N-3-[^{18}F]Fluoropropylputrescine as Potential PET Imaging Agent for Prostate and Prostate Derived Tumors

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A potential PET imaging agent for prostate and prostate derived tumors, N-3-[^{18}F]-fluoropropylputrescine, has been prepared. The radiochemical yield was 7–10% at end-of-synthesis (EOS) and the specific activity was >1.1 Ci/μmol (overall synthesis time was 1.5 hr). In vivo biodistribution in mature male rats showed high prostate uptake. In rats that were pretreated with α-difluoromethylornithine and dihydrotestosterone propionate, the prostate to muscle ratio and prostate to blood ratio increased significantly. This high target uptake and target to nontarget ratio indicates the potential of this compound as a prostate imaging agent.

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Polyamines have long been associated with cell growth (*1*) and cell proliferation (*2*). Higher levels of polyamines were found in rapid growing cells and tumors. While some have suggested that polyamines could be used as a biochemical marker for diagnosis of cancer and monitoring therapy (*3*), others have pointed out that the differential polyamine concentration lacks the sensitivity and specificity of a useful tumor marker (*4*).

In 1975, Clark and Fair (*5*) studied the selective in vivo incorporation and metabolism of ^{3}H-labeled putrescine in adult male rats, and high prostate uptake (0.6% of injected dose) was found 1 hr after i.v. injection of the labeled putrescine (prostate/muscle ratio was 8–10). The possibility of using radiolabeled putrescine as a radiopharmaceutical for imaging the prostate was suggested (*5*), assuming that a suitable isotope could be incorporated into the molecule without altering the in vivo distribution characteristics in the body.

Many positron-labeled putrescine analogs have been prepared, and their in vivo uptake studied. Three N-[^{11}C]methylated polyamines have been evaluated in an animal tumor model, and the highest tumor to nontarget ratio was obtained with a putrescine analog (*6*). Previously, animal studies using 1-[^{11}C]putrescine revealed that the prostate uptake of labeled putrescine was dose-dependent, so the highest uptake was achieved only when high specific activity 1-[^{11}C]putrescine was used (*7*). More recently, 1-[^{11}C]putrescine has been used for imaging human brain tumors (*8,9*).

It has been shown that the in vivo uptake of [^{14}C]-putrescine into rat prostate 3 hr after administration of the compound was high (*10*). These results suggest that for positron emission tomography (PET) imaging of the prostate and prostate-derived tumors with radiolabeled putrescine, the longer half-life of fluorine-18 (^{18}F) ($t_{½}$ = 110 min) may be preferential to carbon-11 (^{11}C) ($t_{½}$ = 20 min). It has also been shown that enhanced uptake of [^{14}C]putrescine in prostate was observed after pretreatment with α-difluoromethylornithine (DFMO) and dihydrotestosterone propionate (DHTP) (*10*). DFMO is an ornithine decarboxylase inhibitor that inhibits polyamine biosynthesis, while DHTP is an androgen that stimulates prostate cell growth. Studying the variation in uptake of an analog by this type of pretreatment can be used to show that a compound behaves as a true polyamine analog.

We have previously reported the carrier-added synthesis of 2-[^{18}F]fluoroputrescine (*11*). Biodistribution studies showed significant bone uptake indicating in vivo defluorination, and the prostate uptake was low. Although in vivo defluorination could be inhibited by the administration of a diamine oxidase inhibitor, guanidine, the prostate uptake did not improve. This finding led us to propose that the defluorination was induced by pyridoxal phosphate dependent diamine oxi-

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dase (*11*). Therefore, when the fluorine atom was attached to the carbon atom γ to the amine group of a putrescine analog, the defluorination might occur to a lesser extent. We have, therefore, investigated the potential of a simple [^{18}F]-labeled N-fluoroalkylputrescine, N-3-[^{18}F]-fluoropropylputrescine, which has the above criteria, as a prostate imaging agent by PET.

MATERIALS AND METHODS

All reagents and solvents (Aldrich Chemical Company, Milwaukee, WI) were reagent grade and used without further purification unless otherwise specified. Anhydrous tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride under nitrogen. 3-Bromo-1-fluoropropane was obtained commercially (Columbia Organic Chemical Co., Inc., Camden, SC). The following chemicals used in the cell culture studies were obtained commercially: DHTP (Steraloids Inc., Wilton, NH), [^{14}C]putrescine (116 mCi/mmol, Amersham, Arlington Heights, IL), ScintiVerse scintillation cocktail (Fisher Scientific Co., Fairlawn, NJ), and all other chemicals and supplies (Sigma Chemical Corp., St. Louis, MO). DFMO was obtained from Merrell Dow Pharmaceuticals Inc. (Cincinnati, Ohio), through the courtesy of Dr. Pete McCann and Dr. W. J. Hudak.

Proton and ^{19}F (external CF_3CO_2H) NMR spectra were recorded in methanol-d4 (Varian EM-360L or XL-500 spectrometer). Melting points were obtained on an open-capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

GC analysis was carried out using a 2 m × 0.125 in. column (10% OV-101, Chromosorb W-HP, 80/100, Alltech; Varian Model 3700 Gas Chromatograph) eluted with Helium at a flow rate of 15 ml/min. The column temperature was 50°C for 2 min followed by a 10°C/min increase to 180°C. A flame ionization detector was used at 200°C. The injector temperature was 220°C.

HPLC analyses of the derivatives of putrescine as well as the purification of [^{18}F]-labeled putrescine derivative were carried out using a column (0.7 × 30 cm) containing Aminex A-25 quaternary amine resin (chloride form, 17.5 μm particle size, converted to the hydroxide form with 0.1 N NaOH; Bio-Rad) eluted with 0.01 N NaOH at a flow rate of 3 ml/min. The radiopurity of [^{18}F]-labeled putrescine was analyzed using an Aminex column (HPX-72-0, 300 × 7.8 mm, Bio-Rad) eluted with 0.01 N NaOH at a flow rate of 0.8 ml/min. The liquid chromatograph was fitted with a uv detector (Lambda-Max model 480, Waters) and a NaI (T1) radioactivity detector.

N-3-Fluoropropylputrescine dihydrochloride (1). Putrescine (0.447 g, 5.08 mmol) and 3-bromo-1-fluoropropane (0.3 ml, 0.41 g, 2.91 mmol) were weighed into a 10 ml reacti-vial. The mixture was vigorously shaked, and acetonitrile (8 ml) was introduced. A white precipitate was seen immediately after the addition of acetonitrile (MeCN). The mixture was sonicated for 5 hr (Bransonic 12 ultrasonic cleaner filled with distilled water; the water temperature increased from 20°C to 45°C after 5 hr). The solution was filtered through a glass pasteur pipet packed with 0.5 cm of glass wool. The vial was rinsed with 10 ml of MeCN which again was filtered through the same pipet. To the MeCN solution was added aqueous HCl (4 N, 10 ml). After vigorous stirring the solution was concentrated in vacuo to leave a brown solid. The solid was dissolved in 5 ml of deionized water and loaded onto a column packed with AG-50W × 4 cation exchange resin (hydrogen form, dry mesh 200–400, Bio-Rad, 3 × 22 cm). The column was eluted with 500 ml of deionized water and then 1.5 l of 1.5 N HCl. The first 650 ml of the eluant was collected in a beaker, and the rest of the eluant was collected as 8-ml fractions. Fractions 97 to 140 contained the desired amine, which were combined and concentrated in vacuo to leave the amine dihydrochloride as a white solid. When analyzed by high performance liquid chromatography (HPLC), the product had a retention time of 7.5 min. The solid was redissolved in methanol and triturated with ether. The solid was then collected by filtration and weighed 0.32 g (47%, based on 3-bromo-1-fluoropropane): m.p. 216–218°C, ^{1}HNMR (CD_3OD) δ 4.57 (dt, J_{HCF} = 47.18 Hz, J_{HH} = 5.62 Hz, 2H) 3.176 (t, J = 7.54 Hz, 2H), 3.079 (t, J = 7.48 Hz, 2H), 2.986 (t, J = 7.26 Hz, 2H), 2.0–2.2 (m, 2H), 1.8 (m, 4H); ^{19}FNMR (CD_3OD) Φ −142.071 (tt, J_{HCF} = 47.2 Hz, J_{HCCF} = 26.8 Hz). Anal. calc'd for $C_7H_{19}Cl_2FN_2$: C, 38.02; H, 8.66; F, 8.59. Found: C, 38.03; H, 8.52; F, 8.08.

N-3-Hydroxypropylputrescine (2). The desired compound was similarly prepared according to the above procedure from putrescine (0.22 g, 2.54 mmol) and 3-bromo-1-propanol (0.11 ml, 1.22 mmol). The crude mixture was purified on AG-50W × 4 cation exchange resin column (1 × 15 cm). The column was eluted with deionized water (80 ml) and then 2 N HCl. The first 80 ml was collected in a beaker and the rest of the eluant was collected as 8-ml fractions. Fractions 7 to 10 contained only putrescine. Fractions 11 to 13 contained the desired 3-hydroxypropylputrescine and a small amount of putrescine, which was concentrated in vacuo to give a white solid weighed 45 mg. The purity of the desired product was estimated to be 85% pure by ^{1}HNMR. HPLC analysis of the product showed two overlapping peaks: one sharp peak with a retention time of 2 min (putrescine) and a broad peak with a retention time of 2.5 min (compound 2). ^{1}HNMR (D_2O, EM-360L) δ 3.6 (t, J = 6 HZ), 3.1 (br m), 1.7 (br m).

N-3-[^{18}F]Fluoropropylputrescine ([^{18}F]-18). Aqueous [^{18}F] fluoride was produced by proton bombardment of an enriched ^{18}O-water target as described previously (*12*). An aliquot of the irradiated water containing 50 mCi of aqueous [^{18}F]fluoride was added to a vacutainer containing 5 μl of 1 *M* aqueous tetrabutylammonium hydroxide (TBAOH). Water was azeotropically removed with MeCN under a stream of nitrogen. The activity was then resolubilized into anhydrous THF (300 μl) (*13*). To the vacutainer was added 2 μl of the triflate of 3-bromopropanol (*14*). The vacutainer was capped and allowed to stay at room temperature for 2 min. The THF solution was passed through a short silica gel (50 mg) column which was washed with 200 μl of MeCN. The organic eluants were combined in a 1 ml reacti-vial and to it was added 50 μl of an MeCN solution of putrescine (42 mg/1 ml) and 50 μl of an aqueous solution of K_2CO_3 (100 mg/ml). The vial was sealed and heated at 110°C for 20 min. After cooling the solution was acidified with 100 μl of 2 N HCl, and concentrated in vacuo to dryness. More than 50% of the radioactivity was lost during the concentration process. The residue was taken up into 200 μl of 0.01 N NaOH and injected onto an Aminex

column. The column was eluted with 0.01 N NaOH at a flow rate of 3 ml/min. The radioactive peak corresponding to that of the labeled product (with a retention time of 7.5 min) was collected in six fractions (total volume ~18 ml). The total amount of radioactivity was 3.6 mCi. The solution was neutralized with 1 N HCl and used for animal studies.

In Vitro Competitive Inhibition of [^{14}C]Putrescine Uptake

Cell culture. The human prostatic carcinoma cell lines PC-3 and LNCaP were obtained from the American Type Culture Collection (Rockville, MD) (*15–17*). The cell lines were maintained in RPMI (Rosewell Park Memorial Institute) 1640 medium supplemented with L-glutamine (4 m*M*), penicillin (100 IU/ml), streptomycin (100 mg/ml), and 10% (V/V) of heat-inactivated FCS (fetal calf serum). Aminoguanidine (100 μM) was added to block the activity of any diamine oxidase enzyme that might be present.

[^{14}C]putrescine uptake. PC-3 cells were plated in a concentration of 5×10^4 cells per well of a 24-well plate in 1 ml of RPMI-1640 medium supplemented with the additives as described. Twenty-four hours after plating, the medium was replaced with fresh plating medium and 1 m*M* DFMO was added to half of the wells. Twenty-four hours later [^{14}C] putrescine (116 mCi/m*M*) at a final concentration of 3 μM was added to all the wells. Upon addition of the [^{14}C]putrescine both groups of wells (with and without DFMO) were each divided into three subgroups: (I) [^{14}C]putrescine alone, (II) [^{14}C]putrescine with an excess (200 μM) of unlabeled putrescine, and (III) [^{14}C]putrescine with an excess (200 μM) of unlabeled N-3-fluoropropylputrescine. All the cells were then incubated for 1 hr at 37°C in an incubator at 7.5% CO_2 and saturation humidity. One milliliter of stop solution (ice cold Hanks' balanced salt solution containing 1 mg of bovine serum albumin and 1 m*M* unlabeled putrescine) was added to each well to terminate the [^{14}C]putrescine uptake. The supernatant was then aspirated and the cells were rinsed twice with stop solution. Following the last rinse, the radioactivity was extracted with 1 ml of 0.1 N NaOH. A 0.5-ml aliquot was added to 2 ml of 2% glacial acetic acid and 10 ml of scintillation cocktail; the radioactive disintegrations were determined in a liquid scintillation counter.

For the LNCaP cells the technique was modified slightly. First, the cells were plated at a concentration of 2.4×10^4 cells per well. Secondly, since these cells did not adhere well to the bottom of the wells before each change of medium, the plates were centrifuged in a refrigerated (4°C) centrifuge for 10 min (Sorvall Centrifuge Model RT 600). The rest of the assay was performed as outlined above.

Each experiment was conducted in triplicate and was repeated twice.

Animal Biodistribution Studies

Biodistribution studies were performed in adult male Sprague-Dawley rats (240 ± 20 g). Each rat was anesthetized with diethyl ether in an open system, injected in a surgically exposed femoral vein, the wound clipped to close, and allowed to recover. The animals were allowed free access to food and water at all times while awake. At the specified times after administration of the radiolabeled compound (20–30 μCi), the rat was reanesthetized with ether and killed by decapitation. The following was removed, weighed, and counted: blood, ventral prostate, dorsolateral prostate, liver, spleen, kidney, bladder, abdominal muscle, and tibia.

Some groups of rats were pretreated with DFMO and DHTP. The treatment involved daily subcutaneous injection of DHTP (2 mg/0.2 ml sesame oil) for 3 days prior to the experiment; additionally, DFMO (0.33 g/1.1 ml saline) was injected intraperitoneally every 4 hr for 24 hr preceeding the experiment. The biodistribution studies were then carried out as previously described.

RESULTS AND DISCUSSION

The desired N-3-fluoropropylputrescine **1** could be prepared by alkylating putrescine with 3-bromo-1-fluoropropane. In general, reactions were carried out using 1.5–2 equivalents of putrescine and one equivalent of 3-bromo-1-fluoropropane. Various combinations of solvents (toluene, o-dichlorobenzene, MeCN, THF, water) and bases (K_2CO_3, $NaHCO_3$, TBAOH) were studied to improve the chemical yields of the desired compound **1**. When reactions were carried out at 90°C for 3 hr in either toluene or o-dichlorobenzene and using TBAOH as base, **1** was obtained in low yield (10%), along with two side products. When reactions were performed in aqueous acetonitrile and using $NaHCO_3$ as base, **1** was obtained in a yield of 5% with no by-products. While attempting to weigh 3-bromo-1-fluoropropane on a balance into a reacti-vial containing neat putrescine, an exothermal reaction ensued, and the addition of MeCN caused the immediate formation of white precipitates. HPLC analysis of the precipitates and the acetonitrile solution revealed that the precipitates were mainly the starting putrescine and the MeCN solution was a mixture of the desired compound, **1** (major), and the starting material, putrescine (minor). With a slight modification of the above procedure, as described in detail in the experimental section, **1** could be obtained in a yield of 47% (based on 3-bromo-1-fluoropropane).

Because 3-bromo-1-[^{18}F]fluoropropane (**[^{18}F]-2**) was obtained as a solution in anhydrous THF in a yield of 60% at EOS (based on [^{18}F]fluoride) according to the published procedure (*14*), a different method was used for the preparation of **[^{18}F]-1**. The reaction conditions, originally developed for the preparation of N-[^{18}F]fluoroalkylspiperone, did not yield good radiochemical yield of **[^{18}F]-1**. When MeCN and aqueous potassium carbonate was used as solvent and base, **[^{18}F]-1** was obtained in a radiochemical yield of 7–10% (EOS) in an overall synthesis time of 1.5 hr.

Since **[^{18}F]-2** was prepared from the trifalte of 3-bromo-1-propanol and tetrabutylammonium [^{18}F]fluoride, the concern of whether the unreacted triflate and other compounds originated from the decomposition of the base-sensitive triflate will also react with putrescine and cause problems in the purification step, and

hence decrease the specific activity of the labeled product, has been raised.

To clarify this concern we have carefully reinvestigated the preparation of [^{18}F]-2. In the preparation of [^{18}F]-2, the reaction mixture was passed through a short silica gel column to remove unreacted [^{18}F]fluoride after a reaction time of 5 minutes at ambient temperature. The silica gel column effectively retained unreacted [^{18}F]fluoride, but it did not hold back unreacted triflate and 3-bromo-1-propanol, which was generated from the triflate by TBAOH. The ratio of 3-bromo-1-propanol to triflate was determined by GC to be greater than 2.5. Since both triflate and 3-bromo-1-propanol were found in the solution of [^{18}F]-2, the by-products from the reaction of the solution and putrescine would be 3-bromopropyl- and 3-hydroxypropyl-putrescine. Because the alkylation reaction was performed in an aqueous solution at elevated temperature, the small amount of triflate was immediately converted to 3-bromo-1-propanol. Therefore, when the reaction was carried out in the presence of excess of putrescine, the main by-product of the reaction would be 3-hydroxypropylputrescine.

The authentic 3-hydroxypropylputrescine was prepared in a yield of 14% (based on 3-bromo-1-propanol) by a procedure similar to that for the preparation of **1**. N-3-hydroxypropylputrescine was well separated from the desired compound, **1**, on the Aminex A-25 resin column eluted with 0.01 N aqueous NaOH at 3 ml/min. The retention time of **1**, N-3-hydroxypropylputrescine, and putrescine was 7.5, 2.5, and 2 min, respectively.

The purification of [^{18}F]-1 needed special attention. Since [^{18}F]-1 was purified on a Bio-Rad A-25 quaternary amine resin column, a small amount of organic solvent (MeCN) interfered with the separation. A major portion of the product was found to coelute at the solvent front when the solvents of the reaction mixture were not completely removed. Therefore, the reaction mixture was thoroughly dried in vacuo, and the residue was redissolved in the HPLC solvent (0.01 N NaOH) and injected onto the Aminex A-25 column. The column did effectively separate the unlabeled by-products, but the desired product was eluted as a broad peak (6 min from the beginning to the end of the peak). Since [^{18}F] fluoride was eluted at the solvent front, it is possible that fluoride will tail into the fractions containing the desired product. To ensure the purity of the labeled product for animal studies, the product eluted from HPLC was collected in six fractions, and the last three fractions were used for animal studies. The radiopurity of [^{18}F]-1 was analyzed on an Aminex column (HPX-72-O) eluted with 0.01 N NaOH at a flow rate of 0.8 ml/min. [^{18}F]-1 was found to be stable at pH 6 for more than 3 hr.

The specific activity of [^{18}F]-1 was determined to be greater than 1.1 Ci/μmol by HPLC using an analytic Chromega γRP-1 column (0.46 × 10 cm, ES Industries) and eluted with 5% CH_3CN/0.05 N NaOH with a flow of 0.8 ml/min.

N-3-Fluoropropylputrescine dihydrochloride effectively blocked the uptake of [^{14}C]putrescine in vitro in cultured human prostate cancer cells, PC-3, and LNCaP (Table 1). Table 1 shows relative inhibition relative to control. The absolute uptake was 8.8 times greater for PC-3 compared to LNCaP, and DFMO increased uptake by a factor of 5.9 in PC-3 cells and 2.4 in LNCaP cells. The difference in absolute [^{14}C]putrescine uptake between these two lines has been observed repeatedly. This is most likely due to a difference in growth rate and consequent polyamine requirements as well as to the different number of cells plated. Other in vitro studies have shown that PC-3 cells take up **1** from the culture medium; and that pretreatment with DFMO enhanced the intracellular concentration of the substance (Kadmon D, unpublished data). It can therefore be inferred that **1** is capable of utilizing the polyamine transport system for its uptake into human prostatic cancer cell lines.

The in vivo biodistribution of [^{18}F]-1 showed relatively high prostate uptakes at 1 hr postinjection, and the prostate uptakes remained high even at 3 hr postinjection (Table 2). The prostate to abdominal muscle ratio increased from 1.76 to 4.70 for dorsal prostate and from 4.01 to 5.7 for ventral prostate.

It has been demonstrated that when rats were pretreated with ornithine decarboxylase inhibitor (DFMO) and androgen (DHTP), the prostate uptakes of [^{14}C] putrescine increased, and the prostate to muscle ratio increased by sixfold at 3 hr after administration. In order to see whether an improvement of the prostate uptake of [^{18}F]-1 by the DFMO and DHTP pretreatment, a similar experiment was carried out using the new agent. The prostate uptakes improved upon pretreatment. The increase in dorsal prostate uptake was statistically (t-test) significant at $p < 0.05$ (Table 3). The

TABLE 1
The Ability of Putrescine Analogs to Inhibit the Uptake of [^{14}C]Putrescine in Cultured Human Prostate Cancer Cells

Tumor cell line	Inhibitors	[^{14}C]Putrescine uptake −DFMO	(% of Control) +DFMO*
PC3	None	100	100
	Putrescine	11	4
	1	12	5
	N-Propylputrescine	27	11
LNCaP	None	100	100
	Putrescine	28	11
	1	37	15

*Cells were pretreated with DFMO.

TABLE 2
Biodistribution of [^{18}F]-1* in Adult Male S.D. Rats (%ID/g)

	1 hr	3 hr
Blood	0.118 ± 0.009	0.074 ± 0.021
V. Prostate	0.669 ± 0.136	0.551 ± 0.267
D. Prostate	0.304 ± 0.084	0.423 ± 0.366
Muscle	0.174 ± 0.027	0.097 ± 0.016
Bone	0.289 ± 0.022	0.315 ± 0.064
D. Pros/Muscle	1.762 ± 0.470	4.700 ± 4.703
V. Pros/Muscle	4.008 ± 1.392	5.736 ± 2.352
D. Pros/Blood	2.562 ± 0.557	5.832 ± 4.907
V. Pros/Blood	5.763 ± 1.495	7.922 ± 3.645

* 20–30 μCi of **[^{18}F]-1** was injected into each rat.

absolute prostate uptake was 2.3 (ventral) to 2.4 (dorsal) times of those of untreated experiments (Table 3). These compare to increases of 5.4 (ventral) and 4.4 (dorsal) for [^{14}C]putrescine studies (*10*). Different batches of **[^{18}F]-1** were used for the biodistribution studies in non-treated (Table 2) and pretreated (Table 3) experiments. The bone uptakes were different between two experiments, so it is possible that the batch of **[^{18}F]-1** used for pretreatment studies contained a slightly higher amount of free [^{18}F]fluoride which caused the higher bone uptake than reported in Table 2. A 5% fluoride impurity would account for the difference in the two sets of experiments.

By comparing the prostate uptakes of radiolabeled putrescine and its analogs (Table 4) it is interesting to know that [^{14}C]- and [^{3}H]-labeled putrescine had prostate to muscle ratios between 3.3 and 13. On the other hand, the [^{18}F]-labeled putrescine derivatives had prostate to muscle ratios (1 hr after administration) between 1.7 and 4 which was only one-half of the values of those of [^{11}C]putrescine. The absolute uptake of the **[^{18}F]-1** is similar or greater than that of [^{14}C]- and [^{3}H]-labeled putrescine while that of 2-[^{18}F]fluoroputrescine (*11*) is significantly lower. There was less response to DFMO and DHTP treatment for the 2-[^{18}F]fluoroputrescine than **[^{18}F]-1**. Although the uptakes of **[^{18}F]-1** are less, as compared to the 20 min half-life of [^{11}C]putrescine, its 2 hr half-life and its high prostate uptake at 3 hr after administration would provide a good means of in vivo imaging of prostate by PET for a longer period of time. The bladder uptake might cause difficulty for prostate imaging, and again the extra time available with ^{18}F will allow voiding prior to imaging. The longer half-life of ^{18}F also allows greater flexibility for coordinating radiopharmaceutical production and imaging.

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TABLE 3
Biodistribution of [^{18}F]-1* in Adult Male s.d. Rats Pretreated with DFMO and DHTP (%ID/g)

	Control	Treated	
	1 hr	1 hr	3 hr
Blood	0.111 ± 0.025	0.86 ± 0.009	0.049 ± 0.007
V. Prostate	0.613 ± 0.151	1.089 ± 0.598	1.297 ± 0.740
D. Prostate	0.347 ± 0.086	1.179 ± 0.257 ($p < .001$)†	1.008 ± 0.234 ($p < .001$)†
Muscle	0.205 ± 0.035	0.233 ± 0.108	0.160 ± 0.068
Bone	0.992 ± 0.097	1.352 ± 0.183	1.524 ± 0.163
Liver	0.444 ± 0.080	0.431 ± 0.094	0.174 ± 0.030
Spleen	0.399 ± 0.035	0.622 ± 0.105	0.337 ± 0.060
Kidney	0.634 ± 0.070	0.605 ± 0.121	0.266 ± 0.046
Bladder	1.670 ± 1.049	1.404 ± 0.919	1.563 ± 0.699
D. Prostate/Muscle	1.88 ± 0.380	5.820 ± 2.420 ($p < .05$)†	6.780 ± 1.860 ($p < .005$)†
V. Prostate/Muscle	3.100 ± 1.100	5.810 ± 4.620	9.540 ± 6.490 ($p < .1$)†
D. Prostate/Blood	3.170 ± 0.760	13.77 ± 2.860 ($p < .001$)†	20.47 ± 3.340 ($p < .001$)†
V. Prostate/Blood	5.660 ± 1.580	13.35 ± 8.500	25.75 ± 12.61 ($p < .05$)†

* 20–30 μCi of **[^{18}F]-1** was injected into each rat.
† Probability determined by nonpaired Student's t-test by comparison of the control with the treated experiment.

TABLE 4
Prostate Uptakes of Radiolabeled Putrescine and Its Analogs (%ID/g)

	^{3}H-* 1 hr	[^{18}F]-1 1 hr	[^{18}F]-1 1 hr treated	[^{18}F]-1 3 hr	[^{18}F]-1 3 hr treated	^{14}C-† 3 hr	^{14}C-† 3 hr treated
D. Prostate	0.36	0.34 ± 0.08	1.18 ± 0.26	0.42 ± 0.36	1.01 ± 0.23		
V. Prostate	0.91	0.67 ± 0.14	1.09 ± 0.60	0.55 ± 0.27	1.30 ± 0.74		
D. Prostate/Muscle	3.3	1.76 ± 0.47	5.82 ± 2.42	4.69 ± 4.68	6.78 ± 1.86	2	12
V. Prostate/Muscle	8.3	4.01 ± 1.39	5.81 ± 4.62	5.73 ± 2.35	9.54 ± 6.49	3	13
D. Prostate/Blood	3.3	2.56 ± 0.58	13.77 ± 2.86	5.82 ± 4.88	20.47 ± 3.34	12	
V. Prostate/Blood	8.3	5.78 ± 1.49	13.35 ± 8.50	7.92 ± 3.65	25.75 ± 12.61	12	

* ^{3}H- = [^{3}H]Putrescine; see Ref. *(5)*.
† ^{14}C- = [^{14}C]Putrescine; see Ref. *(10)*.

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