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Liberation of Histamine by Trypsin.

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Rocha e Silva[1] has reported that trypsin has the capacity of liberating histamine when perfused through the guinea pig lungs and postulates that the toxicity of trypsin when injected intravenously in intact animals may be due to this effect. The present report is concerned with confirming his findings on the isolated perfused guinea pig lung and of reporting observations on the liberation of histamine in intact dogs following its intravenous administration.

The isolated lungs of guinea pigs were perfused through the pulmonary artery with Sollmann-Rademaeker's solution according to the method of Feldberg and Kellaway.[2] They were rhythmically ventilated with air throughout the experiment. After a control perfusion of about 30 minutes a small amount of trypsin was injected into the afferent cannula and the perfusate then tested for histamine activity. Two highly active, but not crystalline, preparations of trypsin were used in amounts from 0.5 to 10 mg. In the experiments done to date the smaller dosage occasionally led to the appearance of histamine activity in the perfusate, while doses of more than 1.0 mg did so regularly. Since this experiment is essentially confirmatory of the findings of Rocha e Silva, further details are omitted.

Four dogs were anesthetized with ether and barbital, and arranged for the recording of blood pressure tracings. Normal blood samples were obtained and then trypsin was injected intravenously in doses of 2 to 5 mg per kilo. Blood samples were obtained 2 to 5 minutes after the injection and all samples of blood then assayed for their histamine content by the method of Barsoum and Gaddum[3] as modified by Code.[4] In one experiment there was but a slight increase in the blood histamine, in 2 experiments there was a moderate increase and in one experiment there was a very marked increase from a normal value of no detectable histamine to a level of 1.8 γ of histamine base per cc after the trypsin injection. There was a marked

1 Rocha e Silva, *Arquivos d. Inst. Biol.*, 1939, **10**, 93.
2 Feldberg, W., and Kellaway, C. H., *J. Physiol.*, 1937, **90**, 257.
3 Barsoum, S. S., and Gaddum, J. H., *J. Physiol.*, 1936, **85**, p. 2.
4 Code, C. F., *J. Physiol.*, 1937, **89**, 257.

fall of blood pressure in each instance, being only temporary in the first 3 instances, while continuing until death of the animal in the last instance. In 2 other animals a portion of the liver was excised (using an electro-surgical knife to obviate bleeding*) before and after the trypsin injection. The liver samples were assayed for their histamine content by the method of Best and McHenry. In one experiment the liver content of histamine decreased from a normal value of 66 γ histamine base per gram to a value of 33 indicating a liberation of 10 mg for the whole liver, and in the other experiment there was a decrease from 50 γ per gram to 17 indicating a liberation of 6 mg from the entire liver.

It is thus clear that trypsin, like proteoses and certain snake venoms has the ability to liberate histamine from the tissues of the intact animal. Enough experiments have not as yet been done to determine whether the toxicity of trypsin can be exclusively related to this property.

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Possible Physiologic Significance of the Zinc Content of Insulin.

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It is known that the effectiveness of insulin in lowering the blood sugar level is dependent upon the integrity of the S-S groups which form part of its protein structure.[1] This suggested the possibility that insulin might exert its physiologic action through the influence of its S-S groups upon such tissue enzymes as are dependent upon S-H groups for their activity.[2-5] We therefore studied the *in vitro* effect of insulin upon succino-oxidase activity. A significant effect was found. But, it soon became apparent that this *in vitro* action

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1 Jensen, H. F., *Insulin*, Oxford University Press, London, 1938.

2 Hopkins, F. G., Morgan, E. J., and Lutwak-Mann, C., *Biochem. J.*, 1938, **32**, 1829.

3 Rapkine, L., *Biochem. J.*, 1938, **32**, 1729.

4 Hellerman, L., *Physiol. Rev.*, 1937, **17**, 454.

5 Purr, A., *Biochem. J.*, 1935, **29**, 5.