Renal iodide clearance in rabbits

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Abstract. The purpose of the study was to compare indirect clearance methods based on plasma values and external detection of activity using small skin attached radioactivity detectors with a direct clearance method based on constant infusion and urine collection. The experiments were performed in anesthetized rabbits. The plasma iodide concentration was increased 100 times to prevent thyroid organization of radioactive iodide. [131I]iodide was infused at a constant rate and [125I]iodide was administered iv as a bolus for indirect clearance determination. The ratio between plasma values and external values 125I-activity was constant in all experiments from 15 min after administration of [125I]iodide and throughout the experiment. The results of 7 experiments in 3 rabbits showed a highly significant correlation (r = 0.98) between direct and indirect values within the range of direct clearance values obtained (0.002–0.6 ml · min⁻¹ · kg⁻¹). The direct and indirect clearances were measured simultaneously during a 2-h period of steady state. The 95% confidence interval of the mean ratio between direct and indirect clearances was ± 20% for plasma activity and ± 26% for externally measured activity. It is concluded that both methods of indirect clearance determination can be applied to rabbits to estimate absolute values of the renal iodide clearance.

The present study was designed to compare an indirect clearance method, previously used in studies of the renal iodide excretion in unrestrained rabbits (1) with a direct clearance method. The purpose was to examine whether the indirect clearance method could be used to estimate absolute values of the renal iodide clearance (C_t).

Information concerning C_t in unrestrained animals of different sizes is important for our understanding of the mechanism of renal excretion of iodide in mammals, which is not yet fully elucidated owing to apparent differences between humans and smaller mammals (2–4).

Material and Methods

Experimental design

The experiments were performed in anesthetized rabbits since they included direct monitoring of C_t by constant infusion technique. The following parameters were measured directly: Plasma disappearance of [125I]iodide following a bolus administration of [125I]iodide. Disappearance from the body of 125I measured by means of 2 small radiation detectors placed on the back of the rabbit. Disappearance of [131I]iodide. Determination of both 131I and 125I excretion in the urine at intervals of 30 min. The thyroid organization of radioactive iodide was blocked by increasing the plasma iodide concentration about 100 times (5) before start of the experiments and non-radioactive iodide was also administered during the experiments in order to ensure an effective blockade of the thyroid organization of iodide.

From the experiments it was tested whether the externally registered disappearance curve of 125I reflected the corresponding plasma disappearance curve of 125I during as well steady state as non-steady state conditions and whether the geometrical localization of the detectors affected the disappearance curves. It was also tested whether a correlation existed between C_t measured by constant infusion technique and the simultaneously determined disappearance slopes of the detector curves and the plasma curve of 125I activity.

Detection of radioactivity

Following an iv bolus of [125I]iodide, the disappearance of the indicator was followed by 2 small Geiger-Müller de-
tectors (GM-detectors) 26 mm in diameter, situated on the upper part of the back of the rabbit, fixed to the skin with adhesive tape after hair removal by shaving. The activity was monitored individually by each detector and the counts were accumulated on a Memolog® (Novo Diagnostic systems, Denmark). The GM-detectors were used since the implantable version of the detector system (6) also uses a similar GM-detector. The GM-detector has also the advantage that it detects 131I with a low efficiency and it is therefore possible to keep the 131I activity so low in comparison with the 125I activity that it constitutes only 5–10% of the total activity. Since the level of 131I in plasma and the body is kept very constant during the experiment, one can subtract the initial 131I activity as constant background during the whole experiment.

An integration period of 4 min was used. The natural background was 5–6 counts/4 min for each detector. After start of 131Iiodide infusion, the count rate increased to 30–40 counts/4 min. After administration of 125Iiodide the count rate increased to more than 500 counts/4 min. The counts obtained after subtraction of natural background plus 131I activity was considered the 125I activity and these counts were pooled for periods of 8 min. The standard deviation of these counts/8 min was 3–5%.

Experimental conditions
The experiments were carried out in male albino rabbits (3.2–3.3 kg). They were fed on pellets and had free access to tap water. The water was supplied with 20 mg KI per 100 ml tap water from the day before start of the experiments and throughout the experimental period of 3 weeks. The rabbits were used in several experiments and at least 2 days elapsed between the experiments in the single rabbit. It was tested by external counting using the GM-detectors that no accumulation of activity occurred from one experiment to another. Neither thyroid nor body accumulation of radioactivity could be detected during the period of 3 weeks, and the initial background level of 5–6 counts/4 min was obtained in each experiment both in the thyroid region and elsewhere.

Experimental procedure
The rabbits were anesthetized with Hypnorm® (Fluanisone 10 g/l and fentanyl 0.2 g/l) at a dose of 0.3 ml/kg im., then catheterized with a No. 8 balloon catheter. The infusion of 125Iiodide (Amersham) was started about 15 min after administration of Hypnorm and consisted of 5 μCi in 12 ml NaI solution (3 g/l). The infusion was administered via an infusion pump at an infusion rate of 0–3 ml/h. The infusion was administered via a very thin polyethylene catheter and a thin needle into an ear vein in order to reduce external radiation near the GM-detectors.

125Iiodide (Amersham) was administered iv after determination of the first renal clearance of 131I. The 131I clearance was determined during a period of 30 min after an initial equilibrating period of 15 min. 125Iiodide was administered in 1 ml NaI solution (3 g/l) as a bolus. During the experiment, the rabbits were placed on the stomach. Additional Hypnorm was sometimes administered. The bladder was emptied at intervals of 30 min using 10 ml water as flushing medium. Blood was drawn from the opposite ear just before the middle of each clearance period into heparinized tubes and centrifuged after completion of the experiment. Aliquots of urine and plasma were counted in a multichannel gamma-spectrometer (Searle Ortec system model 1188). The 125I and 131I counts were corrected for activity of the other isotope within the used spectra. The count rate of 125I in the 131I channel was 0.075% of the activity in the 125I channel and the count rate of 131I in the 125I channel was 14.8% of the activity in the 131I channel.

Calculations
C1 was determined by dividing the activity of 131I in the urine during the 30 min period with the 131I activity in plasma at the middle of this period. As basis to the calculations was used an experiment where C1 was constant during the last 2 h as defined by a coefficient of variation of C1<40% of the mean of 4–5 values of C1 and without systematic increase or decrease in C1 in the course of time. Calculations by regression were made of the slope of plasma disappearance of 125I (rate constant = k1) and the corresponding slope of disappearance of 125I as measured by the GM-detectors (rate constant = Kd).

In all experiments, including experiments without steady state, the ratio between simultaneous values of external activity of 125I and plasma activity of 125I was calculated. The final slope was taken to be present, when this ratio was constant throughout the experiment.

Results
Nine experiments in 3 rabbits showed a variation i C1 measured by constant infusion from 0.002–0.6 ml · min⁻¹ · kg⁻¹. The experiments with very low C1 were performed without manipulation of renal function. It is known from other studies in rabbits that anesthesia and experimental stress affect kidney function very easily in rabbits (7) and this seemed also to be valid as far as Hypnorm is concerned. The experiments with high values of C1 were performed with rabbits where C1 was increased by administration of aminophylline (30 mg iv) or cortisol (Solu cortef®) 50 mg iv, or both. Aminophylline and cortisol increase C1 in anesthetized rabbits (Vadstrup, unpublished results). Aminophylline was administered just before start of the experiment, whereas cortisol was administered 90 min before start of the experiment.
Two experiments, one of which is shown in Fig. 1, were performed during almost zero excretion of iodide in the urine and both experiments showed identical and horizontal slopes of the plasma values and the externally measured values during the whole experiment.

The comparison between the externally measured rate constants ($k_e$) and simultaneously measured $C_t$ and between $C_t$ and simultaneously measured rate constants of the plasma curves ($k_p$) is shown in Fig. 2. When the ratios $C_t/k_p$ and $C_t/k_e$ were used to calculate the 95% confidence intervals of the mean, the respective values were ±20% and ±26%.

The ratio between simultaneously measured plasma activity and external activity of $^{125}$I was calculated in all 9 experiments and expressed relatively to the first ratio in each experiment, 15 min after administration of $[^{125}$I]iodide. With the first ratio being expressed as 1.00, the following ratios of samples at 30 min intervals were (mean of 9 (±SD) 1.00 (0.03), 1.01 (0.04) 1.01 (0.04) and 0.99 (0.04).

The question is first whether external monitoring or plasma sampling can be used as a measure for $C_t$ in rabbits, following an iv bolus of an appropriate iodide indicator.

The data from 9 experiments showed that there was a very constant relation between plasma values and simultaneously measured external count rates during both steady state and non-steady state conditions; furthermore that the obtained ratios were identical to the initial ratio throughout the experiment, thus indicating that the final distribution of the indicator was obtained already after 15 min since the GM detectors detect activity from a fraction of the body and not from plasma. There was no significant differences between these ratios from one detector to the other, indicating that the exact location of the detector is of no importance if
Comparative values of glomerular filtration rate (GFR), the renal iodide clearance ($C_i$), and the excretion fraction of iodide ($EF_i = C_i/GFR$) in man, the rabbit, and the rat during physiological conditions.

<table>
<thead>
<tr>
<th></th>
<th>Weight kg</th>
<th>GFR ml/min</th>
<th>$C_i$ ml/min</th>
<th>$EF_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>75</td>
<td>120</td>
<td>40</td>
<td>0.33</td>
</tr>
<tr>
<td>Rabbit</td>
<td>4</td>
<td>19</td>
<td>4.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Rat</td>
<td>0.2</td>
<td>0.8</td>
<td>0.07</td>
<td>0.09</td>
</tr>
</tbody>
</table>

The data from rabbits and rats are from the active period. The values are based on results from the following studies: (Wayne et al. (9), Pallardo et al. (8), Vadsstrup & Bojesen (1, 11), and the present study).

The plasma iodide concentration is normally very low in mammals (20 nmol/l) or less than $10^{-6}$ times the chloride concentration (9). Studies in rats and dogs have shown that if the plasma iodide concentration is increased above 1–2 mmol/l or $10^5$ times the physiological concentration, $C_i$ increases successively (3, 10). Below this level no ap

![Fig. 3.](image_url)

Comparison between GFR and body mass (○) and between the renal iodide clearance ($C_i$) and body mass (●) based on data from Table 1. The upper regression line is drawn from that of Edwards (12). The formula is $y = a M^b$, where $y = GFR$ and $M =$ body mass in kg. The values of $a$ and $b$ is 5.4 and 0.72. The lower regression line is calculated on basis of data from rats, rabbits and man. If $y = C_i$ and $M =$ body mass, the formula is $y = 0.52 M^{1.07}$.
parent relation exists between the plasma iodide concentration and $C_i$ (3). It seems therefore reasonable to consider the values for $C_i$ as determined by the present method where the plasma iodide concentration is only moderately increased (about 100 times), as valid during physiological conditions.

Data from different mammals can be compared by employing the present ratio between $C_i$ and $k_e$ to calculate $C_i$ from $k_e$ values in unrestrained rabbits glomerular filtration and by using data on rate (GFR) in rabbits (11) (Table 1). The data suggest that $C_i$ falls in relation to GFR when the body weight of the mammal decreases. This can also be expressed graphically, using the method of Edwards (12) (Fig. 3). This figure demonstrates that GFR of rabbits follows the expected regression line, whereas $C_i$ of different mammals follows a regression line with a rate constant near 1.0, suggesting a direct proportionality between $C_i$ and body weight and not between $C_i$ and body surface as is the case for GFR.

In conclusion: The present study demonstrates that the renal iodide clearance can be determined in rabbits with sufficient reliability from the plasma values or external count rates as determined by small external detectors following a bolus administration of $^{125}$Iiodide. The method seems applicable to physiological studies of renal function since the necessary administration of non-radioactive iodide should not interfere with the renal regulation of the renal iodide clearance.

References


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