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Quantitative PET analyses of regional [^{11}C]PE2I binding to the dopamine transporter — Application to juvenile myoclonic epilepsy

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ABSTRACT

The dopamine transporter (DAT) is of central interest in research on the pathophysiology and treatment of neuro-psychiatric disorders. [^{11}C]PE2I is an established radioligand that provides high-contrast delineation of brain regions that are rich in DAT. The aim of the present PET study in eight patients with juvenile myoclonic epilepsy (JME) was to evaluate the kinetics of [^{11}C]PE2I in the brain and to compare binding parameters with those of age-matched control subjects (n = 6). Each patient participated in 90-minute PET measurements with [^{11}C]PE2I. Data were analyzed using kinetic compartment analyses with metabolite-corrected arterial plasma input and reference tissue models using the cerebellum as a reference region. The time-activity curves were well described by the two-tissue compartment model (2TCM) for the DAT-rich regions. The 2TCM with fixed K_1/k_2 ratio derived from the cerebellum provided robust and reliable estimates of binding potential (BP_{ND}) and total distribution volume (V_T). The reference tissue models also provided robust estimates of BP_{ND}, although they gave lower BP_{ND} values than the kinetic analysis. Compared with those of control subjects, we found that BP_{ND} values obtained by all approaches were reduced in the midbrain of the patients with JME. The finding indicates impaired dopamine uptake in the midbrain of JME patients. The three-tissue compartment model could best describe uptake in the cerebellum, indicating that two kinetically distinguishable compartments exist in cerebellar tissue, which may correspond to nonspecific binding and the blood–brain barrier passing metabolite. The reference tissue models should be applied with better understanding of the biochemical nature of the radioligand and the reliability of these approaches.

Introduction

The dopamine transporter (DAT) plays an important role in the reuptake of dopamine into pre-synaptic nerves and regulates dopaminergic transmission in the synaptic cleft. Molecular imaging with positron emission tomography (PET) is a well established tool to evaluate dopaminergic function (Allard et al., 1990; Antonini et al., 2001; Ginovart et al., 1997; Laakso et al., 2001; Meyer et al., 2001; Volkow et al., 2002; Wong et al., 1998).

Among several radioligands for in vivo DAT imaging developed for PET (Chalon et al., 2006; Farde et al., 1994; Goodman et al., 2000; Halldin et al., 1996; Müller et al., 1993; Varrone and Halldin, 2010; Varrone et al., 2009; Wong et al., 1993), [^{11}C]PE2I is an established radioligand with high affinity and selectivity for DAT (Emond et al., 1997; Guilloteau et al., 2003) and has been applied for not only normal human brain but also neuro-psychiatric disorders with quantitative approaches (Arakawa et al., 2009; Ciumas et al., 2008; Ciumas et al., 2010; Halldin et al., 2003; Hirvonen et al., 2008; Jucaite et al., 2005; Jucaite et al., 2006; Leroy et al., 2007; Seki et al., 2010).

More recently, [^{11}C]PE2I and PET studies were performed on patients with juvenile myoclonic epilepsy (JME), and binding potential (BP_{ND}), a parameter for specific binding at equilibrium, was measured (Ciumas et al., 2008). As a result, regional BP_{ND} was found to be reduced in the midbrain and substantia nigra, but not in the striatum, compared with that of age-matched control subjects. These findings suggest that that dopamine signaling is impaired in patients with JME, and a follow up study with an extended number of JME patients (Ciumas et al., 2010) showed that this impairment was related to the breakdown in cognitive control in JME patients. The measuring method applied in these studies was the simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996), a non-invasive approach without arterial plasma input, in which the cerebellum was used as a reference region.

Two potential limitations are, however, suggested for quantification with [^{11}C]PE2I and PET, one of which is late peak equilibrium,

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and the other is radiolabeled metabolite that passes the blood–brain barrier and potentially binds to the DAT, as reported in a rodent experiment (Shetty et al., 2007), but not yet in human brain. These limitations probably make it difficult to obtain robust and reliable values of binding parameters.

The purpose of the present extended analysis was to examine [^{11}C]PE2I uptake in the patients with JME, to measure binding parameters by applying the established kinetic compartment analysis using metabolite-corrected arterial plasma input, to compare the kinetics and binding parameters with those of control subjects, to confirm binding potential reduction in JME patients previously detected, and to evaluate the reliability of non-invasive reference tissue models using the cerebellum as a reference. Particular emphasis was placed on evaluating the binding parameters in the midbrain, the kinetics of [^{11}C]PE2I in the cerebellum as a reference region and additional information about the pathophysiology of JME.

Materials and methods

Patients

The study was approved by the ethics committee of Karolinska Hospital. Eight patients with JME participated in the study, six men and two women, aged 20–56 years (mean ± s.d., 39 ± 12). JME was diagnosed according to the International Classification of Epilepsies from 1989, on the basis of seizure history, seizure semiology as described by relatives or recorded during hospitalization, and results of scalp EEG, the details of which were described previously (Ciumas et al., 2008). The clinical characteristics of the patients and medication are listed in Table 1. Seven patients were medicated with Valproate, but one (patient E) had no medication.

Control subjects

Six men, aged 19–38 years (mean ± s.d., 34 ± 11), were used as control subjects investigated in a previous study (Jucaite et al., 2006).

Radiochemistry

The acid precursor of PE2I was prepared and radiolabeled by O-methylation using [^{11}C]methyl triflate as described in detail elsewhere (Halldin et al., 2003). The decay-corrected radiochemical yield of [^{11}C]PE2I was 50%. The radiochemical purity of the final product was >99%. The specific radioactivity of [^{11}C]PE2I at the time of injection was between 125 and 374 GBq/μmol (mean ± s.d., 220 ± 106 GBq/μmol). The radioactivity injected ranged from 307 to 396 MBq (mean ± s.d., 364 ± 29 MBq) and the injected mass was between 0.42 μg and 1.3 μg (mean ± s.d., 0.86 ± 0.37 μg). The radioligand was injected as a rapid bolus.

MRI and regions of interest

T1-weighted MR images were acquired using a 1.5 T Signa unit (General Electric, Milwaukee). A standard spin-echo sequence with a 256 × 256 matrix and 1 mm slice thickness was used with a repetition time of 400 ms. Echo times were 9 ms for images. A head fixation system was used for both MRI and PET measurements (Bergstrom et al., 1981). Regions of interest (ROIs) were outlined manually on each individual MR image and transferred to the corresponding PET images showing the distribution of [^{11}C]PE2I (Roland et al., 1994). Each ROI set consisted of both sides of caudate and putamen, the midbrain and the cerebellum, as shown in Fig. 1.

Table 1
The list of patients with JME and medication.

Patients	Sex	Age	Medication
A	m	56	Valproate
B	m	45	Valproate
C	m	30	Valproate, Lamotrigine
D	m	42	Valproate, Lamotrigine
E	f	32	No medication
F	f	49	Valproate, Lamotrigine
G	m	20	Valproate, Leviteracetam
H	m	40	Valproate

PET experimental procedure

The PET system (Siemens ECAT Exact HR 47, Siemens/CTI, TN) has been described previously (Jucaite et al., 2006). All PET measurements were carried out in the interictal state for the patients with JME, which was evaluated by the neurologists present during each experiment.

The last seizure (including myoclonia) was reported to be at least 1 week before the PET scan.

Brain radioactivity of the patient with JME was measured in a series of consecutive time frames for 90 min. The frame sequence consisted of eight fifteen-second frames, eight one-minute frames, four two-minute frames, four four-minute frames, four six-minute frames and four eight-minute frames. On the other hand, radioactivity in the brain of a normal subject was measured for 63 min, with three one-minute frames, four three-minute frames and eight six-minute frames.

Arterial blood sampling

To obtain the arterial input function, an automated blood sampling system (ABSS; Scanditronix, Uppsala, Sweden) was used during the first 5 min of each PET measurement. After the first 5 min, arterial blood samples (2 ml) were taken manually at the midpoint of each frame until the end of the measurement (Farde et al., 1989).

Plasma metabolite analysis (HPLC) of [^{11}C]PE2I

The fractions of plasma activity corresponding to unchanged [^{11}C]PE2I and labeled metabolites were determined as described previously (Halldin et al., 2003). Arterial blood samples (2 ml) were drawn at set times: 4, 10, 20, 30, 40, 50 and 60 min after i.v. injection of [^{11}C]PE2I. The in vivo assay of radioactive metabolites was performed using standard procedures developed at Karolinska Institutet for new PET radioligands (Halldin et al., 1995). In short, the supernatant liquid obtained after centrifugation for 2 min was deproteinized with acetonitrile. It was then analyzed by gradient high performance liquid chromatography (HPLC) on a reverse-phase column (Waters μ-Bondapak C18, 7.8 × 300 mm, 10 μm) and eluted at 6 ml/min over 8 min with acetonitrile/0.01 mol/l phosphoric acid, using a gradient of 25/75 to 80/20 from 0 to 4.5 min and 80/20 to 30/70 from 4.5 to 8 min.

The individual time-activity curves (TACs) for fraction (%) of radioactivity in plasma that corresponds to unchanged [^{11}C]PE2I were obtained by fitting with the Hill's function described as follows:

$$m(t) = \left(1 - \frac{\beta t^{\delta}}{t^{\delta} + \gamma}\right) \times 100, \quad (1)$$

where m(t) is percentage of the metabolite fraction in the plasma and β, γ and δ are the parameters of the function form to be estimated under the conditions of $0 < \beta \leq 1$, $0 < \delta$ and $0 < \gamma$ (Gunn et al., 1998; Hill, 1910). Finally, each metabolite-corrected arterial plasma input was derived by multiplying uncorrected plasma input by the function m(t).