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Simplified Reference Tissue Model for PET Receptor Studies

ADRIAAN A. LAMMERTSMA AND SUSAN P. HUME

PET Methodology Group, Cyclotron Unit, MRC Clinical Sciences Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom

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The reference tissue model allows for quantification of receptor kinetics without measuring the arterial input function, thus avoiding arterial cannulation and time-consuming metabolite measurements. The model contains four parameters, of which the binding potential (BP) is the parameter of interest. Although BP is robust, convergence rates are slow and the other parameters can have large standard errors. To overcome this problem, a simplified reference tissue containing only three parameters was developed. This new three-parameter model was compared with the previous four-parameter model using a variety of PET studies: [^{11}C]SCH 23390 (D_1 receptor) and [^{11}C]raclopride (D_2 receptor) in humans, and [^{11}C]SCH 23390, [^{11}C]raclopride and [^{11}C]RTI-121 (dopamine transporter) in rats. The BP values obtained from both models were essentially the same for all cases. In addition, the three-parameter model was insensitive to starting values, produced stable results for the other parameters (small standard errors), and converged rapidly. In conclusion, for the ligands tested the three-parameter model is a better choice, combining increased convergence rate with increased stability.

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INTRODUCTION

Quantification of *in vivo* tracer studies requires not only measurement of the uptake, washout, and retention of the tracer in tissue as function of time (tissue response function), but also of its delivery to the tissue (arterial input function). To measure directly the plasma concentration in arterial blood requires arterial cannulation. For the majority of receptor radioligands, measurement of the total plasma concentration is not sufficient and an additional determination of the fraction of labeled metabolites (as function of time) is required.

Recently, a method has been described (Hume *et al.*, 1992; Lammertsma *et al.*, 1996) which allows for the quantification of receptor kinetics without measuring the arterial input function. This method relies on the presence of a reference tissue, a region without specific binding of the ligand. In the reference tissue model, the time course of radioligand uptake in the tissue of interest is expressed in terms of its uptake in the reference tissue, assuming that the level of nonspecific binding is the same in both tissues. The advantage of the reference tissue method is clear. No arterial cannulation and sampling are required, reducing the degree of invasiveness and the level of complexity of both the scanning protocol and the data analysis procedures. In addition, there is no need for the labor-intensive measurements of labeled metabolites.

The originally described reference tissue model fits four parameters. Although estimation of the parameter of interest (binding potential) is robust, the model provides imprecise estimates of the other parameters, including the rate of transfer from plasma to tissue. In addition, convergence rates are slow and care has to be taken to avoid solutions which correspond to "local" minima rather than true "best fit" parameter values, thereby further increasing the overall analysis time.

The aim of the present study was to develop an alternative reference tissue model with acceptable standard errors for all fitting parameters and with an increased convergence rate.

THEORY

The reference tissue compartment model is based on the following differential equations (Lammertsma *et al.*, 1996):

$$dC_r(t)/dt = K'_1 C_p(t) - k'_2 C_r(t) \quad (1)$$

$$dC_f(t)/dt = K_1 C_p(t) - k_2 C_f(t) - k_3 C_f(t) + k_4 C_b(t) \quad (2)$$

$$dC_b(t)/dt = k_3 C_f(t) - k_4 C_b(t), \quad (3)$$

where C_p is the metabolite corrected plasma concentration (kBq · ml^{-1}), C_r is the concentration in reference tissue (kBq · ml^{-1}), C_f is the concentration of free (i.e., not specifically bound) ligand (kBq · ml^{-1}), C_b is the concentration of specifically bound ligand (kBq · ml^{-1}),

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K_1 is the rate constant for transfer from plasma to free compartment (ml · ml^{-1} · min^{-1}), k_2 is the rate constant for transfer from free to plasma compartment (min^{-1}), k_3 is the rate constant for transfer from free to bound compartment (min^{-1}), k_4 is the rate constant for transfer from bound to free compartment (min^{-1}), K_1' is the rate constant for transfer from plasma to reference compartment (ml · ml^{-1} · min^{-1}), k_2' is the rate constant for transfer from reference to plasma compartment (min^{-1}), and t is time (min).

Equation (1) describes the exchange between plasma and reference tissue, while Eqs. (2) and (3) relate to the free and bound compartments of the region of interest, respectively. In practice, C_f and C_b cannot be measured, but only the total concentration C_t ($=C_f + C_b$). Nevertheless, from Eqs. (2) and (3) it is possible to derive a relationship between C_t and C_p. By using the relationship between C_p and C_r obtained from Eq. (1), a relationship between C_t and C_r can then be derived. This relationship contains six parameters (K_1, k_2, k_3, k_4, K_1', and k_2'). However, K_1 and K_1' only enter as a ratio ($R_1 = K_1/K_1'$), which accounts for any differences in delivery to the region of interest and the reference tissue. The operational equation can be further simplified by assuming that the volume of distribution of the not specifically bound tracer in both tissues is the same, i.e.,

$$K_1'/k_2' = K_1/k_2. \tag{4}$$

Consequently, k_2' can be replaced by k_2/R_1. After replacing k_4 by k_3/BP, an operational equation with four parameters (R_1, k_2, k_3, and BP) is obtained (Lammertsma *et al.*, 1996). From the measured tissue concentrations $C_t(t)$ and $C_r(t)$, best estimates of these parameters can be obtained using standard nonlinear regression analysis.

If the tracer kinetics in the target region are such that it is difficult to distinguish between free and specific compartments, the reference tissue model can be simplified further. This corresponds to the situation where the time–radioactivity curve of the region of interest can be fitted satisfactorily to a single tissue compartment model with plasma input, without significant improvement when a two-tissue compartment model is used. This applies for example to [^{11}C]SCH 23390 and [^{11}C]raclopride (Farde *et al.*, 1989; Lammertsma *et al.*, 1996). In this case, Eq. (1) is still valid, but Eqs. (2) and (3) can be replaced by a single equation

$$dC_t(t)/dt = K_1C_p(t) - k_{2a}C_t(t), \tag{5}$$

where k_{2a} (min^{-1}) is the apparent (overall) rate constant for transfer from specific compartment to plasma. If Eq. (5) provides a good representation of the tracer kinetics, the corresponding total tracer volume of distribution should be the same as that derived from Eqs. (2) and (3):

$$K_1/k_{2a} = (K_1/k_2) \cdot (1 + \mathrm{BP}). \tag{6}$$

From Eqs. (1), (4), (5), and (6) the following expression can then be derived:

$$C_t(t) = R_1C_r(t) + [k_2 - R_1k_2/(1 + \mathrm{BP})]C_r(t) * \exp[-k_2t/(1 + \mathrm{BP})]. \tag{7}$$

In contrast to the original reference tissue model described above, which contains four parameters, the model represented by Eq. (7) contains only three parameters: R_1, k_2, and BP.

MATERIAL AND METHODS

The simplified three-parameter reference tissue model was evaluated by comparing fitted BP results with those obtained from the original four-parameter reference tissue model in both human and rat studies. This comparison was made for a number of ligands where the four-parameter model has been used successfully: [^{11}C]SCH 23390 (D_1 receptor) and [^{11}C]raclopride (D_2 receptor) in humans (Bench *et al.*, 1993, 1996; Lammertsma *et al.*, 1996; Turjanski *et al.*, 1994), and [^{11}C]SCH 23390, [^{11}C]raclopride and [^{11}C]RTI-121 (dopamine transporter) in rats (Hume *et al.*, 1992, 1995, 1996).

Human Studies

[^{11}C]Raclopride and [^{11}C]SCH 23390 studies in 25 and 11 subjects, respectively, were included in the present study. Subjects included normal controls, patients with Parkinson's disease (Turjanski *et al.*, 1994), and normal subjects predosed with varying amounts of the neuroleptic ziprasidone (Bench *et al.*, 1993). The purpose of this diversity of subjects was to test the three-parameter model over a wide range of BP values. The clinical details of the patients are not relevant for the present study and have been reported elsewhere (Bench *et al.*, 1993; Turjanski *et al.*, 1994).

The [^{11}C]SCH 23390 studies were performed on an ECAT 953B (CTI/Siemens, Knoxville, TN), operating in 2D mode, the [^{11}C]raclopride studies on an ECAT 931-08/12 (CTI/Siemens). The scanning protocol was the same for both radioligands. Starting 30 s before time of injection, 22 sequential frames were collected over a period of 60.5 min according to the following protocol: 1 × 30 s (background frame), 6 × 5 s, 3 × 10 s, 4 × 60 s, 2 × 150 s, 2 × 300 s, 4 × 600 s. In both cases a separate transmission scan was used to correct for attenuation. All scans were reconstructed using a Hanning filter with a cut-off frequency 0.5 of maximum.

This resulted in spatial resolutions of 8.0 × 8.0 × 4.3 mm full width at half-maximum (FWHM) at the center of the field of view for the ECAT 953B scanner (Spinks *et al.,* 1992) and 8.4 × 8.3 × 6.6 mm FWHM for the ECAT 931-08/12 scanner (Spinks *et al.,* 1988).

For both [^{11}C]raclopride and [^{11}C]SCH 23390 studies, a standard regions of interest (ROI) template was applied (Sawle *et al.,* 1993). In the present analysis, only whole striatum (average of left and right) data were used, with the cerebellum as the reference tissue.

Rat Studies

[^{11}C]Raclopride, [^{11}C]SCH 23390, and [^{11}C]RTI-121 PET studies in 13, 11, and 22 rats, respectively, were included in the present study. To test the three-parameter model over a large range of BP values, both control animals (tracer alone, high specific radioactivity) and rats predosed or co-injected with the corresponding nonradioactive compound were included.

Preparation of animals and scanning details have been reported previously (Hume *et al.,* 1996). All studies were performed on a dedicated small diameter (11.5 cm) tomograph (CTI, Knoxville, TN). For [^{11}C]raclopride and [^{11}C]SCH 23390, 21 sequential frames were collected over a period of 60 min according to the following protocol: 3 × 5 s, 3 × 15 s, 4 × 60 s, 11 × 300 s. For [^{11}C]RTI-121, the scan time was increased by adding three final frames of 600 s. All scans were reconstructed using a ramp filter with a cut-off frequency 0.5 of maximum. This resulted in a spatial resolution of 2.3 × 2.3 × 4.3 mm FWHM in the center of the field of view, with the transaxial resolution decreasing to 4 mm FWHM at 1 to 2 cm from the center (Bloomfield *et al.,* 1995).

For all studies, a standard ROI template was applied (Myers *et al.,* 1996). As for the human studies, only whole striatum (average of left and right) was used for the present analysis and the cerebellum was used as reference tissue.

RESULTS

An example of a fit to human [^{11}C]raclopride data using the four-parameter reference tissue model has been given previously (Fig. 3 in Lammertsma *et al.,* 1996). Refitting the same data with the three-parameter model resulted in a fit which was visually indistinguishable from the four-parameter fit. Examples of fits to human [^{11}C]SCH 23390 data are given in Fig. 1 for both high and low BP values. Again the three- and four-parameter fits are indistinguishable from each other. This correspondence is reflected in the relationships between striatal BP estimates obtained with both models as shown in Fig. 2 for all human [^{11}C]raclopride and [^{11}C]SCH 23390 studies. In Fig. 3 the same relationships are shown for rat [^{11}C]raclopride, [^{11}C]SCH 23390,

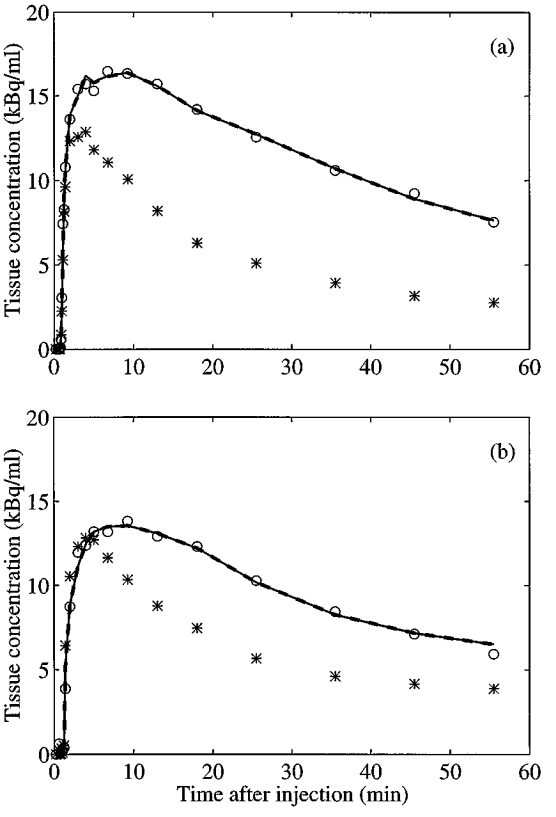

FIG. 1. Examples of fits to human [^{11}C]SCH 23390 data for (a) high and (b) low BP values (1.32 and 0.60, respectively). The three-parameter (solid line) and four-parameter (dashed line) fits to the striatum data (o) are indistinguishable from each other. The cerebellum data (*) are also given.

and [^{11}C]RTI-121 studies (examples of actual fits to region of interest data are given in Hume *et al.,* 1996). In all cases, the fitted lines were not significantly different from the line of identity. The percentage differences of the striatal BP estimates obtained with the three-parameter model compared to those obtained with the four-parameter model are given in Table 1. These differences were not significantly different from zero for all cases. The computation time was an order of magnitude shorter with the three-parameter model than with the four-parameter model.

In Table 2 the results of statistical analyses of individual fits are summarized, giving the number of studies in which the four-parameter model provided a significantly better fit than the three-parameter model according to Akaike (1974) and Schwarz (1978) criteria and the *F* test (1985). Depending on test, tracer, and species, the fraction of studies with this property ranged from 0 to 60%. However, even in these cases the improvement in fit and the Akaike and Schwarz numbers were very small and often merely represented better mathematical solutions. For example, in six of the seven [^{11}C]RTI-121 studies in rats where the Akaike

criterium indicated a better four-parameter fit, this was associated with an unlikely R_1 value (<0.5 or >2.0), whereas the three-parameter fits resulted in R_1 values close to 1.

The three-parameter reference tissue model provided more stable R_1 results for all ligands. The average ($\pm$SD) value of R_1 for all 36 human studies combined was 0.78 $\pm$ 1.24 for the four-parameter model and 0.93 $\pm$ 0.13 for the three-parameter model. For all 46 rat studies, these values were 1.09 $\pm$ 2.69 and 0.96 $\pm$ 0.12, respectively. The large standard deviations for the four-parameter model R_1 values were due to some very high as well as some negative values.

DISCUSSION

The previously reported reference tissue model (Hume *et al.*, 1992; Lammertsma *et al.*, 1996) allows for quantification of receptor studies without the need for measuring the arterial input function, provided that a (reference) tissue exists in which no specific binding of the radioligand occurs. The technique has been successfully used in the study of the dopaminergic receptor system in both humans (Bench *et al.*, 1993, 1996; Turjanski *et al.*, 1994; Lammertsma *et al.*, 1996) and rats (Hume *et al.*, 1992, 1995, 1996). The two main assumptions of the model are that the volume of distribution of not specifically bound ligand is the same in target and reference tissues (i.e., the level of free and nonspecific binding is the same) and that the reference tissue is not affected by the pathology under study. These assumptions have been discussed in detail elsewhere (Lammertsma *et al.*, 1996). It should be noted that the model does allow for differences in delivery (K_1) between target and reference tissues and that it does not

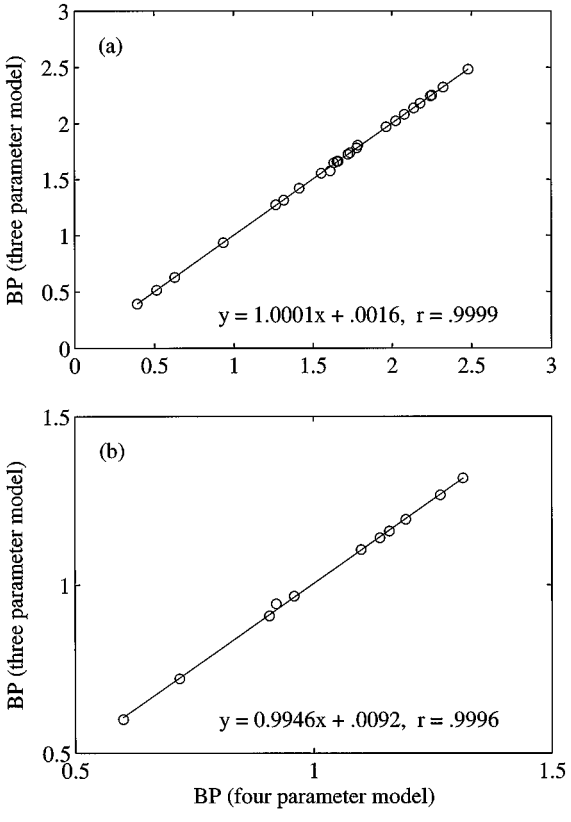

FIG. 2. Relationships between striatal BP estimates obtained with three- and four-parameter models for human (a) [^{11}C]raclopride and (b) [^{11}C]SCH 23390 studies, together with the linear regression results.

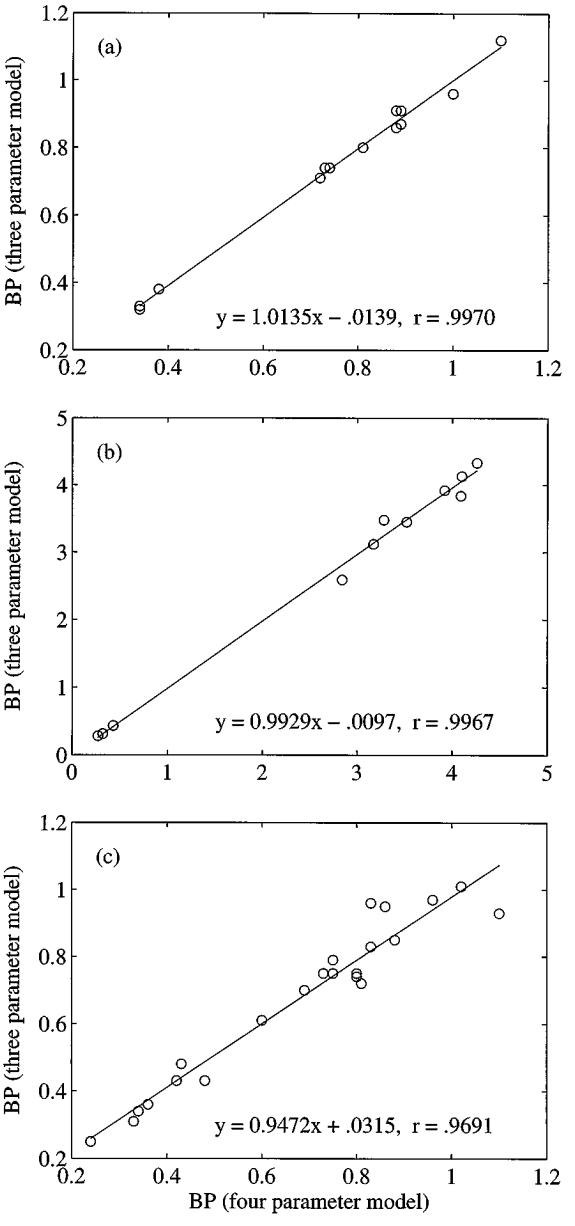

FIG. 3. Relationships between striatal BP estimates obtained with three- and four-parameter models for rat (a) [^{11}C]raclopride, (b) [^{11}C]SCH 23390, and (c) [^{11}C]RTI-121 studies, together with the linear regression results.

TABLE 1

Differences between Three- and Four-Parameter Model Striatal BP Values

Tracer	Species	N^a	Difference[b] Mean ± SD	Maximum
[11C]Raclopride	Human	25	0.13 ± 0.58%	−2.20%
[11C]SCH 23390	Human	11	0.38 ± 0.71%	2.40%
[11C]Raclopride	Rat	13	−0.86 ± 2.67%	−5.88%
[11C]SCH 23390	Rat	11	−0.86 ± 4.21%	−8.80%
[11C]RTI-121	Rat	22	−0.21 ± 7.46%	15.66%

[a] Number of studies.
[b] Difference of three-parameter model BP from four-parameter model BP.

assume that the time course of free and nonspecifically bound ligand is the same in both tissues and in this way differs from an alternative model which uses the cerebellum as a direct input function (Farde *et al.*, 1989).

The underlying assumptions and characteristics of the four-parameter reference tissue model also apply to the simplified three-parameter reference tissue model developed here but, in addition, the three-parameter model assumes that the kinetics of the target tissue can be described by a single compartment. This has been demonstrated for human [11C]raclopride (Farde *et al.*, 1989; Lammertsma *et al.*, 1996) and [11C]SCH 23390 (unpublished data) studies. Although no such evidence is available for rat studies, it could be inferred from the close correlation between BP values obtained from the four- and three-parameter reference tissue models, observed in the present study.

It should be noted that, in theory, both four- and three-parameter reference tissue models are valid only if the reference tissue itself can be described by a single tissue compartment (Hume *et al.*, 1992). For [11C]raclopride, this has been demonstrated in rat cerebellum (Hume *et al.*, 1992), but in human cerebellum the kinetics of [11C]raclopride are best described by two tissue compartments (Farde *et al.*, 1989). Nevertheless, it has been shown that the four-parameter reference tissue model is as sensitive in detecting changes in [11C]raclopride BP in humans as the more laborious and cumbersome method using plasma input and two tissue compartments for both striatum and cerebellum (Lammertsma *et al.*, 1996). In the present study, no differences between the simplified three-parameter reference tissue model and above four-parameter model were found, indicating that the simplified method retains this sensitivity. Simulation studies are required to fully assess the performance of the reference tissue models under different conditions.

TABLE 2

Number of Studies with Significantly Better Four-Parameter Fits Than Three-Parameter Fits

Tracer	Species	N^a	N_4[b] Akaike	Schwarz	*F* test
[11C]Raclopride	Human	25	3	2	1
[11C]SCH 23390	Human	11	2	1	0
[11C]Raclopride	Rat	13	6	3	3
[11C]SCH 23390	Rat	11	7	7	3
[11C]RTI-121	Rat	22	7	5	3

[a] Number of studies.
[b] Number of studies with better 4-parameter fit; *F* test at $P < 0.05$.

In both the three- and four-parameter reference tissue models the intravascular signal in the striatum is ignored. It should, however, be noted that the reference tissue also contains a intravascular component. In the operational equation (e.g., Eq. (7) for the three-parameter model), these two intravascular signals (in target and reference regions) have counteracting effects, i.e., the final error will be small.

From Figs. 2 and 3, it follows that both models provided the same BP values. None of the regression lines were significantly different from the line of identity, nor were the differences between the two sets of data significantly different from zero for all five cases (Table 1). It is clear, however, that there is slightly more scatter for the rat data. This is primarily due to the fact that the rat time–radioactivity curves contain more noise than the corresponding human curves, as a result of the smaller ROI used.

The slight variation between three and four parameter model BP values is probably due to the lower precision of the four parameter model. From Table 2 it follows that in only a small number of studies a significantly better fit was obtained with the four-parameter model. Even in those cases the actual improvement was very small. In addition, they often coincided with very high (>2) or very low (<0.5) values for R_1. Therefore, most of these fits represent best mathematical descriptions of the curves, but are unlikely from a physiological point of view. Although BP is a relatively robust parameter, a small change (<10%) due to "erroneous" R_1 values cannot be excluded. The results of the four-parameter model (in physiological terms) may have been improved by constraining the R_1 parameter. In contrast to the four-parameter model, consistent values of R_1 were found with the three-parameter model, being 0.93 ± 0.13 for the human and 0.96 ± 0.12 for the rat studies. Thus, with the three-parameter model it is possible to estimate not only BP, but also any relative (to reference tissue) change in regional delivery of radioligand.

Also important was the observation that the results of the three-parameter fit were insensitive to the starting values used. This reduces the need for quality

assurance procedures, thereby further decreasing analysis time which was already an order of magnitude less for the three-parameter model compared to the four-parameter model. The insensitivity to starting values and the greater stability of the three parameter fit allows for fitting data with relatively higher noise levels. This can be important in those cases where the amount of radioactivity which can be injected is limited in order to avoid co-injecting too much nonradioactive ligand. It also should improve fitting of postmortem dissection data (e.g. Hume *et al.*, 1994; Ashworth *et al.*, 1996), where time–radioactivity curves are derived from a number of different animals and thus suffer from interanimal variation. In addition, it might become possible to perform pixel by pixel fits, thereby creating functional images of BP. Although further studies are required, the feasibility of this approach is suggested by the stability of the three-parameter fits even for the very small structures in rats.

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