NeuroImage 169 (2018) 278–285

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Non-invasive estimation of [^{11}C]PBR28 binding potential☆

Martin Schain [a,*], Francesca Zanderigo [a,b], R. Todd Ogden [a,b,c,1], William C. Kreisl [d,e,1]

[a] Department of Psychiatry, Columbia University, New York, NY, USA
[b] Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute, New York, NY, USA
[c] Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA
[d] Molecular Imaging Branch, National Institute of Mental Health, Bethesda, MD, USA
[e] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA

ARTICLE INFO

Keywords:
[^{11}C]PBR28
Neuroinflammation
Alzheimer's disease
Kinetic modeling
PET
TSPO

ABSTRACT

[^{11}C]PBR28 is a PET radioligand used to estimate densities of the 18 kDa translocator protein (TSPO) *in vivo*. Since there is no suitable reference region, arterial blood samples are required for full quantification. Here, we evaluate a methodology for full quantification of [^{11}C]PBR28 PET data that does not require either a reference region or blood samples.

Simultaneous estimation (SIME) uses time-activity curves from several brain regions to estimate binding potential (BP_{ND}), a theoretically more sensitive outcome measure than total distribution volume. SIME can be employed with either a measured arterial input function (*AIF*) or a template input function (*tIF*) that has similar shape as the *AIF*, but with arbitrary amplitude.

We evaluated the ability of SIME to detect group differences in TSPO densities using PET and arterial plasma data from 21 Alzheimer's disease (AD) patients and 15 controls that underwent [^{11}C]PBR28 imaging. Regional BP_{ND} obtained with *tIF*s were compared to those obtained using measured *AIF*s. Standard kinetic modeling was also employed for comparison. The sensitivity of each method to detect group differences in TSPO densities were assessed by comparing estimated effect sizes between AD patients and controls. For this purpose, BP_{ND} estimated for one region with high pathological burden (inferior temporal cortex), and for one region with low pathological burden (cerebellum) was used.

BP_{ND} estimates obtained with SIME and *tIF*s were close to identical to those obtained with *AIF* (3.0 ± 21% difference, $r^2 = 0.78$). In this dataset, the effect sizes between AD patients and controls for both SIME with *AIF* and SIME with *tIF* were similar (30.3%, $p = 0.001$ and 31.0%, $p = 0.004$, respectively) and were each greater than the effect size observed using the two-tissue compartment model (16.1%, $p = 0.12$). None of the tested methods showed difference in TSPO binding in cerebellum.

These results demonstrate that BP_{ND} can be estimated for [^{11}C]PBR28 using SIME, and may be useful in clinical studies. In addition, arterial sampling may not be necessary if *tIF*s can be reliably estimated.

Introduction

The possibility to quantify the current inflammatory state in a living human brain has sparked considerable interest in various disciplines of neuroscience (Schain and Kreisl, 2017). A common strategy is to use positron emission tomography (PET) radioligands targeting the 18 kDa translocator protein (TSPO), because TSPO is up-regulated in activated microglia (Venneti et al., 2006). Several second-generation radioligands for TSPO have been developed (Venneti et al., 2013; Herrera Rivero et al., 2015), of which [^{11}C]PBR28 (Briard et al., 2005) is among those most commonly used.

No consensus exists regarding the optimal procedure to quantify [^{11}C]PBR28 PET data. Using compartmental models, such as the standard two-tissue compartment model (2TCM) (Innis et al., 2007), or variants thereof (Rizzo et al., 2014), is considered the conservative option because it is fully quantitative, and it provides estimates of the total distribution volume (V_T) without requiring assumptions regarding the spatial distribution of TSPO. There are three caveats with this approach.

☆ This study was supported by The Paul Janssen Fellowship in Translational Neuroscience.
* Corresponding author. 1051 Riverside Drive, New York, NY, 10032 USA.
E-mail address: ms5234@cumc.columbia.edu (M. Schain).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.neuroimage.2017.12.002
Received 17 October 2017; Accepted 1 December 2017
Available online 5 December 2017

Table 1
Subject demographics.

	AD	HC
N HAB	8	4
N MAB	13	11
Age (years)	63 (9)	65 (5)
Female/Male	11/10	3/12
Education (years)	17.0 (2.2)	16.2 (2.5)
MMSE	18.9 (5.3)	29.9 (0.4)
CDR-sum of boxes	6.3 (3.0)	0 (0.0)
Plasma free fraction (f_p)	0.04 (0.00)	0.04 (0.01)
Spec. Activity (GBq/μmol)	162 (86)	134 (50)
Injected Activity (MBq)	691 (16)	677 (45)

First, it requires measurement of the arterial input function (*AIF*). Arterial blood sampling and analysis require dedicated staff and instrumentation, may be uncomfortable for the research subjects, and introduces a risk of adverse events. Also, measurement errors of the *AIF* increase variability and reduce power for group comparisons. Second, a strong association between V_T in brain and V_T in peripheral organs has been reported (Kanegawa et al., 2016; Gallezot et al., 2016), presumably due to the high concentration of TSPO in these tissues. This association may affect the amount of radioligand that is able to enter brain tissue. Third, the 2TCM only provides reliable estimates of V_T, which represents the sum of non-displaceable and specifically bound radioligand. With V_T as outcome measure, a potential difference in specifically bound radioligand between clinical populations may be obscured by a considerable non-specific signal.

Several strategies for measuring [^{11}C]PBR28 binding without requiring an *AIF* have been proposed. A recent study concluded that using standardized uptake value (SUV) is not reliable due to poor correlation with V_T (Yoder et al., 2015). Several studies have used ratios of either V_T or SUV between different brain regions, or between a particular region of interest (ROI) and the whole brain, similar to assuming a reference region. (Dimber et al., 2016; Lyoo et al., 2015; Zurcher et al., 2015). As TSPO is ubiquitously expressed, however, no true reference region for [^{11}C]PBR28 exists, and therefore these procedures will necessarily result in biased outcomes. Nevertheless, for disorders for which the up-regulation of TSPO varies spatially, tissue-ratio based approaches may be meaningful (Lyoo et al., 2015). To avoid misinterpretation of the results, however, such ratio-based approaches should be validated relative to full quantification before being used in clinical studies. For instance, PET studies in schizophrenia have shown inconsistent findings depending on whether regular kinetic modeling or tissue-ratio methods were employed (Bloomfield et al., 2016; Narendran and Frankle, 2016; Collste et al., 2017; Coughlin et al., 2016). Also, although ratio-based techniques have shown good test-retest variability (Nair et al., 2016), they have been criticized since the outcome measures were uncorrelated with V_T, which raises concern regarding their validity (Matheson et al., 2017).

Here, we evaluate a new method for quantification of [^{11}C]PBR28 binding that avoids the disadvantages of the 2TCM as well as the assumptions implicit when using ratio-based approaches. This method, called *simultaneous estimation of V_{ND}* (SIME) (Ogden et al., 2015), models the time-activity curves (TACs) from several brain regions simultaneously to estimate a brain-wide value for the radioligand non-displaceable distribution volume (V_{ND}). It is commonly assumed that V_{ND} is similar across brain regions, and can be estimated from a reference region. If an estimate for V_{ND} is available, the binding potential BP_{ND} can be calculated. In contrast to V_T, BP_{ND} is not vulnerable to measurement errors in the *AIF* and it implicitly accounts for correction for the radioligand plasma free fraction (f_p). Also, BP_{ND} is theoretically a more sensitive outcome measure than V_T, since it does not contain contribution from non-displaceable radioligand (see Discussion).

The benefit of using SIME may extend beyond the possibility to increase the sensitivity of the outcome measure and reduce measurement error. We recently showed that if V_{ND} can be estimated by SIME, then BP_{ND} can be estimated non-invasively using SIME and a "template" input function (*tIF*) with similar shape as the real *AIF* but with an arbitrary amplitude (Schain et al., 2017). In that study, which included radioligands for the serotonin 1A receptor, the template curves were constructed as an average of normalized input function across subjects, imposing the assumption that the *AIF* shape is similar across individuals. It is not obvious that this strategy to estimate *tIF*s is viable for TSPO tracers. In blood, TSPO is expressed in several cell types, including monocytes, polymorphonuclear neutrophils, and platelets (Canat et al., 1993). The radioligand concentration in blood may therefore depend on peripheral immunoactivation, and thus may vary across diagnostic groups, or even across healthy individuals. It is however unclear whether these (and other) biological factors influence the shape of the *AIF*, or if their effect is limited to a scaling of the curve amplitude, which is key in determining whether the shape of an individual *AIF* can be approximated by a population average. Of interest, a recent study concluded that, for the TSPO radioligand [^{18}F]FEPPA, population-based input functions scaled with a single blood sample could be used to estimate V_T (Mabrouk et al., 2017), indicating that, for that radioligand, the *AIF* shape is similar across individuals.

The objective of the current study was to evaluate the applicability of SIME to [^{11}C]PBR28 PET data. We used SIME to calculate BP_{ND} (with and without the subject-specific measured *AIF*s) in a previously acquired dataset of [^{11}C]PBR28 PET measurements in Alzheimer's disease (AD) patients and controls. Non-invasive estimates of BP_{ND} were compared to those obtained with *AIF*, and their sensitivity to detect up-regulation of activated microglia among the AD group was compared to that observed with standard kinetic modeling.

Materials and methods

Subjects

This study includes a total of 21 AD patients and 15 age-matched controls (demographics shown in Table 1). All patients met National Institute of Neurological Disorders and Stroke (NINDs) criteria for AD, and all controls were cognitively normal on neurological examination. All subjects underwent PET imaging with [^{11}C]PIB, and all AD patients were amyloid-positive while all controls were amyloid-negative. Some of these subjects had been included in previous published studies (Lyoo et al., 2015; Kreisl et al., 2013). Patients who met criteria for logopenic progressive aphasia and subjects who did not have measurement of f_p were excluded. Each subject was genotyped for the rs6971 polymorphism on the 18 kDa gene, and categorized as a high (HAB) or mixed (MAB) affinity binder, using leukocyte-binding assays (Kreisl et al., 2013). Radioligand preparation and details regarding the acquisition and processing of [^{11}C]PBR28 PET and magnetic resonance (MR) images have been previously published (Kreisl et al., 2013). In brief, PET data was acquired on a GE advance PET scanner (GE Healthcare). A head holder was used to minimize motion during the scan. Each acquisition started with an 8-minute transmission scan using ^{68}Ge for attenuation correction. Subsequently, an intravenous bolus injection of [^{11}C]PBR28 was carried out, followed by 90 min acquisition of emission data. Projection data were corrected for attenuation and scatter, and reconstructed into 4D image volumes using filtered back projection. PET data were not corrected for partial volume effects.

T1 weighted MR images were acquired using a 3T Philips Achieva Scanner (Philips), using turbo field echo (TFE) sequence (repetition time (TR) = 8.1 msec, echo time (TE) = 3.7 msec, flip angle = 8°.

All procedures were approved by the Combined Neuroscience Institutional Review Board of the National Institute of Health Intramural Research Program. All subjects or their surrogates provided written informed consent to participate.