0.01. Macroscopical examination of the other organs did not reveal any abnormalities similar to those of the pancreas. Studied histologically, the pancreas from the inhibitor group appeared more fragile though the overall architecture of the tissue was normal. There was increased vascularity. The acinar tissues were hyperplastic with increased basophilic staining of alveolar cells and with less zymogen granules in their cytoplasm. The number of alveolar cells per acinus was significantly increased over the control, but the appearance and distribution of inert cells did not visibly differ. These results compare well with those observed after raw soybean meal in rats.

Although the peanut preparations were impure, the inertness of the heat-treated material would suggest that the trypsin-inhibitor was the responsible agent. The decrease in zymogen granules would suggest that the pancreatic changes were caused by epithelial hyperplasia with increased vascularity and hyperemia. Presence of incompletely digested protein in the intestinal tract has been suggested as a cause of the pancreatic response. This raises the possibility of a yet unknown, feedback mechanism controlling pancreatic size and growth. However, in man protein malabsorption is not correlated with an increase in size of the pancreas[11].

Zusammenfassung. Trypsinhemmende Präparate aus rohen Erdnüssen (*Arachis hypogaea*) wurden während 6 Wochen jungen Ratten verfüttert. Das normale Wachstum wurde verzögert und eine Hypertrophie des Pankreas mit gleichzeitiger Hyperplasie der serösen Drüsenzellen bewirkt. Hitzebehandelte Präparate hingegen waren wirkungslos.

H. C. KWAAN, P. KOK and T. ASTRUP

Veterans Administration Research Hospital, Chicago (Illinois 60611) and The James F. Mitchell Foundation, Institute for Medical Research, Washington (D.C. 20015, USA), 13 May 1968.

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Vasoactivity of Human Plasma and Plasma Protein Fractions

Application of plasma from dogs[1] and rabbits[2] to rabbit aortic strip preparations has been found to cause contractions which cannot be attributed to known vasoactive substances. Several workers[1,3,4] have also referred to a potentiation of responses of this preparation to a variety of substances by small concentrations of plasma and it has been suggested that this is due to the albumen content[4]. During the course of experiments using isolated perfused vessels in the apparatus described by DE LA LANDE and RAND[5], we have found that veins from the rabbit ear are sensitive to small doses of plasma kinins but relatively insensitive to other known vasoactive substances. Such preparations however respond to injections of small amounts of plasma. Further work has shown similar constrictor responses to human plasma in isolated perfused vessels from many sources. These include small subcutaneous and mesenteric veins from man, dog subcutaneous veins and both veins and arteries of the rabbit. However, the most consistently sensitive preparation in this regard is the central vein of the rabbit ear which we have used to investigate the nature of the substance or substances in plasma responsible for the constrictor activities. Injection of as little as 0.002 ml of human plasma into a 10-ml/min flow of Krebs solution through the lumen of the vein may initiate a constriction (Figure 1a). It is usually found that the sensitivity of a vessel to plasma initially increases progressively following successive injections of plasma, but then attains a relatively stable level (Figure 1b). Responses to all other vasoactive agents are also elevated by plasma pretreatment. These results have been interpreted as evidence that plasma has both intrinsic vasoactivity and also non-specific potentiating effect which is only slowly reversible. These actions may or may not be due to the same substance.

The central vein of the rabbit ear and also all other perfused vessels investigated, respond to certain Cohn fractions of human plasma proteins with constrictions similar to those caused by whole plasma. Fraction III-0 is the most potent and many ear veins respond to 0.1 mg or less. There is a close similarity between the dose-response curves for III-0 and plasma (Figure 2). Fresh plasma from 7 subjects was found to have activity equivalent to that of 2.2–4.6 mg/ml of III-0 (Table I). This activity was stable at room temperature for many hours but during storage of plasma at − 20 °C declined slowly relative to freshly prepared III-0 solutions. Constrictor activity in other Cohn fractions is less than that of III-0; fraction IV-1 has approximately 40% of the constrictor activity of III-0/mg dry material. The other fractions tested were III-1, IV-4, IV-5, IV-6, IV-7 and V and all showed less than 10% of the constrictor activity of III-0. Although fraction V, which is 98% albumen, has virtually no constrictor activity it reproduces the non-specific potentiating effect of plasma. Perfusion of albumen concentrations of 1 mg/ml produced detectable potentiation of the effects of noradrenaline in the rabbit ear artery and of bradykinin (BK), III-0 and IV-1 in the rabbit ear vein. There was no conspicuous evidence of potentiation with any Cohn fraction except V.

Constrictor activity in plasma and Cohn fractions can be distinguished from that due to catecholamines, histamine, 5HT, angiotensin, ATP, vasopressin, oxytocin and prostaglandin E_1 by the use of antagonists or by considering the nature of the rabbit ear vein preparation, which is relatively insensitive to most vasoactive substances except plasma kinins. There is, however, marked similarity between responses to bradykinin and the plasma venocon-

[1] D. BOHR and B. JOHANSSON, Circulation Res. *19*, 593 (1966).
[2] M. WURZEL, Archs int. Pharmacodyn. Thér. *143*, 550 (1963).
[3] O. M. HELMER, Am. J. Physiol. *188*, 571 (1957).
[4] M. WURZEL, R. C. BACON, R. B. KALT and B. W. ZWEIFACH, Am. J. Physiol. *206*, 923 (1964).
[5] I. S. DE LA LANDE and M. J. RAND, Aust. J. exp. Biol. med. Sci. *43*, 639 (1965).

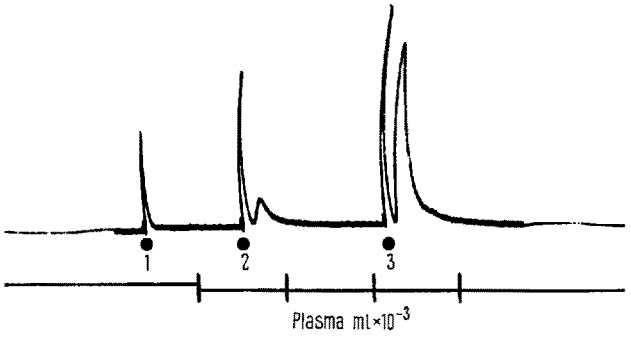

Fig. 1a. Response of rabbit ear vein to human plasma. The initial spike in the pressure tracing marks the injection artefact; the subsequent response to 2 and 3×10^{-3} ml has a much slower time course.

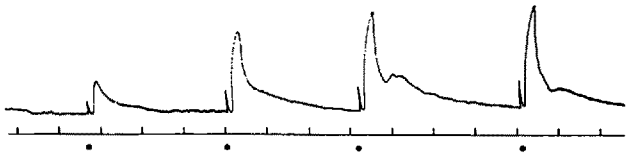

Fig. 1b. Responses of rabbit ear vein to repeated application of 0.1 ml human plasma; note the progressive increase in response to succeeding applications of the same dose.

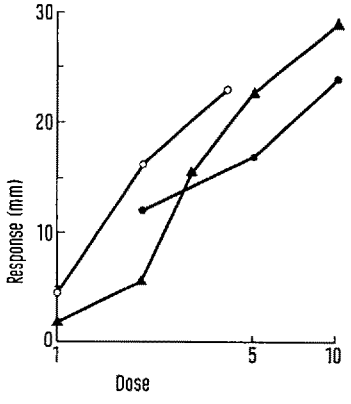

Fig. 2. Dose-response curves for plasma, fraction III-0 and bradykinin. Doses are given as follows: plasma o——o in ml $\times 10^{-1}$, fraction III-0 ▲——▲ in mg $\times 10^{-1}$, bradykinin ●——● in ng. Response given in mm deflection, is an analogue for pressure in the perfusion line.

strictor. The gradients of the dose-response curves and maximum responses are similar for plasma, III-0 and BK in most preparations (Figure 2). Other resemblances to BK of both plasma and III-0 activity are that all are stable to a wide range of pH and temperature and to the action of trypsin and pepsin but are rapidly destroyed by chymotrypsin. Furthermore like BK, III-0 is vasodepressor in the intact rabbit and dog. Increases in carotid and femoral blood flows have been observed in the intact dog following intra-arterial and i.v. injections of III-0 and this plasma fraction is also dilator in the coronary bed of the isolated perfused guinea-pig heart. However there is no constant relationship between sensitivities of different perfused vessel preparations to BK and III-0 (Table II). That is to say, there are marked variations in the relative potency of BK and III-0 on different preparations despite

Table I. Equiactive doses of III-0 and fresh human plasmas assayed on rabbit ear vein preparations

Preparation	Subject	Plasma (ml)	III-0 (mg)
I	J. H.	1	2.2
II	V. H.	1	2.5
	D. A.	1	2.6
III	R. H.	1	2.6
IV	J. B.	1	2.4
	D. M.	1	3.8
	P. W.	1	4.6

Table II. Variations in relative potency of BK and III-0 in 6 different ear vein preparations

Preparation	BK (ng)	III-0 (mg)
1	1	0.1
2	1	0.2
3	1	0.4
4	1	0.5
5	1	0.8
6	1	3.4

parallel dose response curves indicating that despite the many resemblances plasma and III-0 activity is not due to BK.

The venoconstrictor material present in plasma and in Cohn fractions III-0 and IV-1 can further be distinguished from bradykinin on pharmacological grounds since kinins are inactive on human and rabbit mesenteric veins whereas plasma and the active fractions are constrictor on these preparations. In the perfused rabbit ear artery, plasma and III-0 are purely constrictor whereas BK causes small and often biphasic responses. The relative stability of the plasma factor with time also distinguishes it from BK which is very rapidly destroyed by whole blood or plasma. Nonetheless the plasma activity bears a marked resemblance to that of BK and the similar nature of the dose-response curves in certain preparations makes it possible that there is a close relationship between the receptors for them [6].

Zusammenfassung. Blutplasma des Menschen verengt isolierte, durchströmte kleine Blutgefässe. Dieser Effekt kommt nicht durch bekannte, gefässaktive Substanzen, sondern wahrscheinlich durch ein Protein zustande. Eine ähnliche Wirkung wurde in 2 Cohn-Fraktionen von Plasma-Proteinen gefunden, welche sich im Hundeversuch gefässdrucksenkend auswirkten. Plasma-Albumin ist an sich nicht gefässaktiv, es verstärkt aber die Wirkung der andern Substanzen.

J. D. Horowitz and M. L. Mashford

Department of Human Physiology and Pharmacology, University of Adelaide (South Australia), 21 June 1968.

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