Turnover of Interstitial Albumin in the Kidney

The presence of albumin in the renal interstitium has been described in a number of studies and recently reviewed by MOFFAT[1]. In the kidney, albumin can enter the interstitium either directly through the capillary endothelium or indirectly by filtration at the glomerulus and subsequent reabsorption from the tubular fluid. Although protein is known to follow the latter route there is evidence that it may be, at least partially, degraded in its passage through the tubular epithelium[2]. As a maximal value, approximately 10–15% of the total albumin catabolism may take place in the kidneys[3]. Drainage of albumin from the interstitial pool can also be by direct return of the plasma or by way of the lymphatic circulation. A schematic representation of these flows is shown in Figure 1. The functional importance of this turnover of albumin has been related to the concentrating ability of the kidney by a number of authors[4–6].

Materials and methods. Experiments were carried out on 7 anesthetized dogs, weighing between 10 and 31 kg. Renal hilar and occasionally capsular lymphatics were cannulated and lymph samples were collected in sequential 3–5 min periods, in preweighed small tubes. The samples were weighed and counted in a 2 channel, automatic well type scintillation counter. Arterial plasma samples were collected initially at frequent intervals, and thereafter every 15–30 min. An injection of 200–400 μCi of I^{125} albumin (human, Squibb) was given i.v. 24–36 h before the experiment to allow a distribution of the label throughout the entire albumin pool, such that the albumin specific activity (SA) remained stable during the experiment. An injection of I^{131} albumin (human, Squibb) was given i.v. and the appearance of this tracer in renal lymph was studied. Since the molecular weights, shapes and structures of human and canine albumin are similar[7], the use of commercially available labelled human albumin was considered adequate for the purpose of this study. Protein bound I^{131} albumin/I^{125} albumin ratios were taken as a measure of the SA of I^{131} albumin. Correction for lymph cannula dead space was made by taking into account that mean transit times through the interstitial labyrinth and the cannula are additive[8].

The mean transit time of albumin from plasma to lymph was calculated by the equation:

$$A \cdot I(t) = F_{in} \int_0^t P(t)dt - F_{out} \int_0^t L(t)dt \qquad (1)$$

where A is the quantity of interstitial albumin in 100 g renal tissue, $I(t)$, $P(t)$, and $L(t)$ are, respectively, interstitial fluid, arterial plasma and lymph albumin SA, and F_{in} and F_{out} are rates of entry and exit of albumin into and from the interstitium.

If it is assumed that albumin entering the interstitium has the SA of plasma and that all albumin leaving the interstitium has the SA of lymph, $I(t) = L(t)$; and if it is further assumed that the interstitial albumin pool is in a steady state (i.e. $F_{in} = F_{out} = F$), Equation 1 may be solved for mean transit time

$$A/F = \frac{1}{L(t)} \cdot \left[\int_0^t P(t)dt - \int_0^t L(t)dt \right].$$

This solution is equivalent with that derived by ZILVERSMIT, ENTENMAN and FISHLER[9] for the determination of metabolic turnover rates and with that described for measurement of brain blood flow per unit volume of tissue by KETY and SCHMIDT[10]. An assumption implicit in these considerations is the presence of a well mixed compartment. In the case of the interstitial albumin pool this assumption is undoubtedly an oversimplification. Calculations based on this equation should yield the mean transit time of tracer albumin between arterial blood and renal lymph.

Results and discussion. Figure 2 illustrates a representative experiment, in which the mean flow of renal capsular lymph was 2.6 mg/min and of renal hilar lymph was 28.0 mg/min. In spite of this large difference the specific activity curves for hilar and capsular lymph rose in a similar fashion and, when corrected for cannula dead space, the mean transit times were equal (hilar: 32.0 min, capsular: 32.8 min). The slower rise of SA in thoracic duct lymph is also shown in Figure 2. The short duration of the experiments precluded any definite conclusion on the precursor product relationship between plasma and lymph albumin.

The Table shows the data of 11 mean transit time determinations obtained from 8 dogs. An average value of 37.5 min with a standard deviation of 14.5 min was calculated.

The results of these experiments are different from the conclusion of GÄRTNER, VOGEL and ULBRICH[11], who determined the renal distribution volumes of labelled albumin in rats at various times after injection of the tracer. These authors regarded the distribution space after 1 min as a measure of the intravascular fraction of albumin, and accepted the subsequent expansion of this space as a measure of the rate of albumin penetration into the interstitium. GÄRTNER, et al.[11] estimated that the half-time for the extravascular albumin compartment in rat kidney was 1.5 min. The comparable parameter calculated from our experiments for the dog kidney was approximately 25 min. It is not clear whether a species difference could be responsible for this discrepancy.

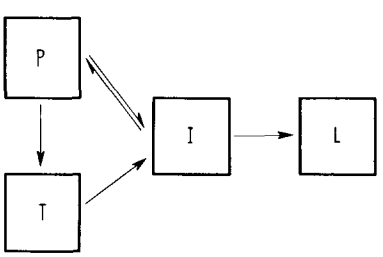

Fig. 1. A block diagram of the flow of albumin in the kidney between blood plasma (P), tubular fluid (T), interstitium (I) and lymph (L).

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In an earlier study it was found that the amount of interstitial albumin in 100 g of dog kidney was equivalent to the albumin content of 6.4 ml of plasma[6]. From this value and the turnover time it can be calculated that the albumin content of $^1/_6$ ml of plasma entered and left the interstitium each minute. This value is in agreement with the estimate by SZABO and MAGYAR[12] of 10 g plasma protein per day. As the albumin concentration in lymph is about 40–70% that of blood plasma, a lymph flow of approximately $^1/_4$ to $^1/_3$ ml per min/100 g kidney can account for all the drainage of interstitial albumin. This corresponds to the value of 0.35 ml per min/100 g, which can be obtained from the figures given by O'MORCHOE and O'MORCHOE[13] if, instead of body weight, kidney weights are taken into account. We conclude from these calculations that renal lymph flow may be sufficient to drain all the albumin from the interstitium of the dog kidney, and that, although a direct reflux of albumin into the capillaries cannot be excluded, the latter process does not seem to play a significant role under our experimental conditions.

Experiment no.	Duration of collection (min)	Mean flow (mg/flow)	Mean transit time (min)
1	0– 50	8.0	15.9[b]
2	0– 43	6.5	58.4
	0– 60	12.8	23.9[b]
3	0– 60	16.5	34.1
	0– 60	23.9	41.8
5	0–180	21.6	63.7
6 Hilar	0– 60	28.0	32.0
Capsular	0– 60	2.6	32.8
7	0– 60	7.9	51.1
	0– 43	2.1	21.1[b]
8	0–105	22.6	38.2

Mean, 37.5; S.D., 14.5. In experiments Nos. 2, 3 and 7 the determination was repeated after 2 h. [b] indicates mannitol diuresis.

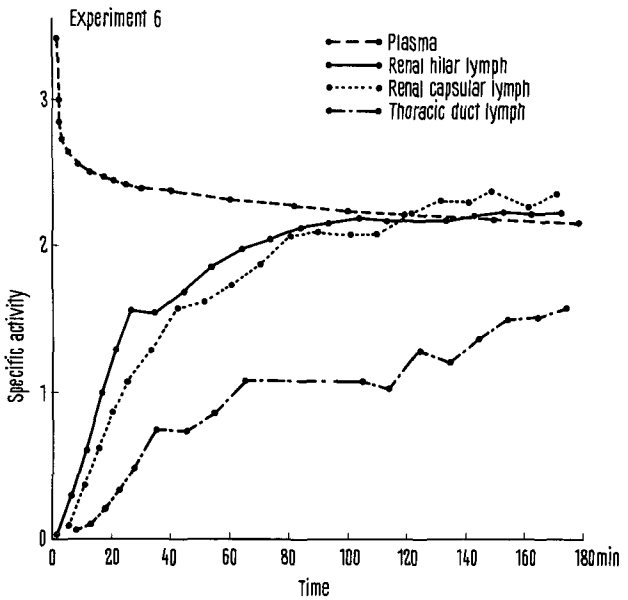

Fig. 2. I^{131}/I^{125} albumin ratio vs. time curves in arterial plasma, renal hilar and capsular lymph and in thoracic duct lymph.

Résumé. On a déterminé le renouvellement de l'albumine plasmatique dans les interstices du rein. Le temps moyens de passage fut de 37,5 min. Un flux lymphatique de 0,3–0,4 ml par min/100 g tissu rénal parut suffisant pour le drainage total de l'albumine interstitiel du rein.

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Calorigenic Effect of Noradrenaline in the Norwegian Lemming, *Lemmus lemmus* (L.)

Control of non-shivering thermogenesis is mediated through the sympathetic nervous system, and noradrenaline (NA) is the main mediating hormone[1–4]. NA may mobilize the release of free fatty acids (FFA) and also activate their subsequent oxidation or re-esterification[5,6]. The calorigenic action has been observed to be mediated by the adrenergic β-receptors[7], and because propanolol (Inderal) is a specific β-receptor blocking agent, it has been used in these studies[8,9]. The aim of the present study was to measure the non-shivering thermogenesis in the lemming and the possible effect of NA on the plasma level of FFA.

Material and methods. Adult male lemmings weighing 60.6 ± 11.7 g were maintained individually in cages at 0 °C or at 30 °C in constant light conditions for 3–4 weeks. Care of animals was as described earlier[10]. Oxygen consumption was measured at 5 °C and at 28 °C using Beckman E 2 oxygen analyzer with open circuit system[10]. Doses of NA and Inderal were 0.3 mg and 10 mg/kg of body weight, respectively. All injections were given i.p. Controls received the same amount of saline solution.

The effect of NA on the FFA content in the blood plasma was measured from the decapitated animals 15 min after the application of 0.3 mg/kg of NA. Blood was heparinized, centrifuged, and 0.5 ml of the serum was analyzed for the FFA content according to the method of DOLE[11] as modified for microdetermination by NOVAK[12].

Results. At 28 °C, which represents the thermoneutral zone, the control level of the oxygen consumption was significantly higher ($P < 0.01$) in cold-acclimatized than in warm-acclimatized animals (Figure). The calorigenic effect of NA seems to depend at this temperature on the acclimatization level. In warm-acclimatized lemmings the metabolic rate increased 105% and in cold-acclimatized lemmings 117% above the basal level. At the same time body temperature was elevated from 37.8–41.1 °C and