Comparison of [¹¹C]flumazenil and [¹⁸F]FDG as PET markers of epileptic foci

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Abstract

Recent PET results indicate that the benzodiazepine (BZ) receptor density measured with the BZ receptor antagonist [¹¹C]flumazenil is reduced in human epileptic foci. The present study examines the applicability of this finding in the presurgical investigation of patients with intractable partial epilepsy. In eight patients, the PET measurements were performed after injection of the BZ receptor antagonist [¹¹C]flumazenil and [2-¹⁸F]2-deoxy-2-fluoro-D-glucose ([¹⁸F]FDG)—a tracer for measurements of the rate of regional glucose metabolism. The focus localising ability of the two PET tracers was examined using extra—and intracranial EEG recordings as reference. The focus was first determined visually on the PET images obtained after a bolus injection of each of the PET tracers. Its anatomical localisation and spatial delimitation was then evaluated for each patient with a computerised anatomical brain atlas. [¹¹C]flumazenil was found to be a more sensitive and accurate focus localiser than [¹⁸F]FDG. This observation was valid both for quantified and non-quantified images. In the preoperative diagnosis of epileptic foci, the PET measurements of BZ receptors may be a suitable and, in some cases, superior method to the generally used "[¹⁸F]FDG-PET" method.

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Surgical resection of the epileptic focus has regained popularity as a method for the treatment of intractable partial epilepsy.¹ Epilepsy surgery, however, requires a complicated and costly preoperative investigation to locate the epileptic focus. In the quest for new diagnostic approaches, the PET method for measurements of the rate of regional glucose metabolism (rCMR_{glu}) with [2-¹⁸F]2-deoxy-2-fluoro-D-glucose ([¹⁸F]FDG) has recently been introduced in clinical practice.^{2,3} It has proved useful but has some limitations: 1) The hypometabolic region associated with the epileptic focus is usually much larger than the epileptic focus as well as the morphologically determined pathological tissue³; 2) In temporal foci, the [¹⁸F]FDG method usually shows maximal hypometabolism laterally in the temporal lobe whereas most foci are localised mesially.^{4,5}

The search for potential biochemical markers of epileptic foci has therefore continued. In a recent PET study, it has been demonstrated that the density of the postsynaptic benzodiazepine (BZ) receptor, a well-known mediator of cortical inhibition, is significantly reduced in human epileptic foci.⁶ This observation suggests that studies of the BZ receptor with [¹¹C]flumazenil might be used for preoperative visualisation and localisation of epileptic foci. In this study we compared the applicability of this method with PET measurements of rCMR_{glu}. The EEG recording from intracranial electrodes was the independent reference method.

The study had the following objectives: 1) to analyse the sensitivity and specificity of [¹¹C]flumazenil and [¹⁸F]FDG as focus markers in relation to other diagnostic methods (seizure presentation, MRI and EEG recordings); 2) to evaluate whether the quantified PET images of glucose metabolism and BZ receptor density offer a better localisation of the epileptic focus than just the uptake images reconstructed after tracer dose injections of [¹⁸F]FDG and [¹¹C]flumazenil; 3) to investigate whether the expected focal hypometabolism and hypodensity of BZ receptors are colocalised; 4) to investigate whether an analysis of BZ receptor density and glucose metabolism in the same patient could offer additional information about the mechanisms behind the phenomenon of interictal hypometabolism in the epileptic foci.

Methods

Patients and controls

Eight patients (five men and three women, age 24 to 37 years), referred for epilepsy surgery were investigated. All had partial complex seizures according to the International Classification of Epilepsies.⁷ Apart from having epilepsy, the patients were healthy. The CT scans and MRIs were normal in all except two cases. The current antiepileptic drugs were phenytoin and/or carbamazepine, compounds that were assumed not to interact with the BZ receptors.⁸ The medication therefore remained unchanged during the PET experiments.

The patients had daily epileptic seizures resistant to the antiepileptic medication. The seizure frequency remained unchanged during the period of PET measurements. These measurements were performed on an outpatient basis. The intracranial EEG

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recordings required admission to hospital and usually caused a temporary decrease in the seizure frequency. To avoid protracted registration time the antiepileptic medication was reduced during this period.

Detailed information about the patients is presented in table 1. The controls for measurements of BZ receptor density consisted of healthy men ($n = 7$, age 28 to 34 years). They had no family or personal history of epilepsy, no current medication, and their blood analyses and EEGs were normal. Details about the controls have been reported in part previously,⁹ the $B_{\max}$ values, recently recalculated (unpublished data) according to a kinetic three compartment model¹⁰ were used in this study.

The controls for measurements of $rCMR_{glu}$ consisted of five healthy men (age 24 to 35 years) chosen according to the above criteria. Informed consent was obtained from each subject and the study was approved by the local ethics and radiation safety committees.

EEG experiments

The preoperative (EEG) recording procedures consisted of: a) three to ten scalp EEGs (10/20 system) with standard activations including sleep deprivation; b) video monitoring of the patient and interictal and ictal recordings from scalp and sphenoidal electrodes; c) video monitoring of the patient and interictal and ictal recordings from subdural plates consisting of 4 electrodes. In patients 1, 3, 6, and 8 one subdural plate was placed subtemporally and one over the temporal convexity on each side. Patient 2 had also two subdural plates over the right and one over the left frontal lobe, patient 4 had in addition

to the temporal electrodes one intracerebral electrode in each orbital gyrus and each amygdala, and patient 7 had in addition to the temporal electrodes two electrode plates over the left and one over the right frontal convexity. In patient 5 the recordings from subdural electrodes were omitted since there was an MRI abnormality that corresponded to the focus localisation of the scalp and sphenoidal electrodes. Six to twenty seizures were recorded for each patient during 10–14 days. In all cases, the dose of the antiepileptic medication was reduced by 50–100%. The patient and his relatives always confirmed that the recorded seizures were of the habitual type. All intracranial EEG recordings were performed after the PET scans; d) peroperative electrocorticography.

Positron emission tomography (PET)

Five patients were examined with the Scanditronix PC 384–7B camera and three with Scanditronix camera PC 2084–15B (General Electronics, USA). The cameras have four and eight rings, respectively, allowing seven and fifteen slices distributed over 10 cm in the axial direction.^{11,12} The spatial resolutions in the transaxial plane are 7.6 mm and 4.5–6.0 mm FWHM, respectively, and in the axial direction 8.6–11.8 mm and 5–8.5 mm. The centre slice distances are 13.5 mm and 6.75 mm.^{11,12} The attenuation correction was based on contour finding (PC 384–7B),¹¹ and transmission scans (PC 2084–15B).

All the PET scans were performed interictally and with approximately the same temporal relation to the last epileptic seizure. The scalp EEGs were recorded during each scan. Ambient light and noise in the laboratory

Table 1 Patient data (Atlas structures with significant reduction of $rCMR_{glu}$ and BZ- $B_{\max}$ are presented)

Patient	Seizure	MRI	EEG	medication	†focus ROI	Atlas structures with reduced	
						a BZ $B_{\max}$	$rCMR_{glu}$
1	Cps with L sided automatisms	normal	SDE-seizure start	phenytoin, carbamazepine	L t ant-mes	L ts, L unc,	L ts, L tm, L ti
2	absences (2–10 seconds), dropping of the head	normal	L mesial temporal SDE-seizure start	carbamazepine	L t lat	L am, L hi	L hi, L sma
			R frontal		R frontal	R fs, R fi,	R fs, R fm,
						R am, R hi	R cin, R rec
						R orb, R cin	R orb, R unc,
3	Cps (derealization)	normal	SDE-seizure start	phenytoin, carbamazepine	R t mes	R hi, R ph,	R ts, R tm,
			R mesial temporal		R t lat #	R am, R unc,	R ti, R orb,
						R ts	R fs, R fi, R prec
4	Cps, sometimes postictal psychosis	normal	SDE-seizure start	phenytoin, carbamazepine	R t mes	R unc, R ph,	none
5	Cps with R sided automatisms	gliosis	R mesial temporal Sphenoid, scalp seizure start	phenytoin	none	R am	none
			L sphenoid, L temporal		L temporal	L ts, L tm, L ti,	L ts, L tm, L ti,
			L lateral temporal		L temporal	L hi, L am, L unc	L unc, L ins
6	Cps (absences, uncinata fits)	normal	SDE-seizure start	carbamazepine	L t mes and	L oct, L orb	L fs, L cin
			L mesial and L lateral temporal		L t lat	L am, L ti	L tm, L ti, L occ
7	jerks R arm, absences (5–30 sec)	atrophy lower R hemisphere	SDE-seizure start	“valproic acid, phenytoin	L frontal		L unc, L rec,
			L frontal		none		L orb, L sma
8	Cps (absences, complex automatisms)	normal	SDE seizure start	carbamazepine	Bil t mes*		L pa, R fs, R ins
			L and R mesial temporal and R lateral temporal		L t lat	bil am, unc, hi, phi, bil ts, L tm, L ti	L tm, L ti, L prec, L sma L phi

†Italics refer to the localisation of the BZ- $B_{\max}$ focus and non italics of the $rCMR_{glu}$ focus.

#The ratio focus/multilobular cortical ROI was not significantly altered from normal.

*Bilateral temporal foci were revealed with the “BZ method” by means of bilaterally low ratios compared with the controls.

**Valproic acid was under withdrawal for clinical reasons (current dose 300mg daily).

amy = amygdala; prec = precentral gyrus; cin = cingular gyrus; rec = gyrus rectus; fi = inferior frontal gyrus;

sma = supplementary motor area; fm = medial frontal gyrus; ti = inferior temporal gyrus; fs = superior frontal gyrus;

tm = medial temporal gyrus; hi = hippocampus; ts = superior temporal gyrus; ins = insula; t ant = anterior temporal cortex;

orb = orbital gyrus; t lat = lateral temporal cortex; oct = occipito temporal gyrus; t mes = mesial temporal cortex

ph = parahippocampus; unc = uncus; pa = parietal lobulus.

Focus ROI = localisation of the visually predetermined focus; R = right; L = left; CPS = complex partial seizures;

SDE = subdural electrodes.

were controlled in a standardised way (eyes open, ears unplugged, a dim and quiet environment).

PET tracers

[^{11}C]flumazenil

The selective benzodiazepine (BZ) receptor antagonist, flumazenil (Ro 15 1788) labelled in the N-methyl group with the positron emitting isotope carbon-11¹³ was used as a marker of BZ receptors. The kinetics and binding properties of this ligand have been described previously.^{6,14–16}

Each subject received two iv bolus injections with about 5 mCi of [^{11}C]flumazenil, one with high (97–486 Ci/mmol) and one with low (0.97–1.2 Ci/mmol) specific activity, respectively. The BZ receptor density was calculated using a kinetic three compartment model¹⁰ with white matter as the reference region.^{6,9,15} Regional uptake of [^{11}C]flumazenil in white matter and cortical regions between 10 and 50 minutes after iv injections of the ligand were used in the analysis. The applied algorithm estimated the receptor density (B_{max}) by a linear least squares method fast enough to enable parameter calculation in each pixel element. The purpose was to demonstrate the regional distribution of benzodiazepine receptor densities (fig).

[2- ^{18}F]2-deoxy-2-fluoro-D-glucose

Regional glucose metabolism was measured after bolus injection of 3.1–4.2 mCi of [^{18}F]FDG. The PET scan lasted 44 minutes, but only data from the last 20 minutes were used for quantification of rCMR_{glu} . The time course for the arterial concentration of [^{18}F]FDG and non-radioactive glucose was followed by automatic and manual sampling.¹⁷ The rCMR_{glu} was calculated using the

autoradiographic method of Sokoloff¹⁸ as applied to [^{18}F]FDG by Reivich and associates.¹⁹ The rate constants K_1 , k_2 , k_3 were 0.08, 0.14 and 0.07 and the lumped constant was 0.52.¹⁹ The rCMR_{glu} was displayed as metabolic colour coded images expressing metabolic rate pixel by pixel in $\mu\text{mol}/100\text{g}/\text{min}$ (fig).

Delineation of regions of interest (ROIs) from MRI images

Six pairs of homotopic regions (inferior and lateral frontal, anterior, mesial and lateral temporal, and parietal cortex) were delineated on the MRI images. Each subject's set of ROIs also included a big multilobar cortical ROI.¹⁵ This ROI sectioned the plane of and the plane above the basal ganglia and thalamus. It comprised the frontal, parietal and occipital cortex. All the ROIs were chosen so that the focus related area of low BZ receptor density and glucose metabolism was excluded as far as possible. The size of the three dimensional ROIs (excluding the multilobar cortical ROI) was about 4.5–6 cm^3 . Each ROI was transferred from the MRI image to four types of corresponding PET images: a) the PET image representing the average concentration of [^{18}F]FDG between 24 and 44 minutes after bolus injection ([^{18}F]FDG uptake image); b) the PET image of rCMR_{glu} ; c) the PET image representing the average concentration of [^{11}C]flumazenil 10–56 minutes after the tracer dose ([^{11}C]flumazenil uptake image); d) The PET image representing regional BZ receptor density (BZ-B_{max}).

The SD of the measured parameters within a PET ROI was about 10%. The transfer of ROIs between MRI and PET images was made possible by use of stereotactic fixation

Figure Regional BZ receptor density in pmol/cc (upper) and regional glucose metabolism in $\mu\text{mol}/100\text{g}/\text{min}$ (lower) in patient 6. A case with two EEG foci (∇), one mesially and one laterally in the left temporal lobe. The BZ method indicates both foci whereas the FDG method reveals only the lateral focus. Black colour indicates low, yellow medium and red high values. The patients right side is to the left.

of the head and the same slice spacing throughout all scans.²⁰

The focus ROI was delineated directly on the PET images ([¹⁸F]FDG-uptake, rCMR_{glu}, [¹¹C]flumazenil uptake, BZ-B_{max}) by two independent investigators (IS and MI) one (MI) uninformed about the patient data. The localisation and extension of the focus ROI was determined visually, guided by the areas where the BZ receptor density, rCMR_{glu} and radiotracer-concentration of [¹¹C]flumazenil and [¹⁸F]FDG were maximally reduced compared with the surrounding tissue and the homotopic cortex. The homotopic reference ROI to the so-defined focus ROI was delineated symmetrically on the contralateral side. In both quantified and non-quantified PET images, the regional asymmetries in the various homotopic ROIs were calculated as asymmetry index (AI) according to:

Asymmetry index =

$$\left(\frac{\text{Right ROI} - \text{Left ROI}}{\frac{\text{Right ROI} + \text{Left ROI}}{2}} \right) \times 100$$

When the asymmetries between the focus and the homotopic region were calculated, the right ROI was substituted with the homotopic ROI and the left ROI with the focus ROI

The average BZ receptor density and rCMR_{glu} from each ROI was divided with the corresponding value from the same subject's multilobar cortical ROI. Each ratio was then compared with the corresponding average ratio from healthy subjects (see statistics). Thereby it was possible to detect a focal alteration in BZ receptor density and glucose metabolism not only in relation to the non-epileptic cortical regions in the patients, but also in relation to the corresponding regions in healthy subjects. The reason for using ratios instead of absolute values was that they yielded lower SDs.⁵ For the final definition of the "PET-FOCUS" two conditions had to be fulfilled: a) the AI between the focus ROI and its homotopic ROI had to be significantly higher than the other regional AIs in this patient (see statistics); b) the ratio between the focus ROI and the multilobar cortical ROI had to be below the value of 95% confidence interval of the corresponding ratios for the same region in the healthy controls.

Delineation of regions of interest with a computerised anatomical atlas

To evaluate the exact anatomical localisation and extension of a statistically significant (see statistics) reduction in the BZ receptor density and rCMR_{glu}, the computerised anatomical brain atlas of Bohm and Greitz was applied.^{21,22} With this approach it was also possible to obtain a spatial correlation between altered BZ receptor density and glucose metabolism in the epileptogenic regions.

The three-dimensional standard brain atlas was first adapted to the MRI images (Siemens Magnetom, Germany; 1.0 tesla, spatial resolution 1.0 mm) of each patient by means of linear and non-linear transforma-

tions. Thereafter, the standard brain atlas was also fitted to the individual PET-images. The anatomical structures of the standard brain atlas were then called in from the data base and presented directly on the BZ-B_{max} and the rCMR_{glu} images. The structures obtained were used as guides for delineation of two dimensional regions. Forty atlas regions, extensively covering the temporal and frontal lobes, including samples from parietal and occipital lobes, were delineated in each patient. The size of the smallest region was about 1.2 cm³.

The mean (SD) values, the highest and lowest value of regional BZ receptor density and glucose metabolism were obtained for each ROI directly from the PET images.

Statistics

The statistical analysis was used to:

- 1) evaluate if the asymmetry between the visually defined focus ROI and the homotopic ROI was significant in relation to all calculated asymmetries in the same patient. This was attained by calculation of the confidence interval with regional asymmetries between various ROIs as input data. An asymmetry was considered as statistically significant if it exceeded the value for the 95% confidence interval. The confidence interval was calculated with the assumption of a t-distribution and DF = n-1
- 2) determine the anatomical atlas structures within and outside each focus ROI that had asymmetries that were significantly higher (= outside the 95% confidence limit) than all the asymmetries of atlas delineated regions in the same patient.
- 3) evaluate if the ratios focus ROI/multilobar cortical ROI and homotopic ROI/multilobar cortical ROI were lower (= outside the 95% confidence limit) than the ratios for the corresponding region in healthy controls. The confidence limit for regional ratios in healthy controls was calculated with the assumption of a t-distribution and DF = n-1
- 4) test whether any of the methods for analysing the data (different types of PET images) gave a significantly better contrast than the other methods used. The applied statistical method was the two way ANOVA with Scheffe's post hoc test. The parameters of variance were the four methods and the regional asymmetries. A p value of < 0.05 was considered significant.

EEG

In patients 1,3,6,7, the intracranial EEG recordings confirmed the localisation of the epileptic focus that had been preliminarily assessed from clinical seizures and/or surface EEGs. Patient 4 had a right-sided temporal focus, whereas the sphenoidal and scalp EEG indicated focus on the contralateral side. Patient 6 presented symptoms of a mesial temporal focus. The EEG recordings showed two foci, one mesially and one laterally in the left temporal lobe. The majority of seizures started from the mesial focus. Patient 8 had

bilateral temporal foci, whereas the scalp EEG indicated only a left sided focus. The results from EEG recordings are presented in table 1.

PET

The areas defined by the two independent investigators (IS and MI) as the epileptic focus almost overlapped in all eight cases each other. These areas comprised 50–80 two dimensional pixels (50–80 × 6.25 mm²) and extended throughout two or three consecutive PET images.

The BZ receptor method (PET images of [¹¹C]flumazenil uptake and BZ-B_{max}) localised an epileptic focus in all eight patients (table 1). All the patients had reduced BZ receptor density within the area of seizure origin as determined with the subdural electrodes. One of them (patient 8) had bilateral temporal foci according to the EEG as well as the BZ receptor method (bilaterally low ROI/multilobar cortical ROI ratios mesially in the temporal cortex). The above observations were valid both for the quantified (BZ-B_{max}) and non-quantified ([¹¹C]flumazenil uptake) images. In one case, however, the AI for the focus and homotopic ROI determined from the [¹¹C]flumazenil uptake images failed to pass the significance level.

The [¹⁸F]FDG method (rCMR_{glu} images and [¹⁸F]FDG-uptake images) localised the epileptic focus in six patients. In one of these patients (patient 8), both types of [¹⁸F]FDG images showed a left sided temporal focus whereas the EEG and the BZ method showed bilateral foci. In the five other patients the lobe with low uptake of [¹⁸F]FDG and low glucose metabolism corresponded well to the lobe of seizure origin. However, in two of these patients the ratio focus ROI/multilobar cortical ROI failed to reach the significance level when the calculation was based on the [¹⁸F]FDG-uptake images. In one of them the same was valid also for the rCMR_{glu}-based ratio. The quantified images offered somewhat better contrast between the normal and hypometabolic regions than the uptake images (table 2a, b).

The comparison between the four types of PET images showed that the B_{max} images

yielded a significantly higher degree of reduction in the focus ROI ($p < 0.001$), than the other three types of PET images (table 2a, b).

According to both the BZ receptor and the [¹⁸F]FDG method there were no significant asymmetries in other ROIs than the focus ROI, which indicated good specificity. However, in the majority of patients with temporal lobe epilepsy the maximal reduction of BZ receptors was found in the mesial temporal cortex, whereas the maximal hypometabolism was confined to the lateral surface of the temporal lobe (the mean asymmetry was, according to BZ-B_{max} images, 50% in the mesial and 17% in the lateral temporal cortex; the corresponding values for the rCMR_{glu} were 8% and 25%). The intracranial EEG recordings from these patients showed that the epileptic seizures started in the mesial temporal lobe. Thus the focus region determined with the BZ receptor method was spatially better correlated to the EEG recordings than the hypometabolic region as determined with the FDG method.

Relationship between the predefined focus ROI and the atlas structures with significantly reduced BZ receptor density and rCMR_{glu}

When the asymmetries of various homotopic atlas structures were analysed, the localisation of the focus ROIs defined visually on the rCMR_{glu} and BZ-B_{max} images was confirmed in all the patients (table 1). The extension of the atlas-determined area with reduced BZ receptor density was in several cases (patients 1,4,6) more limited than that indicated by the focus-ROI (table 1). On the other hand in patients 2 and 5, the atlas analysis showed a significant reduction also outside the focus. In patient 2 this reduction could be related to a possible secondary focus (the EEG recordings showed a few seizures emigrating from the right temporal lobe) whereas in patient 5 the reduction was confined to a projection-area to the focus (table 1).²³

The results from the atlas based evaluation of the FDG method suggested somewhat poorer specificity: in all patients (except in patient 1) there were several hypometabolic atlas-regions outside the visually determined focus ROI (fig 1).

Table 2a Mean BZ receptor density and glucose metabolism in various pairs of ROIs. The corresponding asymmetry indices (AI) as well as mean ratios (ROI/multilobar cortical ROI) are presented. Only the focus ROIs with significant reductions were included. The focus ROI had temporal localisation in six and frontal in two cases.

Region	n	Glucose metabolism			ROI/multilobar cort. ROI	BZ receptor density		
		Mean (SD) rCMR _{glu} (μ mol/100g/min)	asym index			Mean (SD) BZ-B _{max} (pmol/cc)	asym. index	ROI/multilobar cort. ROI
focus (temp)	5	20 (6)	31 (15)	0.61 (0.17)	6	9 (5)	79 (43)*	0.27 (0.16)
homot. ROI		26 (5)		0.82 (0.06)		19 (10)		0.56 (0.31)
focus (front)	1	32	20	0.8	2	15 (8)	77 (5)	0.34 (0.11)
homot. ROI		39		1.0		33 (16)		0.76 (0.21)
i front dx	8	30 (5)	8 (7)	0.92 (0.07)	8	37 (19)	12 (10)	0.94 (0.31)
i front sin		31 (5)		0.98 (0.13)		38 (21)		0.98 (0.37)
temp dx	8	23 (3)	8 (6)	0.69 (0.08)	8	30 (9)	14 (12)	0.82 (0.14)
temp sin		23 (4)		0.69 (0.14)		28 (7)		0.76 (0.13)
front dx	8	32 (5)	6 (2)	0.97 (0.12)	8	35 (18)	9 (5)	0.91 (0.25)
front sin		34 (5)		1.02 (0.09)		37 (20)		0.95 (0.23)
pari dx	8	35 (8)	6 (8)	1.03 (0.13)	8	41 (13)	7 (9)	1.12 (0.17)
pari sin		34 (9)		1.00 (0.17)		41 (15)		1.10 (0.21)

*Patient 8 who had bilateral foci was not included in the calculation of asymmetry index.
i front inferior frontal ROI.

Table 2b Mean asymmetry indices (AI) in the corresponding ROIs, but calculated from the uptake images of [¹¹C]flumazenil and [¹⁸F]FDG. All the six foci with significant asymmetries were included although the ratio focus ROI/multilobar cortical ROI as determined from [¹⁸F]FDG uptake images failed in two cases to pass the confidence limit

n	Radiotracer conc	
	asym index [¹⁸ F] FDG uptake	asym index [¹¹ C]flumazenil uptake
5	25 (11)	22 (8)
1	16	21
8	7 (6)	5 (5)
8	7 (5)	5 (4)
8	5 (2)	3 (3)
8	5 (5)	2 (3)

Discussion

In the present study the ability to localise the region containing the epileptic focus was tested with two PET ligands, [¹¹C]flumazenil and [¹⁸F]FDG. The interictal and ictal EEG recordings from intracranial electrodes were used as a reference method. The focus ROIs were determined visually. The validity of this approach was evaluated with the anatomical brain atlas by testing whether each one of the atlas-data base regions localised within the predefined focus ROI had a significant hypometabolism and hypodensity of BZ receptors compared with other selected atlas regions. The evaluation with the atlas programme confirmed previous studies^{2,24} indicating that the visual method is often satisfactory for PET determination of the epileptic foci in clinical practice. It also confirmed the impression that the hypometabolic region often extends beyond the epileptogenic area, whereas the reduction in BZ receptor density is more confined to the epileptogenic region.⁶

A significant focal reduction in BZ receptor density was found in all eight patients. Measurements of rCMR_{glu} localised the epileptic focus to the correct lobe in five patients, but failed in four cases of temporal lobe epilepsy to select the correct part of the temporal lobe. In relation to EEG recordings, BZ receptor visualisation with [¹¹C]flumazenil appears to offer a better detection of the focus regions than PET measurements of rCMR_{glu} (tables 1, 2). This observation was valid not only for the BZ-B_{max} images, but also for the [¹¹C]flumazenil uptake images.

Despite the limited patient material this study indicates that the BZ receptor method offers a higher contrast between the normal and the dysfunctional areas than the FDG method, making it easier to determine the localisation and extension of the epileptogenic region. It also implies that use of the uptake images of [¹¹C]flumazenil may be a sufficient approach for clinical PET visualisation of epileptic foci. Since this procedure does not require arterial blood sampling and since [¹¹C]flumazenil may, like [¹⁸F]FDG, be prepared batchwise for at least two consecutive PET studies, a "single injection" procedure with [¹¹C]flumazenil is suggested as an alternative, relatively simple PET approach for presurgical investigations of epileptic

patients. The recent study of Koeppel *et al*²⁵ shows that this method could be suitable.

In addition to the methodological evaluation of [¹¹C]flumazenil and [¹⁸F]FDG as focus markers, our study also permitted a comparison of the localisation and extension of the hypometabolic and BZ receptor-reduced areas. Such a comparison was of interest since it has been speculated that altered inhibition may be a possible explanation for interictal focal hypometabolism.³

An interesting observation was that in several patients with mesial temporal EEG foci, the maximum hypometabolism was found laterally in the temporal lobe, whereas the maximum reduction of the BZ receptor density was confined to the mesial temporal lobe. A preliminary report supporting this finding was recently published.²⁶ Since the EEG focus probably reflects pathological firing patterns of a fraction of mesially located neurons,²⁷ the most pronounced activation of GABAergic neurons is expected to be within the same area.^{28,29} Such an activation may lead to a downregulation or blockade of the postsynaptic GABA/BZ receptor complex³⁰ that in addition to the postulated cell loss in the intractable foci could explain the detected reduction of BZ receptor density.³¹ rCMR_{glu} does not necessarily have to be decreased in an area receiving inhibitory input,³² which may explain the relatively sparse hypometabolism in the mesial temporal cortex. However, since the more laterally localised neuronal synapses will not be activated due to the presumably increased mesial inhibition, the net metabolic ratio in the lateral temporal cortex will become considerably decreased. Our observation of maximum reduction of BZ receptor density in the mesio-anterior, and maximum hypometabolism in the lateral temporal lobe, may thus be explained as a mesial inhibition and lateral deactivation.

The results of the present PET studies warrant follow up experiments with a larger number of patients and with evaluation not only of the intracranial EEG recordings but also of the postsurgical outcome. An important future project would be to try to identify if there are subgroups of patients where one tracer is preferable to the other, or where a combination of both tracers will offer additional information for correct focus localisation.

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