume of $30 \times 30 \times 30$ cm^3, which was divided into 16 slices with a thickness of nearly 2 cm each. The matrix size used was 64×64 pixels per slice. The final images were obtained after deconvolution of the back-projected images for the system response function.

Data acquisition and analysis. Via an antecubital vein, the untreated patients (patients 1–4) were given a dose of 37 MBq (1 mCi) ^{11}C-tyr as a rapid bolus. After 30 min, the patient was positioned into the PET camera, and data were acquired between 30 and 62 min after injection. An ^{11}C-tyr study was composed of $2–3 \times 10^5$ counts. From a catheter, temporarily inserted into a contralateral dorsal hand vein, blood samples were obtained to monitor the level of ^{11}C-radioactivity in plasma. The radioactivity measured in the plasma samples was corrected for physical decay to the time of injection, whereupon the level of plasma radioactivity was calculated as the differential absorption ratio:

$$\mathrm{DAR} = \frac{\text{activity plasma sample}}{\text{total activity injected}} \times \frac{\text{weight patient}}{\text{weight plasma sample}}$$

After 3 h, which is 9 times the half-life of ^{11}C, the patient was administered an IV injection of 18.5 MBq (0.5 mCi) ^{18}FDG. With the patient in the same position as in the ^{11}C-tyr study, PET data were acquired between 20 and 45 min after injection. Sensory stimuli (noise, light) were constant during the time the PET studies were being carried out. In the ^{18}FDG studies, $3–4 \times 10^5$ counts were registered.

Within a few days, the patient was intragluteally injected with 50 mg bromocryptine mesylate in a sustained-release form. A second PET study with ^{11}C-try was repeated 18 h after bromocryptine intervention.

In order to compare with the ^{11}C-tyr PET studies, three patients (patients 5–7) were investigated with ^{11}C-me-met. The patients were injected with 37 MBq (1 mCi) ^{11}C-me-met, and data were acquired between 30 and 62 min post-injection. The serum prolactin levels were determined with an radioimmunometric assay at the time the PET studies were done.

The location of the prolactinoma on MRI was used to determine the position of the tumour on the PET images. Regions of interest (ROI) were graphically defined for tumour, cortex and cerebellum, and counts were then measured. ROI for cortex, which consisted mainly of white matter, was delineated in the slice 4 cm cranial to the pituitary tumour, while ROI for cerebellum was delineated 2 cm caudal to the pituitary tumour. The ROIs of the first ^{11}C-tyr study were also used for the radioactivity measurements of the second ^{11}C-tyr study. The uptakes of the ^{11}C-amino acids into the prolactinomas were expressed as tumour/non-tumour (T/NT) ratios.

Results

Prolactinomas of four patients were consecutively investigated with MRI and PET using ^{11}C-tyr and ^{18}FDG, respectively. MRI and PET studies with ^{11}C-me-met were performed in three other patients. Discrepancies were observed among these four imaging methods. Prolactinomas could clearly be visualized with MRI, and

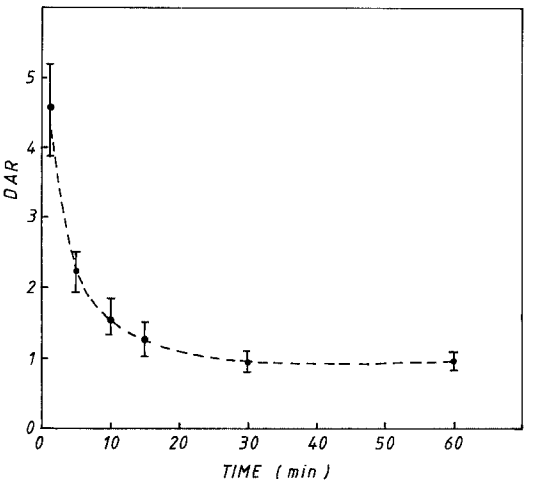


Fig. 3. Time activity curve of L-[1-^{11}C]tyrosine in plasma of four patients measured 1, 5, 10, 15, 30 and 60 min after injection. Plasma activity was calculated as *DAR* and expressed as mean ± SEM

PET using ^{11}C-tyr and ^{11}C-me-met. In Fig. 1, the prolactinoma of untreated patient 4 is shown on MRI (A) and, as indicated by an arrow, on the ^{11}C-tyr PET image (C). In each of the four ^{18}FDG studies, the prolactinomas of the untreated patients could not be delineated. No localized hyper- or hypometabolic regions could be discerned (see Fig. 1 B). In order to visualize the ^{18}FDG and ^{11}C-tyr distribution, different absolute scaling had to be used. This resulted in a visual overestimation of the amount of ^{18}FDG as presented in Fig. 1 B with respect to the ^{11}C-tyr image (Fig. 1 C). In Fig. 2, visualization of prolactinoma (patient 7) is shown with MRI and with PET using ^{11}C-me-met.

The averaged plasma ^{11}C-radioactivity measured in the four ^{11}C-tyr PET studies in the untreated situation is given in Fig. 3. The concentration is given as DAR. This parameter corrects for the injected dose and weight of the patient. Within 15 min after IV injection, ^{11}C-tyr is distributed from plasma into tissue. During the time span of the PET study, between 30 and 60 min after injection, the plasma radioactivity level is observed to be constant.

The tumour-to-tissue uptake ratios of ^{11}C-tyr and ^{11}C-me-met ratios are presented in Table 2. The mean tumour-to-cortex (T/Cor) ratio for ^{11}C-tyr and ^{11}C-me-met amounted 3.20 and 2.78, respectively. The Mann-Whitney test revealed a P-value of 0.32 for the difference. The uptake of ^{11}C-tyr into the prolactinoma, after bromocryptine administration, is also listed in this table. At 18 h after bromocryptine injection, the T/Cor and tumour-to-cerebellum (T/Cer) ratios were decreased in each individual patient, with an average of 28% and 29%, respectively, for the whole group. A 4-paired sample-sign test indicates that bromocryptine is effective on the ^{11}C-tyr uptake ($P < 0.07$). The extent of tumour on the ^{11}C-tyr images did not change 18 h after intervention

Table 2. Tissue uptake ratios of (A) L-[1-^{11}C]tyrosine measured prior to and 18 h after bromocryptine administration (patients 1–4) and (B) L-[methyl-^{11}C]methionine (patients 5–7)

Patient	Untreated			18 h after bromocryptine		
	T/Cor (%)	T/Cer (%)	Cor/Cer	T/Cor (%)	T/Cer (%)	Cor/Cer
A. L-[1-^{11}C]tyrosine						
1	2.73 (100)	3.41 (100)	1.25	2.02 (74)	2.02 (59)	1.00
2	2.00 (100)	1.76 (100)	0.88	1.65 (83)	1.49 (85)	0.90
3	4.05 (100)	2.58 (100)	0.64	3.07 (76)	2.37 (92)	0.77
4	4.00 (100)	2.62 (100)	0.65	2.18 (55)	1.31 (50)	0.60
	–	–	–	–	–	–
Mean	3.20	2.59	0.86	2.23	1.80	0.82
SEM	0.50	0.34	0.15	0.30	0.25	0.09
B. L-[methyl-^{11}C]methionine						
5	3.81	3.58	0.94	–	–	–
6	2.23	2.04	0.91	–	–	–
7	2.27	1.95	0.86	–	–	–
	–	–	–			
Mean	2.78	2.52	0.90			
SEM	0.52	0.53	0.02			

T, Tumour; Cor, cortex; Cer, cerebellum
Percentage for T/Cor and T/Cer ratios in parentheses

Table 3. Bitemporal diameter on MRI in coronal slices and serum prolactin levels of seven patients with untreated prolactinomas. In four patients, serum prolactin was also determined 18 h after administration of bromocryptine

Patient		Serum prolactin levels[a]			
	∅ MRI (mm)	Before (mU/l)	(%)	After 18 h (mU/l)	(%)
1	7	1256	(100%)	251	(20.0%)
2	22	18180	(100%)	1792	(9.9%)
3	30	51000	(100%)	5335	(10.5%)
4	24	15700	(100%)	4191	(26.7%)
5	55	422000	–	–	–
6	37	46600	–	–	–
7	26	39600	–	–	–

[a] Normal values: female 165 (range 50–520), male 110 (range 40–290)

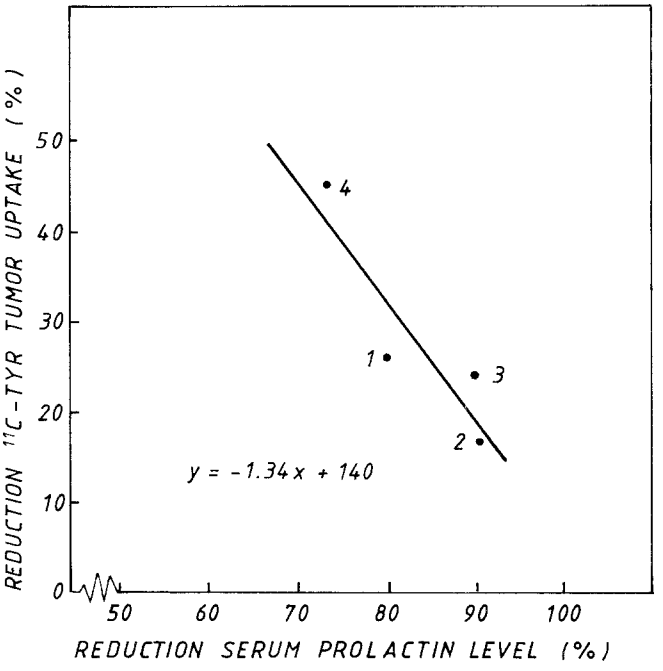


Fig. 4. Graphic comparison in four patients of the percent reduction of L-[1-^{11}C]tyrosine tumour uptake (*Y-axis*) and the percent reduction of the serum prolactin level (*X*-axis) after a bromocryptine injection and measured 18 h after administration. The numbers in the figure represent the respective patients

with bromocryptine. Based on the measured counts in the ROIs, the statistical errors in the T/NT ratios are estimated to be 6%. Consequently, the errors in the bromocryptine-induced differences, as observed in ^{11}C-tyr studies, are about 10%.

The serum prolactin levels for each patient are presented in Table 3. In the untreated situation, the serum prolactin levels measured showed a large variation, with a range between 1.3×10^3 and 411×10^3 mU/l. A coarse correlation was observed between the volume of the tumour, as estimated with MRI, and the serum prolactin level. At 18 h after administration of bromocryptine, serum prolactin had rapidly been reduced to an average residual level of 16±8% (±SD), as compared to the untreated situation.

The percentage of reduction of the ^{11}C-tyr T/Cor

ratio and the reduction of the serum prolactin level per individual patient are compared in graph form in Fig. 4. A correlation was observed between the decreases in the ^{11}C-tyr T/Cor ratio expressed with the x against y line: $y = -1.34x + 140$. Error analysis reveals an error of 0.4 in the slope and of 37 in the intercept.

The parotid salivary glands were depicted in all ^{11}C-tyr studies (e.g. Fig. 1), and in three of these studies the submandibular glands were observed as well. In contrast to ^{11}C-tyr, no notable uptake was observed of ^{11}C-me-met into both kinds of salivary glands. Bromocryptine had no effect on the uptake of ^{11}C-tyr into the salivary glands.

Discussion

The uptake of ^{11}C-tyr, ^{11}C-me-met and ^{18}FDG tumour tissue was investigated with PET in patients with prolactinomas. Furthermore, the effects of a pharmacological intervention with bromocryptine on the amino acid utilization of prolactinoma tissue were measured by the use of ^{11}C-tyr.

A rapid decrease in plasma radioactivity to a low constant level was observed in the four patients after administration of ^{11}C-try (see Fig. 3). A similar profile of the plasma radioactivity curve was observed by Bergström et al. (1987b) for ^{11}C-me-met. The PET data were acquired in the period when the ^{11}C-plasma activity was constant. Therefore, the T/NT ratio measured in this period is considered to be in a steady state.

When compared, nearly the same imaging potentials for prolactinomas were found for ^{11}C-tyr and ^{11}C-me-met. Shome and Farlow (1977), who elucidated the entire linear amino acid sequence of human prolactin, found that of the 198 amino acids present, 4 were methionine and 7 were tyrosine. Sequential PET studies with both tracers in the same patient would provide a clearer answer to the question as to which amino acid is preferred by prolactinomas.

Using ^{18}FDG, prolactinomas could not be visualized because of the lack of contrast in uptake of this tracer between the prolactinoma tissue and the surrounding tissue (cortex, hypothalamus, bone). In patients with a variety of tumours, Minn et al. (1988) found a positive correlation between the fraction S-phase cells and the T/NT uptake ratio for ^{18}FDG. Prolactinomas are slow-growing tumours with very low proliferation rates, which may explain the poor visualization with ^{18}FDG. Consequently, this compound is inappropriate for monitoring therapy of prolactinomas.

Within 18 h after administration, bromocryptine gave a reduction in ^{11}C-tyr uptake into prolactinomas of about 30%. Bromocryptine exerts a two-fold action on the amino acid utilization of prolactin-secreting cells. In cultured pituitary cells exposed to ergocryptine, Maurer (1980) found a rapid reduction in the cellular protein synthesis that could exclusively be ascribed to inhibition to prolactin synthesis. Decreased concentration of prolactin mRNA gave evidence of a dopamine-agonist-mediated specific inhibition on gene transcription for prolactin (Maurer 1981). In rat pituitary adenoma cells, reduction of growth and total cellular protein synthesis were observed at higher bromocryptine concentrations than needed for inhibition of prolactin synthesis (Johansen et al. 1985). The action of bromocryptine was ascribed to a dose-dependent general cytotoxic action on prolactin-secreting adenoma cells.

In a four-patient PET study, Bergström and co-workers (1987a) found a 41% reduction of ^{11}C-me-met uptake into prolactinomas at 2–4 h after an intramuscular injection with the same amount bromocryptine, as used in this study. Even higher reductions of ^{11}C-me-met uptake up to 60% were reported from a two-patient study (Bergström et al. 1988). Compared to our ^{11}C-tyr studies, these reductions in ^{11}C-me-met uptake were higher and measured at an earlier point of time. A possible explanation might be that bromocryptine also has an inhibitory effect on the transmethylation processes occurring in the prolactinoma tissue. This bromocryptine effect was indicated by Bergström and co-workers (1987a) as well.

No positive correlation between the decrease of ^{11}C-tyr uptake into tumour and the decrease of prolactin secretion into serum was found after injection of bromocryptine. Other investigators have also shown discrepancies between the effects of bromocryptine on protein synthesis and on prolactin release. In immunohistochemical studies in prolactinoma cells, Niwa et al. (1987) found that after bromocryptine administration, protein synthesis remained unchanged, while secretion of prolactin was disturbed, associated with a decreased amount of microtubules. Davies et al. (1990) found that secretion of prolactin was reduced by bromocryptine while this agent did not affect the cytoplasmic levels of prolactin mRNA, suggesting a relative autonomy of prolactin synthesis. From the studies of these authors and our own studies, it is suggested that bromocryptine has independent mechanisms of action on the synthesis and the release of prolactin.

The uptake of the different amino acids into prolactinoma tissue was compared with their corresponding uptake into salivary gland tissue. A pronounced preference of ^{11}C-tyr to ^{11}C-me-met was observed for the parotid and the submandibulary glands. Analysis of the free amino acid levels of human saliva showed that tyrosine is found in much higher concentrations compared to methionine (Battistone and Burnett 1961). Furthermore, determinations of the amino acid composition of many proteins in saliva revealed that, in general, these macromolecules are tyrosine-rich, while for methionine only trace amounts are found (Arglebe 1981). The larger amounts of tyrosine in the secretory products of the salivary glands, as compared to methionine, demon-

strate the differences in the biochemistry of the respective amino acids in these glands, which explains the specific high uptake of ^{11}C-tyr observed by PET. From these results it can be concluded that ^{11}C-tyr might be a suitable probe for investigating pathophysiological states of the salivary glands with PET.

In conclusion, ^{11}C-tyr and ^{11}C-me-met are superior to ^{18}FDG for the visualization of prolactinomas. The salivary glands could be visualized with ^{11}C-tyr, but not with ^{11}C-me-met. The utilization of a specific amino acid by tissues for synthesis into molecules that are secreted, such as prolactin and saliva proteins, can be investigated by PET, measuring the uptake of its ^{11}C-labelled counterpart. The bromocryptine-induced reductions in ^{11}C-tyr uptake into prolactinoma tissue did not tally with the decline in prolactin release into serum. Next to MRI and serum prolactin measurements providing information on anatomical structures and hormone function, respectively, PET using ^{11}C-labelled amino acids in a suitable tool for obtaining complementary metabolic information on prolactinoma tissue in relation to bromocrpytine treatment.

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