ELSEVIER

Journal of Fluorine Chemistry 115 (2002) 33–39

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

The effect of aromatic fluorine substitution in L-DOPA on the in vivo behaviour of [^{18}F]2-, [^{18}F]5- and [^{18}F]6-fluoro-L-DOPA in the human brain☆

Raman Chirakal[a,b,*], Neil Vasdev[a], Marie-Claude Asselin[c], Gary J. Schrobilgen[a], Claude Nahmias[b,*]

[a]*Department of Chemistry, McMaster University, Hamilton, Ont., Canada L8S 4M1*
[b]*Department of Radiology, Faculty of Health Sciences, 1200 Main St. West, Hamilton, Ont., Canada L8N 3Z5*
[c]*Department of Physics and Astronomy, McMaster University, Hamilton, Ont., Canada L8S 4M1*

Received 12 December 2001; accepted 7 January 2002

Abstract

Remarkable differences in the human in vivo behaviour of each of the three [^{18}F]-labelled ring fluorinated isomers of L-dihydroxyphenylalanine (L-DOPA) are presented. Unlike [^{18}F]2-fluoro-L-DOPA, which did not appear to cross the blood brain barrier, [^{18}F]5-fluoro-L-DOPA appears to be taken up and cleared from the cerebellum and the striata. In contrast with the 2- and 5-fluoro isomers of L-DOPA, radioactivity derived after injection of [^{18}F]6-fluoro-L-DOPA is specifically retained in the striata. The present study is the first direct comparison of the time course and distribution of radioactivity in the human brain after intravenous injections of [^{18}F]2-, [^{18}F]5- and [^{18}F]6-fluoro-L-DOPA.

Keywords: L-DOPA; Fluoro-L-DOPA; ^{18}F; Brain uptake; Positron emission tomography

1. Introduction

Medical applications of selectively fluorinated biomolecules have a long and successful history in medicinal chemistry [1–3]. However, several physico-chemical properties are affected, and changes in biological activity occur when fluorine is the substituent in a bioactive compound [4]. Kirk [5] has reviewed the pharmacological effects of several selectively ring fluorinated catecholamines and shown that different orientations of aromatic fluorine substitution can display dramatic differences in pharmacological properties from each other and their non-fluorinated derivatives. This remarkable and unexpected phenomenon, which is dependent on the site of the fluorine substituent, has been termed the *fluorine effect* [6,7].

It is known that the clinical features of Parkinson's disease, muscular rigidity, bradykinesia and rest tremor, are associated with marked deficiencies of striatal dopamine [8]. These observations, corroborated many times by means of autopsy examinations [9], have led to the use of L-3,4-dihydroxyphenylalanine (L-DOPA), the metabolic precursor of dopamine, to alleviate the symptoms of Parkinson's disease [10]. A proposal that ^{18}F-(97% β^+, E_{max} = 0.635 MeV, $t_{1/2}$ = 109.7 min) labelled DOPA might be a specific tracer for intracerebral dopamine inspired the synthesis of [^{18}F]5-fluoro-DL-DOPA [11]. Following an intravenous injection of [^{18}F]5-fluoro-DL-DOPA in a monkey, Garnett et al. [12] used simple γ-ray detectors to monitor ^{18}F-activity. These authors used a three-compartment explanatory model to derive fractional rate constants for the forward and backward transport of L-DOPA across the blood–brain barrier, and for the formation and degradation of neuronal dopamine. It was concluded that this technique could be extended to man and used to investigate the role of DOPA and dopamine in the control of mood and locomotion [12]. The lack of an efficient synthesis of [^{18}F]5-fluoro-L-DOPA had prevented it from being studied in the human brain.

Subsequently, Garnett et al. [13] pioneered the use of [^{18}F]6-fluoro-L-DOPA, in conjunction with positron emission tomography (PET), to visualize the regional distribution of

☆ This work was presented in part at the 14th International Symposium on Radiopharmaceutical Chemistry, 10–15 June 2001, Interlaken, Switzerland.

* Corresponding authors. Tel.: +1-905-521-2100x76893; fax: +1-905-546-1125.
E-mail addresses: chiraklr@mcmaster.ca (R. Chirakal), nahmias@mcmaster.ca (C. Nahmias).

0022-1139/02/$ – see front matter
PII: S0022-1139(02)00025-8

intracerebral dopamine in the living human brain. Fluorine-18 labelled 6-fluoro-L-DOPA was further used to show that the accumulation of ^{18}F was reduced in the contralateral putamen of patients suffering from hemiparkinsonism [14]. These findings were the first demonstration of a disturbance of intrastriatal dopamine metabolism in patients suffering from Parkinson's disease. Although the in vivo metabolism of [^{18}F]6-fluoro-L-DOPA in the human brain is known [15,16], the metabolic fate of 2- and 5-fluoro-DOPA in the human brain has not been reported.

The fate of [^{18}F]5-fluoro-L-DOPA in the human brain is not known because low yielding Balz-Schiemann reactions were the only methods described for its synthesis [11,17]. Recently, we have reported a reliable method for the production of MBq quantities of [^{18}F]5-fluoro-L-DOPA by the direct fluorination of L-DOPA with [^{18}F]F_2 [18]. We have described the syntheses of [^{18}F]2- and [^{18}F]6-fluoro-L-DOPA in earlier work [19]. We presently report a comparative study of the time course and distribution of radioactivity in the human brain after [^{18}F]2-, [^{18}F]5- and [^{18}F]6-fluoro-L-DOPA have been injected.

2. Results and discussion

The distributions of [^{18}F]2-, [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA in a transaxial plane at the level of the striata in subject 1 from 60 to 120 min after injection are shown in Fig. 1. There is large accumulation of [^{18}F]6-fluoro-dopamine in the striata, whereas, there is a very small accumulation of radioactivity in the grey matter and basal ganglia following injection of [^{18}F]2- and [^{18}F]5-fluoro-L-DOPA. The time courses of [^{18}F]2-, [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA for subject 1 are shown in Fig. 2. The striatal influx constant (K_i), using a cerebellar input function, was determined to be $0.0027 \pm 0.0026\ min^{-1}$ for [^{18}F]2-fluoro-L-DOPA, $0.0035 \pm 0.0019\ min^{-1}$ for [^{18}F]5-fluoro-L-DOPA and $0.0106 \pm 0.0019\ min^{-1}$ for [^{18}F]6-fluoro-L-DOPA (note the large uncertainty on the K_i value for [^{18}F]2-fluoro-L-DOPA). The very low uptake, if any, of [^{18}F]2-fluoro-dopamine in the brain confirms a previous report that cerebral dopaminergic structures do not accumulate ^{18}F following injection of [^{18}F]2-fluoro-L-DOPA [20]. The distribution and K_i values obtained with [^{18}F]5-fluoro-L-DOPA ($0.0030 \pm 0.0007\ min^{-1}$) and [^{18}F]6-fluoro-L-DOPA ($0.0090 \pm 0.0005\ min^{-1}$) for subject 2 were similar to those for subject 1.

There are marked differences in the distribution and kinetics of the three ring fluorinated isomers of L-DOPA. For example, [^{18}F]2-fluoro-L-DOPA does not appear to cross the blood–brain barrier. In contrast, [^{18}F]5-fluoro-L-DOPA appears to be taken up and cleared from both the cerebellum and striatum as indicated by the shape of the time-activity curves. Fluorine-18 labelled 6-fluoro-L-DOPA clearly enters the brain and shows that ^{18}F preferentially accumulated in the striata. The *fluorine effect* seen in our study is similar to that seen in a previous study [21], which showed that the substitution of fluorine for hydrogen at positions 2, 5 or 6 on the aromatic ring of norepinephrine (NE) dramatically alters the specificity of these analogues to their respective receptors. The 2-fluoro-isomer of NE is a β-adrenergic agonist with little α-activity, 6-fluoro-NE is an α-agonist with little β-agonist activity, whereas, 5-fluoro-NE displays both α- and β-adrenergic activity comparable to endogenous NE.

The distribution of [^{18}F]2- and [^{18}F]6-fluoro-L-DOPA has been studied in the carbidopa-pretreated male hooded rat [22]. These authors showed that [^{18}F]2-fluoro-L-DOPA is not decarboxylated by the enzyme aromatic amino acid decarboxylase (AADC, EC 4.1.1.26) in the rat striatum and is rapidly *O*-methylated by the enzyme catechol-*O*-methyltransferase (COMT, EC 2.1.1.6). Although this study compared the metabolism of [^{18}F]2- and [^{18}F]6-fluoro-L-DOPA,

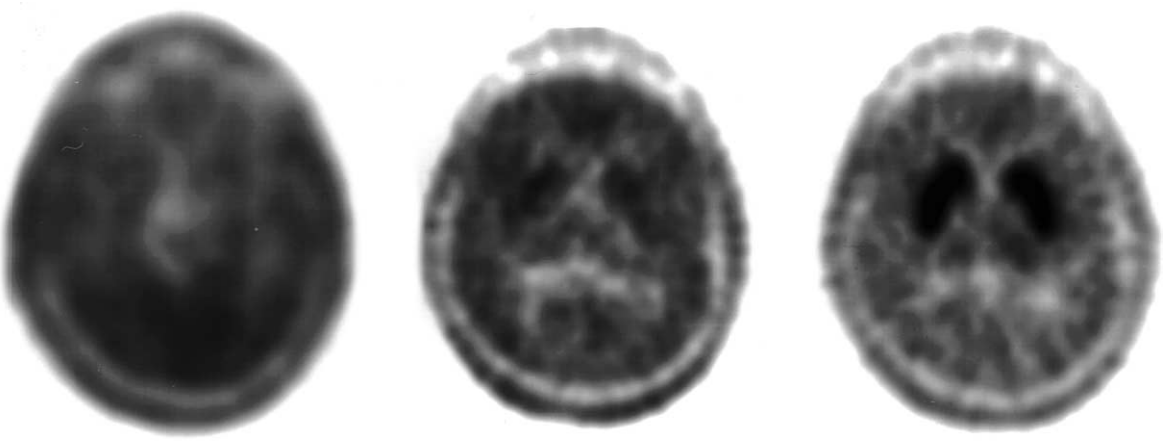

Fig. 1. Distribution of [^{18}F]2-fluoro-L-DOPA (left), [^{18}F]5-fluoro-L-DOPA (middle), and [^{18}F]6-fluoro-L-DOPA (right) in subject 1, 60–120 min after intravenous injection of the tracer. The transaxial section, at the level of the basal ganglia, is at the same level in all three studies. The images have been normalized to each other. Note the intense retention of radioactivity in the striata (darkest regions) following administration of [^{18}F]6-fluoro-L-DOPA.

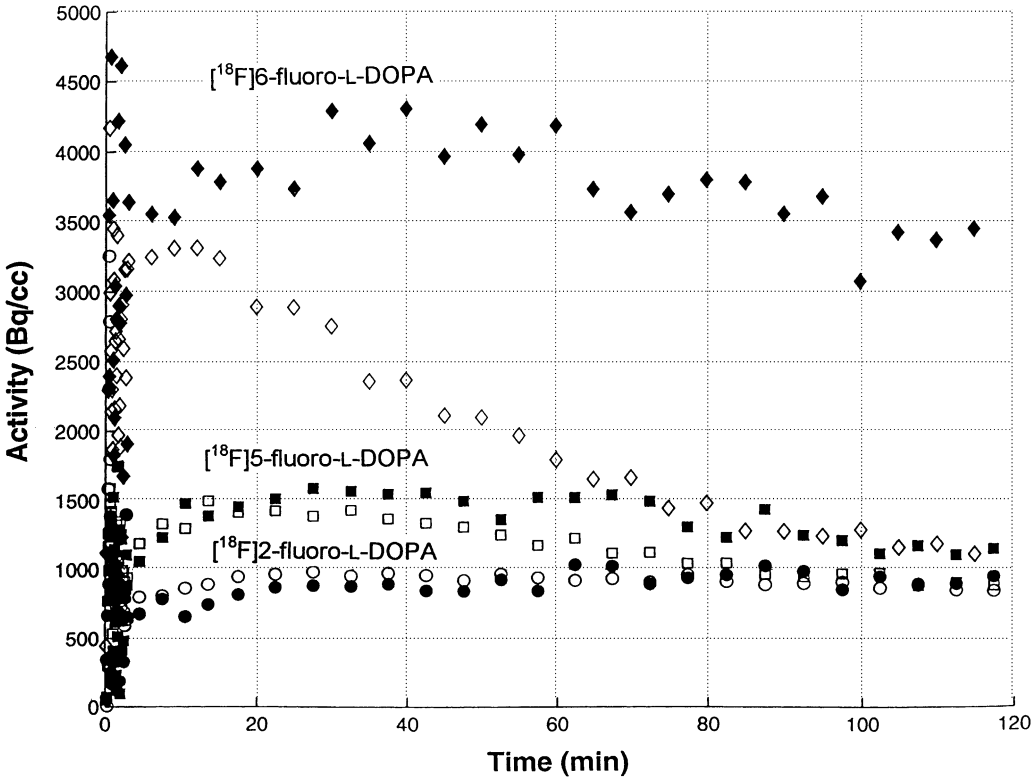

Fig. 2. Time course of radioactivity in the striata (solid symbols) and the cerebellum (open symbols) after an intravenous injection of [^{18}F]2-fluoro-L-DOPA (circles), [^{18}F]5-fluoro-L-DOPA (squares), and [^{18}F]6-fluoro-L-DOPA (diamonds).

these authors did not evaluate the metabolic fate of the 5-fluoro isomer of L-DOPA. Several studies involving 5-fluoro-DOPA have been conducted using racemic mixtures of DL-DOPA, both in vitro [23–25] and in vivo [12,26,27]. Oldendorf [28] has shown that D-DOPA does not cross the blood–brain barrier and in our laboratory, we did not observe uptake of ^{18}F in the striatum when a normal subject was injected with [^{18}F]6-fluoro-D-DOPA [29]. Therefore, evaluations of previous studies using 2-fluoro-DL-DOPA and 5-fluoro-DL-DOPA are further complicated by the presence of D-enantiomers. To our knowledge, only three studies, all of which have been in vitro metabolic studies [30–32], have been reported evaluating [^{18}F]5-fluoro-L-DOPA. Wiese et al. [25,31] have shown that 5- and 6-fluoro-DOPA enantiomers reproducibly undergo *O*-methylation and that COMT inhibitors may prove to be effective for PET application with 5- and 6-fluoro-L-DOPA [32]. Although, these authors compared the metabolism of 5- and 6-fluoro-L-DOPA, the metabolism of the 2-fluoro isomer of L-DOPA was not considered in their studies.

Cross-species determinations of enzymatic activities in [^{18}F]6-fluoro-L-DOPA-PET studies are often equivocal because in vitro determinations obtained from animal models and humans are substantially different [16,33]. Furthermore, a study comparing the 5- and 6-fluoro isomers of DOPA also stated that cerebral metabolism cannot be exclusively elucidated by in vitro enzyme assays [31]. Several factors are involved in human in vivo studies that play a major role in understanding the biological imaging of the dopaminergic pathway using [^{18}F]-fluoro-L-DOPA [16,34]. In addition to transport across the blood–brain barrier, the central availability of fluoro-L-DOPA is affected by peripheral metabolism. The enzymatic reaction rates are dependent upon the availability of the substrate and their affinities for AADC and COMT. The accumulation of fluorodopamine in the striata is further dependent upon its ability to be stored in vesicles within the nigrostriatial neurons, and its later release along with endogenous dopamine [35].

Compared with L-DOPA, 2-fluoro-DOPA has a higher affinity for COMT [24] and a substantially lower affinity for AADC [22]. This suggests that 2-fluoro-L-DOPA is rapidly *O*-methylated (at position 3) in the periphery, thereby depleting the supply of 2-fluoro-L-DOPA to the brain. If present in the brain, [^{18}F]2-fluoro-L-DOPA would be further *O*-methylated, leaving even smaller amounts available for enzymatic decarboxylation to [^{18}F]2-fluoro-dopamine. To our knowledge, no investigation has been carried out to determine if 2-fluoro-dopamine can be stored within the vesicles of the dopaminergic neurons. Alternatively, the very low uptake of [^{18}F]2-fluoro-L-DOPA in the brain could also be attributed to its relatively poor transport across the blood–brain barrier [22].

In contrast with 2-fluoro-DOPA, it has been shown that 5-fluoro-DOPA is comparable with L-DOPA as a substrate for AADC [23], and 5-fluoro-L-DOPA crosses the blood–brain barrier to an extent that is similar to that of L-DOPA [12].

Interestingly, no evidence for substantial retention of 5-fluoro-dopamine in the striatum was obtained in our study. The affinity of 5-fluoro-DOPA for COMT was determined to be higher than L-DOPA and comparable with that of 2-fluoro-DOPA [24]. The increased phenolic ionization produced by fluorine at the 5-position on the aromatic ring of DOPA which, similar to 2-fluoro-DOPA, is situated *ortho* to an activating hydroxyl group, likely promotes the formation of 4-*O*-methylated derivative [30]. The influence of fluorine substitution on the site of enzymatic *O*-methylation when fluorine is situated *ortho* to one of the phenolic groups has also been noted for NE [36]. The relatively high affinity of COMT towards [^{18}F]2- and [^{18}F]5-fluoro-L-DOPA compared with L-DOPA and [^{18}F]6-fluoro-L-DOPA [37] compromises their utility as PET tracers. The use of a COMT inhibitor may reveal specific uptake of [^{18}F]5-fluoro-dopamine in the striata, because 5-fluoro-DOPA was shown to have an affinity towards AADC comparable with that of L-DOPA [23].

The role of COMT cannot be solely responsible for the *fluorine effect* when tracing in vivo dopaminergic function with ring fluorinated isomers of L-DOPA. For example, DeJesus and Mukherjee [38] have proposed ^{18}F-labelled derivatives of L-*meta*-tyrosine (F*m*T) as useful tracers for the study of intracerebral dopamine metabolism. Because the peripheral metabolism of F*m*T is simpler than that of [^{18}F]6-fluoro-L-DOPA, [^{18}F]6-F*m*T has been proposed as a superior agent with which to study intracerebral metabolism in health and disease in humans [39]. Unlike [^{18}F]6-fluoro-DOPA, F*m*T are not substrates for COMT since they lack the necessary enediol moiety [40], but are substrates for AADC [41]. It has since been shown that the site of ring fluorination on L-*meta*-tyrosine alters its biological properties, i.e. [^{18}F]6-F*m*T is superior for the assessment of dopamine metabolism in the brain using PET, when compared with [^{18}F]2-F*m*T [42] and [^{18}F]4-F*m*T [43].

3. Concluding remarks

In the present study, the time course and distribution of [^{18}F]2-, [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA in the human brain are presented. Only [^{18}F]6-fluoro-dopamine shows specific accumulation in the striata, making [^{18}F]6-fluoro-L-DOPA the only useful ring-fluorinated isomer of L-DOPA for the study of the dopaminergic pathway. This study illustrates the importance of isomeric and radiochemical purities in radiopharmaceutical design.

4. Experimental

4.1. General experimental procedures

Caution: Work with anhydrous HF is potentially hazardous. Skin contact with even small amounts of HF can result in painful burns if not properly treated. Before beginning work with HF, first aid-treatment procedures [44–46] should be available and known to all laboratory personnel. Any incident involving direct contact with anhydrous HF or its aqueous solutions, the inhalation of HF gas or eye/skin exposures to HF gas must be immediately treated and brought to the attention of qualified medical personnel for appropriate follow-up treatment.

4.1.1. Materials

Enriched [^{18}O]O_2 (^{18}O, 95.87 at.%, Eurisotop, Saint Aubin, France), neon (99.999%), anhydrous hydrogen fluoride (Air Products), 1% F_2 in neon (Canadian Liquid Air), boron trifluoride, helium (99.9999%, Matheson), potassium dihydrogenphosphate (Aldrich), β-3,4-dihydroxyphenyl-L-alanine (Sigma), 3, 4-dihydroxyphenyl-acetic acid (Sigma), glacial acetic acid (British Drug Houses), potassium acetate (British Drug Houses), formic acid (British Drug Houses), trifluoroacetic acid (Caledon) and HPLC grade acetonitrile (Caledon) were used without further purification.

4.1.2. Syntheses of [^{18}F]2-, [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA

Fluorine-18 labelled F_2 was produced by the ^{18}O(p,n)^{18}F nuclear reaction using a Siemens RDS 112 proton–cyclotron operating at 11 MeV and the ''double shoot'' method [47,48]. Detailed reports on the synthesis and characterization of ^{18}F-labelled 2-, 5- and 6-fluoro-L-DOPA have been published elsewhere [18,19].

4.1.3. Separation and purification of [^{18}F]2-, [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA

After fluorination of L-DOPA with [^{18}F]F_2 in a suitable solvent, [^{18}F]fluoro-L-DOPA was separated from the reaction mixture using a reverse-phase HPLC column (Phenomenex M9 Partisil 10/50 ODS-3) and an aqueous solution of 0.02 M KH_2PO_4 (pH adjusted to 3.0–3.5 with 85% H_3PO_4) containing 5% CH_3CN as the mobile phase, and was eluted at 3.5 ml min^{-1}. The column eluate was monitored using a UV detector (280 nm) and a Geiger-Müller counter (Bicron SWGM B980C) coupled to a rate meter (Bicron Frik-Tech™). HPLC analysis of the reaction mixture gave one broad UV peak having the same retention time as L-DOPA (14 min). The radiochromatograms of all samples showed two major radioactive peaks having retention times between 14 and 17 min. Their identification has been described before [18]. The radiochemical yield of [^{18}F]fluoro-L-DOPA was determined as the ratio of ^{18}F activity in the peaks eluting at 14–17 min to the ^{18}F activity in the reaction vessel. The radioactive peaks were collected and evaporated to dryness. The dry residue was redissolved in 0.5 ml of water and the process was repeated two more times prior to further purification. This was accomplished using a second reverse phase HPLC column (Vydac C_{18}, 0.9 cm × 25 cm) with 0.1% acetic acid in water as the mobile phase and an elution rate of 2.5 ml min^{-1}. The radioactive peak eluting at 12–13 min

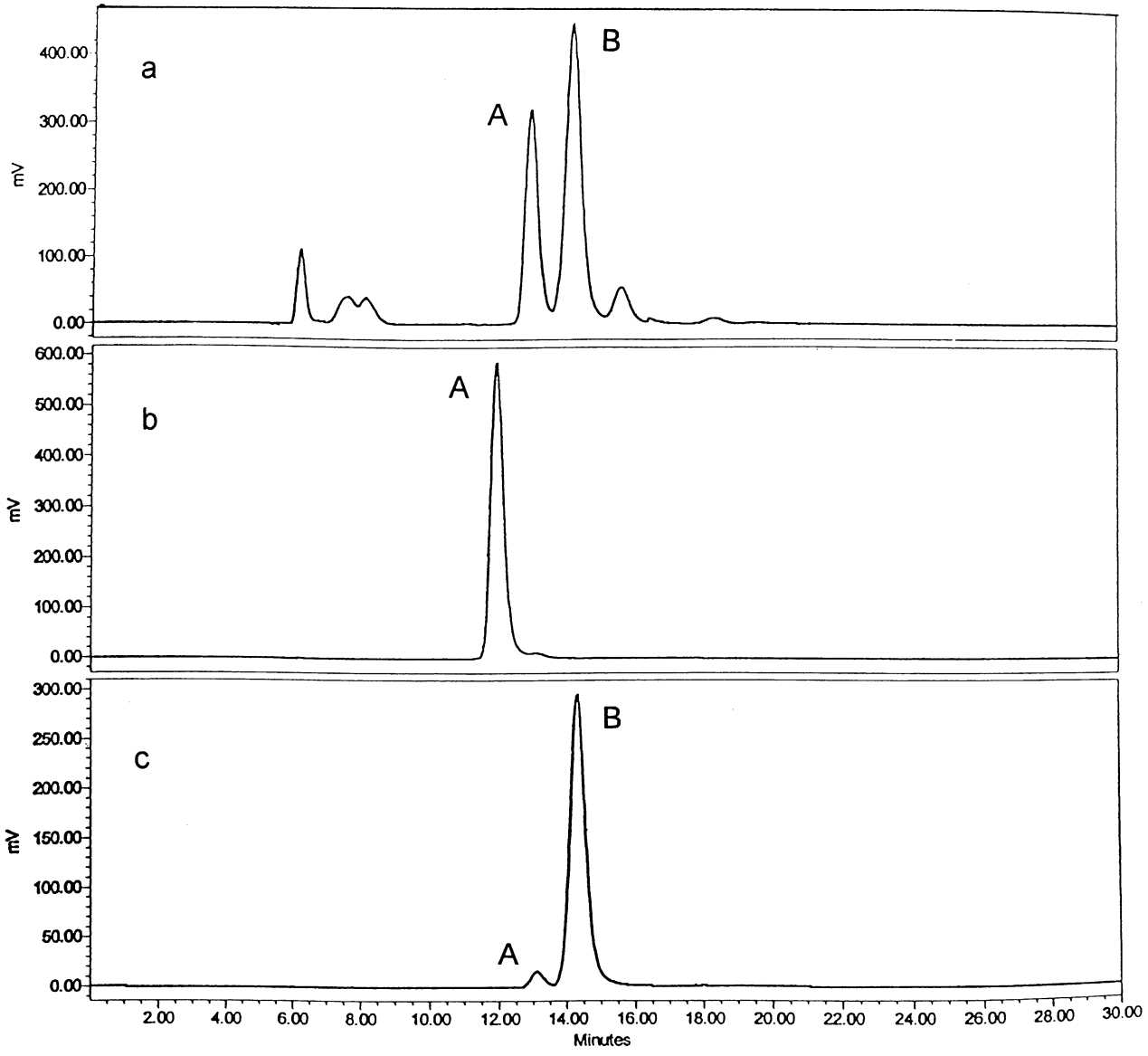

Fig. 3. Radiochromatogram of: (a) the reaction mixture after radiofluorination of L-DOPA in HF/BF_3; (b) [^{18}F]2-fluoro-L-DOPA (A) after final purification; and (c) [^{18}F]6-fluoro-L-DOPA (B) after final purification (see Section 4.1.4 for HPLC conditions). Unlabelled peaks are unknown fluorine-containing species.

corresponded to [^{18}F]2-, [^{18}F]5- or [^{18}F]6-fluoro-L-DOPA and was collected for dose preparation.

4.1.4. Dose preparation and quality control

Pure [^{18}F]2-, [^{18}F]5- or [^{18}F]6-fluoro-L-DOPA in 0.1% acetic acid was collected in a pyrogen-free 10 ml vial and a 0.1 ml sample was removed for quality control. Ascorbic acid (ca. 1 mg) and 0.6 ml of 10% sodium chloride in water (sterile and pyrogen-free) were added and the [^{18}F]fluoro-L-DOPA solution was transferred through 0.22 μm sterile filter (Millipore Corporation, Bedford, MA) into a 10 ml sterile vial. Each batch passed quality control tests for pH (5–6), sterility and pyrogenicity.

The radiochemical purity of [^{18}F]fluoro-L-DOPA (96 ± 2% for 2- and 6- fluoro isomers and 91 ± 4% for 5-fluoro isomer) was determined by passing an aliquot of the QC sample through a reverse phase HPLC column (Vydac C_{18}, 0.9 cm × 25 cm) and 0.1% TFA in water containing 5% CH_3CN as the mobile phase and an elution rate of 2.5 ml min^{-1} (Figs. 3 and 4). The eluate from the column was passed through a Waters 490E Programmable Multi-wavelength detector (280 nm) and Beckman Radioisotope Detector (Model 170).

4.2. PET scanning protocol

Two healthy, neurologically normal 55 year old subjects participated in this study. The study was designed in accordance with the Institutional Review Board, McMaster University. The subjects fasted for 4 h prior to the examination.

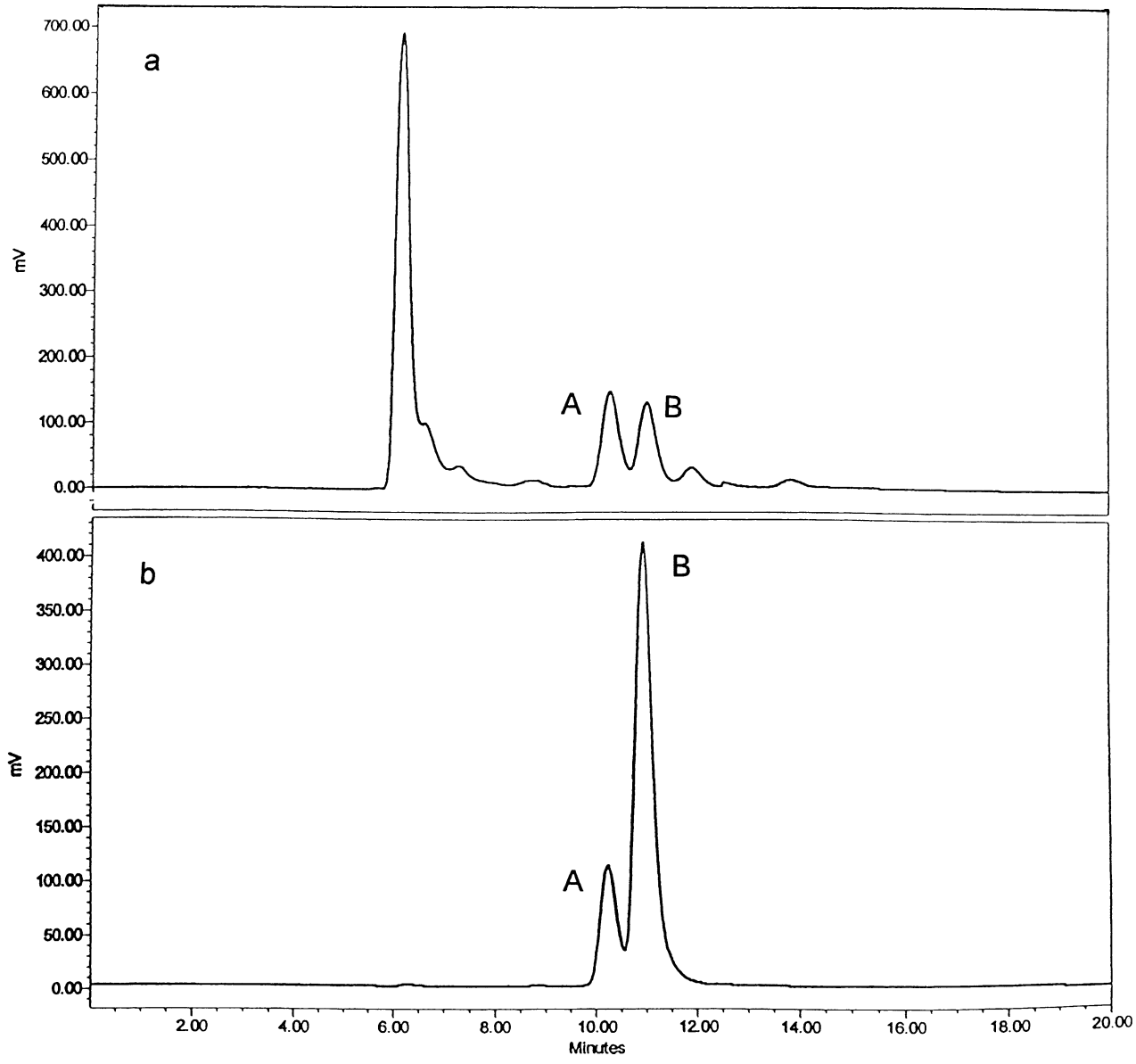

Fig. 4. Radiochromatogram of: (a) the reaction mixture after radiofluorination of L-DOPA in glacial acetic acid containing 10% TFA, showing [^{18}F]2-fluoro-L-DOPA (A) and [^{18}F]5-fluoro-L-DOPA (B); and (b) [^{18}F]5-fluoro-L-DOPA after final purification (see Section 4.1.4 for HPLC conditions). Unlabelled peaks are unknown fluorine-containing species.

They were not pretreated with carbidopa, as it has been shown that this increases the radioactivity in the brain, but not the specific accumulation in the striatum [49]. Subjects were examined in an ECAT ART [50], after intravenous injection of between 110 and 185 MBq of [^{18}F]5-, and [^{18}F]6-fluoro-L-DOPA. Subject 1 was also injected with 150 MBq of [^{18}F]2-fluoro-L-DOPA. Studies were conducted within a 3-month interval. The head was immobilized in a head holder and positioned so that the orbito-meatal line was perpendicular to the axis of the gantry. Subjects were scanned for 2 frames at 10 s per frame, 20 frames at 5 s per frame, 6 frames at 10 s per frame, 4 frames at 180 s per frame, and 21 frames at 300 s per frame for a total of 120 min.

Images were reconstructed using the reprojection algorithm [51] and ramp filters at the Nyquist frequency. An attenuation correction was calculated from a "singles" (^{137}Cs) transmission scan acquired immediately prior to the injection of the tracer [52]. The last 12 frames (60 min) of the study were summed and regions of interest (ROIs) were drawn with reference to a standard neuroanatomical atlas [53] around the right and left caudate nuclei, the right and left putamina, and the cerebellum for the 6-fluoro-L-DOPA study. These regions were then transferred to the 2- and 5-fluoro-L-DOPA studies after careful re-alignment of the three studies based on the blood flow image (first 2 min of study summed). The decay-corrected time activity curves in these ROIs were then obtained for the duration of

the study. An influx constant (K_i) [54] was calculated for each of the regions using the cerebellum as the tissue reference [55].

Acknowledgements

We wish to thank Margo Thompson for her untiring support and Dr. Shigeko Amano for helpful discussions. N.V. and M.C.A. wish to thank the Natural Sciences and Engineering Research Council of Canada for postgraduate scholarships and the Christie Group Ltd. for awarding E.S. Garnett Bursaries in Medical Imaging.

References

[1] M. Silvester, Spec. Chem. 11 (1990) 392–399.
[2] B.K. Park, N.B. Kitteringham, Drug Metab. Rev. 26 (1994) 605–643.
[3] J.H. Clark, D. Wails, T.W. Bastock, Aromatic Fluorination, CRC Press, Boca Raton, 1996, pp. 1–17.
[4] B.E. Smart, J. Fluorine Chem. 109 (2001) 3–11.
[5] K.L. Kirk, J. Fluorine Chem. 72 (1995) 261–266.
[6] K.L. Kirk, C.R. Creveling, Med. Res. Rev. 4 (1984) 189–220.
[7] K.L. Kirk, O. Olubajo, K. Buchhold, G.A. Lewandowski, F. Gusovsky, D. McCulloh, J.W. Daly, C.R. Creveling, J. Med. Chem. 29 (1986) 1982–1988.
[8] L. Iverson, Lancet 2 (1982) 914–918.
[9] O. Hornykiewicz, Pharmacol. Rev. 18 (1966) 925–964.
[10] W. Birkmayer, O. Horneykiewicz, Wien. Klin. Wschr. 73 (1961) 787–788.
[11] G. Firnau, C. Nahmias, E.S. Garnett, Int. J. Appl. Radiat. Isot. 24 (1973) 182–184.
[12] E.S. Garnett, G. Firnau, C. Nahmias, S. Sood, L. Belbeck, Am. J. Physiol. 238 (1980) R318–R327.
[13] E.S. Garnett, G. Firnau, C. Nahmias, Nature 305 (1983) 137–138.
[14] E.S. Garnett, A.E. Lang, R. Chirakal, G. Firnau, C. Nahmias, Can. J. Neurol. Sci. 14 (1987) 444–447.
[15] A. Luxen, M. Guillaume, W.P. Melega, V.W. Pike, O. Solin, R. Wagner, Nucl. Med. Biol. 19 (1992) 149–158.
[16] P. Cumming, A. Gjedde, Synapse 29 (1998) 37–61.
[17] M. Argentini, C. Wiese, R. Weinreich, J. Fluorine Chem. 68 (1994) 141–144.
[18] R. Chirakal, N. Vasdev, G.J. Schrobilgen, C. Nahmias, J. Fluorine Chem. 99 (1999) 87–94.
[19] R. Chirakal, G. Firnau, E.S. Garnett, J. Nucl. Med. 27 (1986) 417–421.
[20] O. Solin, G. Firnau, M. Haaparanta, R. Chirakal, H. Sipila, E.S. Garnett, C. Nahmias, in: Proceedings of the 6th International Symposium on Radiopharmaceutical Chemistry, Boston, MA, 29 June 1986 (paper 36).
[21] D. Cantacuzene, K.L. Kirk, D.H. McCulloh, C.R. Creveling, Science 204 (1979) 1217–1219.
[22] P. Cumming, M. Hausser, W.R.W. Martin, J. Grierson, M.J. Adam, T.J. Ruth, E.G. McGeer, Biochem. Pharm. 37 (1988) 247–250.
[23] G. Firnau, E.S. Garnett, T.L. Sourkes, K. Missala, Experientia 31 (1975) 1254–1255.
[24] C.R. Creveling, K.L. Kirk, Biochem. Biophys. Res. Commun. 130 (1985) 1123–1131.
[25] C. Wiese, M. Cogoli-Greuter, R. Weinreich, K.H. Winterhalter, J. Neurochem. 58 (1992) 219–226.
[26] G. Firnau, E.S. Garnett, P.K.H. Chan, L.W. Belbeck, J. Pharm. Pharmac. 28 (1976) 584–585.
[27] E.S. Garnett, G. Firnau, P.K.H. Chan, S. Sood, L.W. Belbeck, Proc. Natl. Acad. Sci. U.S.A. 75 (1978) 464–467.
[28] W.H. Oldendorf, Am. J. Physiol. 224 (1973) 967–969.
[29] E.S. Garnett, C. Nahmias, R. Chirakal, G. Firnau, unpublished results.
[30] G. Firnau, S. Sood, R. Pantel, S. Garnett, Mol. Pharmacol. 19 (1980) 130–133.
[31] C. Wiese, M. Cogoli-Greuter, M. Argentini, T. Mader, R. Weinreich, K.H. Winterhalter, Biochem. Pharmacol. 44 (1992) 99–105.
[32] C. Wiese, M. Cogoli-Greuter, R. Weinreich, K.H. Winterhalter, Naunyn-Schmiedeberg's Arch. Pharmacol. 349 (1993) 582–585.
[33] R.E. Yee, S.-C. Huang, D.B. Stout, I. Irwin, K. Shoghi-Jadid, D.M. Togaski, L.E. DeLanney, J.W. Langston, N. Satyamurthy, K.F. Farahani, M.E. Phelps, J.R. Barrio, J. Neurochem. 74 (2000) 1147–1157.
[34] J.R. Barrio, S.C. Huang, M.E. Phelps, Biochem. Pharmacol. 54 (1997) 341–348.
[35] C.C. Chiueh, Z. Zukowska-Grojec, K.L. Kirk, I.J. Kopin, J. Pharmacol. Exp. Ther. 225 (1983) 529–533.
[36] C.R. Creveling, E.T. McNeal, D. Cantacuzene, K.L. Kirk, J. Med. Chem. 24 (1981) 1395–1399.
[37] G. Firnau, E.S. Garnett, R. Chirakal, S. Sood, C. Nahmias, G. Schrobilgen, Appl. Radiat. Isot. 37 (1984) 669–675.
[38] O.T. DeJesus, J. Mukherjee, Biochem. Biophys. Res. Commun. 150 (1988) 1027–1031.
[39] C. Nahmias, L. Wahl, R. Chirakal, G. Firnau, E.S. Garnett, Mov. Disorders. 10 (1995) 298–304.
[40] H.C. Guldberg, C.A. Marsden, Pharmacol. Rev. 27 (1975) 135–206.
[41] H. Blaschko, T.L. Chrusciel, J. Physiol. 151 (1960) 272–284.
[42] O.T. DeJesus, C.J. Endres, S.E. Shelton, R.J. Nickles, J.E. Holden, J. Nucl. Med. 38 (1997) 630–636.
[43] J.R. Barrio, S. Huang, D. Yu, W.P. Melega, J. Quintana, S.R. Cherry, A. Jacobson, M. Namavari, N. Satyamurthy, M.E. Phelps, J. Cereb. Blood Flow Metab. 16 (1996) 667–678.
[44] C.F. Reinhardt, W.G. Hume, A.L. Linch, J.M. Wetherhold, J. Chem. Ed. 46 (1969) A171–A179.
[45] D. Peters, R.J. Miethchen, J. Fluorine Chem. 79 (1996) 161–165.
[46] E.B. Segal, Chem. Health Saf. 7 (2000) 18–23.
[47] R.J. Nickles, M.E. Daube, T.J. Ruth, Int. J. Appl. Radiat. Isot. 35 (1984) 117–122.
[48] R. Chirakal, R.M. Adams, G. Firnau, G.J. Schrobilgen, G. Coates, E.S. Garnett, Nucl. Med. Biol. 22 (1995) 111–116.
[49] J.M. Hoffman, W.P. Melega, T.C. Hawk, S.C. Grafton, A. Luxen, D.K. Mahoney, J.R. Barrio, S.C. Huang, J.C. Mazziotta, M.E. Phelps, J. Nucl. Med. 33 (1992) 1472–1477.
[50] D.L. Bailey, H. Young, P.M. Bloomfield, S.R. Meikle, D. Glass, M.J. Myers, T.J. Spinks, C.C. Watson, P. Luk, A.M. Peters, T. Jones, Eur. J. Nucl. Med. 24 (1997) 6–15.
[51] P.E. Kinahan, J.G. Rogers, IEEE Trans. Nucl. Sci. 36 (1989) 964–968.
[52] S.K. Yu, C. Nahmias, Phys. Med. Biol. 40 (1995) 1255–1266.
[53] J. Tailerach, P. Tournoux, Co-planar Streotaxic Atlas of the Human Brain, Thieme, New York, 1988.
[54] C.S. Patlak, R.B. Blasberg, J. Cereb. Blood Flow Metab. 5 (1985) 584–590.
[55] J. Tedroff, S.M. Acquilinius, A. Laihinen, U. Rinne, P. Hartvig, J. Anderson, H. Lundqvist, M. Haaparanta, O. Solin, G. Antoni, A.D. Gee, J. Ulin, B. Långström, Acta Neurol. Scand. 81 (1990) 24–30.