Different Radioactivity Uptake between Somatostatin Analogues Labelled with ^{111}In and $^{90/88}$Y in Rat Kidney

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Abstract. *Somatostatin receptor targeting is a valuable method to treat somatostatin receptor-positive tumours. In peptide receptor radionuclide therapy, it is essential to determine the highest activity that can be safely administered to the patient. As ^{90}Y emits no gamma rays, absorbed doses for ^{90}Y are usually estimated using the same peptide labelled with ^{111}In. The aim of the study was to determine if replacement of $^{90/88}$Y by ^{111}In affects the biodistribution profile of five selected somatostatin analogues in preclinical experiments. Materials and Methods: Radiolabelled peptides were administered intravenously to male Wistar rats. Results: The peptides under study labelled either with ^{111}In or with $^{88/90}$Y showed similar distribution profiles in all tissues excepting the kidney. The kidney radioactivity uptake was significantly lower for $^{88/90}$Y-labeled peptide in comparison with the one of ^{111}In. Conclusion: We conclude that a radiation-absorbed dose after ^{90}Y-labelled somatostatin analogues appears to be lower than that predicted by the ^{111}In-labelled peptide.*

Several types of human neoplasms (especially neuroendocrine tumours and their metastases) overexpress high-affinity somatostatin receptors that allow for tumour imaging and targeted radiotherapy of inoperable and disseminated tumours using radiometal chelator-conjugated somatostatin analogues. This process presents advantages for patients with neuroendocrine malignancies as a result of the early detection and treatment of these tumours and their metastases, and the challenge of tumour therapy with radiolabelled somatostatin receptor–specific peptides is to deliver the highest possible dose to the target while sparing non-target tissues from damage (1-6). A relatively fast renal clearance route for these radiolabelled peptides is favourable. However, due to partial renal reabsorption, the uptake and high renal retention of the radiotracer may lead to renal radiation toxicity, which is a major dose-limiting factor in therapy using these agents (7-9). In order to effectively treat tumours, it is thus essential to assess the doses absorbed by the malignant tissues and to determine the highest activity that can be safely administered to patients. For this reason, it is important to select patient candidates with high expression of the corresponding peptide receptor in the primary tumour and its metastases. ^{90}Y has many desirable properties for radionuclide therapies, and therefore, it is a common radionuclide used for cancer therapy. Unfortunately, ^{90}Y emits no gamma rays that are suitable for gamma camera imaging because of its short-range beta-emission. To determine the radiation dose to the target and non-target tissues (particularly to dose-limiting organs) and for therapy monitoring, the biodistribution data for ^{90}Y are usually estimated using the surrogate ion ^{111}In because the ionic charges for these radiometals are identical (+3) (10). Positive scan results and good radioactivity uptake by the tumour of the diagnostic peptide (preferably the same peptide labelled with gamma-emitting radionuclide) are thus prerequisites for targeted radiopeptide therapy. Only a few studies have examined the effect of radiolabels on the distribution profiles of receptor-specific peptides to date; however, their results concerning individual peptides have often been inconsistent and no general conclusions are thus possible. For example, some studies have shown that there may be significant differences between ^{111}In- and ^{90}Y-labelled agents (11). In our recent study, an approximately three-fold higher kidney uptake of radioactivity was determined after the administration of two ^{111}In-labelled somatostatin derivatives, in comparison with derivatives labelled with ^{88}Y (12). For this reason, there is a need for such information, both from a theoretical and a clinical point of view. The present study compares the distribution profile, of five somatostatin analogues (octreotide and octreotate derivatives), labelled either with ^{111}In or ^{90}Y in rats. In some experiments, ^{88}Y, instead of ^{90}Y, was used due to its longer half-life and simpler detection in biological samples. The aim

Some of the data were presented previously at the Annual Congress of the European Association of Nuclear Medicine in October 2008 in Munich, and were published as an abstract in Eur J Nucl Med Mol Imaging. 2008; 35:S235.

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Key Words: Somatostatin analogue, ^{111}In, $^{90/88}$Y, kidney uptake.

was to determine whether using the radioisotope ^{111}In instead of $^{90/88}$Y influences the distribution pattern of peptidic vectors in somatostatin receptor-rich organs and, specifically, in the kidney.

Materials and Methods

Peptides. All the peptides used were kindly provided by Professor Helmut Mäcke from the University Hospital in Basel, Switzerland. The peptides were modified by Professor Mäcke's team with two different chelators: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid bound to the terminal amino group of the peptide through a carboxyl of acetic acid (DOTA-peptides) and 2-(4,7,10-*tris*(carboxymethyl)-1,4,7,10-tetraaza-cyclododecan-1-yl)glutaric acid, which was attached to the peptide in two different ways (either by binding to the terminal amino group of the peptide through the 5-carboxy group of glutaric acid residue of the chelator (DOTAGA-peptide) or through the carboxyl of acetic acid in position 7 of the same chelator (DOTA-t-GA-peptide). These modifications represent three different coordination environments for the binding of metal radionuclides. The somatostatin analogues used in this study are listed in Figure 1, with indicated net charges at physiologic pH when the chelator is complexed with tri-valent radiometals.

Radiolabelling. Radiolabelling of the peptides was accomplished by adding 10 μg of the peptide in 10 μl of 0.1% trifluoroacetic acid (TFA) to 200 μl of 0.4 M acetate buffer at pH 5 with 0.24 M gentisic acid, together with 0.5 mCi of the radionuclide [$^{90}YCl_3$ in 0.5-2 μl of 40 mM HCl (PerkinElmer Life Sciences, Brussels, Belgium)· $^{88}YCl_3$ in 0.5-2 μl of 50 mM HCl (Los Alamos National Laboratory, NM, USA) or $^{111}InCl_3$ in 50-100 μl of 40 mM HCl (Amersham, United Kingdom)]. After incubation at 90-95˚C for 25 min, the quality control of the product was determined using gradient HPLC analysis on a Pharmacia-LKB system with a Gradient Master GP 962 gradient programmer (Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic) equipped with a LichroCART 125-4 HPLC Purospher RP 18e, 5 μm Cartridge (Merck, Darmstadt, Germany) with a UV monitor and a radioactivity monitoring analyser. 0.1% TFA-water solution was used as a mobile phase A, and CH3CN as phase B. The gradient was as follows: 0-5 min: 0% B; 5-25 min: 0-30% B; 25-30 min: 30% B; 30-35 min: 30-100% B; and 35-40 min: 100% B. The flow rate was 0.5 ml/min. For HPLC analysis, approximately 10 μl of the preparation was dissolved in 30 μl of mobile phase A, to which 2 μl of 10^{-3} M DTPA (pH 5) was also added. The radiochemical purity of the peptides used was greater than 98% in all cases.

Biological experiments. Animals. Animal studies were conducted using male Wistar rats (BioTest, Konarovice, Czech Republic) weighing 190-260 g. The animals were fasted overnight before the experiment (to empty the bowels) but had free access to water. All animal experiments were approved by the Ethics Committee of the Faculty of Pharmacy, Charles University, Hradec Kralove, in accordance with the rules of the Czech Republic State Central Committee for animal protection.

Biodistribution in rats. The agent was administered to rats intravenously under ether anaesthesia in a volume of 0.2 ml (corresponding to a dose of 1 μg of the peptide/kg of body weight and to an activity dose of 50 μCi/kg). During the course of the experiments, the animals were singly housed in cages. At various time points after the injection (5 minutes and 1, 2, 24 and 48 h) the carotid artery was exposed under ether anaesthesia, and a blood sample was collected in a glass tube containing dry heparin. The rats were subsequently sacrificed and dissected. The organs of interest were weighed and tested for radioactivity using a 1480 Wizard 3 automatic gamma counter (Wallac OY, Turku, Finland). To determine the effect of somatostatin receptor blockade on the peptide distribution profile, one group of animals was pretreated with an intravenous injection of 0.1 mg/kg octreotide (Sandostatin, Novartis International AG, Basel, Switzerland) 15 min before the radiolabelled peptide administration. The results were expressed as the mean±standard deviations (SD) of groups of minimally four animals.

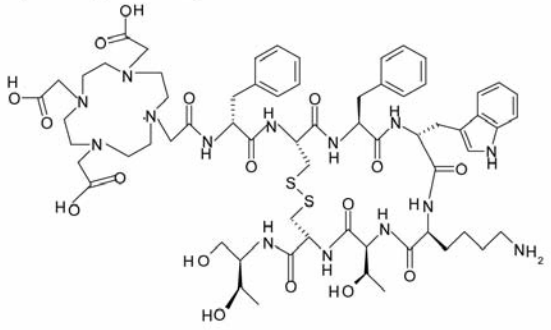
Results

After intravenous administration, radioactivity was rapidly cleared from the blood for all agents under study; significant long-term localisation of radioactivity in somatostatin receptor-rich organs and in the kidney was determined. An example of such distribution-time profile of radioactivity for DOTA-octreotide (DOTA-OC) labelled with ^{111}In and ^{88}Y is shown in Tables I and II. Results are expressed as percent of injected radioactivity because the actual chemical form in which the radioactivity is present may be unknown (especially for the peptide-internalized and metabolized tissues, such as the kidney and somatostatin receptor-rich organs).

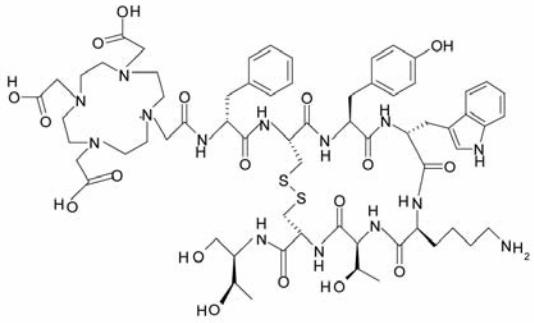
High and long-term radioactivity uptake in organs with high density of somatostatin receptors (mainly the adrenals and pancreas) was observed. The kidneys (the main elimination organ) were the only non-receptor-positive tissue in which high radioactivity accumulation was also found. Non-somatostatin receptor-expressing tissues (except the kidney) exhibited negligible specific uptake of radioactivity and the localisation of radioactivity in these organs and tissues was mutually comparable regardless of the label (wether radioindium or radioyttrium). However, long-term radioactivity localisation in the kidneys over longer time intervals was approximately two-fold higher after ^{111}In-DOTA-OC labelling compared with the same peptide labelled with ^{88}Y. In order to saturate specific binding to somatostatin receptors, non-radioactive octreotide (Sandostatin) was injected before the selected peptide (^{111}In-DOTA-OC) administration. As expected, the activity in somatostatin receptor-rich organs (in the adrenal glands and pancreas and also in the gastrointestinal tract) substantially decreased in the pretreated animals (Table III). No specific somatostatin receptor-mediated kidney uptake of radioactivity was observed.

The retention of radioactivity in the kidneys, adrenals and whole blood of different radiolabelled peptides at selected time points after administration is shown in Figure 2a, b and c. Systematically different radioactivity accumulation in kidney between the same peptide radiolabelled with ^{111}In or $^{90/88}$Y was determined; in other organs and systems, mostly no

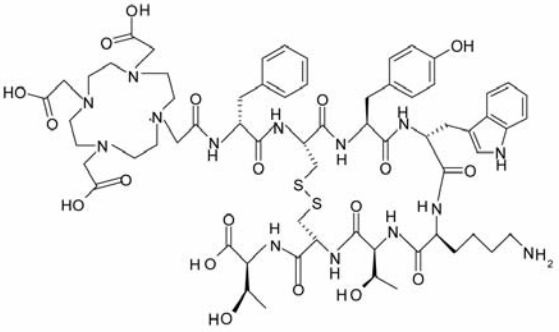
DOTA-octreotide
(DOTA-OC)
(Charge = +1)



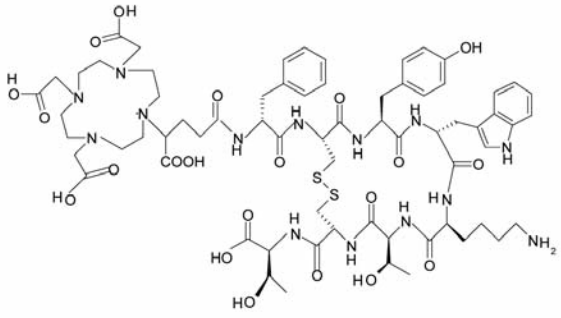
DOTA-Tyr^3-octreotide
(DOTA-TOC)
(Charge = +1)



DOTA-Tyr^3-octreotate
(DOTA-TATE)
(Charge = 0)



DOTAGA-Tyr^3-octreotate
(DOTAGA-TATE)
(Charge = -1)



DOTA-t-GA-Tyr^3-octreotate
(DOTA-t-GA-TATE)
(Charge = -1)

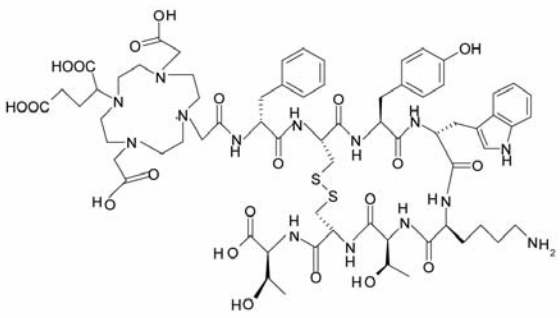


Figure 1. *Structures of the peptides used with indicated net charges at physiological pH when the chelator is complexed with tri-valent radiometal.*

Table I. *Radioactivity uptake in selected organs after administration of ^{111}In-DOTA-OC to rats. Results are expressed as the percentage of injected dose per organ.*

	Percentage dose in whole organ				
	5 min	1 h	2 h	24 h	48 h
Total Blood	16.47±1.61	2.76±0.22	0.68±0.16	0.03±0.01	0.02±0.01
Pancreas	1.40±0.14	1.71±0.16	1.99±0.32	0.93±0.15	0.60±0.10
Liver	2.27±0.06	0.90±0.11	0.64±0.07	0.46±0.04	0.36±0.05
Adrenals	0.37±0.11	0.40±0.24	0.40±0.14	0.20±0.02	0.23±0.04
Kidney	13.59±0.57	8.58±3.10	6.94±1.10	5.12±0.64	4.39±0.68
Lung	1.12±0.11	0.25±0.05	0.09±0.02	0.02±0.01	0.02±0.01
Heart	0.32±0.02	0.07±0.01	0.02±0.01	<0.01	<0.01
Spleen	0.17±0.03	0.07±0.02	0.04±0.01	0.03±0.01	0.02±0.01
Stomach	1.38±0.27	2.04±2.20	1.12±0.54	0.58±0.30	0.37±0.13
Intestine	2.51±0.09	3.77±4.17	6.25±5.31	0.51±0.11	0.31±0.06
Colon	1.71±0.21	0.94±0.06	0.81±0.08	2.89±0.35	1.21±0.75
Testes	0.41±0.08	0.20±0.02	0.07±0.01	0.02±0.01	0.01±0.01
Thyroid	0.09±0.007	0.03±0.01	0.01±0.01	<0.01	<0.01
Brain	0.09±0.03	0.02±0.01	0.01±0.01	<0.01	<0.01

Table II. *Radioactivity uptake in selected organs after administration of ^{88}Y-DOTA-OC to rats. Results are expressed as the percentage of injected dose per organ.*

	Percent dose in whole organ				
	5 min	1 h	2 h	24 h	48 h
Total Blood	12.68±2.34*	2.15±0.46	0.58±0.32	0.04±0.02	0.01±0.01
Pancreas	1.54±0.24	2.21±0.30*	1.92±0.10	0.93±0.10	0.88±0.05*
Liver	1.95±0.36	0.94±0.17	0.67±0.09	0.46±0.03	0.41±0.03
Adrenals	0.35±0.17	0.79±0.35	0.57±0.32	0.25±0.07	0.25±0.05
Kidney	10.16±0.90 **	6.94±2.16	3.26±0.73**	2.73±0.48**	2.45±0.18*
Lung	1.17±0.27	0.26±0.03	0.11±0.04	0.03±0.01	0.02±0.01
Heart	0.33±0.05	0.08±0.02	0.04±0.03	0.01±0.01	<0.01
Spleen	0.18±0.02	0.08±0.02	0.05±0.02	0.03±0.01	0.02±0.01
Stomach	1.53±0.47	1.60±0.56	1.45±0.83	0.64±0.25	0.41±0.04
Intestine	2.78±0.35	2.287±0.67	3.18±1.33	0.66±0.18	0.48±0.18
Colon	1.63±0.17	1.14±0.11*	0.93±0.22	2.16±0.12*	1.28±0.33
Testes	0.32±0.06	0.18±0.05	0.07±0.05	0.02±0.01	0.02±0.01
Thyroid	0.07±0.01*	0.03±0.01	0.01±0.01	0.01±0.01	<0.01
Brain	0.09±0.01	0.02±0.01	0.01±0.01	<0.01	<0.01

Significance of differences between the same peptide labelled either with ^{88}Y or/with ^{111}In at *p=0.05, **p=0.01 (in comparison with data in Table I).

significant differences between accumulation of the two radiolabels were found. Higher concentrations of ^{111}In-labelled peptides in initial time intervals, compared with $^{90/88}$Y-labelled peptides, were found for four out of the five peptides; this result was probably related to the higher lipophilicity of the $^{90/88}$Y-labelled peptides (13). Higher lipophilicity generally results in higher plasma protein binding and lower elimination rate by glomerular filtration (the main elimination pathway for the peptides under study).

Based on inter-peptide comparison, the highest renal radioactivity uptake was found for DOTAGA-TATE and DOTA-t-GA-TATE. The reason for this finding is evidently related to the different charge of the agents (-1), as the net charge of radiolabelled somatostatin analogues significantly affects radioactivity uptake in the kidney (14).

Discussion

In peptide-receptor radiotherapy, the radiosensitive kidney is the dose-limiting organ because of the high uptake and retention of therapeutic radionuclides in the kidney (15). For therapeutic applications, the renal accumulation of

Table III. *The effect of somatostatin receptor blockade (animals were pretreated with Sandostatin 0.1 mg/kg of body weight at 15 min before the peptide dosing) on distribution of radioactivity in rats 2 h after ^{111}In-DOTA-OC administration.*

	Control	Premedication
Blood	0.047±0.010	0.034±0.005
Plasma	0.088±0.012	0.064±0.007*
Pancreas	4.199±0.484	0.621±0.095***
Liver	0.100±0.013	0.088±0.007
Adrenals	6.539±2.840	1.119±0.001**
Kidney	4.022±0.437	4.357±0.142
Lung	0.074±0.010	0.042±0.003**
Heart	0.027±0.005	0.019±0.001
Spleen	0.068±0.010	0.043±0.001*
Stomach	0.607±0.305	0.086±0.024*
Intestine	0.677±0.434	0.111±0.003
Colon	0.112±0.015	0.034±0.003**
Testes	0.026±0.005	0.017±0.000*
Skin	0.057±0.007	0.040±0.011*
Muscle	0.013±0.001	0.010±0.002
Thyroid	0.088±0.016	0.055±0.002*
Brain	0.004±0.001	0.003±0.000

Significance of differences in distribution of radioactivity after premedication of experimental animals with Sandostatin at *p=0.05; **p=0.01; ***p=0.001.

radioligand thus limits the maximum tolerated doses of activity that can be administered without the induction of radionephrotoxicity. Appropriate dosimetry tools are therefore mandatory. As ^{111}In is widely used as an analogue for ^{90}Y in therapy trials, in this study, we compared the biodistribution profiles of five somatostatin analogues labelled with ^{111}In and $^{90/88}$Y to investigate whether the tracer uptake was affected by the choice of radionuclide used for the peptide labelling.

The efflux rate of the radiopeptides from the blood and most tissues (except somatostatin receptor-rich tissues and the kidney) was fast; ^{111}In- and $^{90/88}$Y-labeled peptides exhibited similar distribution in most rat organs. The analysis of the biodistribution at 2, 24 and 48 h after dosing revealed high and long-term radioactivity uptake in somatostatin receptor-positive tissues, such as the pancreas and adrenal glands (biomarkers simulating peptide accumulation in somatostatin receptor-rich tumours). The net retention of radioactivity in these organs was similar for each ^{111}In- and $^{90/88}$Y-labelled peptide. However, the accumulation of radioactivity in the kidneys was approximately two-fold higher for ^{111}In-labelled peptides than for $^{90/88}$Y (an example for DOTA-OC is shown in Tables I and II, but similar results for other peptides were also determined).

Specific targeting of the radiopeptides to somatostatin receptor-expressing tumours and somatostatin receptor-positive tissues is mediated by somatostatin receptors located on the cell membrane. The essential pharmacophore of the peptide responsible for receptor binding is most likely the Phe7-Trp-Lys-Thr$_{10}$ fragment of somatostatin (16). This possibility is based on the lack of significant differences between In- and Y-radiolabelled peptide accumulation in somatostatin receptor-rich organs, as determined in the present study. This finding is consistent with the similar receptor affinity of In- and Y-labelled somatostatin analogues determined under *in vitro* conditions (17). The radiolabel also had no significant effects on the distribution of radioactivity in somatostatin receptor-negative organs and tissues.

In terms of the elimination pathways, the peptidic vectors are eliminated in the kidney by glomerular filtration and are consequently taken up by proximal tubule cells and retained to some extent in this elimination organ. Different mechanisms for renal reabsorption of the peptides may exist. In the kidney, somatostatin analogues are taken up partly through receptor-mediated endocytosis (in which the megalin and cubilin receptor systems are purported to play a major role) and partly through fluid-phase endocytosis (7, 18-21). After binding of the peptides to megalin/cubilin receptors, the plasma membrane invaginates, forming endosomes. The endosomes finally fuse with lysosomes, in which the peptides are digested by proteolytic enzymes (15, 22). Radiolabelled catabolic products (*e.g.* ^{111}In- and $^{88/90}$Y-DOTA-peptide fragments) remain trapped within renal lysosomes (22).

All agents investigated in the present study were mainly excreted *via* the kidney. Both glomerular filtration and tubular reabsorption are known to be charge-dependent processes, and the net charge of radiolabelled somatostatin analogues dramatically changed the kidney retention of radioconjugates, whereas the binding potency to Sstr2 remained similar (14). As electrostatic forces attract the peptide to its binding site on the endocytic receptor, not only net charge, but likely also charge distribution in the chelator part, affects the internalisation of the peptides studied. Our findings show that the kidney uptake of $^{90/88}$Y-labeled peptides was significantly lower than that of the ^{111}In-labelled agent. This result means that although data for ^{111}In-labelled peptides can be successfully used for the calculation of the radiation dose for the ^{90}Y-labelled peptide, absorbed dose estimations for the ^{90}Y-labelled agent based on the ^{111}In-labelled peptide's biodistribution may result in overestimation of the kidney radiation dose. The mechanism of this effect is currently unknown, and the reason for these differences in renal retention of the radioactivity between ^{111}In- and $^{90/88}$Y-labelled peptides will be the subject of further studies. The possible explanations for this particular result include the structural differences between In and Y chelates and the effects of different geometry and local distribution of electrical charges of the radiometal-chelator complex.

A positively charged part of the peptide containing radioligand is probably responsible for the interaction with a renal transmembrane endocytic receptor and the consequent

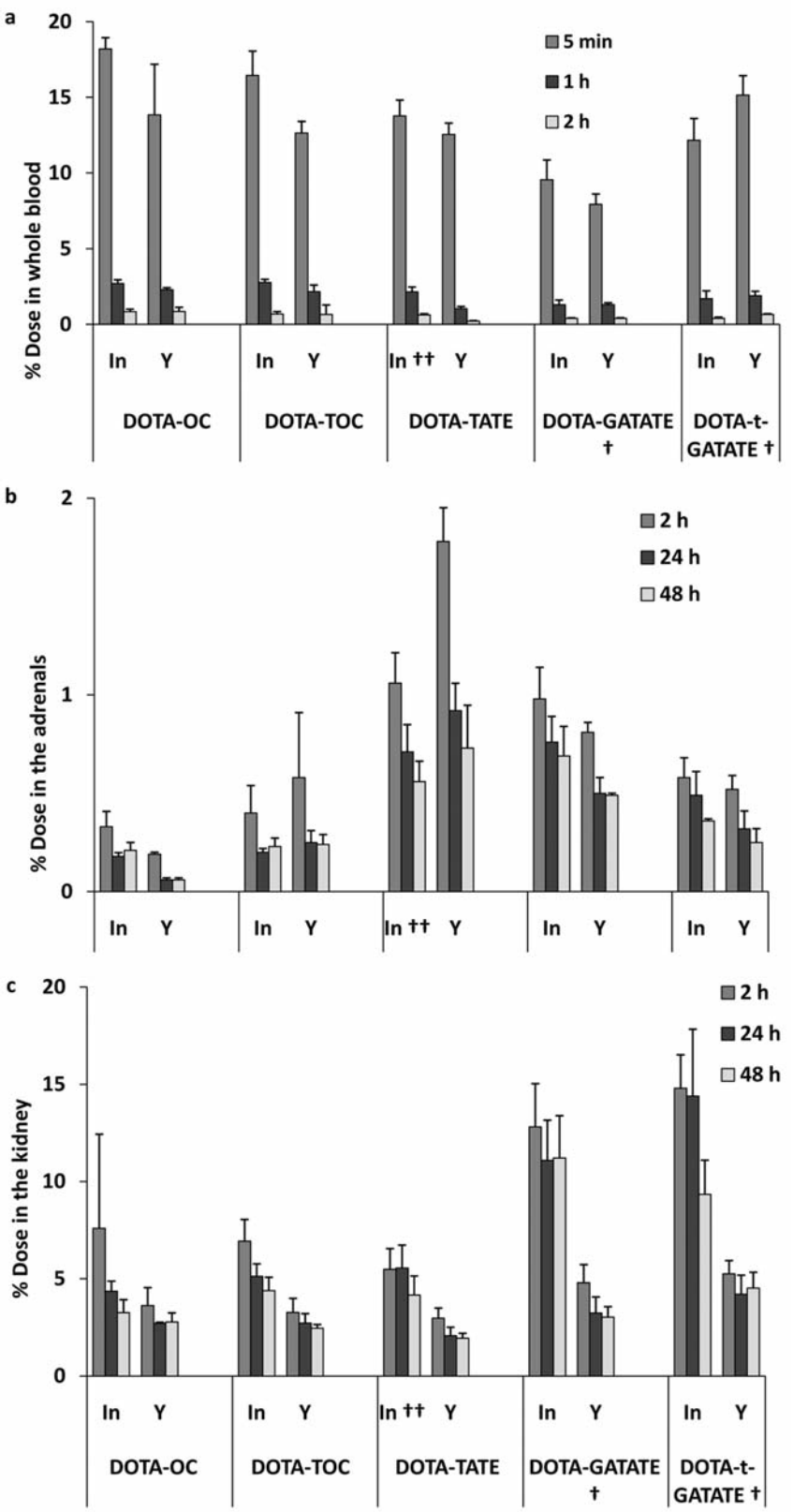


Figure 2. *Uptake of radioactivity into whole blood (a), distribution of radioactivity into adrenals, (an endogenous marker of the affinity to somatostatin receptor, b) and kidney uptake of radioactivity (the dose limiting organ, c). The agent was administered to rats intravenously under ether anaesthesia at a dose of 1 μg of the peptide/kg of body weight (activity approximately 50 μCi/kg). †Data partly derived from (12). ††Data partly derived from (25).*

peptide internalisation, as the only difference between an In-DOTA (or DOTA-like) peptide conjugate and the same peptide conjugate labelled with Y is the metal ion. Recent studies have shown that ^{111}In chelates are more hydrophilic than their corresponding ^{90}Y analogues, suggesting different coordination spheres in In-DOTA and Y-DOTA complexes (13). These structural differences between the yttrium and indium complexes of DOTA may also be due to different ionic radii (89 pm for yttrium and 81 pm for indium), different coordination numbers (usually 8 or 9 for Y^{3+} and 6 or 7 for In^{3+}) and different electron configurations ([Kr] for Y^{3+} and [Kr] $4d^{10}$ for In^{3+}) (1). It was also found that coordination with a water molecule changes the coordination number and position of the metal ion in In-DOTA, whereas Y-DOTA is hardly affected by water coordination (23).

In the literature, there is only a limited number of studies directly comparing biodistribution data for ^{111}In- and ^{90}Y-labelled somatostatin analogues. De Jong and co-workers found 1.66 times higher kidney uptake of radioactivity when ^{111}In-DOTA-TOC and ^{90}Y-DOTA-TOC were compared in rats 24 h after dosing, and they also found similar accumulation of radioactivity in the pancreas (radioactivity as determined in the adrenal gland was, however, surprisingly approximately one half of ^{111}In-DOTA-TOC in comparison with that of ^{90}Y-DOTA-TOC) (11).

The effect of radiolabel (^{111}In, ^{90}Y and ^{67}Ga) on distribution profiles of DOTA-conjugated somatostatin analogues OC, TOC and TATE were also studied by Froidevaux *et al*. (24) in tumour-bearing mice. Whereas after DOTA-TOC administration no significant differences in biodistribution between ^{111}In- and ^{90}Y-labelled agent were found, ^{67}Ga considerably improved distribution and elimination characteristics (mainly higher tumour area under the curve, lower kidney retention and faster clearance of radioactivity from non-target tissues) of all the somatostatin analogues in comparison with the one of ^{111}In. Possible explanation for the differential kidney retention between ^{67}Ga- and ^{111}In-labelled peptides might lie in their different spatial geometry (24). These results also suggest that interspecies differences in distribution profiles of somatostatin receptor-seeking peptides may exist. Although $^{67/68}$Ga-labelled somatostatin analogues appear to be the best choice in the management of somatostatin receptor-positive tumours (24), in current nuclear medicine, ^{111}In- and ^{90}Y-labelled peptides undoubtedly play a dominant role. For this reason, our study focused on these radionuclides and the effect of radiolabel bound was analyzed.

Based on these *in vivo* data, we summarise that ^{111}In-labelled DOTA (or DOTA-like) peptide conjugates are not biologically equivalent to the corresponding ^{90}Y analogue. Even if somatostatin analogues, whether labelled with ^{111}In or with $^{90/88}$Y, exhibit similar patterns of physiological uptake in organs with normal expression of somatostatin receptors, uptake of radioactivity in the kidney and, thus the radiation-absorbed dose with a ^{90}Y-labelled peptide, appears to be lower than the one predicted from ^{111}In peptide distribution in rats, and the difference appears to be statistically significant.

Acknowledgements

The study was supported by the Grant Agency of the Czech Republic – grant no. P304/10/1738. Research originated in collaboration within COST BM0607 and was supported by the Grant of the Ministry of Education of the Czech Republic, no. OC08006.

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Received December 6, 2011
Revised January 9, 2012
Accepted January 10, 2012