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D-Lysine Reduction of Indium-111 Octreotide and Yttrium-90 Octreotide Renal Uptake

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Indium-111-DTPA-octreotide (^{111}In-DTPAOC) is used successfully for imaging somatostatin receptor-positive lesions. A new and promising application is its use in peptide-receptor radionuclide therapy (PRRT). For the latter purpose, [DOTA^0,D-Phe^1,Tyr^3]octreotide (DOTATOC), which is suitable for stable radiolabeling with ^{90}Y, is probably even more promising. Significant renal uptake of these octreotide analogs exists, however, reducing the scintigraphic sensitivity for detection of small tumors in the perirenal region and limiting the possibilities for PRRT. We showed that the renal uptake of ^{111}In-DTPAOC could be reduced to about 50% of control by L-lysine administration in vivo in rats. This study compares the effects of several doses and different methods of administration of D- and L-lysine, in addition to time-related effects of D-lysine, on kidney uptake of ^{111}In-DTPAOC and ^{90}Y-DOTATOC. **Methods:** Male Wistar rats (200–250 g) were given ^{111}In-DTPAOC (0.2 MBq, 0.5 μg-0.5 mg intravenously, intraperitoneally or orally) in the presence or absence of D- or L-lysine. At 1, 4 or 24 hr, the rats were killed, and the organs were isolated and counted for radioactivity. In different experiments, male Wistar rats (200–250 g) were given ^{90}Y-DOTATOC (1 MBq, 0.5 μg intravenously) in the presence or absence of D-lysine. At 24 hr, the rats were killed, and the organs were isolated and counted for radioactivity. **Results:** Administration of D- or L-lysine in a single intravenous dose of 400 mg/kg, resulted in more than 50% inhibition of kidney uptake of ^{111}In-DTPAOC at all time points tested, independently of the mass of ^{111}In-DTPAOC used. Higher or repeated doses of lysine did not give a significantly higher percentage inhibition. D-lysine, given orally in a dose of 400 mg/kg at 30 or 15 min before ^{111}In-DTPAOC injection, resulted in 30% and 20% inhibition of kidney uptake, respectively. L-lysine, given orally 30 min before ^{111}In-DTPAOC administration, resulted in 30% inhibition as well. Inhibition of kidney uptake of ^{111}In-DTPAOC by L-lysine after intraperitoneal administration was 40%. After L-lysine administration, ^{111}In-DTPAOC was decreased in the kidneys and in somatostatin receptor-positive organs such as the pancreas and adrenal glands. In contrast, D-lysine did not have a significant effect on uptake in octreotide receptor-positive organs. Renal uptake of ^{90}Y-DOTATOC was reduced by 65% by intravenous D-lysine, whereas radioactivity in blood, pancreas and adrenal glands was not affected. **Conclusion:** D-lysine may be preferred to L-lysine for reduction of renal uptake of radioactivity during scintigraphy and PRRT because of its lower toxicity and because it should not interfere with the natural amino acid metabolic balance.

Key Words: indium-111-octreotide; yttrium-90-octreotide; renal tubular reuptake; D-lysine; L-lysine; peptide-receptor radiotherapy

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Indium-111 pentetreotide is a radiopharmaceutical that binds to somatostatin receptors present in certain tissues. It is being used for scintigraphic imaging of somatostatin receptor-positive lesions such as gastrointestinal pancreatic tumors, neuroblastoma, pheochromocytoma, breast cancer, Hodgkin's lymphoma and small-cell lung cancer (*1–3*). A new, interesting area of application is PRRT. Promising results have been reported in humans (*4*). However, although it emits Auger electrons, ^{111}In is not an optimal nuclide for radiotherapy. A beta-particle-emitting isotope such as ^{90}Y (maximum beta energy 2.3 MeV, half-life 64 hr) is more suitable for this purpose. However, [^{90}Y-DTPA^0]octreotide is not stable resulting in hematopoietic toxicity in vivo as ^{90}Y escapes to the skeleton (*5,6*). We have

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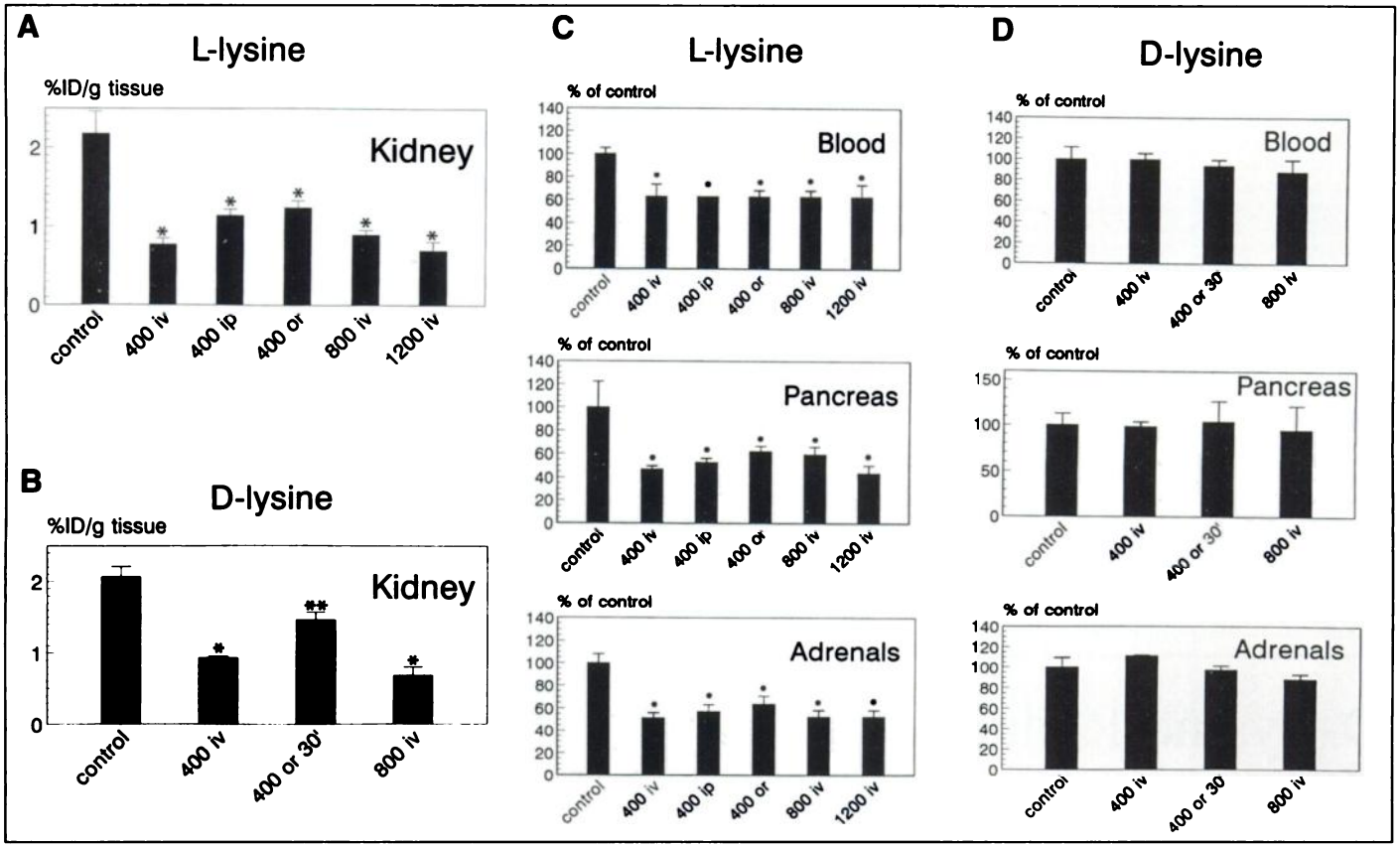

FIGURE 1. (A) Radioactivity in kidneys of control and L-lysine-treated rats, 24 hr after administration of ^{111}In-DTPA-octreotide (0.2 MBq and 0.5 μg). Mean ± 1 s.d. * $p < 0.001$ versus control. (B) Radioactivity in kidneys of control and D-lysine-treated rats, 24 hr after administration of ^{111}In-DTPA-octreotide (0.2 MBq and 0.5 μg). Mean ± 1 s.d. * $p < 0.001$ versus control. ** $p < 0.01$ versus control. (C) Radioactivity in several organs of control and L-lysine-treated rats, 24 hr after administration of ^{111}In-DTPA-octreotide (0.2 MBq and 0.5 μg). Mean ± 1 s.d. * $p < 0.05$ versus control. (D) Radioactivity in several organs of control and D-lysine-treated rats, 24 hr after administration of ^{111}In-DTPA-octreotide (0.2 MBq and 0.5 μg octreotide). Mean ± 1 s.d. iv = intravenous; ip = intraperitoneal; or = oral.

studied the binding of DOTATOC, suitable for stable radiolabeling with ^{90}Y, to octreotide receptors and compared the biodistribution of ^{111}In- and ^{90}Y-labeled DOTATOC with that of ^{111}In-DTPAOC in rats and found that uptake of radiolabeled DOTATOC in the octreotide receptor-expressing tissues pancreas, pituitary, adrenal glands and tumor was a factor of 3–16 that, after injection of ^{111}In-DTPAOC, makes it a promising pharmaceutical for PRRT of patients with octreotide receptor-positive lesions (*7*).

Indium-111-DTPAOC and ^{90}Y-DOTATOC are mostly cleared from the body by the kidneys, 50% within the first 4 hr after injection. However, a significant amount of the dose accumulates in the renal parenchyma reducing the scintigraphic sensitivity for detection of small tumors in the perirenal region in the abdomen. The possibilities of PRRT are reduced as well, as rapid excretion of nontumor-bound radioactivity is necessary to realize this potential.

It has been reported repeatedly that renal accumulation of peptides or proteins can be reduced. Infusion of certain amino acids, particularly lysine and arginine, has been shown to block renal tubular peptide reabsorption in general (*8*). An infusion of synthetic amino acids, containing among others lysine and arginine, significantly reduced kidney uptake of ^{111}In-DTPAOC in eight patients (*9*). Also, in mice, reduction of renal tubular reabsorption of ^{111}In-labeled Fab-fragment was affected by systemic administration of lysine (*10*). We reported on the inhibiting effects of intravenous administration of 400 mg/kg L-lysine on the kidney uptake of ^{111}In- or ^{161}Tb-labeled DTPAOC in-vivo in rats (*11,12*). Behr et al. recently showed that a variety of basic compounds was capable of inhibiting the tubular reabsorption, thus lowering the kidney uptake of antibody fragments significantly (*13*). In patients, renal uptake of monoclonal antibody fragments could be reduced significantly by amino acid infusion (*14*).

Building on the latter studies with antibody fragments, we compared the effects of different doses of D- and L-lysine on kidney uptake of ^{111}In-DTPAOC and ^{90}Y-DOTATOC and the influence on uptake in somatostatin receptor-positive organs. We also examined the effect of different methods of administration (oral, intravenous and intraperitoneal administration) of lysine and the time dependence of its effects on renal uptake of different masses of ^{111}In-DTPAOC.

MATERIALS AND METHODS

Radiolabeling and Quality Control of the Radiopharmaceuticals

The radiolabeling procedures were performed as described by De Jong et al. (*7*) and Bakker et al. (*15*).

Tissue Distribution of Indium-111-DTPAOC

Male Wistar rats (200–250 g) were placed in metabolic cages 24 hr before the start of the experiment. In experiments with fasting rats, food was withdrawn for 24 hr before the start of the experiment. Drinking water was always available ad libitum.

Effect of Peptide Mass

At time t = 0, rats were anesthetized with ether and injected intravenously with 0.2 MBq and 0.5 μg or 0.5 mg ^{111}In-DTPAOC, with or without co-injection of D- or L-lysine (see below).

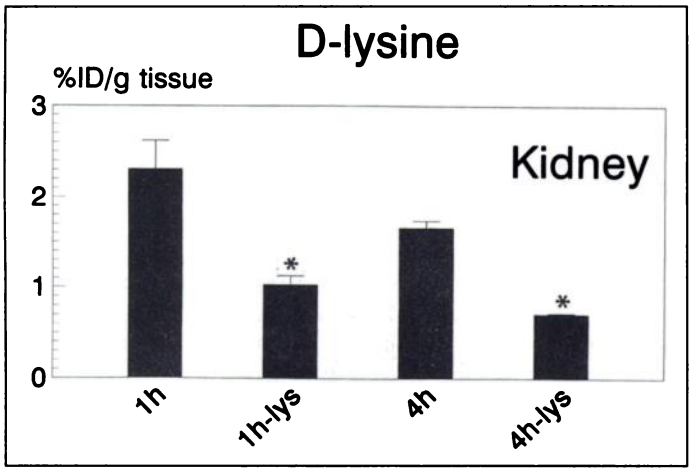

FIGURE 2. Radioactivity in kidneys of control and D-lysine-treated rats, 1 or 4 hr after administration of ^{111}In-DTPA-octreotide (0.2 MBq and 0.5 μg). Mean ± 1 s.d. * $p < 0.001$ versus control.

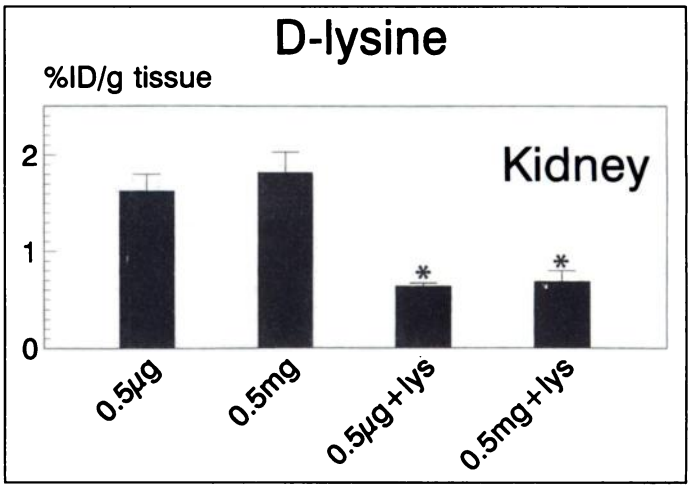

FIGURE 3. Radioactivity in kidneys of control and D-lysine-treated rats, 24 hr after administration of 0.5 μg or 0.5 mg ^{111}In-DTPA-octreotide (0.2 MBq). Mean ± 1 s.d. * $p < 0.001$ versus control.

Time Dependence of Lysine Effects

Rats were killed and organs were isolated 1, 4 or 24 hr after injection of the radiolabeled product and lysine.

D- and L-lysine Administration Methods and Doses

D- and L-lysine were given in doses of 400, 800 or 1200 mg/kg, intravenously or intraperitoneally. Administration consisted of single injections of these doses or repeated injections of 400 mg/kg at the time points indicated in the Results section. Oral administration of 400 mg/kg D- or L-lysine was performed through an oral intubation catheter at time points indicated in the Results section.

Tissue Distribution of Yttrium-90-DOTATOC

Experiments were performed essentially the same as described for ^{111}In-DTPAOC: Wistar rats were injected under ether anesthesia with 1 MBq (0.5 μg) ^{90}Y-DOTATOC intravenously. For reduction of kidney uptake, 400 mg/kg D-lysine was co-injected with the radiopharmaceutical.

Tissue distribution of both radiopharmaceuticals was studied by measurement of radioactivity (in the case of ^{90}Y as bremsstrahlung) in isolated organs, as well as in blood samples, using an LKB-1282-Compu-gammasystem.

Statistical evaluation was performed using one-way analysis of variance followed by comparison among class means and Student's t-test corrected for multiple pairwise comparisons between means. Results are expressed as mean ± 1 s.d.; in each group $n \geq 6$.

RESULTS

The inhibition of renal uptake of ^{111}In-DTPAOC by L-lysine, 24 hr after administration of both, is shown in Figure 1A. The effects of different doses and administration pathways are visualized also. Single doses of 400, 800 or 1200 mg/kg L-lysine, intravenously or intraperitoneally, were co-injected with ^{111}In-DTPAOC; 2 × 400 mg/kg L-lysine intravenously was given at 30 min before and 15 min after administration of ^{111}In-DTPAOC; 3 × 400 mg/kg L-lysine intravenously was given at 30 min before and 15 and 60 min after administration of ^{111}In-DTPAOC. Oral administration of 400 mg/kg L-lysine was 30 min before ^{111}In-DTPAOC. Repeated or higher doses than a single intravenous injection of 400 mg/kg L-lysine did not result in significantly greater inhibition of ^{111}In-DTPAOC kidney uptake. Oral and intraperitoneal administration of L-lysine also had a significant inhibitory effect on kidney uptake. These effects were smaller than those after intravenous administration, albeit not significantly.

In Figure 1B, the inhibition exerted by D-lysine on renal uptake of ^{111}In-DTPAOC, 24 hr after administration, is shown. Doses and timing of D-lysine administration were mostly the same as for L-lysine. Oral doses were given at 30 min prior to ^{111}In-DTPAOC. Again, in accordance with the findings for L-lysine, repeated or higher doses than a single intravenous injection of 400 mg/kg D-lysine did not result in significantly greater inhibition of kidney uptake of ^{111}In-DTPAOC. Oral administration of D-lysine also reduced kidney uptake; however, this effect was significantly smaller than after intravenous administration ($p < 0.05$). The effects of 400 mg/kg D- and L-lysine administered intravenously on kidney uptake of ^{111}In-DTPAOC appeared to be similar.

In Figure 1C, the distribution of radioactivity, expressed as percent of control, 24 hr after administration of ^{111}In-DTPAOC, is given for blood, pancreas and adrenal glands of control and L-lysine-treated rats. Radioactivity in control animals was 0.0017 ± 0.0003% of the injected dose (ID)/g, 1.12% ± 0.35% ID/g and 1.54% ± 0.22% ID/g for blood, pancreas and adrenal glands, respectively. Indium-111-DTPAOC clearance from the blood was faster in L-lysine-treated rats, and uptake in the somatostatin receptor-positive organs pancreas and adrenal glands was less than that in control animals.

In Figure 1D, the distribution of radioactivity expressed as percent of control, 24 hr after administration of ^{111}In-DTPAOC, is given for blood, pancreas and adrenal glands of control and D-lysine-treated rats. No effect of D-lysine was found on both ^{111}In-DTPAOC clearance from the blood and uptake in the receptor-positive organs. The ratios pancreas/kidney (both expressed as %ID/g) and adrenals/kidney of ^{111}In-DTPAOC uptake appeared to be 0.8 and 1.2, respectively, after L-lysine treatment, whereas after D-lysine administration these ratios were 1.4 and 1.9, respectively. For the control rats, the figures

TABLE 1
Radioactivity in Organs and Blood of Rats 24 Hr after Administration of [^{90}Y-DOTA^0,Tyr^3]octreotide without or with Co-injection of 400 mg/kg D-lysine

Organ	Radioactivity (% of control)*
Blood	100.0 ± 0.0
Kidneys	34.8 ± 5.2†
Pancreas	111.0 ± 5.4
Adrenal glands	97.0 ± 6.5

*Data from D-lysine-treated rats are expressed as % of those in controls.
†$p < 0.01$ vs. control.

were 0.5 and 0.7 for pancreas/kidney and adrenals/kidney, respectively.

Figure 2 shows the reduction of ^{111}In-DTPAOC kidney uptake by D-lysine 1 or 4 hr after administration. It shows that the reducing effect of lysine on kidney uptake of ^{111}In-DTPAOC is comparable at the indicated time points. Furthermore, no significant effect was found on the ^{111}In-DTPAOC clearance from blood and uptake in the receptor-positive organs (not shown).

Figure 3 shows that 400 mg/kg D-lysine reduced kidney uptake of 0.5 mg ^{111}In-DTPAOC, which is very high, even blocking the dose for uptake of radioactivity in octreotide receptor-positive organs.

Table 1 shows the distribution of radioactivity in rats 24 hr after administration of ^{90}Y-DOTATOC without or with co-injection of 400 mg/kg D-lysine. Renal uptake was reduced to 35% of control by D-lysine, whereas radioactivity in blood, pancreas and adrenal glands was not affected.

DISCUSSION

Peptides (and proteins less than 60 kD) in plasma are filtered through the glomerular capillaries in the kidneys and subsequently reabsorbed almost completely ($\geq$ 99%) by the proximal tubular cells through saturable receptor-mediated endocytosis. The peptide then may be intracellularly routed to the lysosomes where degradation takes place. Lysosomal degradation also has been described for ^{111}In-DTPA-labeled peptides, its radiolabeled degradation products are retained in the lysosomes and likely transferred to intracellular metalloproteins (*16*).

It has been shown repeatedly that renal accumulation of peptides or proteins can be reduced. Administration of amino acids, among others lysine and arginine, has been shown to block renal tubular peptide or protein reabsorption (*8–15*). It was concluded that the mechanism of the reduction of the renal uptake of radiolabeled peptides seemed to rely on an inhibition of the tubular reabsorption so that they appear directly in the urine without prior lysosomal degradation to low-molecular weight compounds (*14*). Membranes of renal tubular cells contain negatively charged sites, to which positively charged amine or guanine groups of peptides can bind (*8*). So, decreased binding of ^{111}In-DTPAOC after administration of the positively charged amino acids lysine and arginine can be explained by this phenomenon (*9*).

An important finding of the experiments described here is that L- and D-lysine were equally potent in inhibiting kidney uptake of ^{111}In-DTPAOC, but that after L-lysine administration the uptake in the somatostatin receptor-positive organs was reduced as well. This reduction of uptake of ^{111}In-DTPAOC in the receptor-positive organs was not found after administration of D-lysine. These findings in rats may have implications for the clinical use of lysine as an inhibitor of kidney uptake of ^{111}In-DTPAOC. For both diagnostic and radiotherapeutical use of ^{111}In-DTPAOC, it is important that a maximal uptake of radioactivity in the tumor is achieved. Therefore, D-lysine is the preferred agent for inhibition of kidney uptake of ^{111}In-DTPAOC. Another advantage of D-lysine is that toxicity of lysine at high doses seems to be restricted to the L-isomer (LD_{50} in fasted rats 4000 mg/kg (*17*)) and that D-lysine should not interfere with the natural amino acid metabolic balance as D-lysine is not used as a source for L-lysine in humans (*18*).

An increase in glomerular filtration rate (GFR) and renal plasma flow (RPF) after administration of L-lysine, but not after D-lysine, could at least partially explain our findings. The measured radioactivity in the blood, 24 hr after administration of ^{111}In-DTPAOC, was significantly lower after L-lysine administration than in control rats ($p < 0.05$). It may be hypothesized from these experiments that a lower blood concentration, because of a higher renal clearance, results in a lower uptake of ^{111}In-DTPAOC in the organs, except for the kidneys. This is in accordance with our opposite findings with regard to increased uptake of ^{111}In-DTPAOC in all organs, except for the kidneys, after sodium maleate administration, explained by the inhibitory effect of this compound on the GFR (*11*).

Our findings of reduced radioactivity in receptor-positive organs after L-lysine administration are in contrast with those of Behr et al. (*13*) and Pimm et al. (*10*) who did not find a significant effect of L-lysine on the uptake and retention of radiolabeled antibody fragments in tumor or normal organs in mice. This discrepancy may be due to species differences (mice versus rats), or by the fact that their experiments were performed with radiolabeled monoclonal antibody fragments, whereas ours were done with radiolabeled peptides. Peptides are cleared faster from the circulation and receptor binding and uptake processes occur at higher rates than those of the bigger monoclonal antibody fragments. In the period just after injection of ^{111}In-DTPAOC, lysine concentration in the circulation is relatively high and may hamper ^{111}In-DTPAOC binding to its receptors by the same mechanism as described for the kidneys (see above). When binding of monoclonal antibody fragments to their receptors occurs, lysine concentration in the blood decreases and may not influence the binding process. Furthermore, an increased GFR by L-lysine will affect the rapid ^{111}In-DTPAOC clearance more than that of monoclonal antibody fragments.

From our data, we conclude that the maximal inhibitory effect of both L- and D-lysine is reached after intravenous administration of 400 mg/kg as higher doses or repeated doses of 400 mg/kg do not result in an increased reduction of ^{111}In-DTPAOC uptake in the kidneys. After intraperitoneal administration, lysine was less effective than after intravenous injection. The same holds for a single oral administration. Overnight fasting, thereby emptying the stomachs of the rats, did not improve the effect of orally administered D-lysine on kidney uptake (results not shown). It may be useful to further investigate the effects of oral administration of higher doses of D-lysine as this means of administration avoids long intravenous infusion of lysine in humans. The different time point measurements showed that D-lysine had the same reducing effect on kidney dose measured at 1, 4 and 24 hr after administration of ^{111}In-DTPAOC.

Currently, PRRT of octreotide receptor-positive lesions is explored by repeated administration of high doses of radiolabeled octreotide. Promising results have been reported both in human and in rat studies (*4,19*). Stolz et al. (*19*) found up to 100% longer survival of tumor-bearing rats after radionuclide therapy with [^{90}Y-DTPA-benzyl-acetamido]-octreotide. We investigated in vivo in rats the effect of PRRT, using ^{111}In-DTPAOC, on the development and growth of somatostatin receptor-positive tumors (CA20948) inoculated in the liver. Treatment was given at Day 1 and/or Day 8 after inoculation with: (a) 0.5 μg unlabeled DTPA-octreotide, (b) 10 mCi ^{111}In-DTPAOC (0.5 μg) or (c) 10 mCi ^{111}In-DTPAOC after saturation of the receptors with 1 mg unlabeled octreotide. Significantly fewer tumors were found in animals of Group B compared to the other groups (manuscript submitted for publication). As for PRRT in humans, we treated 11 end-stage patients with neuroendocrine tumors with ^{111}In-DTPAOC, up to a cumulative dose of 53 GBq (for dose estimates (*20*)) per patient, in a Phase I trial (*4*). There were no major side effects after up to 2 yr of treatment and positive effects were found on

clinical symptoms, hormone production and tumor proliferation (*4*). However, ^{111}In is not the most appropriate radionuclide for PRRT; it lacks the preferable higher energies of beta particles. Yttrium-90 is a good candidate with its maximum beta energy of 2.3 MeV and high affinity for the DOTA chelator. Radiotherapeutic use of ^{90}Y-DOTATOC will lead to a higher and more evenly distributed radiation dose to the tumor because of its larger particle range and tissue penetration. With respect to in vivo tissue distribution in the rat, we showed that specific uptake of both ^{90}Y- and ^{111}In-labeled DOTATOC in octreotide receptor-expressing tissues was significantly higher than that of ^{111}In-DTPAOC, making radiolabeled DOTATOC favorable for both scintigraphy and radiotherapy of receptor-positive lesions (*7*).

D-lysine administration resulted in a significant reduction of labeled DOTATOC uptake in the kidneys without affecting uptake in receptor-positive tissues, thus bringing the application of the labeled compound for radionuclide therapy further within reach. In this respect, it is also interesting to note that the D-lysine dose (400 mg/kg) used in rats was able to reduce kidney uptake of up to 0.5 mg ^{111}In-DTPAOC, which is a very high and blocking dose of octreotide for uptake in the octreotide receptor-positive organs.

More knowledge of ways to decrease renal uptake of radiometals is of great value for tumor scintigraphy and PRRT as this may lead to better protection of the kidneys and, thus, less radiotoxocity in this organ, especially after PRRT with high-energy beta-emitters, such as ^{90}Y, coupled to octreotide analogs.

CONCLUSION

While this article was in press, further experiments in CA20948 tumor-bearing rats showed that the tumor uptake after ^{111}In-DTPAOC injection was not affected by 400 mg/kg L-lysine. We still conclude, however, that D-lysine may be preferred to L-lysine for reduction of renal uptake of radioactivity during scintigraphy and PRRT because of its lower toxicity and because it should not interfere with the natural amino acid metabolic balance.

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