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Semiquantification of the peripheral-type benzodiazepine ligand [^{11}C]PK11195 in normal human brain and application in multiple sclerosis patients

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Abstract

Objectives : [^{11}C]PK11195 is a peripheral-benzodiazepine-receptor radioligand used for detection of microglial inflammation. Normal uptake by means of semiquantification was measured in order to establish reference data. The applicability of this semiquantitative approach was tested in three multiple sclerosis patients.

Materials and methods : Seven controls and three patients underwent MR and PET scanning. Coregistered static scans 40 minutes postinjection of [^{11}C]PK11195 were used for assessment of relative ligand uptake by comparison to whole-brain uptake.

Results : For static scans acquired in near steady-state, the relative ligand uptake was significantly higher in gray matter structures as compared to the whole brain (ratio : 1.041 ± 0.06, p = 0.036) whereas it was comparable in white matter (1.010 ± 0.035). Intersubject reproducibility was 11.4% and 12.9% for white and grey matter. Intrasubject reproducibility was of the same order : 14.0% and 14.5% respectively. In two clinically active patients with Gadolinium-positive T1-weighted lesions on MRI the focal ligand uptake was significantly increased (1.36 and 1.14, p = 0.001). In one clinically stable patient, the uptake value corresponding with a T2-weighted MR lesion was not different from normal brain measurements.

Conclusion : The current investigations show that normal brain uptake of [^{11}C]PK11195 is very low and shows the feasibility of a semiquantitative method which can be applied to larger cohorts of patients subgroups.

Key words : [^{11}C]PK11195 ; semiquantification ; positron emission tomography ; healthy volunteers ; multiple sclerosis.

Introduction

PK11195 [1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinolinecarboxamide] is a specific high-affinity ligand for the peripheral-type benzodiazepine binding site (PBBS) (Le Fur *et al*. 1983). In humans and animals, PBBS are mainly distributed in peripheral tissues such as heart, adrenal gland, testis, liver and hemopoietic cells (Woods & Williams 1996) but they have also been discovered in glial cells of the central nervous system (Marangos *et al*. 1982). In normal human and cat brain, PK11195 exhibits only minimal binding (Benavides *et al*. 1983). Autoradiographically, binding sites are restricted to grey matter and absent in white matter (Benavides *et al*. 1984 ; Doble *et al*. 1987). Histological observations showed that resting microglia in the adult human brain form a stable population of ramified cells, where more microglia are found in grey than white matter (Lawson *et al*. 1990). In pathological conditions however, microglia rapidly transform into an activated state with proliferation and ensuing increases of PBBS (Banati *et al*. 2000 ; Dubois *et al*. 1988). In human post-mortem tissue and animal models of brain damage, high densities of PK11195 were demonstrated, reflecting glial proliferation (Benavides *et al*. 1988 ; Diorio *et al*. 1991 ; Myers *et al*. 1991). Activated microglia are the predominant site of PK11195 binding as confirmed by photo-emulsion micro-autoradiography in lesions causing a retrograde neuronal reaction (Banati *et al*. 1997). PK11195 has been labelled with ^{11}C for the in vivo study of normal and lesioned brain by positron emission tomography (PET) (Camsonne *et al*. 1984). In order to use [^{11}C]PK11195 as a tool for PET imaging of microglial activation in acute and chronic pathology, a baseline level of ligand uptake in a control population is required. No generally accepted model of absolute quantification of [^{11}C]PK11195 specific binding in normal brain has been validated yet (Banati *et al*. 1999 ; Banati *et al*. 2000). The

heterogeneous distribution of microglia even in brain regions without pathology and the inconsistent blood flow hamper the selection of a reference tissue in brain and the establishment of a model for absolute quantification. For selected cases, a cluster analysis based on assumption of a receptor free region may provide an approach to absolute quantification, as has been elaborated by Banati *et al.* (Banati *et al.* 1999 ; Banati *et al.* 2000). However, in a number of pathological conditions where brain inflammation is likely involved in a widespread fashion, such as multiple sclerosis, true receptor-free regions are not present.

Therefore, in the present study, a straightforward semiquantitative method for measuring the uptake of [^{11}C]PK11195 in normal brain was tested, in order to establish normative baseline data with an estimate of the reproducibility. The semiquantitative method is based on measuring an activity ratio at a fixed time interval after tracer injection under the assumption of subject-independent near steady-state between brain regions. A second aim was to test the applicability of this semiquantitative approach for the in vivo detection of significant [^{11}C]PK11195 uptake value increases in a feasibility study of three multiple sclerosis (MS) patients with chronic and active white matter lesions on MR imaging.

Materials and methods

Subjects

The study was approved by the Ethical Committee of the Ghent University Hospital. Written informed consent was obtained from each subject. Seven consecutive healthy volunteers with a normal physical examination [4 female, 3 male, average age 33 yrs (SD 7.5, range 23-41 yrs)] and three MS patients with definite proven MS referring to new MS diagnostic criteria of McDonald *et al.* (McDonald *et al.* 2001) [average age 43.5 yrs (SD 7.0, range 37-51 yrs)] were included. All three patients had relapsing-remitting MS. No treatment with anti-inflammatory drugs such as steroids and β-interferon was applicated. Patient 1 and 2 had a relapse at the time of [^{11}C]PK11195 scanning and both showed one Gd-enhancing lesion on T1-weighted MR images, in the left frontal periventricular region for patient 1 and the centrum semiovale for patient 2, respectively with an extent of 15/15 ml and 5/5 ml. Patient 3 was 'clinically stable' at the time of [^{11}C]PK11195 scanning. The MR scan revealed no T1 – weighted Gd-uptake. The three patients had several T2-weighted paraventricular hyperintensities on the T2 – weighted MR and the FLAIR sequences. The lesion load was rather low and there was minimal disability.

Radiochemistry

PK11195 was obtained from RBI (Natick, MA, USA). [^{11}C]PK11195 was synthesized according to a procedure described by Camsonne *et al.* (Camsonne *et al.* 1984). Briefly, 3 µmol N-desmethyl PK11195 was dissolved in 150 µL dimethylsulphoxide, containing 3 µmol tetrabutylammonium hydroxide. After trapping of [^{11}C]CH_3I, the vial was closed and heated at 80°C for 3 min. Purification was done by HPLC using a RP-C18 column (Econosil, 250 × 10 mm, 10 µm particle size) and an ethanol/water (70/30) mixture as mobile phase. Radiochemical yield towards [^{11}C]CH_3I was 57 ± 2.35%. Finally, 3.7 GBq [^{11}C]PK11195 was obtained with a specific activity of 25 GBq/µmol. Chemical and radiochemical purity were higher than 99%. All subjects were injected intravenously with 370 ± 10% MBq [^{11}C]PK11195 with a slow bolus in a time course of 30 s. For regional cerebral blood flow (rCFB) imaging in PET the steady state technique using [^{15}O]CO_2 was applied (Frackowiak *et al.* 1980). Its automated production and quality control is described elsewhere (Strijckmans *et al.* 1985, 1989). The absorbed dose for the [^{15}O]CO_2 scan yields 16 mGy for the lung, which is considered as the dose-limiting or critical tissue. The effective dose-equivalent is 6 mSv (Bigler *et al.* 1983).

Data acquisition and reconstruction

All subjects underwent MR and PET scanning. To determine intrasubject reproducibility, five volunteers were submitted twice to another PET session within one week. Both MR and the first PET scan were carried out on the same day. MR imaging was performed on a 1.5 T commercial MR scanner (Siemens, Magnetorn 1.5 T, SP4000). Prior to the administration of gadolinium (Gd), standard spin-echo imaging was carried out in 5 mm thick axial planes (pixel size = 0.9 * 0.9 mm^2) with proton-density (TR/TE/NEX = 2170/20/1), T2-weighted (TR/TE/NEX = 2170/80/1) and T1-weighted (TR/TE/NEX = 600/12/1) contrast. Five min after Gd injection, the axial slices were rescanned with T1-weighting (TR/TE/NEX = 800/20/1). PET studies were performed on a Siemens ECAT 951/31 PET scanner with a transaxial resolution (FWHM) of 5.8 mm and an axial resolution of 5 mm, values provided by Siemens, Knoxville, TN, USA operating in 2D mode. All subjects were placed in supine position with dimmed lights and low ambient noise. Realignment of the head to the orbitomeatal line was performed by laser guidance. Recontruction was done using filtered back projection with a Hanning filter with cut-off 0.5 cycles/cm. Sequential transmission scanning was performed using a germanium-68/germanium-68 ring source. Correction for scatter was done

using the standard software provided by the manufacturer (CTI). Subsequently, cerebral blood flow images were acquired by [15O]CO_2 inhalation at 900 MBq/min (Frackowiak *et al*., 1980). Eight minutes later, a one-hour dynamic PET study was conducted following injection of 370 MBq [11C]PK11195. Thirty-one planes of 3.375 mm thickness and 19 frames were recorded over 60 min with an increasing duration of 2 * 5 s, 5 * 10 s, 4 * 1 min, 2 * 3 min, 1 * 4 min, 1 * 5 min, 4 * 10 min. Data obtained from 40-60 min postinjection were summed and defined as activity on the static scans. Automatic radioactive decay correction was applied to all images. Individual coregistration of perfusion data in the MRI orientation was achieved using SPM99 (Statistical Parametric Mapping, Functional Imaging Laboratory, The Wellcome Department, London, UK) (Friston *et al*. 1991). The same spatial transformation parameters were subsequently applied to the PK11195 data.

Descriptive kinetics and semiquantification

In three volunteers, a tissue time-activity curve (TAC) of the [11C]PK11195 uptake over 60 minutes was determined for three global regions, namely white matter, cortical grey matter and subcortical grey matter, normalised to the final frame whole brain uptake value. The data for these regions are the weighted average of the individual normalised VOI data. Since no generally accepted model of absolute quantification of specific binding of [11C]PK11195 in normal brain has been widely validated and moreover, and as no dynamic data for all volunteers were available and no arterial sampling was carried out, a semiquantitative approach was carried out on the static images. Volumes-of-interest (VOIs) were defined on each individual subject's reoriented high-resolution MR scans and automatically transferred on the reoriented [11C]PK11195 scans. Three global regions were defined namely, white matter, cortical and central grey matter (thalamus and striatum) (figure 1). The latter was done because high labelling of [3H]PK11195 was described in diencephalic structures notably in several thalamic nuclei (Doble *et al*. 1987). The relative activity normalised to the mean activity per volume unit in the total brain was taken as outcome parameter. This was attained by defining a single whole-brain volume-of-interest (VOI) on the MR anatomic template. Care was taken to avoid the carotid and major cerebral arteries, ventricles and venous sinuses which was verified in each individual case.

Statistical analysis

Data were analysed by means of the software package SPSS v10.0 for Windows (SPSS, Heverlee, Belgium). Unless specified otherwise,

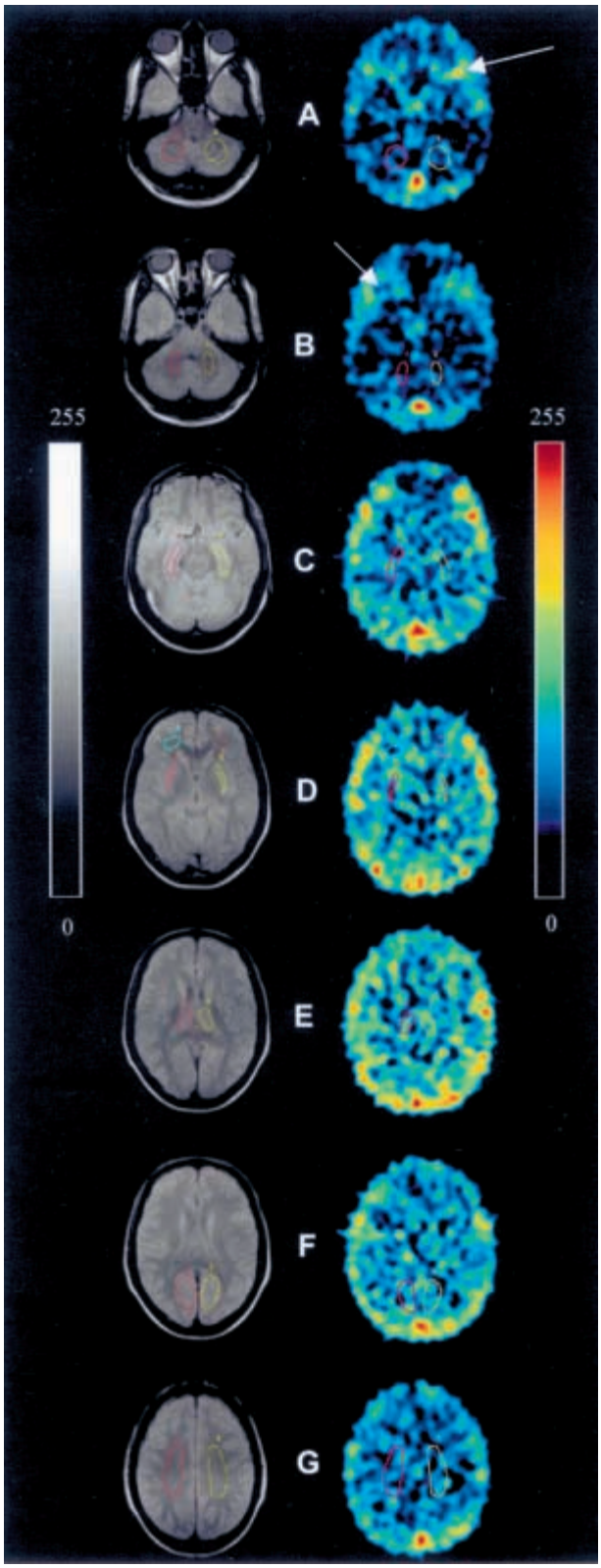

Fig. 1. — ROI localization on three different regions (grey, white, and subcortical grey matter) in coregistered MR - [11C]PK11195 scan pairs. A : cerebellar cortex, B : cerebellar white matter, C : temporal cortex, D : frontal white matter and striatum, E : thalamus, F : occipital cortex, G : parietal white matter.

Arrowheads represent "aspecific activity" in extracerebral structures (figure A : retro - orbital fat tissue figure B : masticatory muscles).

Color scales are given for the [11C]PK11195 image and the grey scales for MR.

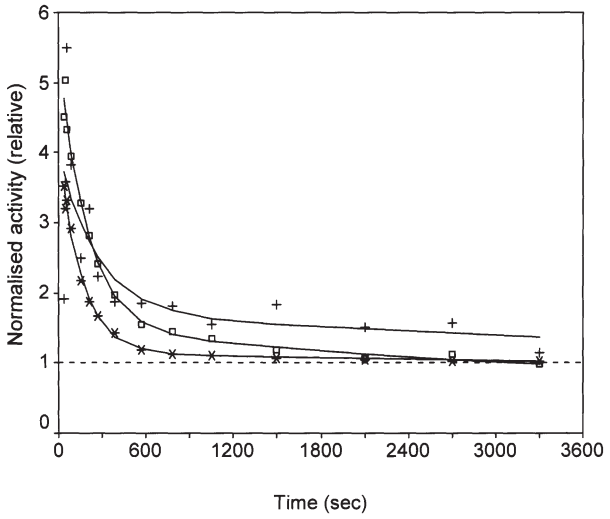

FIG. 2. — A representative sixty-minutes time activity curve from one volunteer and patient (patient 1) after injection of [11C]PK11195. Lines of data represent bi-exponential fits through measured activity data. Static scans were obtained between 40 and 60 min. (2400-3600 sec).

* = normal white matter, □ = normal cortical grey matter, + = lesional activity white matter (patient).

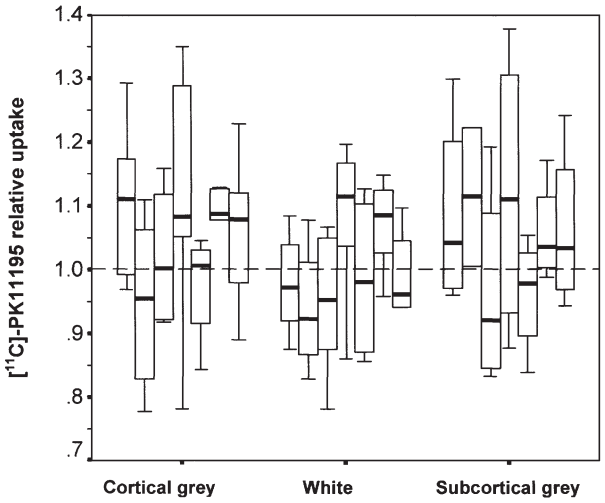

FIG. 3. — Intersubject reproducibility of [11C]PK11195 uptake (defined as relative to the intersubject mean value), partitioned as cortical and subcortical grey and white matter for seven healthy volunteers. Each bar represents one subject.

data are expressed as mean ± one SD. For descriptive kinetics, a non-linear bi-exponential least-square fitting of the time-activity curves was used to produce TAC parameters for white and grey matter. Intersubject reproducibility was defined as the standard deviation of the normalised [11C]PK11195 uptake in the various brain regions. This intersubject reproducibility estimate might be able to differentiate individuals with abnormal [11C]PK11195 uptake from normal subjects. The intraindividual reproducibility is defined as one standard deviation (%) in [11C]PK11195 uptake obtained from scan 1 and scan 2 from all subjects in whom repeated scanning was performed (Jonsson *et al*. 2000). This measure is based on the intra-individual difference defined as 200 * (scan 1 – scan 2) / (scan 1 + scan 2) (%). Differences between groups were calculated by means of the Wilcoxon Rank Sum test. To explore significant ratios, a t-test was performed after Kolmogorov-Smirnov testing for normality. Uptake values in MS patients were assessed by means of a one-sample t-test.

Results

Descriptive kinetics and time-activity curves

Figure 2 shows a representative example of a TAC for one volunteer (white matter and cortical grey matter) and one clinically active MS patient (corresponding with T1-weighted Gd white matter lesion). A fast decay of [11C]PK11195 before reaching steady-state is seen with an uptake half-life of 1.40 min (95% asymptotic confidence interval 1.12 – 1.84) for white matter, 2.63 min (2.06 – 4.10) for grey matter and 2.88 min (2.13 – 4.42) for subcortical grey matter. The second exponential component was characterized by a half-life value over 2 hours for all regions.

Intersubject reproducibility

The average normalised activity in white and grey matter of the static scans for the first PET session of the seven volunteers is shown in figure 3. Intersubject reproducibility was 12.9% for grey matter, while it was 11.4% for white matter. When difference was made between cortical and subcortical grey matter, the intersubject reproducibility values were 12.6% and 13.7% respectively.

Intrasubject reproducibility

Intrasubject reproducibility was calculated by comparison of the values obtained from the single repeated scan in the five volunteers. The average intrasubject reproducibility for white and grey matter was 14.8 and 14.0% respectively (figure 4). There was no difference between neocortical and subcortical grey matter activity in normal volunteers.

Overall uptake

For all volunteers, a mean uptake value of 1.010 ± 0.035 in white and 1.041 ± 0.060 in grey matter was found. The latter normalised activity is significantly different from unity (t-test, $p = 0.036$) (figure 5). However, white and grey matter did not differ significantly from each other (Mann-Whitney U, $p = 0.19$). There were also no significant differences between cortical and central grey matter (Mann-Whitney U, $p = 0.70$).

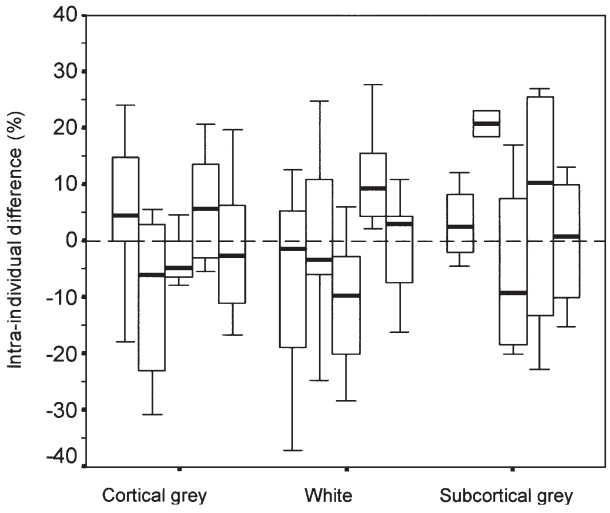

FIG. 4. — Box plot of the intrasubject differences of [11C]PK11195 uptake for five healthy volunteers. The standard deviation of these differences is defined as the intraindividual reproducibility. Each bar represents one subject.

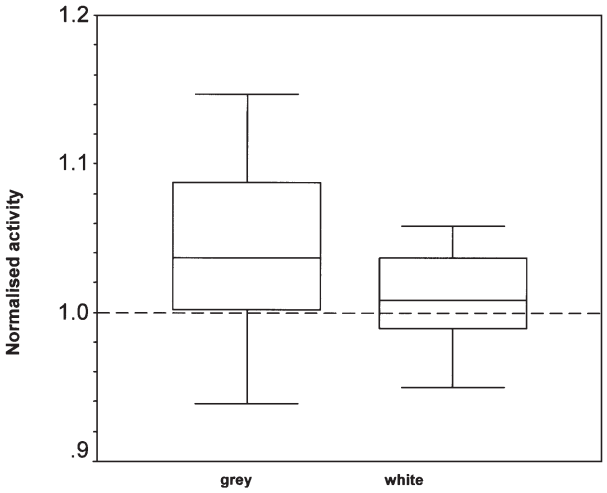

FIG. 5. — Normalised relative [11C]PK11195 activity for the whole group of volunteers and in all regions, partitioned as grey and white matter.

APPLICATION OF SEMIQUANTITATIVE APPROACH IN MS PATIENTS

Patient 1 (figure 6) and 2 showed an intense focal uptake on the [11C]PK11195 images corresponding to the Gd enhancement on the coregistered T1-weighted MR scan. Normalised activity of the lesion yielded 1.36 for patient 1 and 1.14 for patient 2 which both differed significantly from normal white matter uptake (t-test, $p < 0.001$). Patient 3 showed a lesion on the T2-weighed MR scan with a normalised [11C]PK11195 uptake of 1.02, which did not reach significance compared to normal subject measurements ($p = 0.4$).

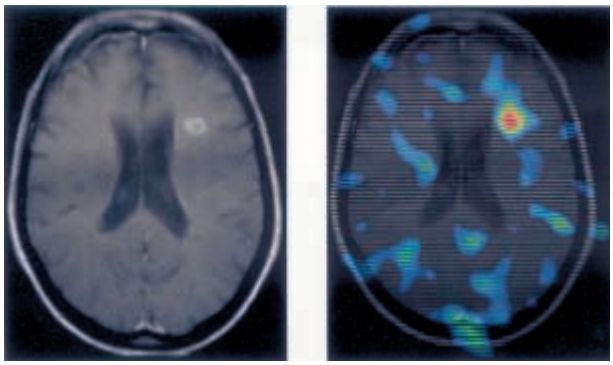

FIG. 6. — Pathological uptake of [11C]PK11195 in a focal white matter lesion observed on the corresponding T1-weighted Gd MR scan in a patient with active relapsing-remitting MS.

Discussion

PK11195 AS MARKER FOR MICROGLIOSIS

The rationale to use [11C]PK11195 as an in vivo marker of microgliosis is based on the demonstration in ample neuropathological and animal experimental work of the association of microglial proliferation and increased densities of PBBS in the lesioned brain (Benavides *et al*. 1983 ; Benavides *et al*. 1988 ; Streit & Kreutzberg 1988). Displacement studies have proven that the human peripheral-type benzodiazepine receptor shows selective affinities for isoquinoline ligands (Rao & Butterworth 1997). Although most of the PBBS are located in peripheral tissue and cells, nearly 10% binding of PK11195 is found in cerebral structures, mainly to microglia (Awad & Gavish 1991 ; Woods & Williams 1996). Specific immunocytochemical staining in the adult mouse brain has determined a considerable variability in the distribution and morphology of the microglial population. They are present in every region and occupy 5 to 12% of the total number of cells in the brain. Grey matter contains more microglia than white matter, especially in sensory, limbic and subcortical grey structures (Lawson *et al*. 1990), which is reflected in the present study where, although not significant, a slightly higher [11]IPK11195 uptake for the static scans was detected in grey matter. However, the heterogeneous distribution of [3H]PK11195 uptake in post-mortem human brain is less striking in the present in vivo study. High aspecific activity of the [11C]PK11195 ligand is consistently observed in extracerebral structures including the masticatory muscles, retro-orbital fat tissue, cavernous and sagittal sinuses, carotid artery and skull (figure 1).

The functional role of resting microglia is not well understood yet in the normal adult nervous system. In pathology however, microglia rapidly transform into an activated state with cytotoxic and tissue destructive properties. As such, microglial

activation is involved in most conditions associated with neuronal injury, ischemia, inflammation and neurodegeneration (Gehlert *et al*. 1997). This has been extensively demonstrated in vitro by autoradiography using animal and human post-mortem tissue with focal brain damage. Also, high concentrations of [^{3}H]PK11195 were observed in rat and human brain tumour, specifically in glioma where a striking correspondence of PBBS with the histological topography and the activity grade was demonstrated (Black *et al*. 1989 ; Black *et al*. 1990). Enhanced PBBS densities have been observed on the edge of active inflammatory lesions in MS (Banati *et al*. 2000 *;* Benavides *et al*. 1988) and in stroke patients (Myers *et al*. 1991 ; Ramsay *et al*. 1992). Moreover, a dramatic increase of [^{3}H]PK111195 uptake was demonstrated in the facial nucleus a few days after facial nerve axotomy. Even with an intact blood-brain barrier, activated microglia are the predominant source of lesion – induced increases of PK11195 binding (Gehert *et al*. 1997). Focal PBBS upregulation was preferentially situated on activated but still ramified microglia suggesting a high and rapid expression of this receptor in the absence of blood-brain barrier damage. Even in chronic neurodegenerative disorders such as Alzheimer's and Huntington's disease, a significant increase in PBBS have been described, possibly due to a relative gliosis associated with neuronal loss (Diorio *et al*. 1991). (Messmer & Reynolds 1998). The potential value of PET and [^{11}C]PK11195 for the in vivo imaging of the lesioned brain is clearly demonstrated in human glioma (Junck *et al*. 1989). High accumulation of [^{11}C]PK11195 reached equilibrium in tumour tissue about 80 min postinjection. Most of the PBBS were occupied with high specificity, confirmed by displacement with saturating doses of cold ligand. The metabolisation of [^{11}C]PK11195 has been studied in normal healthy volunteers (De Vos *et al*. 1999). For humans, rapid metabolisation of [^{11}C]PK11195 was observed at 5, 20 and 35 min post injection. 5%, 22% and 32% respectively, of the plasma activity consisted of at least two more polar metabolites. Despite the extensive metabolisation rate in mice (up to 42% at 10 min post injection of [^{11}C]PK11195), no ^{11}C-labelled metabolites could be detected by HPLC in the extracts of brain.

In focal ischemic lesions, transient specific [^{11}C]PK11195 uptake was found after occlusion of the middle cerebral artery in an experiment with anaesthetised baboons (Sette *et al*. 1993). An equal observation was made in MS where the high [^{11}C]PK11195 uptake occurs in active white matter inflammation defined by MR and thus reflects the presence of activated microglia, which are known to be involved in autoimmune demyelinating diseases (Vowinckel *et al*. 1997). The latter findings were confirmed in the present study where significantly increased [^{11}C]PK11195 uptake values were found in two patients with active inflammatory lesions.

Methodological aspects

Until now there is no widely accepted method for the absolute quantitative measurement of [^{11}C]PK11195 in diffuse brain pathology. The simplified reference tissue model (Gunn *et al*. 1997), recently applied in two cases of Rasmussen's encephalitis (Banati *et al*. 1999) cannot be used in MS and other diseases with non-focal brain pathology due to a lack of a suitable region devoid of active binding for use as a single reference compartment. The recently introduced cluster analysis (Myers *et al*. 1999), applied to MS (Banati *et al*. 2000), has not been widely validated. Especially in MS patients with extensively affected white matter where the amount of healthy tissue, from which a normal input function needs to be derived for the kinetic modelling, the assumption for the simplified reference method is questionable (Banati *et al*. 2000). For this reason we tested a more straightforward semiquantitative method in healthy volunteers for the eventual clinical detection of significant increases in [^{11}C]PK11195 uptake values of MS patients without the need of full arterial sampling and dynamic scanning. Applying this semiquantitative procedure on VOI data, normalised on total brain activity with a careful avoiding of the large venous and arterial vessels, yielded accurate semiquantitative data in normal volunteers.

Although patients and controls are not age-matched, we anticipate no differences in [^{11}C]PK11195 uptake in normal brain that would influence the results. This is in spite of the demonstration of an increased [^{11}C]PK11195-binding in the thalamus correlated with age by Cagnin *et al*. (Cagnin *et al*. 1999). However, this finding, derived from a small sample of 10 healthy volunteers, was especially significant for the older ages above 60 years.

It was demonstrated from the comparison of the inter – versus intrasubject reproducibility, that, with the current procedure, the strongest component of uncertainty in the [^{11}C]PK11195 uptake is the measurement of background noise and not the physiological variability between subjects. In this respect, three-dimensional PET and [^{11}C]PK11195 could be a more accurate tool for visualizing global increases of activated microglia due to the higher count rate and therefore image quality (Myers *et al*. 1998).

Concerning the kinetics, a fast decay of [^{11}C]PK11195 was demonstrated suggesting aspecific binding both in grey and white matter. However, the fact that the time-activity curves for both volunteers and patients had a similar decline with a near-steady-state from 40 min postinjection on, indicates that a semiquantitative index of binding

with normalisation on total counts is acceptable. This assumption is in concordance with the kinetic results of previous [11C]PK11195 PET studies by Sette *et al*. where uptake ratios became stable approximately 20 minutes after injection, minimizing confounding effects of perfusion (Sette *et al*. 1993). The difference in half-life between grey and white matter is confounded by perfusion dynamics and could not be fully evaluated in this study due to the lack of full kinetic modelling.

As with any semiquantitative approach, the choice of the normalisation area affects the sensitivity of the method to detect significant changes. As no true reference region may be found in MS, globally increased PK11195 activity may be masked by normalisation on the total activity. Also for intense increased uptake, global normalisation may somewhat reduce the sensitivity of the method, but it was considered as a viable option in the absence of full kinetic data. Similar normalisation problems are present in non-absolutely quantified routine clinical PET and SPECT perfusion or metabolism evaluations (Van Laere *et al*. 2001).

The intersubject reproducibility range of [11C]PK11195 uptake resulted in an average standard deviation of 12.5%. These baseline data are able to detect significant pathological uptake of [11C]PK11195 as demonstrated in the three MS patients giving rise to a focal uptake in two patients with clinical relapse, strong enough to significantly rise above the signal-to-noise ratio. This high [11C]PK11195 uptake occurred in active white matter inflammation defined by gadolinium – enhanced T1 – MRI. The increased uptake for [11C]PK11195 in gadolinium lesions is in accordance with the known histology of the conventional MRI lesions were the blood-brain barriere breakdown is related to an extensive invasion of blood - borne cells such as macrofages (Banati *et al*. 2000). On the other hand one patient without clinical attack did not reach significance concerning the [11C]PK11195 uptake values in focal T2-weighted MR lesions. Further studies with PET and [11C]PK11195, as are currently carried out in an extended series of multiple sclerosis patients, will evaluate the final sensitivity of this semiquantitative methodology in cerebral pathology.

Conclusion

There is a minimal specific binding of [11C]PK11195 in normal brain. Near-steady-state [11C]PK11195 activity is not significantly different between grey and white matter. Since absolute quantification of [11C]PK11195 uptake remains problematic, reproducibility intervals for semiquantification may allow for the characterisation of physiological variability between subjects or even a measurement of signal-to-noise variation and thus knowledge of normal range values of [11C]PK11195 uptake. In our series of healthy volunteers, an intersubject reproducibility of 12.5% was found. This value allows definition of an accurate confidence interval for the detection of microglial activation in acute and chronic neuroinflammatory diseases, as indicated in the present study for focal white matter lesions in two clinically active MS patients. The simple approach by this semiquantification method might prove to be a feasible and useful application to measure the [11C]PK11195 uptake as a marker for the peripheral type benzodiazepine receptor on the microglia in the course of the multiple sclerosis process in individual patients and provide additional information over other anatomical imaging modalities such as MR.

This method opens a perspective in providing functional information in addition to anatomical imaging. Additional studies should further assess the usefulness of this simplified PET procedure in questionable cases.

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