RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Studies with 17β(16α-[^{125}I]Iodo)-Estradiol, an Estrogen Receptor-Binding Radiopharmaceutical, in Rats Bearing Mammary Tumors

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We have studied the distribution of 17β(16α-[^{125}I]iodo)-estradiol (I-E_2) in tumor-bearing and normal rats. High early adrenal-to-blood ratios (up to 22 at 5 min) were seen in all groups, but this fell to six at 1 hr. Uterus-to-blood ratios of 15 were found, and these were fairly constant up to 2 hr after administration. Uptake of label in the uterus, but not in the adrenals, was sensitive to excess diethylstilbestrol, which competes with I-E_2 for estrogen receptors. Mean tumor-to-blood ratios of 1.4, 5.5, and 8.7 were seen at 1 hr in rats with transplanted, spontaneous, and N-nitrosomethylurea-induced tumors, respectively. Diethylstilbestrol was shown to reduce uptake of label by spontaneous tumors. Most of the radioactivity was excreted in the bile by 1 hr. Better estrogen-receptor-binding radiopharmaceuticals can probably be designed.

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In women with breast cancer, the rate of response to anti-estrogenic treatment increases with the content of estrogen receptors in the tumor. Levels of hormone receptors are determined in biopsy samples and used as a guide to therapy.

A gamma-emitting compound that would bind to the receptors in vivo might allow a noninvasive, more accurate screening of these tumors using conventional nuclear medicine instruments. Krohn (*1*) has recently reviewed progress in this area. Among compounds evaluated as estrogen-receptor binding radiopharmaceuticals are estradiol, radioiodinated at C-2 and C-4 (*2,3*), and the corresponding F-18 compounds (*4*). Failure of the latter was unavoidable because of the low specific radioactivities, and the iodo compounds were also unsuccessful because binding to the receptor is hindered by bulky substituents on the aromatic ring (*5,6*). In a study of two other estrogen analogs, Mazaitis et al. (*7*) showed that the binding of monoiodohexestrol to receptors in vivo is masked by nonspecific protein binding, and that 17α-iodoethynyl estradiol suffers rapid de-iodination in the presence of proteins. Katzenellenbogen et al. (*8*) have prepared a series of four tritium-labeled halogenated derivatives of hexestrol that bind to the estrogen receptor in vivo. Two of these, *o*-fluorohexestrol and 1-fluorohexestrol, bind more tightly to the estrogen receptor than estradiol and hold out great promise if they can be labeled with fluorine-18 at a high enough specific radioactivity.

Recently, Hochberg (*9*) introduced 17β(16α-[^{125}I]iodo)estradiol (I-E_2) and showed that it binds to rat uterus in vivo. We report our studies with this compound in normal rats and rats with mammary tumors.

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MATERIALS AND METHODS

Animals. Unless stated otherwise, we used Fischer female rats (150–250 g) bearing transplanted mammary adenocarcinoma 13,762.* Sprague-Dawley rats bearing spontaneous mammary tumors† or tumors induced with *N*-nitrosomethylurea (NMU)‡ were also used (*10*). All

animals were allowed free access to food and water.

Tissue distribution experiments. Five rats were used per time point unless otherwise stated. About 1 μCi of I-125-E_2[‖] (280 Ci/mmol) in 10 μl of ethanol was diluted with 0.4 ml of 0.9% NaCl and injected into the tail vein. After intervals of 5 and 15 min, and 1, 2, 4, and 8 hr, the animals were anesthetized with ether and blood was drawn from the heart. The chest cavity was then opened and the heart excised. Organs were rinsed, blotted, and dropped into preweighed counting tubes. Whole liver and tumor were weighed and 1- to 2-g samples transferred to counting tubes. Tubes were reweighed and then assayed for radioactivity in an automatic gamma well counter. Standards containing one tenth of the injected dose were counted with each experiment and % dose/g, % dose/organ, and organ-to-blood ratios were calculated for each tissue. The tail from each animal was assayed separately in a single-channel gamma well counter to check for residual radioactivity. Differences between groups of animals were assessed statistically using Student's t-test.

Surgical procedures. Operations were done under ether anesthesia. Ovariectomies were performed 3 days before the animals were used in experiments. Adrenalectomies and bile-duct cannulations were done immediately before administration of I-E_2.

Radiochemicals. Each batch of I-125-E_2 (280 Ci/millimol) was subjected to thin layer chromatography (TLC)[§] in chloroform:acetone (95:5, v/v). Spots were located by autoradiography on XRP-1 film.[¶] Over 98% of the radioactivity was associated with a single spot, R_f = 0.3. No spots could be seen under ultraviolet light. On prolonged exposure of the film, other radioactive spots became apparent at R_f = 0.0, 0.4, and 0.6.

RESULTS

Tumor-bearing rats. The tissue distribution of I-125 in rats bearing transplanted mammary tumors after intravenous injection of I-E_2 is shown in Table 1. The blood level of radioactivity declined from 0.28 ± 0.06% dose/g at 5 min to 0.09 ± 0.03 at 1 hr; thereafter it fell more slowly to 0.05 ± 0.04 at 8 hr. The uteri accumulated approximately 1% dose/g by 5 min and stayed fairly constant to 2 hr.

Ovariectomy might be expected to increase receptor-mediated uptake of I-E_2 by depleting endogenous estrogens able to compete for binding to receptors. However, in four castrated female rats, two carrying transplanted tumors and two normal, we found that uteri had 1.27 ± 0.35% dose/g at 1 hr and this was not significantly different from normal, uncastrated female rats (0.99 ± 0.47% dose/g).

Mammary tissue and ovaries behaved like uteri except that the concentration was lower and declined more rapidly after 2 hr. The ovaries lost half of their radioactivity between 5 and 15 min. This behavior was paralleled by blood, bone, brain, heart, kidney, lungs, muscle, pancreas, spleen, thyroid, and tumor. It probably largely represents movement down concentration gradients between blood and the lipid content of the various tissues. Some breakdown of I-E_2 to iodide would account for the later accumulation of label by the thyroid. At 1 hr, bone was the least radioactive tissue at 0.06% dose/g.

At 5 min the adrenal glands had the highest uptake of any tissue, 6.12 ± 1.32% dose/g (Table 1). The adrenal-to-blood ratio fell from 22 at 5 min to 6 at 1 hr.

The distribution pattern in adrenalectomized animals at 1 hr did not differ from that obtained with sham-operated controls, but blood levels in both of these groups were higher (0.20 ± 0.03 and 0.21 ± 0.04% dose/g) than those shown in Table 1. This was probably due to the anesthesia.

The transplanted mammary tumor exhibited about 10% of the uterine uptake at 1 hr; the mean tumor-to-blood ratio was only 1.3. Table 2 shows that in the

TABLE 1. TISSUE DISTRIBUTION (% DOSE/g) of I-125 AFTER I.V. ADMINISTRATION OF 17β(16α-[^{125}I]-IODO)ESTRADIOL TO RATS BEARING TRANSPLANTED MAMMARY TUMORS

Tissue	5 min*	15 min	1 hr	2 hr	4 hr	8 hr
Adrenals	6.12 ± 1.32	1.70 ± 0.67	0.53 ± 0.05	0.32 ± 0.12	0.06 ± 0.04	<0.01
Blood	0.28 ± 0.06	0.17 ± 0.03	0.09 ± 0.03	0.08 ± 0.01	0.06 ± 0.02	0.05 ± 0.04
Kidney	1.73 ± 0.35	0.78 ± 0.28	0.30 ± 0.08	0.20 ± 0.04	0.12 ± 0.02	0.06 ± 0.04
Liver	2.67 ± 0.47	1.82 ± 0.66	0.65 ± 0.09	0.57 ± 0.17	0.57 ± 0.18	0.39 ± 0.26
Lungs	1.34 ± 0.37	0.72 ± 0.15	0.21 ± 0.08	0.12 ± 0.07	0.07 ± 0.02	0.03 ± 0.04
Ovaries	1.84 ± 0.44	0.89 ± 0.40	0.63 ± 0.08	0.59 ± 0.12	0.20 ± 0.05	0.07 ± 0.06
Muscle	0.59 ± 0.09	0.22 ± 0.10	0.10 ± 0.03	0.06 ± 0.02	0.02 ± 0.02	0.01 ± 0.01
Thyroid	0.99 ± 0.31	0.46 ± 0.28	0.58 ± 0.30	1.08 ± 0.90	1.36 ± 0.87	3.70 ± 1.58
Tumor	0.53 ± 0.33	0.25 ± 0.15	0.12 ± 0.02	0.12 ± 0.06	0.05 ± 0.03	0.03 ± 0.02
Uterus	1.12 ± 0.27	0.87 ± 0.42	0.99 ± 0.47	1.25 ± 0.37	0.70 ± 0.26	0.24 ± 0.18

* All values are the mean ± 1 s.d. for five animals.

TABLE 2. TISSUE DISTRIBUTION (% DOSE/g, MEAN AND RANGE) OF I-125 AFTER ADMINISTRATION OF 17β(16α-[^{125}I]IODO)ESTRADIOL TO TUMOR-FREE RATS

Animals	Normal males		Normal females		
Time	15 min	1 hr	15 min	15 min*	1 hr
No. of animals	4	4	4	4	4
Weight (g)	104(100–111)	111(103–125)	127(110–136)	180(160–195)	128(115–140)
Adrenals	3.10(2.19–3.96)	1.09(0.54–1.84)	2.91(2.42–3.47)	0.86(0.19–1.16)	0.50(0.19–0.77)
Blood	0.31(0.21–0.41)	0.15(0.10–0.18)	0.24(0.20–0.28)	0.15(0.11–0.18)	0.10(0.09–1.12)
Kidney	2.04(1.22–2.83)	1.06(0.64–1.39)	1.28(0.96–1.93)	1.25(1.14–1.32)	0.35(0.32–0.43)
Liver	3.56(2.22–4.92)	2.22(1.63–2.62)	2.55(1.74–2.96)	1.32(0.93–1.56)	1.00(0.59–2.01)
Lungs	1.02(0.63–1.69)	0.43(0.25–0.71)	0.87(0.72–1.29)	0.41(0.19–0.81)	0.24(0.20–0.28)
Ovaries/testes	0.86(0.29–1.52)	0.41(0.25–0.51)	1.34(0.67–1.71)	0.38(0.20–0.72)	0.83(0.63–1.24)
Muscle	0.66(0.40–0.84)	0.24(0.13–0.39)	0.43(0.34–0.77)	0.08(0.02–0.17)	0.12(0.10–0.14)
Thyroid	1.10(0.56–1.46)	1.47(0.81–2.31)	0.84(0.61–0.99)	1.20(0.92–1.41)	1.08(0.48–1.85)
Uterus/prostate	1.03(0.60–1.28)	0.78(0.36–1.68)	1.27(0.54–2.08)	0.18(0.03–0.40)	1.81(1.33–2.59)

* 2 nmol of diethylstilbestrol was given intravenously 20 min before 17β(16α-[^{125}I]iodo)estradiol.

Sprague-Dawley rats bearing spontaneous mammary neoplasms, tumors also exhibited little uptake of I-E_2 compared with their uteri (0.11 ± 0.03 and 0.84 ± 0.50% dose/g, respectively), but tissue-to-blood ratios were much higher, at 5.5 ($p < 0.01$ compared with the transplanted tumors). A still higher average value (8.7) was obtained for NMU-induced tumors, but because the range was wider (2–25), a t-test gave only $p < 0.2$ for this group compared with the transplanted tumor group. When diethylstilbestrol was administered 20 min before I-E_2, the uterus-to-blood ratios in rats with spontaneous tumors were markedly lowered ($p < 0.025$). This confirms Hochberg's observations (*9*) and shows that the uterine binding of I-E_2 is to estrogen receptors. Diethystilbestrol also lowered tumor-to-blood ($p < 0.025$) and ovary-to-blood ratios ($p < 0.2$), suggesting involvement of estrogen receptors in the uptake of I-E_2 in these tissues.

Rats without tumors. To determine whether tumor transplants might affect the distribution of I-E_2, a series of experiments was done with tumor-free animals (Table 3). No great differences in tissue-to-blood ratios were seen in females at 15 min or 1 hr. However, the tissue concentrations were higher at 15 min than in tumor-bearing Fischer rats. We found 1.81 ± 0.55% dose/g in the uteri of these animals at 1 hr, the highest values of any animals we studied. As with the tumor-bearing animals, prior administration of diethylstilbestrol reduced the uptake of I-125 in the uteri (and to a lesser extent in the ovaries), but not in the adrenals. A t-test gave $p < 0.1$ for the difference in uterus-to-blood ratio between plus and minus diethylstilbestrol groups. The value for the ovaries was $p < 0.4$. Thus, the adrenal uptake is not mediated by classical saturable estrogen receptors.

Male rats had greater uptake of I-E_2 radioactivity in the adrenals, liver, and skin than females, but statistically these differences were not very reliable ($0.4 > p > 0.2$). Levels in skin (not shown in Tables 1 and 2) were 0.81 ± 0.39 and 0.61 ± 0.22% dose/g at 15 min and 1 hr; in normal females these levels were 0.40 ± 0.20 and 0.28 ± 0.06, while in rats with transplanted tumors they were 0.26 ± 0.18 and 0.25 ± 0.04. The greater liver uptake may be related to the presence in male rat liver of large amounts of a nonreceptor steroid-binding protein (*11*), although much of the liver uptake in both sexes is probably due to metabolites of I-E_2. As expected, testes and the prostate accumulated less radioactivity than normal female ovaries and uteri at 15 min and 1 hr.

Metabolism and excretion. The liver cleared most of the radioactivity from the blood and secreted it into the bile. At 1 hr the small intestine contained 48% of the dose in four animals with transplanted tumors and 71% in four animals with spontaneous tumors. Two rats kept in a metabolism cage excreted 65% of the administered I-125 in the feces and 9% in the urine by 21 hr. At 4 days 81% had appeared in the feces and 16% in the urine. The thyroid contained 0.7% dose, the liver 0.5%, and the gut 0.3% after 4 days.

Bile was collected from four rats with cannulated bile ducts at 5-min intervals for 1 hr after injection of I-E_2. There was a lag of about 10 min before radioactivity began to appear, and thereafter the rate of I-125 excretion was fairly constant. In 1 hr 21–55% of the injected dose was collected. This variability was probably due to different degrees of anesthesia. Analysis of the bile by TLC did not reveal any I-E_2 or $^{125}I^-$. The radioactivity in bile had R_f = 0, 0.5, and 0.95, respectively, in chloroform:acetone (95:5, v/v), water, and water:ethanol (1:1, v/v). After bile had been incubated with glucuronidase,** the R_f values were 0, 0, and 0.95. In water:ethanol, however, the spot showed more "tailing" after the treatment with the enzyme. Thus, although glucuronidation appears to be involved in hepatic metabolism of I-E_2, glucuronidase (with or without sulfatase)†† did

not release I-E_2 from bile. We have not investigated the chemical state of I-125 in feces and urine.

DISCUSSION

The distribution data reported here confirm that I-E_2 binds to the estrogen receptor in vivo (*9*). This is supported by the high uptake in the uteri of all female animals tested, and by the abolition of high uptake by excess diethylstilbestrol, which can compete with I-E_2 for the receptor.

Uptake of I-E_2 by spontaneous and NMU-induced mammary tumors, and our demonstration that DES significantly lowers uptake of label by spontaneous tumors, suggest that it may be possible to visualize human breast tumors and/or metastases with I-E_2. This would depend on the tissue richness of estrogen receptors. Human breast tumors exhibit concentrations of estrogen receptors as high as 500 fmol/mg protein, about ten times the maximum concentrations reported for rat mammary tumor (*12,13*). The best nuclide for this purpose would be I-123, with its short half-life (13.6 hr) and lack of particulate emission, and its gamma energy well suited for Anger-camera imaging. A positron-emitting label (perhaps F-18 or Br-75) on the 16α position of estradiol might be preferable to I-123. Positron emission tomography would then enable binding to estrogen receptors in tumors or normal tissues to be measured quantitatively. A preliminary report of the synthesis of the Br-77 compound has appeared recently (*14*).

It is clear that factors other than the distribution of estrogen receptors must be considered in order to explain the distribution of label from I-E_2. It is important to understand that the sub-pharmacological dose used here does not provide for an assay of tissue receptor content. Rather, it samples the available receptors. The specific radioactivity of the I-E_2 used in the experiments summarized in Table 1 was 280 Ci/mmol. Therefore, the amount bound in the uteri at 1 hr was 5–10 fmol. This involves only around 1% of the receptors in mature rat uteri (*15*), which might explain why ovariectomy did not markedly increase uterine uptake of I-E_2. Other explanations are possible, however; for instance, a fall in estrogen level will decrease uterine perfusion (*16*). Thus, in ovariectomized animals, increased uptake of I-E_2, because of decreased competition from endogenous estrogens, might be offset by a reduced supply of I-E_2 from the blood.

After intravenous injection, I-E_2 can move from blood and be held in the tissues by cytoplasmic estrogen receptors or by other nonspecific binding, including simple lipid solubility. However, the availability of I-E_2 to receptors will depend on the vascularity of each tissue, so that the amount of I-E_2 specifically bound will depend on blood supply as well as the concentration of receptors. As the concentration in the blood falls, I-E_2 dissolved in lipid material in the tissues or loosely bound to proteins, can re-enter the blood. Although I-E_2 binds reversibly to the cytoplasmic estrogen receptors, the dissociation constant is so small (10^{-10} *M*) that loss of I-E_2 from the uterus is very slow. Thus, the percent dose per gram in the uterus is essentially constant from 5 min to 2 hr, whereas the level of radioactivity in the other tissues (except the thyroid) falls to 1/3 or less (Table 1). Most of the I-E_2 is metabolized and cleared by the liver into the bile within an hour after administration. Some radioactivity was excreted in urine, and it is likely that this

TABLE 3. TISSUE DISTRIBUTION (% DOSE/g) OF I-125 AFTER ADMINISTRATION OF 17β(16α-[^{125}I]IODO)-ESTRADIOL TO RATS WITH SPONTANEOUS AND NMU-INDUCED MAMMARY TUMORS*

Animals	NMU	Spontaneous	
Time	2 hr	1 hr	1 hr†
No. of animals	5	4	4
Weight (g)	230 ± 6	394(325–495)	335(285–420)
Adrenals	0.05 ± 0.05‡	0.12(0.03–0.18)‡	0.20(0.15–0.23)‡
Blood	0.04 ± 0.02	0.02(0.02–0.04)	0.03(0.02–0.03)
Kidney	0.08 ± 0.03	0.11(0.08–0.14)	0.05(0.04–0.06)
Liver	0.43 ± 0.21	0.30(0.25–0.35)	0.26(0.10–0.41)
Lungs	0.05 ± 0.02	0.06(0.05–0.08)	0.05(0.03–0.06)
Ovaries	0.14 ± 0.18	0.27(0.18–0.36)	0.12(0.11–0.14)
Muscle	0.02 ± 0.01	0.03(0.02–0.04)	0.03(0.02–0.04)
Thyroid	0.34 ± 0.20	0.45(0.35–0.75)	0.41(0.19–0.59)
Tumor	0.18 ± 0.07	0.11(0.07–0.15)	0.05(0.04–0.07)
Uterus	0.48 ± 0.23	0.84(0.34–1.52)	0.05(0.04–0.06)

* All animals were female Sprague–Dawley rats.

† 2 nmol of diethylstilbestrol was given intravenously 20 minutes before 17β(16α-[^{125}I]iodo)estradiol.

‡ Values are the mean ± 1 s.d. or the mean and range.

would represent relatively polar (i.e., more water soluble) metabolites of I-E_2.

Two observations argue against the adrenal uptake being due to "classical" estrogen receptors. They are that the time course of radioactivity in the glands is completely different from that in the uterus (Table 1), and that the uptake was not abolished by excess diethylstilbestrol (Tables 2 and 3). Limited amounts of estrone and estradiol are made in the adrenals, and the functions of these glands are affected by exogenous estrogens (*17*,*18*). Conceivably, binding by one or more enzymes involved in steroid interconversions could account for the high adrenal-to-blood ratio of radioactivity at 5 min. Early accumulation of tritiated E_2 has been reported in dogs (*19*) and mice (*20*), with the latter study showing the radioactivity concentrated in the adrenal cortex. Nuclear medicine adrenal studies are currently done with I-131-labeled 19-iodocholesterol and 6-iodomethyl-19-norcholesterol (*21*). With these agents, imaging must be done after a 3- to 7-day delay. E_2 labeled with a gamma-emitting nuclide would have the potential advantage of immediate imaging.

The scanning potential of I-E_2 for breast cancer and for diseases of the uterus, ovary, and adrenals should be further investigated. However, better estrogen-receptor-binding radiopharmaceuticals can probably be designed. An agent that is metabolized more slowly than I-E_2 would probably show higher target-tissue uptake, because the receptors would have longer access to the compound in the blood. Eckelman et al. (*22*) have developed a model for predicting tissue-to-blood ratios of receptor-binding radiopharmaceuticals from tissue-receptor concentrations and affinity constants. Similarly, Katzenellenbogen and his colleagues (*23*) have formulated a "binding selectivity index" to predict from in vitro tests the likelihood that a given compound will show a high ratio of specific to nonspecific binding. A previous report from our own laboratory (*24*) also stressed the need to consider nonspecific binding in explaining the biodistribution of potential radiopharmaceuticals that bind to enzymes. The results of the present work remind us that metabolism and excretion also have to be taken into account in the design of receptor-binding radiopharmaceuticals.

FOOTNOTES

* Mason Research Institute, Worcester, MA.
† Harlan Sprague-Dawley, Madison, WI.
‡ Kindly provided by Dr. D. P. Rose.
‖ New England Nuclear, North Billerica, MA.
§ Polygram SilG/uv plates from Brinkman Instruments, Westbury, NY.
¶ Kodak.
** Type VIII, Sigma Chemical Company, St. Louis, MO.
†† Type V, Sigma Chemical Company, St. Louis, MO.

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6th ANNUAL WESTERN REGIONAL MEETING SOCIETY OF NUCLEAR MEDICINE

October 8-11, 1981 **Hilton Hotel** **San Francisco, California**

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The abstracts will be printed from camera-ready copy provided by the authors. Therefore, only abstracts prepared on the official abstract form will be considered. These abstract forms will be available from the Western Regional Chapter office (listed below) after March 1, 1981. Abstract forms will be sent to members of the Northern California, Pacific Northwest, Southern California, and Hawaii Chapters in a regular mailing in early May, 1981. All other requests will be sent on an individual basis.

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SOCIETY OF NUCLEAR MEDICINE PEDIATRIC NUCLEAR MEDICINE CLUB ANNUAL MEETING

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The Pediatric Nuclear Medicine Club will hold its annual meeting in conjunction with the 28th Annual Society of Nuclear Medicine Meeting on Thursday, June 18, 1981, Las Vegas Convention Center, Room E at 12:30 following the pediatric session (Room D). There will be a 30 minute lunch break between the pediatric session and the meeting. Lunches may be brought to the meeting room. Anyone interested in pediatric nuclear medicine is invited to attend. If you have any interesting cases to share with the club, please bring them on 2 in. by 2 in. slides.

For further information contact:

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