Kallikrein and Histamine

KALLIKREIN, Frey and Kraut's circulatory hormone, has been extensively studied from the pharmacological point of view by Frey, Kraut and Werle¹ and considered by Szakall² as the regulator of the capillaries and small vessels. This last condition would introduce some relationship between kallikrein and histamine. Recently, Ungar and Parrot³ have shown that kallikrein produces secretion of gastric juice, and more recently Schneider and Springorum⁴ have demonstrated the close similarity between the circulatory effects of kallikrein and histamine in the dog. All these facts have justified the inclusion of kallikrein among the histamine-like substances, although its physical and chemical properties exclude the idea of its being histamine itself.

To demonstrate the effects produced by kallikrein upon the small vessels of the rabbit skin we employed the trypan blue test. Kallikrein (= padutin) was injected intracutaneously in the adult rabbit and, five minutes after, a solution of trypan blue (1 per cent) was injected into the ear vein. A more and more extensive and beautiful blue spot appears in the locality of the intradermal injection. This positive reaction has been obtained by injection of irritant substances⁵ and by a proper concentration of histamine⁶. Since the rabbit's skin is very rich in histamine, one might be induced to interpret this positive test as characteristic of a liberation of histamine. By assuming that kallikrein exerts its action by liberating histamine from the tissues, this would provide an explanation for its pharmacological properties.

Initially, a difficulty for this hypothesis would be the inactivity of kallikrein upon the isolated guinea pig gut. Moreover, we have verified that kallikrein inhibits the contracting action of histamine upon that organ; therefore, even if it liberated histamine from the smooth muscle, this last active substance would have its action inhibited by kallikrein itself. But in another way the hypothesis has been rendered very improbable by the fact that we have verified that kallikrein is also extremely active even upon the skin of very young rabbits (200 gm.), while histamine and a substance liberating histamine (turpentine) are not active or only very slightly so. Furthermore, in perfusion experiments with guinea pig lung kallikrein has been found devoid of any histamine liberating activity. Thus the pharmacological activity of kallikrein does not involve a liberation of histamine.

Indirect evidence has been put forward by Frey and Kraut¹ as well as by Szakall² for an increase of the capillary permeability after injection of large amounts of kallikrein. Since the seepage of the trypan blue into the intradermal injected area is very characteristic of an increase of capillary permeability, the experiment described above is a direct demonstration that kallikrein produces an abnormal filtration of colloidal matter through the walls of the capillaries.

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¹ Frey and Kraut, *Archiv. exp. Path. u. Pharm.*, **133**, 1 (1928); Werle, *Klin. Woch.*, **15**, 848 (1936); *Muench. Med. Woch.*, **11**, 407 (1937).

² Szakall, *Biochem. Z.*, **269**, 92 (1934).

³ Ungar and Parrot, *C.R. Soc. Biol.*, **122**, 1052 (1936).

⁴ Schneider and Springorum, *Z. klin. Chir.*, **194**, 373 (1939).

⁵ Rocha e Silva and Bier, *Arg. Inst. Biol.*, **10**, 219 (1939).

⁶ Bier and Rocha e Silva, *Virchows Archiv.*, **303**, 325 (1939).

The Herring Material in the Perch Pituitary

IN an investigation of the histology of the pituitary of the perch (*Perca fluviatilis*) a process of some general interest has come to light. Cells having the appearance of eosinophile leucocytes are present in the middle glandular or transitional lobe, and from them can be traced a succession of cells with fewer and larger inclusions to precise and brightly staining eosinophilic spheres which come ultimately to lie free among the cells of the lobe. In some series these spheres can be seen in all locations from the transitional to the nervous lobe, where they represent the larger elements of the Herring material in this form. Here in turn they appear to break down and form a characteristic granulation.

Photograph No. 1 (all photographs $\times$ about 1,000) shows two of these 'sphere cells' at an early stage among transitional lobe eosinophiles, No. 2 shows later stages, and No. 3 shows some spheres among the transitional lobe cells (T.l.) and some in a process of the nervous lobe (N.l.). No. 2 recalls certain cells noticed by Charipper¹ in the pituitary of *Necturus*, in which they appear to discharge directly into blood vessels. Herring² first described this material in the nervous lobe and looked upon it as probably secretion passing up to the third ventricle, but it has since been claimed to be simply unusual nerve endings in the lobe or an artefact due to precipitation. The sequence described here, however, including the demonstration of its origin, suggests that it is definitely secretory.

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¹ Charipper, H. A., *Anat. Rec.*, **49**, 345 (1931).

² Herring, P. T., *Quart. J. Exper. Physiol.*, **1**, 121 and 261 (1908).