Comparative evaluation of two serotonin transporter ligands in the human brain: $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoimipramine

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Abstract. Serotonin (5-HT) is considered to be an important transmitter underlying mood and behaviour. Abnormalities of the 5-HT transporter have been suggested in mood disorders, since it is one of the major binding sites of antidepressants. A number of ligands have been developed to visualise the 5-HT transporter in vivo, but only a few have successfully visualised specific binding in vivo. In this study, we comparatively evaluated two ligands for 5-HT transporter, $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoimipramine, in the human brain. Brain uptake of $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoimipramine was measured with PET in 15 healthy volunteers. Second PET scans were performed after pretreatment with the potent 5-HT reuptake inhibitor clomipramine. Data were analysed as regional brain uptake as well as whole brain uptake. In six healthy volunteers uptake of the two ligands was also measured in the lung since it is one of the high-uptake organs in the body. In the brain, high accumulation was observed in the thalamus and striatum, the regions known to contain high densities of 5-HT transporter, for both $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoimipramine. The average ratio of thalamus to cerebellum uptake at 90 min after the tracer injection was approximately 1.6 for $^{11}$C$^{(+)}$McN5652 and 1.7 for $^{11}$Ccyanoimipramine, while the ratios obtained after pretreatment with clomipramine were approximately 1.2. However, the whole brain uptake of $^{11}$C$^{(+)}$McN5652 was approximately twice that of $^{11}$Ccyanoimipramine, while the lung uptake of $^{11}$C$^{(+)}$McN5652 was approximately half that of $^{11}$Ccyanoimipramine. Both $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoimipramine showed sufficient specific binding for performance of a quantitative analysis in the brain. $^{11}$C$^{(+)}$McN5652 could be superior because of its higher distribution to the brain.

Keywords: Serotonin transporter – $^{11}$C$^{(+)}$McN5652 – $^{11}$Ccyanoimipramine – Brain – Lung

Introduction

The serotonin (5-HT) system plays an important role in mood and behaviour. Abnormalities of serotonergic transmission have been suggested in mood disorders and several psychiatric disorders [1]. 5-HT transporter has been reported to be one of the major binding sites for a number of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) [2, 3]. Several SSRIs, such as fluoxetine, paroxetine and citalopram, have been labelled with carbon-11 or fluorine-18 to visualise the 5-HT transporter in vivo [4, 5, 6, 7, 8]. However, most ligands were not suitable for visualisation of the 5-HT transporter owing to difficulties in evaluating their specific binding in vivo. Recently a series of N-methyl-2-(aryltio)benzylamine analogues were synthesised and radiolabelled with $^{11}$C for 5-HT transporter ligand [9, 10]. Some of these compounds showed nanomolar affinity for 5-HT transporter and one of them, $^{11}$C$^{[3]}$DASB ($^{[11]}$C$^{[3]}$-amino-4-(2-dimethylaminomethyl-phenylsulphanyl)-benzonitrile), gave promising results in human studies [11]. $^{11}$Ccyanoimipramine was developed in the late 1980s [12]. Although Suhara et al. have reported the lung uptake with the ligand, it has not been evaluated thoroughly as a 5-HT transporter ligand in the brain [13]. $^{11}$C$^{(+)}$McN5652 is a selective 5-HT reuptake inhibitor that has nanomolar potency for 5-HT transporter and is currently being used as a positron emission tomography (PET) tracer for 5-HT transporter [14, 15, 16, 17, 18, 19, 20].

The aim of this study was to compare the two $^{11}$C-labelled compounds, $^{11}$C$^{(+)}$McN5652 and $^{11}$Ccyanoim-
ipramine, as brain 5-HT transporter ligands, and to examine their characteristics.

Materials and methods

Subjects

Twenty-one healthy male volunteers (age 19–34 years; mean±SD, 22.9±4.0 years) participated in this study. Fifteen subjects were included in the brain uptake study and six in the lung uptake study. All subjects were recruited from the university campus, were well screened, and had no history of present or past psychiatric, neurological or somatic disorders. They also had no alcohol- or drug-related problems. They had not taken any kind of medication for at least the 2 weeks prior to the start of the study. The study was approved by the ethics and radiation safety committees of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from each subject.

Radioligands

\[ ^{11}C\]cyanoimipramine was labelled with \[ ^{11}C\]CH\(_3\)I by N-demethylation reaction on N-desmethyl-cyanoimipramine (supplied by F Hoffman-La Roche Ltd., Basel, Switzerland) [13]. The radiochemical purity was higher than 95% and the specific radioactivity was more than 37 TBq/mmol at the time of injection. \[ ^{11}C\]cyanoimipramine was injected intravenously at a dose of 179–759 MBq (mean±SD, 581±200 MBq).

PET study

Brain uptake study

Nine subjects took part in the \[ ^{11}C\](+)McN5652 study and six subjects in the \[ ^{11}C\]cyanoimipramine study. The brain PET scans were carried out with an ECAT 47 (CTI-Siemens, Knoxville, Tenn., USA) scanner, which provides 47 planes and a field of view of 16.2 cm. A head fixation device with an individual mouthpiece was used during the brain scans (Fixster Instruments, Stockholm, Sweden). A 10-min transmission scan was performed to correct for attenuation. Dynamic PET scans with \[ ^{11}C\]cyanoimipramine were carried out for 90 min (2 min \(\times\)15, 4 min \(\times\)5, 8 min \(\times\)5) in 2D mode. Because of the limited availability of technical staff, arterial blood samples were taken only from three of the nine subjects in the \[ ^{11}C\](+)McN5652 study.

Pretreatment with the 5-HT reuptake inhibitor clomipramine. Three of the nine subjects with \[ ^{11}C\](+)McN5652 and three of the six subjects with \[ ^{11}C\]cyanoimipramine were studied again after the administration of the potent 5-HT transporter inhibitor clomipramine. Each subject was orally administered 50 mg of clomipramine 5 h before the PET scan, as the peak plasma level has been reported to occur 2–4 h after a single oral dose [21].

Brain uptake study with arterial blood sampling. Three of the nine subjects with \[ ^{11}C\](+)McN5652 underwent serial arterial blood sampling. Arterial blood samples were taken ten times during the initial 3 min after tracer injection, then eight times during the next 17 min, and then once every 10 min until the end of the scan. Metabolite analysis was carried out at ten time points during the scans. The subjects then underwent second scans 5 h after being pretreated with 10 mg, 25 mg or 50 mg of clomipramine, again with arterial blood sampling.

Metabolite analysis. The supernatant obtained by centrifuging the plasma fraction with acetonitrile was analysed by radio-HPLC analysis (column, µBondapak C18; mobile phase, 50/50 acetonitrile/0.1 M ammonium formate).

Data analysis of the brain uptake study. Brain scans were reconstructed with a Ramp filter cut-off frequency of 0.5. The full-width at half-maximum (FWHM) in the transaxial direction was 6.0 mm at the centre and 6.7 mm at 10 cm offset from the centre, which was determined with a line source. With reference to a brain atlas and individual magnetic resonance imaging, circular (10 mm diameter) regions of interests (ROIs) were drawn manually on transverse slices of summed images in the following areas: cerebellum, striatum, frontal cortex and thalamus. The whole brain volume of interest was drawn manually on all 47 slices including the cerebellum and cerebrum. Regional radioactivity was normalised to 370 MBq. The whole brain uptake was expressed as the average radioactivity (kBq/ml) multiplied by the whole brain volume of interest. The average radioactivity of the whole brain uptake was compared between \[ ^{11}C\]cyanoimipramine using the areas under the time activity curves from 0 to 90 min.

The distribution volumes of the cerebellum, frontal cortex, thalamus and striatum were calculated using metabolite-corrected arterial plasma data [22]. Kinetic analysis was performed based on the two-compartment model. The two-compartment configuration consisted of the metabolite-corrected arterial plasma compartment \(C_d\) and one tissue compartment \(C_t\) that included the ligand free and non-specifically bound and specifically bound compartments. The distribution volume \(D\) (ml of plasma/g of tissue) was defined as the ratio of the unidirectional forward rate constant \(K_1\) (ml g\(^{-1}\) min\(^{-1}\)) and backward rate constant \(k_2\) (min\(^{-1}\)) between \(C_d\) and \(C_t\):

\[
D = \frac{K_1}{k_2}
\]

The percent changes of distribution volumes were calculated as follows:

\[
\%\text{change} = 100 \times \frac{(D_{V_d} - D_{V_c})}{D_{V_c}}
\]

where \(D_{V_d}\) is the distribution volume with clomipramine and \(D_{V_c}\) the distribution volume without clomipramine.

Lung uptake study

Three subjects each took part in the \[ ^{11}C\](+)McN5652 study and the \[ ^{11}C\]cyanoimipramine study. PET scans for the lung were carried out with an ECAT 47 scanner, except for one \[ ^{11}C\](+)McN5652 lung scan done with an ECAT EXACT HR+ (CTI-Sie-