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An alternative synthesis of [^{11}C]raclopride for routine use

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The standard method of [^{11}C]raclopride synthesis requires a large amount of its desmethyl precursor. We prepared [^{11}C]raclopride by methylation of a small amount of desmethyl derivative (0.3–0.5 mg) with [^{11}C]methyl iodide in a DMF solution containing NaH, with a decay-corrected radiochemical yield of 11–14% based on [^{11}C]methyl iodide and with a specific activity of 48 TBq/mmol for 25 min from EOB. The reaction was reproducible and reliable.

Key words: [^{11}C]raclopride, dopamine D_2 receptor, PET

INTRODUCTION

[^{11}C]Raclopride is a standard ligand for investigating dopamine D_2 receptors by positron emission tomography (PET) because of its high selectivity. For the radiosynthesis of [^{11}C]raclopride, *N*-ethylation of the *N*-desethyl derivative with [^{11}C]ethyl iodide was first reported by Ehrin et al.[1] Later another method was proposed using *O*-methylation of desmethyl precursor with [^{11}C]methyl iodide,[2,3] which has now become a standard method for [^{11}C]raclopride production and is used world-wide because of higher yield and shorter-time synthesis. Chemical and biological issues related to [^{11}C]raclopride have been reviewed in detail.[4,5]

The current method of [^{11}C]raclopride synthesis (at least in its original form), requires a far larger amount of the precursor (2.3–2.5 mg) than is used in most other types of ^{11}C-methylating radiosynthesis (usually 0.5–1 mg). This leads to a considerable amount of the precursor present as a concomitant with the [^{11}C]raclopride preparation, so when the amount of the precursor was decreased, so was the radiochemical yield (unpublished data in our laboratory).

In the present study we describe an alternative method for the production of [^{11}C]raclopride by *O*-methylation of the precursor with [^{11}C]methyl iodide in the presence of NaH. Under similar conditions, we successfully performed *O*-^{11}C-methylation of the hydroxy group of the benzene ring for preparing a sigma receptor ligand [^{11}C]NE-100.[6] With this new method, reaction was reproducible and reliable, the reaction time was slightly shortened, the amount of precursor was much smaller, and the radiochemical yield was not much worse than with the original method.

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MATERIALS AND METHODS

[^{11}C]CO_2 was prepared by proton irradiation of N_2 gas at 25 μA for 20 min, and was converted to [^{11}C]methyl iodide by means of the automated synthesis system.[7] The [^{11}C]methyl iodide was trapped in 0.25 mL of dimethylformamide (Aldrich, Milwaukee, WI, USA) solution containing 0.2–0.5 mg of desmethyl raclopride (NCQ 259, (*S*)-3,5-dichloro-2,6-dihydroxy-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]benzamide hydrobromide) and 1–5 mg NaH, which had been preheated to 80–120°C for 5–6 min. The solution was heated at 120°C for 1–3 min. After adding 1.3 m*l* of a mixture of CH_3CN and 5 mM H_3PO_4 (17.5/82.5, v/v), the reaction mixture was applied to HPLC separation. The column used was a YMC-pack ODS (20 mm i.d. × 150 mm length, YMC, Kyoto) with the mixture of CH_3CN and 10 mM H_3PO_4 (35/65) as a mobile phase at a flow rate of 15 m*l*/min. The [^{11}C]raclopride fraction (retention time: desmethyl raclopride, 4.0–4.5 min; and [^{11}C]raclopride, 6.5–7.0 min) was collected and evaporated to dryness. The residue was dissolved in physiological saline containing

Table 1 Radioactivity yield of [^{11}C]raclopride by *O*-methylation of desmethyl raclopride with [^{11}C]methyl iodide in the presence of NaH

Precursor/DMF (mg/m*l*)	*O*-Methylation		Radiochemical yield* (%)
	Temperature (°C)	Time (min)	
0.5/0.25	120	1	13.9 (15.5–12.2, n = 3)
0.4/0.20	120	1	11.3 (15.0–8.4, n = 3)
0.3/0.30	120	3	11.8 (12.0–11.6, n = 3)
0.2/0.20	120	1	6.7 (8.6–5.1, n = 4)
0.2/0.20	120	3	8.3 (11.7–6.2, n = 3)

*Decay-corrected, based on [^{11}C]methyl iodide (range, number of runs).

$NaHCO_3$ to adjust the pH to 7–8. The solution was sterilized by filtration through a 0.22 μm membrane. The radiochemical purity was analyzed by HPLC on a TSKgel super ODS column (4.6 mm i.d. × 50 mm length, Toso, Tokyo) with a mixture of CH_3CN and 10 mM H_3PO_4 (25/75) as the mobile phase at a flow rate of 1 m*l*/min. The retention times of the precursor and [^{11}C]raclopride were 2.1 min and 3.2 min, respectively.

RESULTS AND DISCUSSION

As shown in Table 1, [^{11}C]raclopride was prepared with a decay-corrected radiochemical yield of 11–14% based on [^{11}C]methyl iodide in the reaction with 0.3–0.5 mg of the precursor. A longer reaction time (3 min) for methylation did not essentially increase the yield. With the smallest amount of the precursor (0.2 mg) the yield slightly decreased, and a 3-min reaction time slightly increased the yield. The preparation time was approximately 25 min after the EOB and the mean specific activity was 48 TBq/mmol (range: 33–91 TBq/mmol, n = 16). At 10–20 min before the end of irradiation, we preheated the DMF containing precursor and NaH to 80°C or 120°C for 5–6 min to ensure deprotonation of the hydroxy group of the precursor. The DMF solution became pale yellow or pale blue, and a reproducible radiochemical yield was achieved, even if NaH was not freshly prepared. When the solution remained colorless, the radiochemical yield was low (< 5%). Although the radiochemical yield in the present method was not better that in the standard method, we reproducibly prepared up to 1.3 GBq of [^{11}C]raclopride after 20-min irradiation at 25 μA in our [^{11}C]methyl iodide production system.[7]

The radiochemical yields by the original method reported were 20–50% and approximately 40% based on [^{11}C]CO_2 and [^{11}C]CH_3I, respectively,[2,3,5] but we could not reproducibly prepare [^{11}C]raclopride by the original method. Furthermore, we confirmed that the radiochemical yield significantly decreased (8.3%, n = 3) when the amount of precursor was decreased (0.5 mg).

The amount of precursor used in the present study was much smaller than in the original method (2.3–2.5 mg/m*l* DMSO). Consequently, HPLC separation produced a [^{11}C]raclopride preparation with a much smaller amount (approximately 10% or less of raclopride) of the precursor without any device such as a back-flushed technique.[4] Although the precursor is known to be inactive in an *in vitro* dopamine D_2 receptor blocking assay,[5] minimizing the concomitant is always recommended to avoid any possible *in vivo* confounding effect.

The use of DMF instead of DMSO as a reaction solvent has another benefit. Because of the lower melting point (–61°C) of DMF, the DMF solution can be cooled to a sufficiently low temperature to efficiently trap [^{11}C]methyl iodide. In our synthesis system the trapping efficiency was 85–96% (n = 7) at –16– –20°C even to 0.2 m*l* of DMF solution. In the standard method with DMSO solution, with a melting point of 18.5°C, [^{11}C]methyl iodide is usually trapped at room temperature, which may have resulted in a lower trapping efficiency of [^{11}C]methyl iodide.

In conclusion, the *O*-methylation of desmethyl raclopride with [^{11}C]methyl iodide in a DMF solution containing NaH as base is a reliable alternative for routine [^{11}C]raclopride production.

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