CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 28, Number 9, 2013

DOI: 10.1089/cbr.2013.1483

Biodistribution and Dosimetry of Free ^{211}At, $^{125}I^-$ and $^{131}I^-$ in Rats

Johan Spetz, Nils Rudqvist, and Eva Forssell-Aronsson

Abstract

^{131}I is widely used for therapy in the clinic and ^{125}I and ^{131}I, and increasingly ^{211}At, are often used in experimental studies. It is important to know the biodistribution and dosimetry for these radionuclides to determine potential risk organs when using radiopharmaceuticals containing these radionuclides. The purpose of this study was to investigate the biodistribution of $^{125}I^-$, $^{131}I^-$, and free ^{211}At in rats and to determine absorbed doses to various organs and tissues. Male Sprague Dawley rats were injected simultaneously with 0.1–0.3 MBq $^{125}I^-$ and 0.1–0.3 MBq $^{131}I^-$, or 0.05–0.2 MBq ^{211}At and sacrificed 1 hour to 7 days after injection. The activities and activity concentrations in organs and tissues were determined and mean absorbed doses were calculated. The biodistribution of $^{125}I^-$ was similar to that of $^{131}I^-$ but the biodistribution of free ^{211}At was different compared to $^{125}I^-$ and $^{131}I^-$. The activity concentration of radioiodine was higher compared with ^{211}At in the thyroid and lower in all extrathyroidal tissues. The mean absorbed dose per unit injected activity was highest to the thyroid. ^{131}I gave the highest absorbed dose to the thyroid, and ^{211}At gave the highest absorbed dose to all other tissues studied.

Key words: $^{125}I^-$, $^{131}I^-$, ^{211}At, biodistribution, dosimetry

Introduction

Radioactive iodine has long been used for medical purposes. ^{131}I is the radionuclide most widely used for treatment of various thyroid disorders, such as hyperthyroidism and thyroid cancer. This is due to the fact that iodide mainly accumulates in the thyroid gland and in differentiated thyroid carcinoma cells, but also since ^{131}I has decay properties favorable for treatment. Iodine is transported into the thyroid follicular cells by the sodium iodide symporter (NIS).[1]

Astatine is the heaviest of the halogens, the chemical group also containing iodine. Astatine is thought to have properties similar to iodine in regard to thyroid uptake and excretion, for example, ^{211}At is probably transported partly by NIS,[2,3] although ^{211}At seems to have metallic properties resembling those of polonium.[4,5] Due to an assumed near optimal LET for therapy ^{211}At is very suitable for therapeutic applications.[6] ^{211}At emits, for example, α-particles with a very short range in tissue compared to most of the electrons emitted by ^{131}I, together with a lower photon emission.

Animal models are often used to test new radiopharmaceuticals for treatment of tumor diseases, including both mice and rats. This is an important area of research to improve already existing and new treatment methods, especially for disseminated tumor disease, when using radioactive substances labeled with ^{131}I or ^{211}At. It is common that a small amount of $^{131}I^-$ or free ^{211}At is released from the radiopharmaceutical *in vivo*. It is then important to know the biodistribution and the absorbed dose to normal tissues for ^{131}I and ^{211}At to determine potential risk organs when using such radiopharmaceuticals for treatment. To our knowledge, no biodistribution data of free ^{211}At can be found in humans. For pharmaceuticals directly labeled with radioiodine the released iodine will most probably be in the iodide chemical form. For indirectly iodinated pharmaceuticals, the chemical form of the released radioiodine might vary. For astatine At^- is the best defined valence state and it is expected to be stable in acidic and basic solutions containing reducing agents.[7] However, to our knowledge no information can be found on the behavior of At^- in solutions

Department of Radiation Physics, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden.

Address correspondence to: Johan Spetz; Department of Radiation Physics, Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital; Gula Stråket 2B, SE-413 45 Göteborg, Sweden
E-mail: **johan.spetz@gu.se**

without reducing agents. In this article, we therefore, use the term "free astatine" to include all possible oxidation states of astatine occurring *in vivo.*

The biodistribution of $^{125}I^-$, $^{131}I^-$ and free ^{211}At has been studied in mice.[8–12] The results demonstrate clear differences between the radionuclides and show a higher accumulation of ^{211}At compared to radioiodine in all organs and tissues except the thyroid. The difference in size between rats and mice makes organ sampling easier in rats, particularly for the smaller organs (such as thyroid which is one of the risk organs), which can be difficult to entirely excise alone in mice. This may result in a more extensive use of rat animal models. To our knowledge, biodistribution data of iodide and free ^{211}At in rats has been presented in only one article, published in 1953.[13] There is thus, a need to repeat such a study. Furthermore, at that time the astatine chemistry was only known to some extent.

The purpose of this study was to investigate and compare the biokinetics of $^{125}I^-$, $^{131}I^-$, and free ^{211}At in rats and to determine absorbed doses from these radionuclides to various organs and tissues.

Materials and Methods

Animal model

Male Sprague Dawley rats (Scanbur AB) weighing 180–210 g were used in all studies. The rats were kept in groups of 5 individuals per cage. Drinking water and autoclaved food were given *ad libitum*. For 5 days, before injection, the animals were given autoclaved food with reduced iodine content (0.05 ppm), at all other times it was regular autoclaved laboratory food (iodine content 2 ppm). The studies were approved by the Ethics committee for Animal Research at University of Gothenburg.

Radionuclides

^{125}I was delivered (as NaI) from PerkinElmer and ^{131}I was delivered (as NaI) from GE Healthcare. ^{211}At was produced through the $^{209}Bi(\alpha,2n)^{211}At$ reaction and delivered from the Cyclotron and PET Unit at Rigshospitalet in Copenhagen, Denmark. The extraction procedure of the ^{211}At has previously been presented.[14] Throughout this article, ^{211}At refers to "free astatine" which probably consists not only of $^{211}At^-$ but also, to some extent, of other oxidation states.

The decay data for ^{125}I, ^{131}I and ^{211}At is shown in Table 1.

Table 1. Decay Data for ^{125}I, ^{131}I, and ^{211}At[17]

			Energy per decay (keV/Bq·s)		
Radionuclide	*Decay mode*	$T_{1/2}$	*Electrons*	*α-Particles*	*Photons*
^{125}I	EC	59 days	17	—	42
^{131}I	β^-	8.0 days	190	—	380
^{211}At	α, EC	7.2 hours	0.048	6900	27

α-particle data for ^{211}At was calculated from the complex disintegration of ^{211}At and ^{211}Po.

Administration and organ sampling

Radioactive solutions were prepared using sodium radioiodide dissolved in phosphate-buffered saline (PBS, pH 7.2). The syringes and needles were weighed individually before and after adding the solution, and also after injection, to determine the amount of radioactive solution administered. The rats were divided into two study groups. The first study comprised of 30 animals, which were further divided into six groups with 5 animals in each group. These were injected intravenously with 0.1–0.3 MBq $^{125}I^-$ and 0.1–0.3 MBq $^{131}I^-$ in 0.15 mL of PBS. The rats were sacrificed by cardiac puncture under anaesthesia with Mebumal (sodium pentobarbital 60 mg/mL; Apoteksbolaget AB) at 1, 6, 18, 24, 72 hours, or 7 days after injection. The animals were immediately dissected and radioactivity measurements were made *ex vivo* on trachea (including thyroid), salivary glands, blood (0.5–1 mL, from cardiac puncture), lungs, heart, liver (right lobe), kidney (right), stomach, muscle from neck, brain, spleen, and sections of large and small intestine.

The second study involved 20 rats divided into four groups with five animals in each group and injected with 0.05–0.2 MBq ^{211}At in 0.15 mL of PBS. Also here, the syringes and needles were weighed individually before and after adding the solution, and also after injection. The rats were sacrificed as described above at 1, 5, 18, or 24 hours after injection. The animals were immediately dissected and all tissue samples were weighed. Radioactivity measurements were made *ex vivo* on thyroid, salivary glands, blood (1 mL, from cardiac puncture), lungs, heart, liver (right lobe), kidney (right), stomach, muscle from neck, spleen, and sections of large and small intestine.

Radioactivity measurements

Injected activity was individually determined by measurements on the syringes before injection using an ion chamber (CRC-15 dose calibrator; Capintec), and also by measuring syringe remnants and batch solutions in a gamma-counter (Wallac 1480 WIZARD® 3"; Wallac Oy). Radioactivity measurements made *ex vivo* on the rat organs were performed using the gamma-counter. Corrections were made for dead time loss, self-attenuation, spill-over (when performing measurements on ^{125}I and ^{131}I simultaneously), radioactive decay, and background. The measurement time was adjusted to allow the counts in the sample to exceed 1000 counts above the background level; this resulted in a detection error, which was less than 3%.

The activities in the organs and tissues at time t, $a_{tissue}(t)$, were calculated as percent of the injected activity (%IA):

$$a_{tissue}(t) = \frac{A_{tissue}(t)}{A_{inj}} \cdot 100\% \,, \qquad \text{Eq. 1}$$

and the activity concentrations at time t, $c_{tissue}(t)$, as percent of the injected activity per gram tissue (%IA/g):

$$c_{tissue}(t) = \frac{A_{tissue}(t)}{A_{inj} \cdot m_{tissue}} \cdot 100\% \,, \qquad \text{Eq. 2}$$

where $A_{tissue}(t)$ is the activity in the sample at time t corrected for radioactive decay to $t = 0$, A_{inj} is the activity injected at time $t = 0$, and m_{tissue} is the mass of the tissue sample.

The total blood volume (in mL) of the animal, V_{blood}, was determined using

$$V_{blood} = 0.06 \cdot m_{body} + 0.77 \ , \qquad \text{Eq. 3}$$

where m_{body} is the body weight in grams.[15]

For those tissues where the entire organ was not measured (blood, liver, small intestine and large intestine), calculations of $a_{tissue}(t)$ were performed by correcting $A_{tissue}(t)$ to correspond to the whole of the organ (assuming homologous activity distribution inside the organ). The total organ mass was calculated using previous measurements.[13,15] When calculating the $c_{thyroid}(t)$ from the trachea sample (including thyroid) it was assumed that the trachea had no uptake of iodine and the weight used in this calculation was the mean weight of the thyroids collected in the second study.

Absorbed dose calculations

The mean absorbed dose to the various organs and tissues from the different radionuclides was calculated according to the Medical Internal Radiation Dose (MIRD) formalism:

$$D_{tissue} = \tilde{A}_{tissue} \cdot E \cdot \frac{\emptyset}{m_{tissue}} \ , \qquad \text{Eq. 4}$$

where $\tilde{A}_{tissue}$ is the cumulated activity in the organ, E is the mean emitted energy per disintegration and ø is the absorbed fraction. For absorbed dose calculations on thyroids containing radioiodine, the mean weight of the thyroids collected in the biodistribution study of ^{211}At was used.

$\tilde{A}_{tissue}$ was calculated from the data using

$$\tilde{A}_{tissue} = A_{inj} \cdot \int_0^{t_D} a_{tissue}(t) \cdot e^{-\lambda t} dt \ , \qquad \text{Eq. 5}$$

where t_D is the time to which the absorbed dose contribution is to be calculated, and λ is the radioactivity decay constant. Due to the short range of α-particles and electrons compared to the size of most of the rat organs, the self-absorbed fraction was set to 1.0 for ^{125}I and ^{211}At. For ^{131}I the self-absorbed fraction was calculated from previously presented results.[16] The cross-absorbed fraction was set to 0 for all organs for all three radionuclides. The activity distribution in the source-organs was assumed to be homogeneous.

E was assumed to include only the electrons emitted for the radioiodine isotopes, and for ^{211}At E was assumed to concern only the α-disintegrations and was calculated from the complex disintegration of ^{211}At and ^{211}Po (Table 1).[17]

Table 2. The Activity Concentration [$c_{tissue}(t)$], %IA/g, of $^{125}I^-$ and $^{131}I^-$ in Rats (N=5) at 1 Hour to 7 Days After Simultaneous Injection of 0.1–0.3 MBq of $^{125}I^-$ and 0.1–0.3 MBq of $^{131}I^-$

	$c_{tissue}(t)$ (%IA/g)					
Tissue	*1 hour*	*6 hours*	*18 hours*	*24 hours*	*72 hours*	*7 days*
$^{125}I^-$						
Blood	0.44 (0.02)	0.26 (0.02)	0.09 (0.01)	0.10 (0.01)	0.023 (0.002)	0.006 (0.001)
Brain	0.023 (0.003)	0.018 (0.003)	0.007 (0.001)	0.009 (0.002)	0.0042 (0.0004)	0.0007 (0.0001)
Heart	0.150 (0.003)	0.13 (0.02)	0.035 (0.005)	0.039 (0.005)	0.011 (0.001)	0.0028 (0.0005)
Kidneys	0.30 (0.01)	0.19 (0.02)	0.07 (0.01)	0.07 (0.01)	0.023 (0.002)	0.007 (0.001)
Large intestine	0.22 (0.02)	0.16 (0.01)	0.05 (0.01)	0.05 (0.01)	0.012 (0.003)	0.0035 (0.0005)
Liver	0.18 (0.01)	0.12 (0.01)	0.056 (0.003)	0.06 (0.01)	0.025 (0.003)	0.007 (0.001)
Lungs	0.29 (0.01)	0.27 (0.07)	0.11 (0.01)	0.07 (0.01)	0.019 (0.002)	0.0057 (0.0004)
Muscle	0.081 (0.004)	0.15 (0.09)	0.04 (0.01)	0.14 (0.05)	0.011 (0.003)	0.005 (0.001)
Salivary glands	0.19 (0.01)	0.15 (0.02)	0.05 (0.01)	0.07 (0.01)	0.017 (0.002)	0.005 (0.001)
Small intestine	0.28 (0.04)	0.37 (0.12)	0.10 (0.02)	0.13 (0.04)	0.024 (0.003)	0.004 (0.001)
Spleen	0.20 (0.02)	0.25 (0.11)	0.044 (0.003)	0.04 (0.01)	0.011 (0.002)	0.0029 (0.0003)
Stomach	1.2 (0.1)	4.1 (0.6)	0.61 (0.12)	0.64 (0.13)	0.10 (0.01)	0.006 (0.001)
Thyroid	50 (6)	270 (60)	400 (40)	340 (40)	110 (40)	40 (14)
$^{131}I^-$						
Blood	0.46 (0.03)	0.22 (0.02)	0.09 (0.01)	0.09 (0.01)	0.022 (0.002)	0.006 (0.001)
Brain	0.025 (0.003)	0.017 (0.003)	0.007 (0.001)	0.008 (0.001)	0.0045 (0.0004)	0.0011 (0.0001)
Heart	0.16 (0.01)	0.11 (0.02)	0.039 (0.005)	0.036 (0.004)	0.010 (0.002)	0.0030 (0.0005)
Kidneys	0.27 (0.02)	0.17 (0.02)	0.07 (0.01)	0.06 (0.01)	0.023 (0.002)	0.007 (0.001)
Large intestine	0.23 (0.02)	0.13 (0.01)	0.06 (0.01)	0.046 (0.004)	0.011 (0.003)	0.0035 (0.0004)
Liver	0.18 (0.02)	0.11 (0.01)	0.059 (0.005)	0.05 (0.01)	0.024 (0.003)	0.007 (0.001)
Lungs	0.32 (0.02)	0.18 (0.03)	0.07 (0.01)	0.06 (0.01)	0.019 (0.002)	0.0061 (0.0005)
Muscle	0.09 (0.01)	0.14 (0.08)	0.05 (0.01)	0.13 (0.05)	0.012 (0.003)	0.005 (0.001)
Salivary glands	0.20 (0.02)	0.13 (0.02)	0.047 (0.005)	0.07 (0.02)	0.017 (0.002)	0.005 (0.001)
Small intestine	0.30 (0.05)	0.30 (0.10)	0.11 (0.02)	0.11 (0.03)	0.025 (0.003)	0.004 (0.001)
Spleen	0.22 (0.03)	0.19 (0.08)	0.045 (0.005)	0.036 (0.004)	0.011 (0.002)	0.0031 (0.0004)
Stomach	1.2 (0.1)	3.9 (0.6)	0.62 (0.12)	0.54 (0.09)	0.10 (0.01)	0.006 (0.001)
Thyroid	50 (9)	270 (70)	430 (60)	360 (80)	110 (40)	40 (14)

Data are given as the mean (SEM). The data are corrected for physical decay.
SEM, standard error of the mean.

Table 1 also shows the contribution calculated from the EC disintegration chain of ^{211}At to ^{207}Bi.

Statistical analysis

The statistical uncertainties in the measurements are represented by standard error of the mean (SEM).

Results

Biodistribution of $^{125}I^-$, $^{131}I^-$ and ^{211}At

The biodistribution of $^{125}I^-$ and $^{131}I^-$ was determined 1 hour to 7 days after injection [Table 2 shows $c_{tissue}(t)$, and Fig. 1 shows $a_{tissue}(t)$], and the biodistribution of ^{211}At was

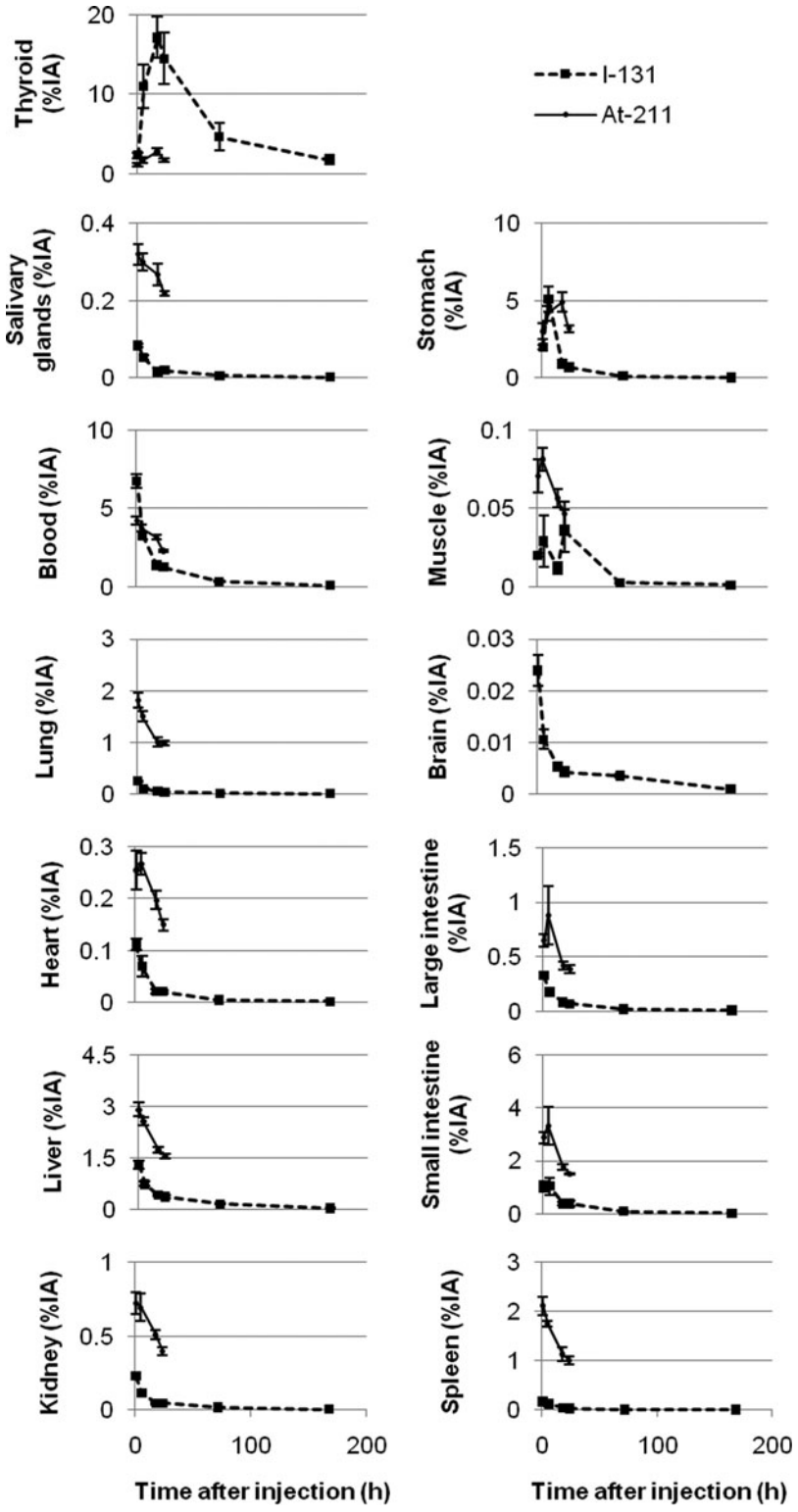

FIG. 1. The mean activity [$a_{tissue}(t)$], %IA, of $^{131}I^-$ and ^{211}At in rats ($n=5$) at 1 hour to 7 days after simultaneous injection of 0.1–0.3 MBq $^{125}I^-$ and 0.1–0.3 MBq ^{131}I or 0.05–0.2 MBq of ^{211}At. Data are given as the mean ± standard error of the mean. The data from $^{125}I^-$ was similar to that of $^{131}I^-$.

determined 1–24 hours after injection [$c_{tissue}(t)$ is shown in Table 3, and $a_{tissue}(t)$ in Fig. 1]. The biodistribution of $^{125}I^-$ was similar to that of $^{131}I^-$ and only the data from $^{131}I^-$ is shown in Figure 1. The thyroid gland showed the highest accumulation of all three radionuclides with $a_{thyroid}=16\%$IA (SEM=1.5%IA) or $c_{thyroid}=400\%$IA/g (SEM=40%IA/g) for ^{125}I, while for ^{131}I the uptake was 17%IA (SEM=2.6%IA) or 430%IA/g (SEM=60%IA/g), and for ^{211}At 2.8%IA (SEM= 0.5%IA) or 75%IA/g (SEM=15%IA/g) after 18 hours. For thyroid, the activity concentration was highest at 18 hours for all three radionuclides. In all organs and tissues except the thyroid, the activity concentration of ^{211}At was higher compared with $^{125}I^-$ and $^{131}I^-$. This was particularly evident for lungs and spleen. ^{211}At was also retained longer in extrathyroidal tissues compared to $^{125}I^-$ and $^{131}I^-$. The stomach, which is known to express NIS,[18] had a high concentration of all three radionuclides. The activity concentration in the stomach was highest after 6 hours for $^{125}I^-$ and $^{131}I^-$ and after 18 hours for ^{211}At. The brain had the lowest activity concentration of radioiodine of all organs and tissues studied.

Dosimetry

The dosimetric calculations for ^{125}I, ^{131}I, and ^{211}At show that the thyroid received the highest absorbed dose per injected activity, with $D_{thyroid,\ I\text{-}125}=2600$ mGy/MBq and $D_{thyroid,\ I\text{-}131}=21000$ mGy/MBq (Table 4) and $D_{thyroid,\ At\text{-}211}=18000$ mGy/MBq (Table 5) at $t=\infty$. The highest mean absorbed doses to extrathyroidal tissues and organs were found in stomach, heart, and small intestine for ^{125}I and ^{131}I, and in stomach, lungs and spleen for ^{211}At. ^{211}At delivered a much higher absorbed dose per injected activity to all extrathyroidal organs compared to ^{125}I and ^{131}I (at $t=\infty$), and ^{125}I delivered the lowest absorbed dose per unit injected activity.

Discussion

No significant difference was found between the biodistributions of $^{125}I^-$ and $^{131}I^-$ (Table 2). This was expected since the very small difference in atomic mass should not have an impact on the biokinetics of a radionuclide. Results showed that the trachea (including thyroid) and stomach selectively accumulated iodide over time (Table 2 and Fig. 1). This was also true for ^{211}At (Table 3 and Fig. 1) and was expected since both organs are known to express NIS.[18] The higher concentration of $^{125}I^-$ and $^{131}I^-$ than ^{211}At in thyroid could only to a low extent be explained by the difference in thyroid tissue sampling technique between the studies (a possible overestimation of $^{125}I^-$ and $^{131}I^-$ concentration). No other organs showed significant increase in activity concentration from 1 to 5–6 hours after injection. The salivary glands, which are also known to express NIS,[18] showed low activity concentrations of all three radionuclides. The biodistribution of ^{211}At also showed high activity concentrations in lungs and spleen and to a lesser extent in the kidneys. This supports our previous findings that the uptake/transport of ^{211}At is also dependent on mechanisms other than NIS.[3] Results also showed that the retention time of ^{211}At was longer compared with $^{125}I^-$ and $^{131}I^-$. A possible explanation for this is that the biochemical properties of ^{211}At *in vivo*, which are largely unknown, might change after injection. Another possibility is the existence of an uptake mechanism different from NIS.

Two animals showed unexpectedly low activity concentrations of both $^{125}I^-$ and $^{131}I^-$ in the thyroid at 6 and 72 hours and 7 days and resulted in high SEM values for these time points (Table 2). No obvious abnormalities could be found in these individuals, and the activity concentrations in other organs and tissues did not differ. A possible reason is that the animals in question had a slower metabolic rate. The individual food intake of the animals was not monitored and differences might change the amount of stable iodine accumulated in the thyroid before injection with radioiodide. Results from our pilot studies without the reduced iodine diet showed similar unexpectedly low activity concentrations of radioiodide, but in a larger number of animals (data not shown). The findings might be explained by the relatively high iodine concentration (2 ppm) in regular laboratory food compared to normal human diets (about 0.1 ppm). Therefore, the food with reduced iodine content (0.05 ppm), which better resembles a normal human diet was used, which seems to have reduced the effect.

TABLE 3. THE ACTIVITY CONCENTRATION [$c_{TISSUE}(T)$], %IA/G, OF ^{211}At IN RATS ($N=5$) AT 1–24 HOURS AFTER INJECTION OF 0.05–0.2 MBQ OF ^{211}At

	$c_{tissue,\ At\text{-}211}(t)$ (%IA/g)			
Tissue	*1 hour*	*5 hours*	*18 hours*	*24 hours*
Blood	0.29 (0.02)	0.26 (0.01)	0.22 (0.01)	0.160 (0.005)
Heart	0.53 (0.04)	0.49 (0.03)	0.34 (0.01)	0.29 (0.01)
Kidneys	1.2 (0.1)	1.1 (0.1)	0.72 (0.04)	0.61 (0.02)
Large intestine	0.46 (0.04)	0.63 (0.19)	0.30 (0.02)	0.28 (0.03)
Liver	0.41 (0.03)	0.36 (0.02)	0.25 (0.01)	0.22 (0.01)
Lungs	3.0 (0.2)	2.50 (0.05)	1.8 (0.1)	1.60 (0.03)
Muscle	0.32 (0.04)	0.34 (0.05)	0.24 (0.02)	0.23 (0.04)
Salivary glands	0.95 (0.11)	0.76 (0.03)	0.52 (0.01)	0.47 (0.02)
Small intestine	0.82 (0.06)	0.95 (0.21)	0.50 (0.03)	0.43 (0.01)
Spleen	3.0 (0.2)	2.4 (0.1)	1.7 (0.1)	1.5 (0.1)
Stomach	2.3 (0.4)	3.1 (0.3)	3.6 (0.5)	2.4 (0.2)
Thyroid	35 (9)	41 (11)	75 (15)	37 (3)

Data are given as the mean (SEM). The data are corrected for physical decay.

Table 4. The Mean Absorbed Dose Per Unit Injected Activity, mGy/MBq, of ^{125}I and ^{131}I in Rats Obtained at Different Points in Time After Injection ($N=5$) and the Corresponding m_{TISSUE} Used for Calculations ($N=30$)

		D(t) (mGy/MBq)				
Tissue	m_{tissue} *(g)*	*18 hours*	*24 hours*	*72 hours*	*7 days*	∞
^{125}I						
Blood	0.67 (0.01)	0.40 (0.01)	0.46 (0.01)	0.72 (0.04)	0.85 (0.05)	0.87 (0.05)
Brain	0.76 (0.04)	0.027 (0.002)	0.033 (0.002)	0.05 (0.01)	0.08 (0.01)	0.08 (0.01)
Heart	0.59 (0.02)	1.3 (0.1)	1.3 (0.1)	1.4 (0.1)	1.5 (0.1)	1.5 (0.1)
Kidney	0.71 (0.02)	0.30 (0.02)	0.34 (0.02)	0.56 (0.03)	0.70 (0.04)	0.74 (0.04)
Large intestine	0.33 (0.01)	0.20 (0.02)	0.23 (0.02)	0.38 (0.03)	0.44 (0.04)	0.46 (0.03)
Liver	1.95 (0.05)	0.18 (0.01)	0.22 (0.01)	0.45 (0.03)	0.58 (0.04)	0.61 (0.04)
Lung	0.66 (0.03)	0.34 (0.08)	0.40 (0.09)	0.61 (0.08)	0.70 (0.08)	0.73 (0.08)
Muscle	0.23 (0.01)	0.15 (0.05)	0.21 (0.05)	0.63 (0.15)	0.74 (0.15)	0.76 (0.15)
Salivary glands	0.36 (0.01)	0.22 (0.02)	0.26 (0.02)	0.44 (0.05)	0.55 (0.05)	0.57 (0.05)
Small intestine	0.74 (0.02)	0.39 (0.08)	0.46 (0.08)	0.89 (0.20)	1.0 (0.2)	1.0 (0.2)
Spleen	0.71 (0.02)	0.25 (0.06)	0.28 (0.06)	0.40 (0.08)	0.46 (0.08)	0.48 (0.08)
Stomach	1.41 (0.03)	3.9 (0.4)	4.3 (0.4)	5.9 (0.5)	6.3 (0.5)	6.3 (0.5)
Thyroid	0.040 (0.002)	470 (60)	680 (80)	1700 (100)	2400 (200)	2600 (300)
^{131}I						
Blood	0.67 (0.01)	4.4 (0.1)	5.0 (0.1)	7.4 (0.3)	8.5 (0.4)	8.6 (0.4)
Brain	0.76 (0.04)	0.30 (0.02)	0.36 (0.02)	0.58 (0.04)	0.78 (0.07)	0.82 (0.07)
Heart	0.59 (0.02)	13 (1)	14 (1)	15 (1)	16 (1)	16 (1)
Kidney	0.71 (0.02)	3.0 (0.2)	3.4 (0.2)	5.6 (0.2)	6.8 (0.3)	7.0 (0.4)
Large intestine	0.33 (0.01)	2.1 (0.1)	2.4 (0.1)	3.7 (0.2)	4.1 (0.2)	4.2 (0.2)
Liver	1.95 (0.05)	2.1 (0.1)	2.4 (0.1)	4.5 (0.3)	5.7 (0.4)	5.9 (0.4)
Lung	0.66 (0.03)	3.2 (0.3)	3.6 (0.3)	5.5 (0.3)	6.3 (0.3)	6.5 (0.3)
Muscle	0.23 (0.01)	1.5 (0.5)	2.0 (0.4)	5.8 (1.2)	7.0 (1.2)	7.1 (1.2)
Salivary glands	0.36 (0.01)	2.2 (0.2)	2.5 (0.3)	4.1 (0.5)	4.9 (0.5)	5.0 (0.5)
Small intestine	0.74 (0.02)	4.2 (0.8)	4.9 (0.9)	8.8 (2.0)	10 (2)	10 (2)
Spleen	0.71 (0.02)	2.5 (0.5)	2.8 (0.5)	3.9 (0.7)	4.5 (0.6)	4.6 (0.6)
Stomach	1.41 (0.03)	41 (4)	45 (4)	60 (5)	64 (5)	64 (5)
Thyroid	0.040 (0.002)	4200 (700)	6100 (800)	15000 (2000)	19000 (2000)	21000 (2000)

Data are given as the mean (SEM).

In the previous study, from 1953 on female Long-Evans rats kept on standard laboratory chow, the maximum uptake in thyroid for ^{131}I and ^{211}At occurred 24 hours after injection.[13] In the present study, the maximum activity of ^{131}I found in the thyroid was about half of the maximum activity found by Hamilton et al. (17%IA compared to 28%IA), although our rats had probably received food with lower iodide content (the iodide content was not specified in the older study). Similar relations (lower concentrations in the present study) were found for most of the other organs and tissues (except spleen which had a similar maximum uptake). The reason for this discrepancy is not known;

Table 5. The Mean Absorbed Dose Per Unit Injected Activity, mGy/MBq, of ^{211}At in Rats Obtained at Different Points in Time After Injection ($N=5$) and the Corresponding m_{TISSUE} Used for Calculations ($N=20$)

		D(t) (mGy/MBq)		
Tissue	m_{tissue} *(g)*	*18 hours*	*24 hours*	∞
Blood	0.96 (0.04)	87 (3)	93 (3)	98 (3)
Heart	0.53 (0.02)	170 (10)	180 (10)	190 (20)
Kidney	0.65 (0.02)	370 (20)	390 (20)	390 (20)
Large intestine	0.35 (0.01)	200 (40)	210 (40)	210 (40)
Liver	1.97 (0.08)	160 (10)	160 (10)	230 (20)
Lung	0.60 (0.01)	1000 (100)	1100 (100)	1100 (100)
Muscle	0.23 (0.01)	120 (10)	120 (10)	130 (10)
Salivary glands	0.43 (0.02)	250 (10)	270 (10)	280 (10)
Small intestine	0.78 (0.02)	310 (50)	330 (50)	340 (50)
Spleen	0.69 (0.02)	950 (50)	1000 (50)	1000 (50)
Stomach	1.33 (0.02)	1000 (100)	1200 (100)	1200 (100)
Thyroid	0.040 (0.002)	16000 (4000)	17000 (4000)	18000 (4000)

Data are given as the mean (SEM).

however, the most possible explanation is differences in stable iodine intake via the food and rat strain. The differences in sex and amount of administered ^{131}I (0.1–0.3 vs. 1.4 MBq) would most probably not affect the biodistribution. In the older study no organs or tissues except the thyroid gland showed a selective accumulation of radioiodide over time. This is in contrast to the results found in the present study, which also showed a selective accumulation in the stomach.

The maximum activity of ^{211}At found in the thyroid in the older study was about one-tenth of the maximum activity of radioiodide, while it was about one-fifth in the present study. The maximum activity of ^{211}At in the thyroid in our study (at 18 hours) was similar to that found previously (at 24 hours), (2.8%IA compared to 2.7%IA). For the other organs and tissues, the older study gave somewhat higher maximum activities in general. In both studies, only the thyroid gland and the stomach showed selective accumulation of ^{211}At over time.

In a third limited study from 1954, the thyroidal uptake of ^{211}At was 1.2%IA 1.5 hours after injection.[19] This is comparable to the results found in the present study (1.1%IA 1 hour after injection).

Studies on the biodistribution of ^{211}At in nude mice[11,12] have shown that the uptake of ^{211}At was highest in the thyroid gland, lungs, spleen, and stomach. These studies also demonstrated higher activity concentrations of ^{211}At compared to radioiodine in extrathyroidal organs and tissues and Lundh et al.[12] also showed a longer retention time of ^{211}At compared to $^{125}I^-$. These results are all in accordance with the results found in this study. In contrast to the results found in this study, previous studies on nude mice present a maximum thyroidal uptake of ^{211}At at approximately 4 hours after injection.[10,12] The reason for this difference is probably due to lower metabolic rates in rats compared to mice.[20]

In the dosimetric calculations, only the electrons and α-particles were considered (see Table 1 for decay data). This assumes no photon contribution to the absorbed dose and resulted only in a small underestimation of the absorbed dose. Previous studies have shown that the photon absorbed dose contribution is, for example, about 7% for the mouse thyroid gland for ^{125}I.[21] Concerning ^{211}At the energy released from electrons and photons per decay is negligible compared to that from the alpha particles. However, these results are from animal models and a translation of this data to the human system must be performed with caution, for all three radionuclides, as the photon contribution may be higher in clinical situations.[22,23]

Results from the absorbed dose calculations showed that the thyroid received the maximum mean absorbed dose per unit injected activity, for all three radionuclides (Tables 4 and 5). This was expected due to the high activity concentration (400%IA/g for $^{125}I^-$, 430%IA/g for $^{131}I^-$ and 75%IA/g for ^{211}At). The highest mean absorbed dose per unit injected activity to the thyroid was found for ^{131}I followed by ^{211}At ($2.1 \cdot 10^4$ mGy/MBq compared to $1.8 \cdot 10^4$ mGy/MBq, values compared at $t = \infty$), which is explained by the much higher activity concentrations found for $^{131}I^-$ and the much shorter half-life of ^{211}At. For the other organs and tissues ^{211}At delivered a higher absorbed dose per unit injected activity in general, due to the larger amount of energy deposited per disintegration and longer retention time of ^{211}At compared to $^{125}I^-$ and $^{131}I^-$. In a clinical application, the tissue accumulation of ^{211}At may be blocked, which would potentially reduce the mean absorbed dose to extrathyroidal tissue.[11]

Conclusions

The biodistribution of free ^{211}At is different compared to $^{125}I^-$ and $^{131}I^-$. The thyroid gland was found to accumulate $^{125}I^-$, $^{131}I^-$, and ^{211}At selectively, although the activity concentration of ^{211}At was only about one-fifth of that of radioiodide. Absorbed dose calculations showed that ^{211}At gave the highest mean absorbed dose per unit injected activity to all extrathyroidal tissues.

Acknowledgments

The authors thank Lilian Karlsson for her skillful handling of the animals and Dr. Sture Lindegren for the generous supply of ^{211}At. This study was supported by grants from the European Commission FP7 Collaborative Project TARCC HEALTH-F2-2007-201962, the Swedish Research Council, the Swedish Cancer Society, BioCARE—a National Strategic Research Program at University of Gothenburg, the Swedish Radiation Safety Authority and the King Gustav V Jubilee Clinic Cancer Research Foundation. The work was performed within the EC COST Action BM0607.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

1. Dohan O, De la Vieja A, Paroder V, et al. The sodium/iodide symporter (NIS): Characterization, regulation, and medical significance. Endocr Rev 2003;24:48.
2. Hamilton JG, Soley MH. A comparison of the metabolism of iodine and of element 85 (eka-iodine). Proc Natl Acad Sci U S A 1940;26:483.
3. Lindencrona U, Nilsson M, Forssell-Aronsson E. Similarities and differences between free ^{211}At and ^{125}I- transport in porcine thyroid epithelial cells cultured in bicameral chambers. Nucl Med Biol 2001;28:41.
4. Corson DR, Mackenzie KR, Segré E. Artificially radioactive element 85. Phys Rev 1940;58:672.
5. Visser GWM, Diemer EL. The synthesis of organic at-compounds through thallium compounds. Int J Appl Radiat Isot 1982;33:389.
6. Brown I. Astatine-211: Its possible applications in cancer therapy. Int J Rad Appl Instrum A 1986;37:789.
7. Vasáros L, Berei K. General properties of astatine. In: Kugler HK, Keller C, eds. *Gmelin Handbook of Inorganic Chemistry-Astatine*, 8th ed. Berlin: Springer-Verlag; 1985:107.
8. Cobb LM, Harrison A, Dudley NE, et al. Relative concentration of astatine-211 and iodine-125 by human fetal thyroid and carcinoma of the thyroid in nude mice. Radiother Oncol 1988;13:203.
9. Garg PK, Harrison CL, Zalutsky MR. Comparative tissue distribution in mice of the alpha-emitter ^{211}At and ^{131}I as labels of a monoclonal antibody and F(ab')2 fragment. Cancer Res 1990;50:3514.
10. Harrison A, Royle L. Determination of absorbed dose to blood, kidneys, testes and thyroid in mice injected with ^{211}At and comparison of testes mass and sperm number in x-irradiated and ^{211}At treated mice. Health Phys 1984;46:377.

11. Larsen RH, Slade S, Zalutsky MR. Blocking [211At]astatide accumulation in normal tissues: Preliminary evaluation of seven potential compounds. Nucl Med Biol 1998;25:351.
12. Lundh C, Lindencrona U, Schmitt A, et al. Biodistribution of free ^{211}At and ^{125}I- in nude mice bearing tumors derived from anaplastic thyroid carcinoma cell lines. Cancer Biother Radiopharm 2006;21:591.
13. Hamilton JG, Aisling CW, Garrison WM, et al. The accumulation, metabolism, and biological effects of astatine in rats and monkeys. Univ Calif Publ Pharmacol 1953;2:283.
14. Lindegren S, Back T, Jensen HJ. Dry-distillation of astatine-211 from irradiated bismuth targets: A time-saving procedure with high recovery yields. Appl Radiat Isot 2001;55:157.
15. Lee HB, Blaufox MD. Blood volume in the rat. J Nucl Med 1985;26:72.
16. Endo S, Nitta Y, Ohtaki M, et al. Estimation of dose absorbed fraction for ^{131}I-beta rays in rat thyroid. J Radiat Res (Tokyo) 1998;39:223.
17. Eckerman KF, Endo A. MIRD: Radionuclide Data and Decay Schemes, 2nd ed. Reston, VA: Society of Nuclear Medicine; 2007.
18. Spitzweg C, Joba W, Eisenmenger W, et al. Analysis of human sodium iodide symporter gene expression in extrathyroidal tissues and cloning of its complementary deoxyribonucleic acids from salivary gland, mammary gland, and gastric mucosa. J Clin Endocrinol Metab 1998; 83:1746.
19. Shellabarger CJ, Godwin JT. Studies on the thyroidal uptake of astatine in the rat. J Clin Endocrinol Metab 1954;14:1149.
20. Kleiber M. Body size and metabolic rate. Physiol Rev 1947;27:511.
21. Aronsson EF, Gretarsdottir J, Jacobsson L, et al. Therapy with ^{125}I-labelled internalized and non-internalized monoclonal antibodies in nude mice with human colon carcinoma xenografts. Nucl Med Biol 1993;20:133.
22. Uusijärvi H, Bernhardt P, Forssell-Aronsson E. Translation of dosimetric results of preclinical radionuclide therapy to clinical situations: Influence of photon irradiation. Cancer Biother Radiopharm 2007;22:268.
23. Josefsson A, Forssell-Aronsson E. Microdosimetric analysis of ^{211}At in thyroid models for man, rat and mouse. EJNMMI Res 2012;2:29.