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Measurement of dopamine D_2 receptors in living human brain using [^{11}C] raclopride with ultra-high specific radioactivity

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Abstract

Introduction: High specific radioactivity is preferable in the measurement of neuroreceptor bindings with positron emission tomography (PET) because receptor occupancy by mixed cold ligand hampers the accurate estimation of receptor binding. Recently, we succeeded in synthesizing [^{11}C]raclopride, a dopamine D_2 receptor ligand, with ultra-high specific radioactivity, i.e., several thousand GBq/μmol. In the present study, we compared the [^{11}C]raclopride bindings to dopamine D_2 receptors between radioligands with ultra-high specific radioactivity and ordinary high specific radioactivity in healthy human subjects.

Methods: Two PET studies using [^{11}C]raclopride with ultra-high specific radioactivity (4302–7222 GBq/μmol) or ordinary high specific radioactivity (133-280 GBq/μmol) were performed on different days in 14 healthy men. Binding potential (BP) was calculated by the simplified reference tissue method, peak equilibrium method, and area-under-the-curve method for each region-of-interest using time-activity data in the cerebellum as a reference brain region.

Results: BP values for radioligands with ultra-high specific radioactivity and ordinary high specific radioactivity calculated by the simplified reference tissue method were 4.06±0.29 and 4.10±0.25 in the putamen, 0.44±0.07 and 0.47±0.07 in the thalamus and 0.37±0.06 and 0.38±0.06 in the temporal cortex, respectively (mean±S.D.). No significant difference in BP was observed between ultra-high specific radioactivity and ordinary high specific radioactivity in any of the brain regions.

Conclusion: BP values of [^{11}C]raclopride with ultra-high specific radioactivity did not differ from those with ordinary high specific radioactivity in the measured brain regions, including striatal and extrastriatal regions.

Keywords: [^{11}C]raclopride; Ultra-high specific radioactivity; Dopamine D_2 receptor; Binding potential; Positron emission tomography

1. Introduction

[^{11}C]Raclopride, a substituted benzamide, is a ligand for visualization and quantification of dopamine D_2 receptors by positron emission tomography (PET) [1]. Using [^{11}C]raclopride, dopamine D_2 receptors have been studied in relation to the pathophysiology of several neuropsychiatric disorders [2–8]. [^{11}C]Raclopride can be applied to estimate the binding to receptor-rich regions such as the striatum, but the binding in extrastriatal regions with low density of D_2 receptors is too low for accurate quantification. On the other hand, [^{11}C] raclopride can be used to measure striatal endogenous dopamine release due to its low affinity to receptors. A decrease in binding of [^{11}C]raclopride was observed when endogenous dopamine release was increased by D-amphetamine [9,10]. The development of radioligands with higher affinity to dopamine D_2 receptors, such as [^{11}C]FLB457, have enabled us to measure the extrastriatal D_2 bindings [11–14]. However, these radioligands have difficulties when they are used to measure small differences of endogenous dopamine release in these regions because they have high affinity to receptors [15].

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The carrier mixed with the radioligand binds to receptors competitively, hampering the measurement of receptor binding, and especially in brain regions with a low density of receptors. Thus, the radioligand with extremely high specific radioactivity might enable us to measure receptor binding in brain regions with a low density of receptors. We recently developed an automatic synthesis system for preparing [^{11}C]ligands with extremely high specific activity (SA) [16]. Using this system, we have succeeded in synthesizing [^{11}C]raclopride with extremely high specific radioactivity, i.e., several thousand GBq/μmol [16,17]. Applying this radioligand, we succeeded in detecting two-affinity binding sites of [^{11}C]raclopride not only in the striatum, but also in the cerebral cortex of rat brain [18]. We assumed that this radioligand might also allow us to measure the dopamine D_2 receptor binding in extrastriatal regions with higher signal and to increase the detectability of endogenous dopamine release in extrastriatal regions. In this study, we investigated the effect of ultra-high specific radioactivity on [^{11}C]raclopride in living human brain.

2. Materials and methods

2.1. Subjects

Fourteen healthy male volunteers (age 21–33 years; mean±S.D., 25.7±3.29 years) participated in this study. The subjects were free of somatic, neurological and psychiatric disorders on the basis of their medical history and magnetic resonance (MR) imaging of the brain. All volunteers had no history of current or previous drug abuse. This 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 all subjects.

2.2. PET procedure

All participants underwent two [^{11}C]raclopride PET studies – one with ordinary high specific radioactivity (ordinary high SA) and the other with ultra-high SA. The two studies were performed on different days within a two-week period. The studies were performed first with ordinary high SA and then with ultra-high SA in seven subjects, and in reverse order in the other seven subjects. The radiochemical purity of all [^{11}C]raclopride used was higher than 95%. Specific radioactivity of ordinary high SA was from 133 to 280 (mean±S.D., 216±65) GBq/μmol, and that of ultra-high SA was from 4302 to 7222 (mean±S.D., 5514±997) GBq/μmol at the time of injection. The injected doses of [^{11}C]raclopride with ordinary and ultra-high SA were 195–247 MBq (mean±S.D., 227±13), and 192–242 MBq (218±15), respectively.

The PET scans were carried out using Siemens ECAT EXACT HR+ (Siemens, Knoxville, TN, USA) in three-dimensional (3D) mode, which provides 63 planes and a 15.5-cm field of view. To minimize head movement during each scan, a head fixation device with an individual mouthpiece was used during the scans (Fixster Instruments, Stockholm, Sweden). A 10-min transmission scan was performed with a ^{68}Ge-^{68}Ga source to correct for attenuation. Radioactivity in the brain was measured by 43 series of frames for 90 min starting immediately after the intravenous injection of [^{11}C]raclopride. All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (full-width half-maximum=7.5 mm).

2.3. MR imaging study

T1-weighted MR images of the brain were obtained in all subjects using Phillips Intera, 1.5 Tesla (Philips Medical Systems, Best, The Netherlands). The scan parameters were 1 mm thick, 3D, T1 images with a transverse plane (repetition time/echo time 21/9.2 ms, flip angle 30°, matrix 256×256, field of view 256×256 mm).

2.4. Data analysis

The MR images were coregistered to the summated PET images using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Polygonal volumes-of-interests (VOIs) were defined manually on the coregistered MR images to cover 3 adjacent slices for the caudate nucleus, putamen, thalamus, frontal cortex, temporal cortex, occipital cortex, parietal cortex, anterior part of cingulate gyrus, pons, parahippocampal gyrus, and cerebellar cortex. The regional radioactivity of each brain region was obtained for these VOIs. Binding to receptors was estimated from time-activity curves of each region using a simplified reference tissue method (SRTM), peak equilibrium method and area under the curve (AUC) method. For each method, the cerebellum was used as a reference brain region with no specific binding.

2.5. Calculation of binding potential

2.5.1. SRTM

The binding to dopamine D_2 receptors was estimated by the three-parameter simplified reference tissue model [19]. The cerebellum was used as a reference brain region because it has been shown to be almost devoid of D_2 receptors [14,20]. This model provides an estimation of the binding potential (BP), which is defined by the following equation:

$$BP = k_3 / k_4 = f_2 B_{max} / \{K_d[1 + \Sigma_i F_i / K_{di}]\},$$

where k_3 and k_4 describe the bidirectional exchange of tracer between the free compartment and the compartment representing specific binding, f_2 is the "free fraction" of nonspecifically bound radioligand in brain, B_{max} is the receptor density, K_d is the equilibrium dissociation constant for the radioligand [21] and F_i and K_{di} are the free concentration and the dissociation constant of