

RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Radiolabeled Adrenergic Neuron-Blocking Agents: Adrenomedullary Imaging with [¹³¹I]iodobenzylguanidine

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The tissue distributions of three radioiodinated neuron-blocking agents have been determined in dogs. Iodine-125-labeled meta- and para-iodobenzylguanidines show a striking affinity for, and retention in, the adrenal medulla. Peak concentrations of the two isomers exceed those of previously reported adrenophilic compounds. High myocardial concentrations were also observed at early time intervals. Images of the dog's adrenal medullae have been obtained with para[¹³¹I]-iodobenzylguanidine.

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The adrenal gland consists of two embryologically and functionally distinct regions, the cortex and the medulla. Imaging of the human adrenal cortex and its neoplasms has been possible for nearly a decade through the use of radioiodinated cholesterols (1,2). However, no comparable radiopharmaceutical has yet been developed for the adrenal medulla and its neoplasms, such as pheochromocytoma and neuroblastoma.

The central role the adrenal medulla plays in the synthesis and storage of catecholamines has led to previous radiopharmaceutical approaches based on labeled dopamine and its analogs (3,4). A second but closely related approach derives from the functional similarity between the chromaffin cells of the adrenal medulla and adrenergic neurons (5). If one considers the adrenal medulla a specialized sympathetic ganglion, then compounds known to have an affinity for adrenergic nerves might be expected to localize in the adrenal medulla. This rationale led to the first imaging of the adrenal medulla with a radioiodinated analog of the antiadrenergic agent bretylium (6).

In the early 1960s, both bretylium and guanethidine

were found to be potent neuron-blocking agents that act selectively on adrenergic nerves (7). Since that time, the combination of the benzyl portion of bretylium with the guanidine group of guanethidine has led medicinal chemists to a variety of substituted aralkylguanidines with even greater antiadrenergic potency (8). This development has prompted us to begin an evaluation of radioiodinated aralkylguanidines as potential adrenal medulla and myocardial imaging agents. We report here the striking affinity of these compounds for the adrenal medulla and the imaging of this organ in the dog using para[¹³¹I]iodobenzylguanidine.

MATERIALS AND METHODS

Microanalyses were performed commercially. Thin layer chromatography was done on precoated, 250- μ silica gel plates.[†] The Cellex D anion-exchange cellulose (hydroxide form)[†] and the three isomeric iodobenzylamines[‡] were obtained from commercial sources.

Proton magnetic resonance (PMR)[§] and infrared (IR)[¶] spectra were obtained; high pressure liquid chromatography (HPLC)** data were also determined.

Synthesis of unlabeled compounds. The ortho- and para-iodobenzylguanidine sulfates were prepared by the method of Short and Darby (8) by reaction of the appropriate iodobenzylamine with 2-methyl-2-thiopseudourea sulfate in refluxing water. The previously unreported meta-iodobenzylguanidine sulfate was syn-

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thesized as follows:

A mixture of *m*-iodobenzylamine hydrochloride (539 mg, 2.0 millimol) and cyanamide (127 mg, 3.0 millimol) was stirred and heated in an oil bath at 100°C for 4 hr. The resulting glassy solid was dissolved in 1 ml of water, and a solution of KHCO₃ (200 mg, 2.0 millimol) in 1 ml of water was added dropwise with stirring. The precipitated *m*-iodobenzylguanidine bicarbonate was collected, washed with cold water, and dried in vacuo: yield 575 mg (85%), mp 124–126°C.

To the *m*-iodobenzylguanidine bicarbonate (539 mg, 1.6 millimol) in 5 ml of water were slowly added 0.8 ml (1.6 mEq) of 2 *N* H₂SO₄. The resulting suspension was warmed to solution, and the desired guanidinium sulfate crystallized on cooling to room temperature. The colorless crystals were collected, washed with cold water and dried in vacuo: yield 403 mg (78%), mp 164–165°C. Recrystallization from H₂O-EtOH provided *m*-iodobenzylguanidine sulfate as colorless crystals: mp 166–167°C, HPLC [THF/0.1 *M* NaH₂PO₄ 12/88, 3.0 ml/min] showed only one peak *t*_R = 8.6 min, IR (nujol) 3340 (NH), 3160 (NH), 1660 and 1630 (C=N), 1090 (S=O), 780 and 695 cm⁻¹ (1,3-disubstituted benzene); PMR (CD₃OD) δ 4.36 (S,2,CH₂), 6.96–7.73 [m(seven peaks), 4, arom]. The aromatic peak pattern is identical to that observed for *m*-iodobenzylamine hydrochloride in CD₃OD. Anal: calcd. for C₈H₁₀IN₃·0.5 H₂SO₄: C, 29.64, H, 3.42; found: C, 29.55, H, 3.40.

Synthesis of radiolabeled compounds. The following radiosynthesis of para-[¹²⁵I]iodobenzylguanidine sulfate exemplifies the general procedure used in this study.

Radioiodide exchange. Two milliliters of deionized and redistilled water and 5 mg of para-iodobenzylguanidine sulfate were added to approximately 5 mCi of carrier-free Na¹²⁵I. The solution was refluxed for 72 hr, cooled to ambient temperature, and passed through a glass column packed with 1.5 g of Cellex D anion exchange cellulose to remove unreacted radioiodide and iodate. The radiochemical yield was 60–80%, resulting in a specific activity of 0.6–0.8 mCi/mg. Specific activities up to 10 mCi/mg could be obtained by this procedure but with a concomitant decrease in radiochemical yield.

Purity determination. The radiochemical purity was greater than 98% as determined by thin layer chromatography on silica gel G using two solvent systems: (a) 1:1 ethyl acetate:ethanol (*R*_f = 0.0; *R*_f of free radioiodide = 0.60); (b) 3:1 *n*-propanol:10% ammonium hydroxide (*R*_f = 0.15, *R*_f of free radioiodide = 0.75; *R*_f of para-iodobenzylamine = 0.35). The radiolabeled compound showed no detectable decomposition for up to 8 wk when stored as the sulfate salt in water or physiological saline at 4°C.

Since the *R*_fs of the three isomeric guanidines were nearly identical in the above TLC systems, radio-HPLC was needed to verify the absence of rearranged isomeric

impurities. The radiochemical purity of para-[¹²⁵I]iodobenzylguanidine was routinely found to be >98% on a μ Bondapak C18 column (THF/0.1 *M* NaH₂PO₄ 12/88, 2.0 ml/min). With this HPLC system, the retention times (*t*_R) of the para-, meta-, and ortho- isomers were 15 min 20 sec, 12 min 20 sec, and 6 min 40 sec, respectively. The absence of 3,4-di-[¹²⁵I]iodobenzylguanidine (*t*_R = 32 min 25 sec at 3.0 ml/min), a potential impurity that could arise from electrophilic addition to the aromatic ring, was also verified.

Further details of this radiosynthesis and the purity determination will be published elsewhere, including the production of these compounds in carrier-free form by a different synthetic scheme (9).

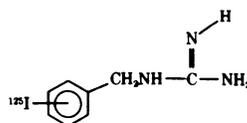
Tissue distribution studies. These were performed on 41 mongrel dogs injected intravenously with 100 μ Ci of the I-125-labeled compounds as the sulfate salts in approximately 2 ml of water. Two or three dogs were injected with each isomer and killed by i.v. injection of sodium pentobarbital at the time intervals shown in Table 1. Duplicate samples of 18 different tissues from each dog were counted in an autogamma counter, with corrections made for radioactive decay, background, and counter efficiency. Blood samples were obtained by cardiac puncture. To normalize for differences in animal weights, tissue concentrations were expressed as percentage kilogram dose per gram (10). The canine model was selected because of the ease with which its adrenomedullary and adrenocortical tissues can be separated.

Imaging studies. Three male dogs weighing 22.1 kg, 30.0 kg, and 34.0 kg were injected intravenously with 1.0 mCi of para-[¹³¹I]iodobenzylguanidine. With the dogs anesthetized (sodium pentobarbital), a large-field-of-view camera (high-energy, parallel-hole collimator), interfaced to a minicomputer, was used to obtain posterior adrenal images at 1, 2, 3, 5, 6, and 10 days after injection. Confirmation of adrenal localization was made by subsequent injection of 2 mCi of Tc-99m DTPA into the immobilized animal without altering position. The resultant renal images were superimposed over the adrenal scans using the computer.

Analysis of radioactivity in adrenal glands. Two dogs were injected with 1 mCi of para-[¹³¹I]iodobenzylguanidine and killed 5 days later. The adrenal medullae were removed and homogenized for 5 min with a ground-glass homogenizer in 6.4 ml of 0.4 *M* HClO₄ containing 2 mg/ml of unlabeled para-iodobenzylguanidine. The homogenate was centrifuged at 2000 *g* for 10 min, the supernatant decanted, and the residual pellet resuspended in 6.4 ml of 0.4 *M* HClO₄. One-milliliter aliquots were taken from both fractions and counted in a gamma counter. Based on the total radioactivity in both fractions, the extraction efficiency was 75–80%.

Approximately 0.2 ml of the supernatant was streaked

TABLE 1. TISSUE DISTRIBUTION[†] OF [¹²⁵I]IDOBYENZYLGUANIDINES IN THE DOG



Compd. No.	Position of radioiodine	Time (hr)	Tissue concentration (% kg dose/g) ^{1,2}										
			Adrenal medulla	Adrenal cortex	Liver	Heart	Blood	Lung	Spleen	Kidney	Thyroid		
1	para	0.5	3.2 (2.1-5.0)	0.42 (0.28-0.55)	0.69 (0.63-0.78)	0.59 (0.45-0.75)	0.02 (0.02-0.03)	0.38 (0.24-0.49)	0.33 (0.21-0.49)	0.64 (0.40-0.88)	0.5 (0.3-1.0)		
		2.0	9.5 (6.7-11.1)	0.58 (0.48-0.78)	0.37 (0.35-0.40)	0.53 (0.43-0.65)	0.04 (0.02-0.05)	0.53 (0.46-0.64)	0.46 (0.44-0.47)	0.25 (0.24-0.28)	0.9 (0.6-1.0)		
		24.0	9.2 (8.7-9.5)	0.12 (0.08-0.18)	0.08 (0.06-0.10)	0.17 (0.10-0.27)	0.02 (0.01-0.02)	0.13 (0.09-0.16)	0.31 (0.28-0.33)	0.06 (0.05-0.07)	9.0 (4.3-17.3)		
		48.0	14.3 (11.6-17.2)	0.17 (0.11-0.28)	0.04 (0.03-0.06)	0.09 (0.06-0.11)	0.02 (0.01-0.02)	0.08 (0.05-0.10)	0.27 (0.21-0.37)	0.04 (0.03-0.05)	13.8 (3.7-27.4)		
		72.0	14.0 (10.5-18.9)	0.18 (0.12-0.28)	0.03 (0.02-0.04)	0.04 (0.03-0.07)	0.01 (0.01-0.01)	0.05 (0.03-0.07)	0.18 (0.13-0.24)	0.03 (0.02-0.03)	33.6 (27.4-42.4)		
		120.0	13.3 (9.2-17.7)	0.10 (0.08-0.12)	0.01 (0.00-0.02)	0.02 (0.01-0.03)	0.00 (0.00-0.00)	0.03 (0.01-0.05)	0.06 (0.04-0.09)	0.01 (0.01-0.02)	22.5 ³ (15.0-28.6)		
		192.0	9.1 (6.8-13.1)	0.12 (0.05-0.22)	0.01 (0.00-0.01)	0.01 (0.00-0.01)	0.00 (0.00-0.00)	0.01 (0.00-0.01)	0.01 (0.00-0.02)	0.00 (0.00-0.01)	21.3 (12.2-38.0)		
		2	ortho	0.5	1.7 (1.5-1.9)	0.29 (0.26-0.32)	0.44 (0.43-0.45)	0.51 (0.51-0.52)	0.07 (0.07-0.07)	0.23 (0.17-0.28)	0.13 (0.10-0.16)	0.66 (0.51-0.80)	0.3 (0.2-0.3)
				2.0	2.0 (1.9-2.0)	0.16 (0.16-0.16)	0.17 (0.17-0.17)	0.36 (0.35-0.36)	0.06 (0.06-0.06)	0.17 (0.17-0.17)	0.10 (0.10-0.10)	0.26 (0.25-0.28)	0.4 (0.2-0.6)
				24.0	2.7 (2.0-3.4)	0.05 (0.03-0.06)	0.03 (0.03-0.04)	0.02 (0.01-0.03)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.03 (0.02-0.05)	2.6 (1.2-4.0)
48.0	1.3 (1.2-1.4)			0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.01 (0.01-0.01)	0.00 (0.00-0.00)	0.01 (0.01-0.01)	9.4 (9.0-9.8)		
3	meta			0.5	5.4 (4.1-6.6)	0.61 (0.58-0.65)	0.34 (0.29-0.39)	0.47 (0.44-0.50)	0.02 (0.02-0.03)	0.22 (0.13-0.32)	0.30 (0.24-0.36)	0.54 (0.49-0.59)	0.6 (0.5-0.7)
		2.0	6.3 (5.9-6.7)	0.39 (0.30-0.48)	0.17 (0.08-0.26)	0.50 (0.33-0.67)	0.02 (0.02-0.03)	0.46 (0.29-0.64)	0.29 (0.21-0.37)	0.26 (0.21-0.30)	0.6 (0.5-0.6)		
		24.0	7.9 (7.3-8.5)	0.17 (0.07-0.27)	0.03 (0.02-0.23)	0.10 (0.08-0.11)	0.02 (0.02-0.03)	0.05 (0.03-0.07)	0.20 (0.18-0.23)	0.04 (0.04-0.05)	3.4 (2.1-4.7)		
		48.0	13.6 (11.8-15.4)	0.10 (0.08-0.11)	0.02 (0.02-0.03)	0.06 (0.05-0.08)	0.01 (0.01-0.01)	0.03 (0.02-0.03)	0.19 (0.19-0.20)	0.03 (0.02-0.04)	1.3 (0.5-2.1)		
		120.0	13.3 (10.9-15.7)	0.12 (0.09-0.16)	0.01 (0.01-0.01)	0.02 (0.02-0.02)	0.00 (0.00-0.00)	0.01 (0.01-0.01)	0.06 (0.02-0.09)	0.01 (0.01-0.01)	0.8 (0.2-1.4)		
		192.0	9.3 (8.9-9.8)	0.03 (0.03-0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.01 (0.00-0.02)	0.01 (0.01-0.01)	0.00 (0.00-0.00)	2.3 (1.6-2.9)		

¹ Tissue data for all organs are available from authors on request.

² All other tissues except urine showed concentrations of 0.16% kg dose/g or less at 1-8 days.

³ N = 3 for Compound 1, N = 2 for Compounds 2 and 3. All values expressed as % kg dose/g; numbers in parentheses give the range.

⁴ This value was 0.15 when two dogs were maintained on a regimen of potassium iodide before and after injection.

on a silica-gel-G plate and developed with 3:1 n-propanol:10% ammonium hydroxide. The radiochromatograms were subsequently obtained following 1- or 2-day exposure on XRP-5 x-ray film.^{††} Zones of radioactivity were quantitated by adding the scraped-off silica-gel samples directly to tubes for gamma counting.

Thyroid-blocking study. Two dogs were administered 300 mg of potassium iodide orally each day for 7 days before tracer injection, with the same regimen continued until sacrifice at 5 days after injection.

RESULTS

Table 1 summarizes the tissue concentrations of the three isomeric [¹²⁵I]iodobenzylguanidines in nine selected tissues of the dog. Both the meta- and para- isomers showed great affinity for the adrenal medulla, with high concentrations appearing as early as 2 hr and per-

sisting throughout the 8 days of the study. Besides the adrenal medulla, only the thyroid demonstrated high levels of radioactivity at 8 days, with all other tissues approaching background. The meta- isomer (Compound 3) showed a strikingly lower thyroid radioactivity concentration than the para- isomer (Compound 1) at longer time intervals. The heart showed relatively high radioactivity concentrations with all three isomers at early time intervals, an observation consistent with the rich sympathetic innervation of the heart. In contrast to the previously reported bretylium analogs (6), the iodobenzylguanidines show negligible biliary excretion.

With Compound 1, low thyroid activity (0.15%) was obtained in two dogs maintained on oral potassium iodide and killed 5 days after injection of 100 μCi of 1. Thin layer chromatography of the supernatant of the adrenal homogenate at 5 days revealed that >95% of the

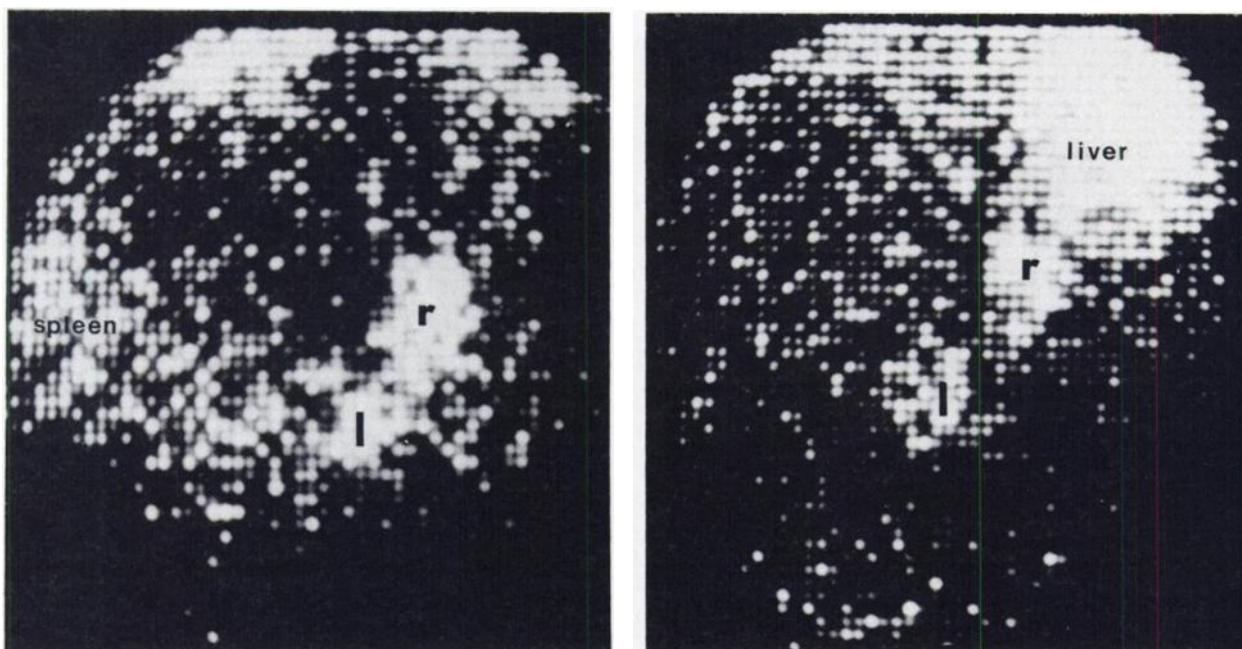


FIG. 1. Computer displays of the same male dog (30.0 kg) at 3 days (left) and 5 days (right) after injection of Compound 1 labeled with I-131, showing posterior images of the dog's adrenal medullae.

extracted radioactivity was unchanged Compound 1.

The three dogs injected with Compound 1 labeled with iodine-131 all gave clear and nearly identical images of the adrenal medullae. Figure 1 includes scintigrams of a dog's adrenal medullae obtained at 3 and 5 days after injection. Adrenal images in the dog were visible at 2 days, but satisfactory resolution from background activity (particularly in the spleen and liver) was attained only after 3 days.

DISCUSSION

The high affinity of Compound 1 for the dog adrenal medulla can be put into perspective by comparing it with other adrenophilic radiochemicals. Its peak adrenomedullary concentration is nearly an order of magnitude higher than that obtained with labeled dopamine (3,10), and four times that of ortho-[¹³¹I]iodobenzyl dimethyl- β -hydroxyethyl ammonium, the bretylium analog that was recently reported to give the first images of a dog's adrenal medullae (6). In addition, the adrenal medullary concentration of 1 is 90% higher than the corresponding peak adrenocortical uptake of 6 β [¹³¹I]iodo-19-norcholesterol (11). The latter steroid has found wide clinical use in diagnosing adrenocortical disease (12).

Of special note is the prominent liver activity near the dog's adrenal images despite the fact that the adrenomedulla-to-liver concentration ratio approaches 1000 at 5 days after administration. This underscores the stringent requirements placed on an adrenomedullary imaging agent. The dog adrenal medullae are not only small (1/5 the size of the thyroid glands) but are sur-

rounded by large, metabolically active organs. On a % dose/organ basis, the uptake of Compound 1 at 5 days in the dog's adrenal medullae is 0.16%, whereas in the liver, which is approximately 3000 times as heavy, the % dose is 0.35% (13). Target-to-nontarget concentration ratios ranging from 10 to 50 are generally sufficient for most organ-imaging radiopharmaceuticals, but they appear to be inadequate to visualize the adrenal medullae by conventional gamma-imaging techniques.

As in the bretylium series, the pharmacological potency (neuron-blocking activity) of the isomeric iodobenzylguanidines parallels their respective affinities for the adrenal medulla, but in contrast to the bretylium series, it is the para- isomer and not the ortho- isomer that shows the greater potency and higher adrenomedullary uptake (6,8).

With Compound 1, nearly all of the radioactivity in the thyroid is due to sequestration of free radioiodide, as evidenced by the low thyroid activity in two dogs maintained on an oral potassium iodide supplement. The thyroid concentrations of all three isomers indicate that the meta- isomer is the most resistant to *in vivo* deiodination.

From the standpoint of possible myocardial imaging, the heart concentration of 1 was equivalent to that of thallium-201, and the heart-to-blood concentration ratio was favorable (~25 at 30 min). However the heart-to-liver and heart-to-lung ratios were near unity.

Although the iodobenzylguanidines, like norepinephrine, are most likely taken up into adrenergic nerves by a saturable, carrier-mediated process, we have observed no increase in uptake in either the heart or adrenal

medulla with carrier-free I-125-1. Details of this experiment will be included in the final full paper.

The remarkably long retention of **1** and **3** in the adrenal medulla may derive from their sequestration within the chromaffin storage granules. In adrenergic nerves, guanidines such as guanethidine and phenethylguanidine are thought to share the same transport pathway as norepinephrine and to accumulate in and displace norepinephrine from intraneuronal storage granules (7,14). If **1** and **3** are mimicking norepinephrine in both transport and storage, their lengthy medullary retention is reasonable in view of the physiological role the adrenal medulla plays in the long-term storage of catecholamines. The study of subcellular elements in the adrenal medulla should help to clarify the mode of retention of these compounds.

Although adrenomedullary images in this report were obtained with the I-131-labeled compound, efforts are currently used to shorten the radiosynthesis time so that I-123-1 or I-123-3 can be utilized. This is important because the avidity of these radiochemicals for the adrenal medulla results in a high radiation dose to that organ. The combined use of I-123-1 or I-123-3 with a tomographic imaging technique, such as the coded aperture (15), may provide images of the human adrenal medullae in less than 1 day.

FOOTNOTES

† Analtech Silica GF,

‡ Bio Rad,

§ Pfaltz and Bauer, Inc., Stamford, CT.

¶ Varian EM360A Spectrometer,

† Beckman Acculab 8,

** Waters Model ALC/GPC 204 Chromatograph with a μ Bondapak C18 column (3.9 mm \times 30.9 cm) from Waters Associates, Milford, MA.

†† Kodak

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