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Research Article

An improved method for the radiosynthesis of [^{11}C]*d-threo*-methylphenidate

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Summary

An improved method to remove the 2-nitrophenylsulfenyl protecting group in the conventional radiosynthesis of the PET radiotracer [C-11]*d-threo*-methylphenidate was developed. The method uses the nonvolatile reagents sulfuric acid and L-cysteine. In addition it was demonstrated that solid phase extraction (SPE, C18 and ion exchange) can be used to purify the final product instead of semi-preparative HPLC. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: [C-11]methylphenidate; dopamine transporter; SPE purification

Introduction

Changes in the dopamine system are observed in a number of diseases such as Parkinson's disease, schizophrenia and substance abuse.[1] The conventional method for the radiosynthesis of a radiotracer for the dopamine transporter, [^{11}C]*d-threo*-methylphenidate ([^{11}C]MP),[2] producing adequate quantity and quality of the radiotracer, has been successfully used for over a decade. Our research was aimed at making the radiosynthesis safer for radiochemists, simpler, faster and more reliable. The original reference[2] and our research suggests that the synthesis of [^{11}C]MP by direct ^{11}C-iodomethylation of ritalinic acid is impractical. Alternative ^{11}C-methylation agents such as

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[^{11}C]methyl triflate[3] and [^{11}C]CH_3OH/BF_3-Et_2O[4] were also unsuccessfully tried.

The use of a *t*-Boc-protecting group-containing precursor and dilute aqueous HCl for deprotection was proven feasible but low yielding. However, substitution of HCl-diethyl ether with concentrated H_2SO_4 and mercaptoacetic acid with L-cysteine, while retaining the protecting 2-nitrophenylsulfenyl-(Nps) group, worked well and eliminated the disadvantages associated with the volatile reagents. To accelerate [^{11}C]MP purification, a previously developed[5] solid phase extraction (SPE) system utilizing two Sep-Paks was considered for the final product purification as an alternative to HPLC.

Experimental

Chemicals were purchased from Aldrich or Across. [^{11}C]CH_3I was produced using gas-phase method from in-target generated [^{11}C]CH_4. The final solution of radiotracer was filtered through sterile Acrodisc^{TM} filter (0.22 μm, 25 mm, Pall Corp.). [^{11}C]MP quality control was accomplished using Waters HPLC with Nova-Pak, C18, 5 μm, 150 × 4.6 mm column; 0.17 M ammonium formate – 30% acetonitrile eluent at 1.5 ml/min; UV 225 nm; t_R 2.5 min.

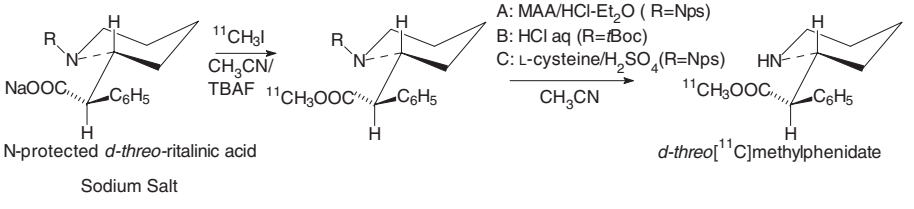

Figure 1. Radiosynthesis of [^{11}C]*d-threo*-methylphenidate; MAA-mercaptoacetic acid

[^{11}C]MP radiosynthesis[2]

[^{11}C]CH_3I in a stream of helium was bubbled through the cooled (aluminum cylinder, 5–10°C) solution of MP precursor [*d-threo-N*-(2-Nitrophenylsulfenyl) ritalinic acid sodium salt, 0.3 mg, 0.8 μmol, JML Biopharm, Vancouver, BC, Canada] and tetrabutylammonium fluoride (1.3 μmol) in anhydrous acetonitrile (0.4 ml). The mixture was heated (oil bath, 80°C, 5 min), and a solution of 5.5–8.5 mg (45–70 μmol) of L-cysteine and 17 μl (340 μmol) of concentrated sulfuric acid in 0.4 ml of acetonitrile was added via a remote addition line. After stirring at room temperature for 3 min, the reaction was quenched with 3 ml of saturated sodium tetraborate. The solution was loaded onto C18 Light Sep-Pak (Waters), and the cartridge was washed with water (4 ml) (Figure 1).

HPLC Method

[^{11}C]MP was eluted (methanol, 2 ml) from the Sep-Pak into the 2-ml injector loop. The product was purified by HPLC (Phenomenex, Partisil, 10 μm, 250 × 9.4 mm column; 0.17 M ammonium formate–25% acetonitrile eluent at 5 ml/min; UV 254 nm; t_R 10–12 min). Collected product fraction was rotary evaporated (60–70°C); ethanol (5 ml) was added and evaporated to remove traces of acetonitrile, and the radiotracer was reconstituted in saline (10 ml). The decay corrected radiochemical yield with respect to [^{11}C]CH_3I was 50 ± 15% ($n = 6$) 45 min after EOB; radiochemical purity was >99%; and EOS specific radioactivity, 8 ± 5 ($n = 6$) Ci/μmol.

SPE Method

The solution of product, eluted from C18 Sep-Pak with ethanol (2 ml), was mixed with water (20 ml) and passed through Waters CM Sep-Pak. After the cartridge was washed with water (2 × 5 ml), [^{11}C]MP was eluted with saline (10 ml). The decay corrected radiochemical yield with respect to [^{11}C]CH_3I was 45 ± 15% ($n = 4$) after 45 min of radiosynthesis; radiochemical purity was >99%, and EOS specific radioactivity was 1.8 ± 0.5 ($n = 4$) Ci/μmol.

Results and discussion

Although ritalinic acid has two potential sites for ^{11}C-methylation, it has been shown that chemoselective ^{11}C-methylation can, in principle, be achieved by changing the reaction solvent or ^{11}C-methylating agent.[4,6–8] In our case, however, no formation of [^{11}C]MP was observed in the reaction of ritalinic acid with carbon-11- methyl iodide, methyl triflate and CH_3OH/BF_3-Et_2O. In the conventional radiosynthesis a mixture of HCl-diethyl ether and mercaptoacetic acids is required for deprotection of the Nps- group;[2] both reagents are volatile irritants, and HCl-diethyl ether is unstable upon storage. The use of *t*-Boc as a protecting group in the radiosynthesis of [^{11}C]MP afforded the use of a milder deprotection system (1 M aqueous HCl). However, this resulted in a 30% lower radiochemical yield compared to the original radiosynthesis.

Another proposed improvement to the radiosynthesis was the development of a better method to remove the Nps-protecting group in the conventional radiosynthesis. These attempts have proven successful; a new deprotection system using a solution of nonvolatile L-cysteine and sulfuric acids in acetonitrile avoids the disadvantages associated with HCl-diethyl ether/ mercaproacetic acid without sacrificing radiochemical yield.

Due to the unlikely formation of *l-erythro*-[^{11}C]MP, the final product can be purified using the Sep-Pak method;[5] completion of QC, however, would be required prior to administration. Meanwhile, preparative HPLC indicates, in

the course of the radiosynthesis, whether significant amount of *l-erythro*-[^{11}C]MP is formed and separates these two diastereomers. Another disadvantage of the Sep-Pak radiosynthesis is a requirement for a dedicated setup as opposed to the use of universally applicable radioHPLC with multi- column/eluent selectors. An initial believe in a shorter time of Sep-Pak radiosynthesis was deceptive, especially considering the added time for QC release.

Conclusions

Use of the L-cysteine/H_2SO_4 deprotection system with the conventional radiosynthesis proved to be advantageous compared to the mercaptoacetic acid/HCl-diethyl ether method. Our other experiments showed that a one-step conversion of ritalinic acid into [^{11}C]methylphenidate is not practical, while the search for an alternative protective group to the currently used Nps-group is nontrivial.

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