RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Development of I-123-Labeled Amines for Brain Studies: Localization of I-123 Iodophenylalkyl Amines in Rat Brain

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Localization in rat brain of forty iodophenylalkyl amines labeled with I-123 was evaluated in an attempt to develop I-123-labeled amines useful for brain studies. For the amines studied, the highest activity in brain and the brain-to-blood activity ratios ranked *p* > *m* > *o* as related to iodine position on the benzene ring: for alkyl groups the rank order was α-methylethyl > ethyl > methyl > none; for N additions it was single lipophilic group > H > two lipophilic groups. It is suggested that introduction of a halogen into the ring structure of many amines results in greater concentration of the agent in brain than is seen with the nonhalogenated parent compound.

Thirty-four of the forty compounds showed higher rat brain activity, and higher brain-to-blood activity ratios at 5 min than did [^{123}I]-4-iodoantipyrine. Ten of the compounds showed a tenfold or greater brain-to-blood ratio at 5 min than did [^{123}I]-4-iodoantipyrine. We propose that while initial uptake of these agents in the brain is a consequence of their lipophilicity and that such initial uptake may be a measure of perfusion, progressive brain accumulation of these agents is probably a combined consequence of intravascular/extravascular intracerebral pH gradients, favorable brain lipid/aqueous partition coefficients, and the affinity of the agents for high-capacity, relatively nonspecific binding sites for amines located in the brain and/or brain capillary endothelium.

The agent N-isopropyl-*p*-iodoamphetamine was chosen for further study because, in the rat, it showed high brain activity (1.57%/g) and brain-blood ratio (12.6) at 5 min; these increased to 2.14%/g and 20.7 at 60 min (R isomer) following its intravenous administration.

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Amines are prominent among the chemical mediators of brain function. While a limited number of physiologically occurring amines are normally involved in the function of the brain, a substantially larger number of pharmacologically active amines can alter such function. They do so by influencing transport and uptake; rates of synthesis, storage, and release; reuptake; and degradation. They may also mimic effectors, their precursors, or their metabolites.

Consideration of the central role of amines in brain function makes it appear likely that most of the pathologic states of the brain—including functional disorders, such as schizophrenia and manic-depressive psychoses—manifest themselves as abnormalities in neurohumeral amine metabolism or kinetics. The unique ability of tracer materials to assess biochemical kinetics in vivo suggests a major role for labeled amines in the study of normal and altered brain function.

Given present limitations of radiopharmaceutical design, production, and distribution, and the available instrumentation, we believed it prudent to begin development of amine radiopharmaceuticals for brain studies using radioiodine as the label. The physical advantages of I-123 over other radioiodines with respect to the above

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parameters further suggested the use of this radionuclide (*1*).

While certain specific iodine-containing amines had been shown to localize in the brain (*2,3*), the known relationships between structure and in vivo distribution appeared to us to be too meager, in general, to predict that a given iodoamine would show sufficient in vivo localizing behavior to prove useful in clinical scintigraphic studies for defining aspects of amine metabolism. Consequently, we embarked upon a program to define structure against distribution relationships directed at maximizing brain uptake, brain retention, and brain-to-blood ratios for radioiodinated amines, with the hope that such values would correlate with ability of the agent to diffuse, or be transported, into the brain and to interact with sites involved in neurohumeral amine storage or metabolism in a manner that would provide clinically useful information. The results of in vivo distribution studies in rats are described herein.

MATERIALS AND METHODS

The nonradioactive iodinated form of each compound studied was synthesized, purified, characterized, and exchange-labeled with I-123 (RM Baldwin and TH Lin, unpublished data).

Rat bioassays were performed in female Sprague-Dawley rats weighing 150–175 g. Under sodium pentobarbital anesthesia they were injected in a tail vein with 0.05–1.0 mCi of the I-123-labeled compound in a volume of 0.2 to 0.5 ml containing 0.1–2.0 mg/ml of carrier compound. Generally each rat received between 0.1 and 1.0 mg of compound. At the time of injection, the external urethral meatus was clamped with a hemostat to prevent loss of urine before killing. Rats were killed by thoracotomy and cardiectomy. Each organ to be assayed was weighed wet and counted in standardized geometry with a NaI(Tl) scintillation counter. The energy window was centered on the 159-keV emission of I-123. Except where noted, tissue activity data from at least two rats were averaged to yield the data value presented in the tables.

RESULTS

Table 1A presents the activity in the brain for several [^{123}I]iodoaniline derivatives, expressed as percent administered dose per gram of wet rat brain, and also an activity ratio for brain to whole blood (each cpm/g), at 5 and 60 min following i.v. administration. Each point represents the average of data from two rats.

TABLE 1A.
LOCALIZATION IN RAT BRAIN OF I-123 ACTIVITY IODOANILINE DERIVATIVES

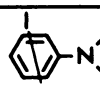
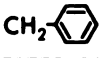
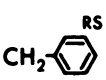
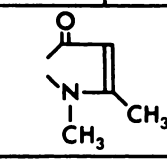
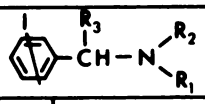
No.	Position of *I*			% Dose per gram		Brain/blood ratio	
		R_1	R_2	5 min	60 min	5 min	60 min
1A	o	−H	−H	0.47	0.03	0.28	0.07
2A	p			1.09	0.80	1.12	1.00
3A	o		−H	0.67	0.29	2.23	0.80
4A	p			1.57	0.44	1.57	0.51
5A	p			0.35	0.22	0.53	0.54
6A	o		−H	1.29	0.16	1.24	0.33
7A	p			0.93	—	1.06	—
8A	o	−CH−$(CH_3)_2$	−H	0.88	0.13	1.13	0.26
9A	p			1.23	0.26	2.55	0.33
10A	p		−H	0.92	—	1.30	—
11A	o		−H	0.96	0.41	1.81	0.75
12A	p			**0.61**	**0.17**	**0.48**	**0.18**

TABLE 1B.

LOCALIZATION IN RAT BRAIN OF I-123 ACTIVITY
IODOBENZYL AMINE DERIVATIVES

No.	Position of I				% Dose per gram		Brain/blood ratio	
		R_1	R_2	R_3	5 min	60 min	5 min	60 min
1B	o	$-CH_2-CH_3$	$-H$	$-H$	1.06	0.44	4.22	1.31
2B	o	$-CH_2-CH_2-CH_3$	$-H$	$-H$	1.03	0.59	3.81	1.84
3B	o	$-CH-(CH_3)_2$	$-H$	$-H$	1.21	0.64	7.63	1.04
4B	m				1.61	0.85	7.35	4.16
5B	o	$-CH-(CH_3)_2$	$-CH-(CH_3)_2$	$-H$	1.40	0.46	5.73	1.31
6B	o	$-C-(CH_3)_3$	$-H$	$-H$	1.49	0.89	8.85	8.16
7B	o	$-CH_2-CH_2-$ 	$-H$	$-H$	0.68	0.14	2.52	0.96
8B	o	$-CH_2-CH_2-$ 	$-CH_2-CH_2-$ 	$-H$	1.06	–	1.03	–
9B	o	$-CH_2-$ 	$-CH_2-CH_3$	$-H$	0.36	0.25	0.68	0.88
10B	o		$-H$	$-H$	1.02	0.17	1.70	0.41
11B	o			$-H$	0.93	0.29	1.56	0.91
12B	o			$-H$	1.01	0.32	3.32	1.59
13B	o			$-H$	1.16	0.22	3.17	1.52
14B	o		$-H$	$-H$	1.06	0.36	3.93	1.89
15B	o	$-H$	$-H$	$-C\equiv N$	0.58	–	1.74	–
16B	o		$-H$	$-C\equiv N$	0.80	0.14	4.68	1.41

Tables 1B and C present similar data for I-123 iodobenzylamine derivatives and I-123 iodophenethylamine derivatives, respectively.

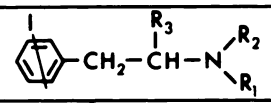
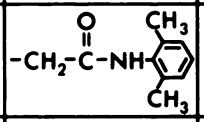
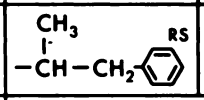
The upper portion of Table 2 presents the activity in various tissues of the rat at 5, 60, and 180 min after i.v. injection of S-(+)-N-isopropyl-*p*-[^{123}I]iodoamphetamine. Data are expressed as percent administered dose per gram of tissue (wet weight). Given in the lower portion of the table are the total activities in the entire bladder including urine, the entire small and large bowel including contents, and entire stomach including contents.

For N-alkyl iodoaniline derivatives (Table 1A), iodination in the *p* position generally resulted in greater brain activity than for the *o* position at both 5 and 60 min (compounds 2A as opposed to 1A, and 9A as opposed to 8A). Results with N-aryl derivatives of iodoaniline are ambiguous, since such compounds can be considered N-iodophenyl derivatives of the corresponding aryl amine (e.g., 3A, 4A, 6A, 7A). N-substitution with a single lipophilic group resulted in greater brain activity than that noted with the primary amine (compounds 3A, 6A, 8A, as opposed to 1A). Generally, the highest brain activity was seen with benzyl, isopropyl, and phenethyl N-substitution (compounds 3A, 4A, 8A, 9A, and 6A, as opposed to 1A and 2A). The highest brain-to-blood ratio at 5 min was seen with N-isopropyl-*p*-iodoaniline. N-substitution with two lipophilic groups (cpd. 5A) or incorporation of the N into a ring structure (cpd. 12A), resulted in lower brain activity than that seen with a single N-substitution. Except for *o*-iodoaniline, and N,N-dibenzyl-*p*-iodoaniline, all iodoaniline derivatives showed higher absolute concentration of activity in brain, and higher brain-to-blood ratios, at 5 min than did 4-iodoantipyrine (I-123), which can also be considered a *p*-iodoaniline derivative (cpd. 12A).

For N-isopropyl iodobenzylamine (Table 1B), iodination in the *m* position resulted in greater brain activity than in the *o* position at both 5 and 60 min (compound 4B as opposed to 3B). N-substitution by a tert-butyl or isopropyl group resulted in higher brain activity than by ethyl, propyl, phenyl, phenethyl, or α-methylphenethyl groups (compounds 6B and 3B as opposed to 1B, 2B, 10B, 7B, and 14B). N-substitution with two

TABLE 1C.

LOCALIZATION IN RAT BRAIN OF I-123 ACTIVITY IODOPHENETHYL AMINE DERIVATIVES

No.	Position of I				% Dose per gram		Brain/blood ratio	
		R_1	R_2	R_3	5 min	60 min	5 min	60 min
1C	o	−H	−H	−H	0.70	—	0.49	—
2C	o	$-CH_3$	−H	−H	0.57	—	0.49	—
3C	o	$-CH_2-CH_2-CH_3$	−H	−H	1.17	0.44	4.03	2.20
4C	o	$-CH-(CH_3)_2$	−H	−H	1.03	0.67	8.58	5.83
5C	o	$-CH_2-CH_2-$ 	−H	−H	0.74	0.48	4.77	5.17
6C	o		−H	−H	0.73	0.08	1.33	0.31
7C	o	$-CH_2-CH_2-$ 	$-CH_2-CH_2-$ 	−H	0.20	0.11	0.24	0.17
8C	o		−H	−H	0.82	0.83	7.13	7.86
9C	o			−H	1.08	—	2.35	—
10C	p	−H	−H	$-CH_3{}^R$	1.38	2.07	10.60	18.50
11C	p	−H	−H	$-CH_3{}^S$	1.22	1.88	7.04	11.30
12C	p	$-CH-(CH_3)_2$	−H	$-CH_3{}^R$	**1.57**	**2.14**	**12.60**	**20.70**
13C	p	$-CH-(CH_3)_2$	−H	$-CH_3{}^S$	1.32	1.93	12.80	15.40

isopropyl or phenethyl groups generally resulted in lower brain-to-blood ratios than did a single N-substitution with these groups (compounds 5B and 8B as opposed to 3B and 7B). N-substitution with an *o*-iodobenzyl group and an ethyl group (compound 9B) clearly resulted in decreased brain activity. Incorporation of the nitrogen of the benzylamine in a piperidine or pyrrolidine nucleus did not result in any improvement in brain uptake over simpler N-substituted amines (compounds 11B, 12B, and 13B as opposed to all others). Nitrile substitution on the α carbon appeared to decrease absolute brain uptake somewhat but may have increased the brain-to-blood ratio (compound 16B as opposed to 10B). Except for one compound containing a nitrile in the α position (15B) and one containing an N-substitution with an *o*-iodobenzyl and an ethyl group (9B), all iodobenzylamine derivatives studied showed higher absolute brain activities and higher brain-to-blood ratios at 5 min than did 4-iodoantipyrine (I-123).

For the iodophenethylamine derivatives (Table 1C), N-substitution by a propyl or isopropyl group improved brain uptake and the brain-to-blood ratio over the primary amine (3C and 4C as opposed to 1C). N-methyl substitution was comparable to the primary amine (2C as opposed to 1C). N-substitution with phenethyl, β-methylphenethyl (RS), or 2,6-dimethylphenylcarbamoylmethyl did not appear to increase the absolute level of brain activity over that seen with the primary amine, but they did appear to increase the brain-to-blood ratio (5C, 8C, and 6C as opposed to 1C). N-substitution with two phenethyl groups resulted in lower brain uptake and lower brain-to-blood ratios than a single N-substitution with this group (7C as opposed to 5C). Incorporation of the nitrogen of the phenethylamine into a piperidine nucleus did not result in any appreciable difference in results from those obtained with simpler N-substituted amines (9C as opposed to most others). Addition of a methyl group in the α position resulted in an increase in brain activity and an increase in the brain-to-blood ratio at 60 min, compared with that seen at 5 min (10C, 11C, 12C, and 13C). This finding was not seen with any other group of compounds studied. In this series of experiments, R isomers showed somewhat higher brain activities than did S isomers (10C and 12C as opposed to 11C and 13C). N-substitution with an isopropyl group showed somewhat higher brain uptake and higher brain-to-blood ratios than did the unsubstituted primary amine (12C and 13C as opposed to 10C and 11C). Eleven out of 13 compounds in this series showed higher brain activity and much higher brain-to-blood ratios than did 4-iodoantipyrine (I-123) at 5 min.

If we compare the brain-to-blood activity ratio at 5

TABLE 2.
TISSUE ACTIVITY IN RAT AFTER ADMINISTRATION OF S(+)-N-ISOPROPYL-p-IODOAMPHETAMINE

Tissue	Percent of dose per gram of tissue		
	5 min[1]	60 min[1]	180 min[2]
Lungs	11.45	9.51	9.84
Adrenals	4.40	2.62	2.42
Kidneys	3.17	1.82	0.99
Pancreas	2.68	1.88	1.39
Liver	2.64	1.89	1.58
Brain	**1.32**	**1.93**	**1.49**
Heart	1.28	0.85	0.72
Skeletal muscle	**0.42**	**0.29**	**0.31**
Blood	**0.11**	**0.13**	**0.12**
	Percent dose per whole organ plus contents		
Total bladder plus urine	0.12	2.16	6.30
Total small and large bowel plus contents	11.62	10.53	11.52
Total stomach plus contents	1.42	3.46	9.21

[1] Data are averages from two rats. [2] Data from one rat.

min for N-isopropyl derivatives of *o*-iodoaniline (cpd. 8A, ratio 1.13) with that of *o*-iodobenzylamine (cpd. 3B, ratio 7.63) with that of *o*-iodophenethylamine (cpd. 4C, ratio 8.58), the data suggest that for this series of compounds the highest brain-to-blood ratio is achieved with derivatives of phenethylamine, followed by benzylamine, followed by aniline.

Compound 12C was studied using the system of Oldendorf et al. (*4,5*). It was concluded that its BUI was comparable to that of nicotine. Retention time in the brain exceeded that of nicotine. It is estimated that extraction efficiency of the brain for the compound was essentially 100% per single pass (*6*).

The in vivo distribution of compound 13C was studied in rats on eight occasions for eight separate batches of the I-123-labeled material. The results were comparable in each study. The results of one of these studies are shown in Table 2. The urethra was clamped immediately after injection to retain urine in the bladder during the course of the study, and the rats were maintained under pentobarbital anesthesia. Only 6.3% of the administered activity was excreted in the urine during the first 3 hr of the study, and essentially none was excreted into the small or large intestine as evidenced by failure of activity in the bowel to increase with time (lower portion of table). Progressive increase in stomach activity was seen, suggesting either a degree of in vivo deiodination of the agent or accumulation of the agent in the stomach consequent to the physiological pH gradient across the gastric mucosa. Lungs showed the highest tissue activity, which did not decrease to any great extent within 180 min. All other tissues showed decreasing activity with time except for brain, which showed increase in activity during the first 60 min. At all times the brain-to-blood ratio was greater than 10 and the brain-to-skeletal-muscle ratio was greater than 3.

Iodine-123-labeled N-tert-butyl-*p*-iodobenzylamine was administered intravenously to rats at carrier doses of 0.28 mg/rat and 6.08 mg/rat. The two carrier doses caused no observable difference in brain activity at 5 and 60 min. Compound 13C labeled with I-123 was also administered to rats at carrier dose levels ranging from 0.1 mg/rat to 1.0 mg/rat and again the carrier dose levels gave no difference in brain activity at 5 and 60 min. This compound and compounds 12C and 13C were studied in dogs and monkeys. The results confirmed high brain uptake of the compounds in both nonrodent species (*6*).

DISCUSSION

In this study, iodine at the para position gives greater brain uptake than at the ortho position for N-alkyl aniline derivatives, and iodine at the meta position gives greater brain uptake than at the ortho position for N-isopropyl benzylamine. Shulgin and Sargent have demonstrated that 2,5-dimethoxy-*p*-bromoamphetamine has greater psychotomimetic activity than the unhalogenated parent 2,4,5-trimethoxyamphetamine (*2*). Retention of *p*-chloroamphetamine in the brain appeared to be much greater than that of the parent amphetamine (*7*). Kuntzman, Tsai, and Burns report greater tissue uptake in general, and greater brain uptake specifically, for chloronorchlorcyclizine than for the unhalogenated parent norcyclizine (*8*). Iodinated antipyrine has a greater brain uptake (BUI = 130) than antipyrine itself (BUI = 68) (*9*). As a working hypothesis, we suggest that for a variety of nitrogen-containing

compounds, introduction of a halogen in the structure may improve brain accumulation and retention of the compound, and that for amines containing a benzene ring addition of a halogen results in increased brain accumulation in the following order of position of the halogen: $p > m > o$.

From the present work, we may conclude that for ring-iodinated phenylalkylamines, the brain uptake, retention, and brain-to-blood ratios are greatest when the alkyl group is α-methylethyl (amphetamine derivatives), followed by ethyl (phenethylamine derivatives), followed by methyl (benzylamine derivatives). The presence of any of these alkyl groups results in greater brain activity than when none of these is present (iodoaniline derivatives).

For derivatives of iodoaniline, benzylamine, and phenethylamine, N-addition of a single lipophilic group usually increases brain uptake. Addition of a single lipophilic group (secondary amine) shows greater brain-to-blood ratios than when two lipophilic groups are added on the nitrogen (tertiary amine), or when the nitrogen is incorporated in a ring structure, such as in a piperidine nucleus.

Remarkably, 34 out of the 40 compounds reported in this paper had brain uptake and brain-to-blood activity ratios greater than that for iodoantipyrine at 5 min. Most of the agents showed brain-to-blood ratios over three times that of iodoantipyrine at 5 min, and ten showed a tenfold or greater brain-to-blood ratio than that seen at 5 min with 4-iodoantipyrine. The *p*-iodoamphetamines generally showed brain-to-blood ratios of over 20 times that of iodoantipyrine at 5 min, and 100 times at 60 min. Clearly the size of their "distribution space" in the brain is substantially greater than that of the brain's freely equilibratable tissue water.

Generally, noncarrier-mediated passage of an amine across a cell membrane is ascribed to free diffusion of its non-ionized lipophilic form. If the concentration of the free amine is rate-limiting in its diffusion across cell membranes, we would anticipate that the lower the pKa of an amine, the greater will be the fraction of the non-ionized lipophilic form at physiological pH and the more rapid will be its diffusion across cell membranes. In the present study, the brain activity and brain-to-blood ratios at 5 and 60 min did not correlate with the relative amount of free base at body pH anticipated from the compound's structure. Aniline derivatives have a much lower pKa than benzylamine or phenethylamine derivatives (*10*), yet in general, brain activity and brain-to-blood ratios were lower at 5 min for the aniline derivatives. Similarly, placement of a halogen on the ortho position of the benzene ring should result in a lower pKa than its placement on the para position, and primary amines should have a lower pKa than secondary amines (*10*); yet para-iodinated secondary amines showed higher brain activity and brain-to-blood ratios at 5 min than did their ortho-halogenated or primary amine analogs. Moreover, even the anticipated relative lipophilicity of the free base did not correlate simply with brain activity or brain-to-blood ratio at 5 and 60 min (e.g., tertiary amines showed less brain-to-blood ratios than did their primary amine analogs). These data suggest that neither concentration of the free amine at body pH nor lipophilicity alone is rate-limiting in determining brain activity or brain-to-blood activity ratios at 5 and 60 min.

One may ascribe a degree of tissue retention of amines with a pKa in excess of 7.4 to an extravascular-intravascular concentration gradient arising from a lower pH in the extravascular against the intravascular space. Possibly such is the case in accumulation of activity in the stomach and in the urine. However, in order for pH gradients to account for more than a tenfold difference in brain and blood activity observed with the amphetamine derivatives, the intracerebral pH would have to be over 1 pH unit lower than that in the blood. Moreover, if such pH gradients were the major factor in establishing a high brain-to-blood ratio, similar ratios should have been observed for all benzylamine and phenethylamine derivatives, since they all have pKa values substantially in excess of 7.4.

One may also ascribe a degree of brain accumulation of these agents to a favorable partition coefficient between brain lipids and blood. However, if lipophilicity, as classically defined, were the major factor in producing high brain-to-blood ratios at 5 and 60 min, such ratios should correlate with the compounds' lipophilicity as anticipated from their chemical structure. As noted previously, the brain-to-blood ratios for these compounds do not correlate directly with anticipated lipophilicity.

We propose that, at least in part, the agents studied are found to localize in the brain at 5 and 60 min primarily because of the presence in the brain or brain vasculature of high-capacity, relatively nonspecific binding sites for amines. Data presented elsewhere demonstrate the ability of N-isopropyl-*p*-iodoamphetamine to interact with the brain's cortical synaptosome mechanisms for uptake and release of neurohumeral amine transmitters (*5*).

Certain characteristics of the postulated binding sites interacting with the agents in the present study are suggested from our data and those in the literature. At least one surface of the N region of the agent must be free to interact with the binding site (i.e., not sterically hindered). The binding site should be electronegative to allow it to bind to the nitrogen of the agent through hydrogen bonding, and the affinity of such binding may be proportional to the pKa of the agent. The regions around the binding site must be lipophilic to allow for optimized interaction with lipophilic groups surrounding the N region of the agent; minimizing degrees of rotational freedom of such lipophilic groups surrounding the N

region of the agent favors binding (such as is present with α-methyl and N-isopropyl or N-tert-butyl substitution). The region surrounding the electronegative N binding site of the receptor is sufficiently cramped that a benzene ring is best accommodated by being removed from the N binding region by one or preferably two carbon atoms, and whereas one or two benzene rings can be accommodated in the region if they are removed from the N region by a distance of one or two carbon atoms, three benzene rings cannot be so accommodated.

Based upon the known metabolism of amphetamine (*11*), and the probability that the *p* iodo group of *p*-iodoamphetamine will also block *p*-hydroxylation (*12*) and that its α-methyl group will inhibit monoamine oxidase (*13*), we anticipate that if N-dealkylation occurs, the principal routes of metabolism of N-isopropyl-*p*-iodoamphetamine will be oxidative deamination (primarily in hepatic microsomes) to form *p*-iodophenylacetone. The compound may be subject to β-hydroxylation (largely by dopamine hydroxylase) to form *p*-iodonorephedrine or N-isopropyl-*p*-iodonorephedrine. It is further anticipated that *p*-iodophenylacetone will be metabolized to *p*-iodobenzoic acid (*11*), which will be largely conjugated with glycine to form *p*-iodohippuric acid or with glucuronic acid to form *p*-iodobenzoylglucuronic acid. Since *p*-hydroxy-norephedrine has been shown to be stored in sympathetic nerve endings and also to localize in brain (*11*), it is possible that a portion of the delayed concentration and retention of I-123 activity in the brain, following administration of *p*-iodoamphetamine, is a result of concentration and retention of the hypothesized metabolite *p*-iodonorephedrine or its N-isopropyl derivative. Moreover, the early high concentration of activity in the adrenals, with subsequent clearance, seen with *p*-iodoamphetamine (I-123) and its derivatives herein noted, may be related to the action of dopamine β-hydroxylase on *p*-iodoamphetamine to form *p*-iodonorephedrine, which is lost from the adrenals and concentrates elsewhere. (Note that sympathetic nerve endings are rich in dopamine β-hydroxylase.)

Others have observed that, in general, N-alkyl-amphetamines de-alkylate more rapidly as the N-substitution is increased from methyl to isopropyl (*11*), and that N-isopropyl-*p*-chloroamphetamine is largely de-alkylated to *p*-chloroamphetamine (*12*), and it is on this basis that it is reasonable to assume that the N-isopropyl derivative of *p*-iodoamphetamine will de-alkylate yielding the *p*-iodoamphetamine parent. If the N-isopropyl group is not rapidly de-alkylated in the metabolism of the agent, then oxidative deamination pathways could be largely blocked and the principal metabolites of the agent may be N-isopropyl derivatives of *p*-iodonorephedrine.

It is anticipated that a large portion of N-isopropyl-*p*-iodoamphetamine excreted in the urine will, like other amphetamine derivatives, be relatively unchanged (e.g., N-isopropyl-*p*-iodoamphetamine or the de-alkylated product *p*-iodoamphetamine). If such proves to be the case, marked enhancement in the urinary excretion rate should be seen when steps are taken to acidify the urine, as is seen with amphetamine (*11*).

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