Intra- and Extravascular Distribution of Albumin and Immunoglobulin in Man

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Summary

The plasma proteins are constantly shuttling between intravascular and extravascular spaces until catabolism. The intravascular mass of a specific plasma protein is determined by its individual rate of synthesis and the mean total time it spends in plasma. The ratio of intravascular to total mass (distribution ratio) is determined by the relative rate, at which it passes from plasma to interstitial spaces (transcapillary escape rate: TER) and the relative return rate via lymph. TER in a specific organ depends on the local leakiness of the microvasculature. The overall value in normal man varies with the molecular weight of the protein being about 5%/h of the intravascular albumin mass, 3%/h for IgG and less than 1%/h for IgM. The higher the TER, the lower is the intravascular fraction. Hypertension, diabetes mellitus, burns, myxedema and certain types of liver cirrhosis will increase TER. In hypertension and diabetes this may be compensated for by an increased lymphatic return rate. Hypoproteinemia due to malnutrition or urinary or gastrointestinal loss is accompanied by a shift from the extravascular to the intravascular space.

Introduction

Socalled "plasma proteins" are present not only in plasma but also in interstitial fluid and lymph. Metabolic studies with radioactive labelled, metabolically pure and native proteins have taught us that during the life-span of the protein molecules, they pass from the blood stream to the interstitial fluid and back again if not caught and destroyed in action.

The *quantitative* aspects of this molecular behaviour are specific for each type of protein. This means that each protein has its own typical average life-time, its own speed of circulation from intravascular to extravascular space and hence its own intravascular to extravascular ratio.

As for the *qualitative* aspects of the behaviour of the plasma proteins questions such as "by which mechanism does intra- and extravascular protein exchange?" and "which mechanisms are involved in catabolism?" are very difficult if not impossible to answer at present. Furthermore, what may be known about one protein does not necessarily apply for the other.

The Model

The study of the turnover of endogenous plasma proteins by means of radioactive labelled protein tracers will only give correct results, when the tracer and the mothersubstance have identical fate, and when the model used for calculation is in agreement with reality.

Fig. 1 shows the model of tracer and tracee for albumin. Just as the liver injects albumin directly into the blood stream, we inject the tracer in the vein. We assume that the organism does not distinguish between labelled and unlabelled protein, and we also assume catabolism to occur within or in close relation to the intravascular space. With these conditions fulfilled we can calculate the variables of an albumin turnover study from tracer curves as those shown in Fig. 2 obtained from a normal subject.

Plasma volume (PV) = distribution volume of ^{131}I-albumin, 10 min after i.v. injection (ml).

Intravascular albumin (I) = PV multiplied by plasma albumin concentration (g).

Fractional catabolic rate (FCR) = 1/sojourn time in plasma = 1/area under plasma activity curve extrapolated to infinity (d^{-1}).

Distribution ratio (D) = area under plasma curve/area under wholebody curve = intravascular albumin/total albumin (I/I + E).

Extravascular albumin (E) = (I + E) − I (g).

Distribution ratio

As seen above, the determination of the wholebody and plasma disappearance curves makes an indirect determination of the extravascular albumin mass possible. If we assume, that the studied protein is synthethized into the blood

circulation and also that final catabolism takes place intravascularly, then we have for a steady-state organism

$$I \cdot TER = E \cdot ERR$$

and

$$\frac{I}{I + E} = \frac{ERR}{TER + ERR} = D$$

where ERR is the extravascular return rate (fraction of extravascular albumin returning to blood per unit time) and TER is the trans-capillary escape rate (fraction of intravascular albumin mass passing to the extravascular space per unit time).

The calculation of the extravascular protein mass via calculation of the distribution ratio holds true for *albumin* known to be produced only in the liver and assumed to be catabolized in close relation to the intravascular space. For plasma cell produced *immunoglobulins* the calculations can be invalid, if the immuno-globulins are synthethized and maybe also catabolized extravascularly. Usually it is sup-posed, that the variables of IgG and IgM metabolism can be calculated from tracer stu-dies like those used for albumin.There is, howe-ver, an uncertainty mainly resting with the evaluation of the extravascular amount, and especially so in pathological cases, since the proteins may actually be produced and destroy-ed without entering plasma at all. As for IgA known to be mainly an extravascularly loca-ted surface protein the described principles can not be employed at all.
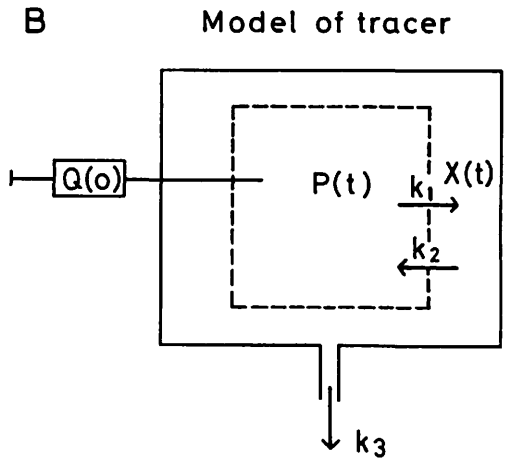

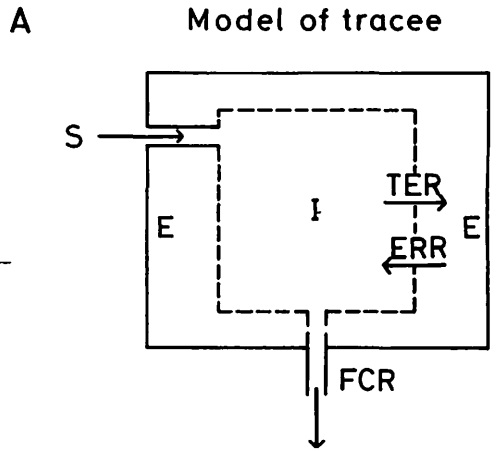**A** Model of tracee

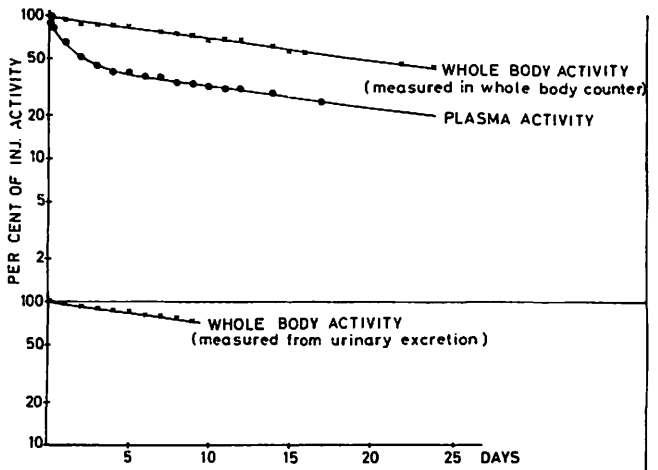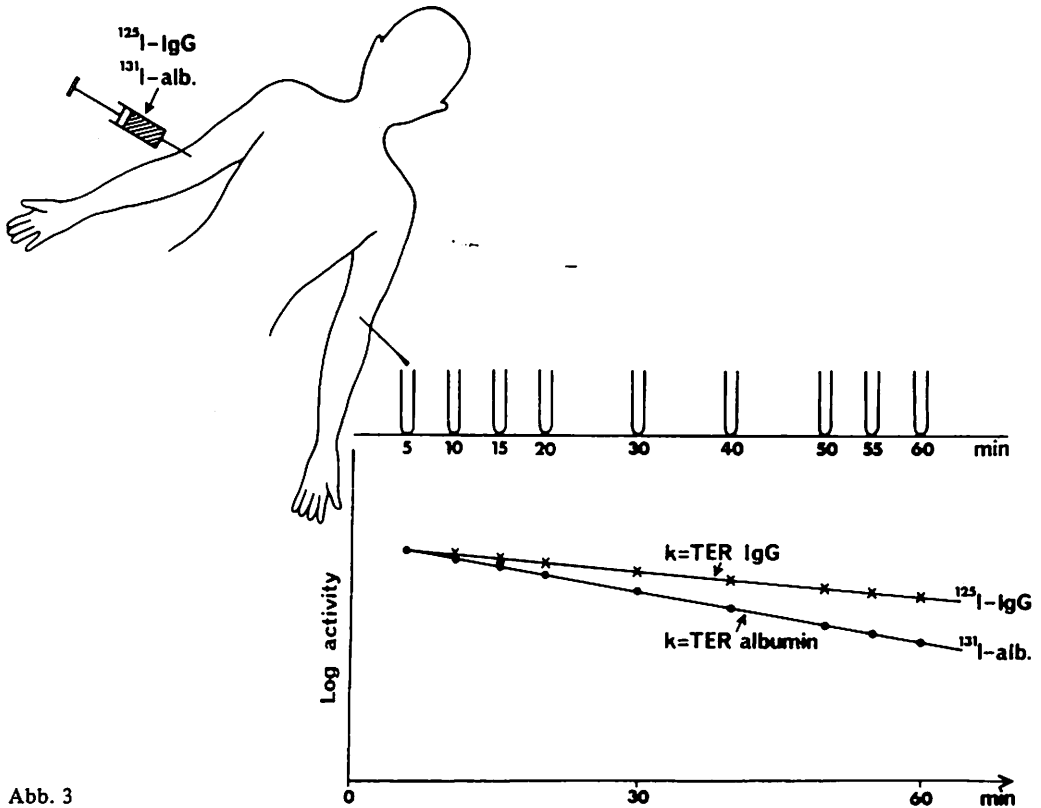**B** Model of tracer

Fig. 1

Fig. 2

Abb. 3

The *transcapillary escape rate* is the reciprocal of the intravascular transit time of the protein. It signifies the net passage from intravascular to extravascular space and hence the leakiness of the microvasculature to the protein. Fig. 3 shows, how TER for two proteins (albumin and IgG) can be determined with tracers labelled with two iodine radionuclides. It is calculated as the rate constant of the plasma activity disappearance after intravenous injection measured for 60 or 120 min.

Albumin

Albumin fulfills — as far as we know — all the conditions of the described model. After synthesis it is released to the blood stream directly, and its existence is divided between intravascular and extravascular transits. Catabolism occurs in close relation to the blood stream by some unknown mechanism. Catabolism seems to be ubiquitous and may be related to the passage across the endothelial lining of the vessels.

Albumin functions are all rather unspecific and seem to be exerted as a consequence of its relative abundance. It is a vehicle for a variety of endogenous and alien substances, it has a buffer effect in plasma and above all, it is of paramount importance for the oncotic pressure of plasma. It has been put very aptly, that the molecular weight of about 69,000 is a compromise between its being small enough to exert a sufficient oncotic pressure and large enough not to be wasted in the urine when passing through the glomeruli. Its average life time in the body of man is about 28 days. This period is spent on about 14 passages from intravascular to extravascular space and back again. In normal man the average transit in blood lasts 18 h. In the extravascular space including interstitial fluid and lymph, the average visit lasts 30 h, but with a considerable deviation. Thus, 40% of albumin is in plasma and 60% in the extravascular space. Transit in liver, kidneys and lungs is rapid compared with the transit time of 5—6 days through skin and

skeletal muscle. This means that the latter organs contain most of the extravascular albumin.

In pathological cases the distribution of albumin may be disturbed. Thus in hypoalbuminaemia due to protein deficiency distribution is in favour of the intravascular space thus depleting the interstitial fluid disproportionally. This is also the case, when albumin is lost as in the nephrotic syndrome, and protein-losing gastroenteropathy. In cirrhosis distribution ratio is normal or reduced, especially so when ascites is present. It is remarkable, that in hypertension and diabetes mellitus, where TER is increased, distribution ratio is normal, meaning that the extravascular return rate or lymph flow keeps pace with the increased leakage of the microvasculature. This is in contrast to untreated myxedema, in which condition an extraordinary high fraction of albumin is located extravascularly. This also goes for patients with cancer, in whom much albumin may be located either in the tumormasses or in ascites.

Immunoglobulins

IgG with a molecular weight of about 170.000 is distributed evenly between intravascular and extravascular spaces. The transcapillary escape rate of 3%/h corresponds to an intravascular transit time of about 30 h. The extravascular passage must average the same time. Thus, the extravascular return rate of IgG and albumin is about the same. Supposedly, the distribution of extravascular IgG is identical with that of albumin. At least we have found the ratio of subcutaneous albumin to IgG concentration to be identical to the ratio of albumin to IgG TER.

IgG distribution ratio in pathological cases has not been examined to the same extent as has that of albumin. Distribution ratio is known to be high in the nephrotic syndrome, and some cases of proteinlosing gastroenteropathy. As with albumin it is normal in diabetes mellitus and hypertension in spite of the fact, that TER is increased in these cases to the same extent for IgG and albumin.

IgM has a molecular weight of about 1,000,000. Between 80 and 90% of the total mass is located intravascularly. TER is determined with some uncertainty to be around 1%/h. Abnormal patterns of intravascular to extravascular distribution are not well examined. There is evidence, however, that when TER is experimentally increased for albumin by large infusions of dextran or albumin TER of IgM will increase relatively more.

Conclusions

See Table 1.

1. The intravascular masses of albumin and IgG depend on the rates of synthesis and fractional catabolic rates.

2. The ratios of intravascular to total masses of these proteins depend on the transcapillary escape rates and the extravascular return rates.

3. The transcapillary escape rates correlate inversely with the molecular weights of the proteins. The transcapillary escape rate increases with the filtration pressure within the vessels and in diabetes mellitus due to leaky microvasculature.

4. The extravascular return rate reflects the lymphatic protein transport and is the reciprocal of the extravascular transit time. It is of the same order of magnitude for albumin and IgG and maybe shorter for IgM.

5. The extravascular transit time covers a wide range of transit times: short in liver, kidneys and lungs, and long, up to 5–6 days in muscle and skin containing the largest depots of extravascular protein.

6. In most cases of hypoproteinaemia intravascular to extravascular distribution ratio of plasma proteins is changed in favour of the intravascular space.

7. Pathological extravascular accumulation of plasma proteins occurs in few diseases when TER is increased without corresponding increase in the lymphatic return rate. This is seen in cirrhosis with ascites, in untreated myxedema and in some cases of

Tab. 1

	IVM (g)/TM (g)	Plasma transit time (h)	Interstit. transit time (h)	Number of "transit tours"
Albumin 6.9 x 10^4	150/340 = 0.4	20	30	14
IgG 1.7 x 10^5	35/ 70 = 0.5	30	30	14
IgM 1 x 10^6	2.1/ 2.6 = 0.8	100	(15)	2–3

cancer, notably those with liver affection and ascites. Eventually, extravascular accumulation of plasma proteins occurs in tumor tissue and postoperatively in wound tissue.

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