

## Somatostatin receptor subtype 2-mediated uptake of radiolabelled somatostatin analogues in the human kidney

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### Abstract

**Purpose** Renal irradiation is a dose-limiting factor in peptide receptor radionuclide therapy using radiolabelled somatostatin analogues. This irradiation is mainly caused by reabsorption of radiolabelled peptides in the proximal tubule. In the human kidney, somatostatin receptors are expressed in the vasa recta, tubuli and glomeruli. It is not clear to what extent these receptors contribute to the total kidney radioactivity uptake.

**Methods** Retrospectively, [ $^{111}\text{In}$ -DTPA $^0$ ]octreotide scans of ten selected patients with carcinoids (well-differentiated gastrointestinal endocrine tumour) with liver metastases were evaluated. For each patient, two scans were obtained: one scan was performed without (control) and one during treatment with unlabelled octreotide. Kidney, tumour, spleen and liver uptake was measured in both scans.

**Results** The interval between the two scans per patient varied from 50 to 397 days. Octreotide treatment substantially lowered kidney [ $^{111}\text{In}$ -DTPA $^0$ ]octreotide uptake in eight out of ten patients. Kidney uptake in all patients was reduced to  $82\% \pm 15\%$  of control, ( $p < 0.01$ ). A correlation between kidney uptake and spleen uptake was found ( $r = 0.67$ ,  $p < 0.05$ ). Serum creatinine was unchanged. Surprisingly, tumour and liver [ $^{111}\text{In}$ -DTPA $^0$ ]octreotide uptake was not significantly influenced by unlabelled octreotide

therapy, but spleen uptake was significantly lowered by treatment (30.6% of control,  $p < 0.002$ ).

**Conclusion** We conclude that the somatostatin receptor plays a role in the total renal uptake of radiolabelled somatostatin analogues. The long interval between scans might explain the finding that tumour and liver metastasis uptake of [ $^{111}\text{In}$ -DTPA $^0$ ]octreotide was unchanged. Further studies are needed to confirm and elucidate the results of this study.

**Keywords** PRRT · Kidney · Somatostatin receptor subtype 2 · Carcinoid · Octreotide

### Introduction

The finding that neuroendocrine tumours have a high expression of somatostatin receptors has led to new diagnostic and therapeutic strategies for these tumours. In recent years many peptide receptor radionuclide therapy (PRRT) clinical trials have been conducted using radiolabelled somatostatin analogues, with promising results [1–6].

In PRRT, the kidney radiation dose is the major dose-limiting factor, being caused by uptake of a few percent of the injected dose after glomerular filtration and the subsequent long residence of radioactivity in the kidney cells. Based on external beam radiation data, kidney radiation doses of 23–27 Gy are generally accepted as safe [7]. Follow-up studies after PRRT have suggested that the maximum safe kidney dose, calculated as the biological equivalent dose using the linear quadratic model, might be about 37 Gy [8, 9]. When renal uptake of radiolabelled somatostatin analogues can be significantly lowered, larger total radioactivity doses can be injected within the boundaries of these maximum renal radiation doses, thereby enlarging the therapeutic window for PRRT.

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It was recently shown that renal uptake of somatostatin analogues can be inhibited by maleic acid, which interferes with cellular energy supplies [10], by colchicine [11] due to dysfunction of proximal tubule reabsorption processes and by positively charged amino acids such as lysine and arginine [10, 12, 13]. Based on animal studies and clinical data [6, 14–17], PRRT is nowadays performed by co-infusion of lysine and arginine for kidney protection. All these data point to the proximal tubule as the main site of kidney uptake, but the specific mechanism of renal uptake has not yet been fully elucidated. From in vitro studies with opossum kidney cells it was suggested that megalin, a multiligand endocytic protein, is involved in the uptake process [18], which is strongly supported by our recent findings of low renal uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide in kidney-specific megalin-deficient mice [19]. For more specific renal prevention strategies it is important to know the mechanism and site of renal uptake of somatostatin analogues.

Using binding and immunohistochemistry studies, Reubi et al. [20] found that the vasa recta in human kidney express somatostatin type 2 ( $\text{sst}_2$ ) receptors in a high density.  $\text{Sst}_2$  receptors were also demonstrated in tubular cells of the renal cortex, but at a lesser density. Balster et al. [21] showed mRNA of the somatostatin receptor subtypes 1 and 2 in nine out of nine human kidneys. With antisera they found that  $\text{sst}_2$ , but not  $\text{sst}_1$ , was expressed on the glomeruli, whereas both subtypes could be demonstrated on distal tubule cells and on the thick ascending limb of Henle's loop.

The aim of the present study was to establish the contribution of renal  $\text{sst}_2$  receptors to the total kidney uptake of radiolabelled somatostatin analogues. Because a rat model is not suitable—the rat kidney does not express somatostatin receptors—we retrospectively examined [ $^{111}\text{In-DTPA}^0$ ]octreotide scans of carcinoid patients with and without high-dose octreotide therapy.

## Materials and methods

### Patients

From our database, ten patients with a carcinoid tumour (well-differentiated gastrointestinal endocrine tumour) were selected who had been investigated with two diagnostic [ $^{111}\text{In-DTPA}^0$ ]octreotide scans. One scan was performed without treatment and one during treatment with high-dose octreotide for relief of carcinoid syndrome symptoms. The interval between scans was 50–397 days (mean 275 days, SD 102 days). No other medical anti-tumour therapy or surgery was given in between scans. Octreotide was either administered as the short-acting Sandostatine (Novartis, Brussels, Belgium) or the long-acting Sandostatine LAR. Doses varied between 200 and 300  $\mu\text{g}$  per day and between 20 and 30 mg per 28 days, respectively. Patients initially were treated with octreotide as the gold standard in our hospital, but after the long-acting Sandostatine LAR became available, this became the treatment modality of choice. Doses were adjusted individually on the basis of symptoms. For the patients treated with the LAR-octreotide, the interval between the last octreotide-LAR injection and the scan was 4–21 days. Table 1 summarises the patients' characteristics.

### Radiolabelling

Commercially available kits of [DTPA $^0$ ]octreotide and  $^{111}\text{InCl}_3$  were obtained from Mallinckrodt (Petten, The Netherlands). The radiolabelling procedure was performed in accordance with standard procedures [22, 23].

### Measurement of kidney uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide

Uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide in left kidney, spleen, liver and tumour was calculated as percentage uptake of the

**Table 1** Patient characteristics

Patient	Localisation	Octreotide	Octreotide dose
PB	75/F	Small intestine + appendix	LAR-octreotide
JD	75/F	Unknown origin	LAR-octreotide
AJ	52/M	Small intestine	LAR-octreotide
HM	64/F	Small intestine	LAR-octreotide
MS	75/M	Small intestine	LAR-octreotide
JJ	65/F	Small intestine	Octreotide
AS	62/F	Unknown origin	Octreotide
RW	60/M	Small intestine	Octreotide
JB	47/M	Appendix	Octreotide
PP	38/F	Unknown origin	Octreotide

LAR-octreotide the long-acting Sandostatine LAR

**Table 2** Left kidney uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide during octreotide treatment, expressed as % of the scan performed without octreotide treatment (% of control)

Patient	Age (yrs)/sex	Kidney uptake during octreotide treatment (% of control)
PB	75/F	83
JD	75/F	91
AJ	52/M	74
HM	64/F	68
MS	75/M	109
JJ	65/F	74
AS	62/F	101
RW	60/M	80
JB	47/M	87
PP	38/F	58
Mean $\pm$ SD		82 $\pm$ 15*

\* $p < 0.01$ 

injected dose using conjugate-view abdominal planar scintigraphy at 24 h post injection of 220 MBq [ $^{111}\text{In-DTPA}^0$ ]octreotide. Planar scintigraphy was performed with a dual-head gamma camera (2000XP, Philips Medical Systems, Eindhoven, The Netherlands) fitted with a medium-energy collimator. The energy windows were set at  $\pm 15\%$  and acquisition times were 15 min.

### Statistics

Wilcoxon paired non-parametric test was used for intra-patient comparisons.  $p$ -values  $< 0.05$  were considered statistically significant.

### Results

Left kidneys were clearly visible on all scintigrams, but overprojection of the liver made measurement of the right kidney unreliable.

Table 1 shows the characteristics of the ten included patients, who all had liver metastases.

Left kidney radioactivity at 24 h p.i. ranged from 0.2% to 1.05% of the injected dose; during octreotide treatment, left kidney radioactivity ranged from 0.2% to 1.07% of injected dose. Table 2 shows the left kidney uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide during octreotide treatment, expressed as percentage of the scan performed without octreotide treatment. In eight out of ten patients, substantial reductions in renal radioactivity were found, ranging from 58% to 91% of the scan without octreotide treatment, but in two of the ten patients no reduction in kidney radioactivity uptake was found. The kidney uptake in all patients was

reduced by 18%, to 82% $\pm$ 15% of the scan without octreotide treatment ( $p < 0.01$ ).

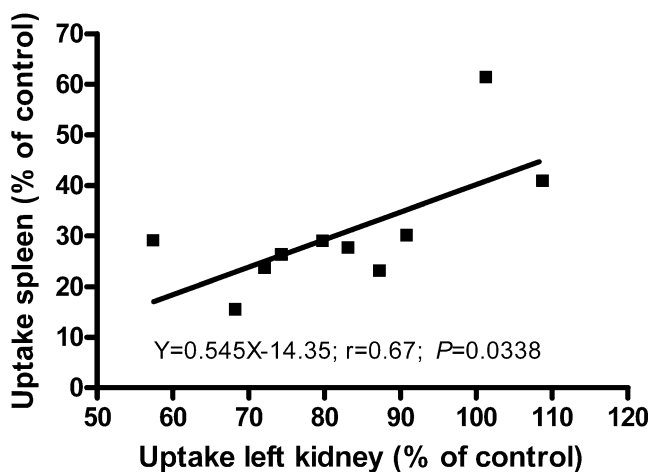
Figure 1 shows the weak but significant correlation that was found between kidney and spleen uptake ( $r = 0.67$ ;  $p < 0.05$ ). There was no correlation between reduction in renal uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide and the length of the interval between scans (not shown). In addition, no correlation was found between reduction in renal uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide and the dose of octreotide administered (not shown).

Figure 2 shows the serum creatinine values at the time of the standard scan and at the time of the scan during octreotide treatment. During octreotide treatment, the serum creatinine was not significantly different from that during the control situation.

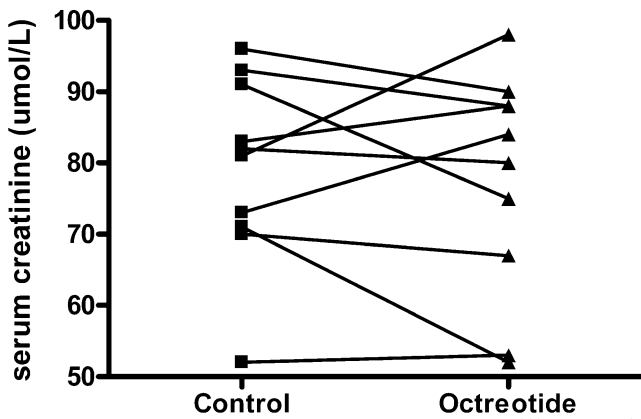
Table 3 shows the uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide in the left kidney, liver, spleen and tumour in patients receiving octreotide therapy, expressed as percentage of the uptake measured without this treatment. Spleen uptake was significantly reduced by octreotide treatment, but tumour and liver uptake was not.

Table 4 summarises the individual values for tumour uptake (expressed as percentage of control) in each patient. Table 4 also shows the changes in disease during the interval between scans, as measured by computer tomography (CT) or magnetic resonance imaging (MRI). No clear correlation could be found between increases in tumour uptake and changes in disease activity, e.g. progression.

The patients who were treated with LAR-octreotide had tumour uptake values of 97 $\pm$ 35% of control, not significantly different from control. The patients who were treated with octreotide had tumour uptake values of 74 $\pm$ 32% of control, again not significantly different from control.



**Fig. 1** Correlation of effects of octreotide treatment on kidney uptake and on spleen uptake 24 h after injection of 220 MBq [ $^{111}\text{In-DTPA}^0$ ] octreotide. Data are expressed as percentage of the scan without octreotide treatment



**Fig. 2** Serum creatinine values at the times of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide scintigrams before and during octreotide treatment

**Discussion**

During PRRT, the kidney radiation dose is the major factor that limits the total administered dose and the radiation dose to the tumour. Renal uptake of radiolabelled somatostatin analogues and subsequent long retention of radioactivity are responsible for this kidney radiation.

In order to interfere with this uptake successfully, it is essential to understand the exact uptake mechanism. The major part of kidney uptake of radiolabelled somatostatin analogues is via proximal tubular reabsorption. This is supported by the finding of several groups that positively charged amino acids, like lysine and arginine, can reduce the kidney uptake of radiolabelled somatostatin analogues by about 40–50% [10, 15, 17]. These amino acids are known to interfere with the proximal tubular reabsorption of small proteins and peptides [24]. Furthermore, we have shown that the kidney uptake of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide in megalin-deficient mice is significantly reduced as compared with normal mice [19]. Megalin is a multi-scavenger molecule that is essential for proximal tubular reabsorption of many low molecular weight proteins. Despite this, the exact localisation and mechanism have not been fully elucidated. As the renal uptake of somatostatin analogues cannot be completely blocked, other mechanisms may be involved.

**Table 3** Spleen, liver and tumour uptake of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide during treatment with unlabelled octreotide, expressed as percentage of uptake without treatment

	Uptake (% of control)
Spleen	31%±13%*
Liver	83%±32%**
Tumour	85%±37%**

\**p*<0.002, \*\**p*=NS

**Table 4** Tumour uptake of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide during treatment with unlabelled octreotide, expressed as percentage of a scan without treatment in each individual patient

Patient	Tumour (% control)	Disease <sup>a</sup>
PB	119	Stable (MRI)
JD	145	Progression (MRI)
AJ	70	Stable (MRI)
HM	46	Stable (CT) <sup>b</sup>
MS	104	Stable (CT) <sup>b</sup>
JJ	70	Stable (CT) <sup>c</sup>
AS	93	Stable (CT)
RW	117	Regression (CT) <sup>d</sup>
JB	67	Stable (CT)
PP	22	Stable (MRI)

<sup>a</sup> Course of the disease during the interval between scans

<sup>b</sup> Stable disease on CT, but new lesions on SMS scan

<sup>c</sup> On CT the metastasis volumes were unchanged, but there was less necrotic tissue in metastases

<sup>d</sup> Minimal reduction of metastasis size

In the past, sst<sub>2</sub> have been demonstrated in cells of glomeruli [21], tubuli and vasa recta [20]. The present study was performed to elucidate the role of these receptors in renal uptake during scintigraphy and PRRT using somatostatin analogues. We showed that renal uptake of somatostatin analogues is significantly reduced by concomitant treatment with unlabelled octreotide for relief of carcinoid syndrome symptoms. This indicates that binding to the renal sst<sub>2</sub> plays a role in the total uptake of radiolabelled somatostatin analogues in the kidneys and thus in the resulting renal radiation dose. We could not find a clear dose relationship in these ten patients, but the correlation observed between spleen uptake and kidney uptake suggests a dose dependency.

One could argue that the effects of octreotide treatment on kidney uptake of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide might not be caused by ousting of the radioligand from the sst<sub>2</sub> by the cold octreotide, but by other factors, such as haemodynamic changes due to high octreotide levels. There is some controversy in the literature on the effects of somatostatin and somatostatin analogues on kidney function parameters. Table 5 summarises all human data on the effects of somatostatin or octreotide on kidney function. Somatostatin and octreotide have been described in healthy subjects and patients with diabetes mellitus and acromegaly to decrease renal plasma flow (RPF) and concomitantly decrease glomerular filtration rate (GFR) with an unchanged filtration fraction [25–32]. However, it should be noted that some of these studies administered supraphysiological doses of somatostatin [100–420 µg/h intravenously (IV) or 600 µg/day subcutaneously (SC)]. In contrast, the study by Castellino et al. [33] applied 480 µg/h somatostatin in 18 healthy subjects and did not find any effect on the GFR. Studies that applied octreotide doses comparable to the

doses in our patient group showed conflicting results as well. Tulassay et al. [34] administered 100 µg octreotide subcutaneously and found a significant decrease in GFR of 47%, which lasted up to 8 h. Studies performed in cirrhotic patients, growth hormone-deficient patients and patients with mild to moderate renal insufficiency did not find significant changes in either RPF or GFR [33, 35–42]. It must be stressed that the studies listed in Table 5 describe the relatively short-term (hours to months) effects of somatostatin or its analogues on kidney function. Patients suffering from neuroendocrine tumours are usually treated for years with unlabelled somatostatin analogues. In our study, serum creatinine values did not change during treatment with octreotide, suggesting that there were no major changes in GFR in our patients that could have biased our findings.

In the present study, the variable effects of octreotide treatment on tumour and liver uptake were unexpected. As these tumours and metastases are somatostatin receptor-positive, one would expect an unequivocal reduction in [ $^{111}\text{In-DTPA}^0$ ]octreotide uptake in them. A possible expla-

nation for our findings could be progression of the tumour at the time of the scan during octreotide treatment. As shown in Table 4, in only one patient with an increase in tumour [ $^{111}\text{In-DTPA}^0$ ]octreotide uptake during octreotide treatment was disease progression present. Two patients with progressive disease, however, had a strong reduction in tumour and liver uptake. Patients with stable disease could have had either a strong reduction or an increase in [ $^{111}\text{In-DTPA}^0$ ]octreotide uptake during octreotide treatment.

Interestingly, patients treated with the long-acting LAR-octreotide seemed to have a smaller reduction (3%±35%) in tumour uptake of [ $^{111}\text{In-DTPA}^0$ ]octreotide than those treated with octreotide (26%±32%), although this difference was not statistically significant and large variations were present in both groups. This, taken together with the reduced kidney uptake caused by both octreotide and LAR-octreotide, might provide a basis in the future for continuation of LAR-octreotide treatment during PRRT as it causes little reduction in tumour uptake but sustained kidney uptake reduction, enlarging the therapeutic window of PRRT. Larger studies that apply smaller intervals

**Table 5** Summary of human studies on renal effects of somatostatin or octreotide

Authors	Subjects	Dosage	Major finding
Serri et al. [25]	Diabetics ( $n=11$ )	Cont. SC infusion of 300 µg octreotide/day for 12 weeks	GFR 136 ml/min vs 157 ml/min in placebo group
Luksch et al. [26]	Healthy ( $n=3$ )	6 µg/kg/h somatostatin IV, for 3 h	Inulin clearance 131→124 ml/min
Schmidt et al. [27]	Healthy ( $n=9$ )	6 µg/kg/h somatostatin IV, for 3 h	Inulin clearance 138→119 ml/min
Tulassay et al. [28]	Healthy ( $n=7$ )	250 µg somatostatin/h IV, for 2 h	Inulin clearance 131→62 ml/min
Vora et al. [29]	Healthy ( $n=6$ ) and diabetics ( $n=9$ )	100 µg somatostatin/h IV, for 2 h	$^{51}\text{Cr-EDTA}$ clearance 112→95 ml/min
Dullaart et al. [30]	Acromegaly ( $n=7$ )	T.i.d. 100 µg octreotide, for 3 months	$^{125}\text{I-iodothalamate}$ clearance 132→117 ml/min
Kalambokis et al. [31]	Cirrhotics ( $n=25$ )	B.i.d. 300 µg octreotide SC, for 11 days	Higher RPF flow but $^{99\text{m}}\text{Tc-DTPA}$ clearance 95→79 ml/min
Kalambokis et al. [32]	Cirrhotics ( $n=20$ )	B.i.d. 300 µg octreotide SC, for 14 days	$^{99\text{m}}\text{Tc-DTPA}$ clearance 79→72 ml/min
Castellino et al. [33]	Healthy ( $n=18$ )	480 µg/h somatostatin IV, for 3 h	No effect of somatostatin on inulin clearance
Tulassay et al. [34]	Healthy ( $n=8$ )	100 µg octreotide SC, once	Creatinine clearance 124→66 ml/min
Krempf et al. [35]	Diabetics ( $n=5$ )	480 µg octreotide IV/h, for 10 h	$^{99\text{m}}\text{Tc-DTPA}$ clearance unchanged
Malesci et al. [36]	Cirrhotics ( $n=11$ )	T.i.d. 100 µg octreotide SC, for 2 weeks	Inulin clearance 99→99 ml/min
Ruggenenti et al. [37]	Cystic kidneys ( $n=14$ )	40 mg LAR-octreotide SC every 4 weeks, for 6 months	Unchanged iothexol plasma clearance
Sabat et al. [38]	Cirrhotics ( $n=20$ )	B.i.d. 250 µg octreotide SC, for 5 days	Creatinine clearance 61→65 ml/min
Dullaart et al. [39]	GH-deficient ( $n=7$ )	10 µg/h IV plus 4 injections 100 µg octreotide SC	$^{125}\text{I-iodothalamate}$ clearance unchanged
Mountokalakis et al. [40]	Cirrhotics ( $n=9$ )	40 µg/h octreotide IV, for 2 h	Creatinine clearance higher
Ottesen et al. [41]	Cirrhotics ( $n=25$ )	20 mg LAR-octreotide SC every 4 weeks	$^{51}\text{Cr-EDTA}$ clearance 120→114 ml/min (NS)
Pomier-Layrargues et al. [42]	Hepatorenal syndrome ( $n=14$ )	50 µg/h IV, for 2 days	Creatinine clearance unchanged



between the scans are needed before such a strategy can be implemented in PRRT protocols, however. In our study, the interval between the scan without and that with octreotide treatment was long, and it is hard to tell exactly what happens in the tumours at the level of receptor numbers and receptor density.

Dorr et al. [43] previously showed diminished kidney, liver and spleen uptake during octreotide treatment with 600 µg per day, yet improved tumour visualisation by somatostatin analogue treatment. Our results are not in line with their findings: indeed we found significant reduction in kidney uptake, but in four of five patients treated with three daily injections of octreotide we also found a considerable reduction in tumour uptake, applying even a lower dose (200 or 300 µg/day) than Dorr et al. Owing to the small number of patients and the large inter-individual variation, the mean tumour uptake was not significantly reduced by unlabelled octreotide treatment.

## Conclusion

We showed that during treatment with octreotide for symptom relief, kidney uptake of [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide was decreased by about 18% in ten patients with carcinoid tumours. This indicates a substantial contribution of renal sst<sub>2</sub> to the total kidney uptake of radiolabelled somatostatin analogues. The effects of octreotide and LAR-octreotide on tumour and liver metastases were not expected: we did not find a significant reduction of tumour uptake. The large interval between scans might be a confounding factor, as might the small number of patients evaluated.

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