8123 C

Inactivation of Histamine in Vivo.

CARL A. DRAGSTEDT AND FRANKLIN B. MEAD.

From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Illinois

One of us with Gebauer-Fuelnegg[1] has previously reported on the appearance of a physiologically active substance in the blood and lymph of dogs during anaphylactic shock and on the basis of a pharmacological and chemical study[2] concluded that the active substance was apparently histamine. It was noted in this study that this active substance may be only temporarily detectable and it was concluded that it disappeared rapidly from the blood as it circulates. Various workers have noted the inactivation or detoxication of histamine in intact animals, organ perfusions, etc. (see Best and McHenry[3, 4] for discussion and literature). None of these studies, however, provide the necessary data to enable us to compare the fate of intravenously injected histamine with that liberated during shock. We were interested, therefore, in inducing shock of varying degrees of severity by intravenous injection of histamine at different dosage levels into dogs and of studying the blood and thoracic duct lymph for its presence and disappearance and of correlating these findings with our observations in anaphylactic shock.

Dogs were anesthetized with ether and sodium barbital and freshly prepared solutions of histamine acid phosphate (1-500) injected into the femoral vein. Samples of blood and thoracic duct lymph were collected at various time intervals thereafter. These samples were kept from clotting by means of heparin, the bloods in addition were centrifuged to obtain the plasma, and then assayed for their histamine activity by intravenous injection into cats (under ether or ether and barbital anesthesia and after the preliminary administration of atropine). The essential data of these experiments are outlined in Table I.

The degree of sensitivity of the cats used was always such that samples of blood or lymph recorded as negative contained a concentration of histamine less than 1-200,000. It is therefore apparent that injected histamine disappears very rapidly from the blood

1 Dragstedt, C. A., and Gebauer-Fuelnegg, E., *Am. J. Physiol.*, 1932, **102**, 512.

2 Gebauer-Fuelnegg, E., and Dragstedt, C. A., *Am. J. Physiol.*, 1932, **102**, 520.

3 Best, C. H., and McHenry, E. W., *J. Physiol.*, 1930, **70**, 349.

4 Best, C. H., and McHenry, E. W., *Physiol. Rev.*, 1931, **11**, 371.

TABLE I.
Duration of Detectable Histamine in Blood Plasma and Thoracic Duct Lymph after Intravenous Injection of Histamine. (Dog.)

Exp. No.	Histamine Ac. Phos. mg. per kilo	Calculated Initial conc. of H. in plasma	Degree of shock	Duration of detectable Histamine in blood plasma: Last positive sample, min.	Duration of detectable Histamine in blood plasma: First negative sample, min.	Duration of detectable Histamine in thoracic duct lymph: Last positive sample, min.	Duration of detectable Histamine in thoracic duct lymph: First negative sample, min.
A50	0.1	1-500 M	+	—	1	—	0-10
A168	0.5	1-100 M	++	2	5		
A6	0.66		++				0-20
1	1.0	1-50 M	++	3	10		0-20
A168	1.0	"	++	2	10		
5	1.0	"	++		5		0-22
2	1.0	"	++				0-20
A173	1.0	"	++	1	5		
A134	1.5	1-37.5 M	++			0-10	10-20
A14	1.5	"	++				0-20
10	1.5	"	++++(10′)	10			
12	1.5	"	++	10	20		
A18	1.6		++				0-20
4	2.0	1-25 M	++++(7′)				0-7
3	2.0	"	++				0-20
6	2.0	"	++	10	15	10-20	20-30
8	3.0	1-16.6 M	+++	15	20	15-20	20-28
7	3.0	"	+++	10	20	5-10	10-20
11	3.0	"	++	30	40		
9	4.0	1-12.5 M	+++	40	50	20-33	33-43
3	4.0	"	++++(15′)	15		0-15	
5	4.0	"	++++(7′)	7		0-7	

Explanatory: Degrees of shock: ++ = definite shock but recovery of blood pressure within 30 min.; +++ = severe shock, blood pressure still at shock level at 30 min.; ++++ = fatal shock. Time refers to minutes elapsed since injection of histamine.

stream. When a dose of 0.5 mg. per kilo is injected, which would give an approximate initial concentration in the plasma of 1 to 100,000 (assuming the plasma volume to be 1/20 body weight) histamine is detectable by this method of assay 2 minutes after the injection but not at 5 minutes. At 1.0 mg. per kilo it is also as a rule not detectable at 5 minutes. At 2.0 mg. per kilo, traces are still present for 10 minutes but usually gone by 15 or 20 minutes. At doses of 3.0 to 4.0 mg. per kilo (if not fatal sooner) traces are present for 30 to 40 minutes. We were never able to detect histamine in the thoracic duct lymph after doses of 1.0 mg. per kilo or less, occasionally after doses of 1.5 to 2.0 mg. per kilo, and regularly after doses of 3.0 to 4.0 mg. per kilo.

The similarity of these findings in the case of histamine with our experiences with the "anaphylatoxin" of anaphylactic shock is striking. In the great majority of the experiments on anaphylactic shock which were done early in our work, blood samples were fre-

quently taken at what was assumed to be the "height" of shock, namely 5 to 15 minutes after the shocking dose of serum. Consequently we had many experiments of moderate degrees of shock in which the blood samples examined were negative, although the thoracic duct lymph samples were positive. These latter were, however, collected continuously from the onset of shock. In view of our findings on the rapidity of the disappearance of injected histamine we have repeated a number of experiments on anaphylactic shock and are now able to report that in anaphylactic shock of moderate degrees of severity, blood samples taken at one, 2 or 3 minutes after the shocking dose of serum are usually active, although later samples may be negative. It is also seen from this work that an occasional animal may die from a dose of histamine (1.5 mg. per kilo) which is insufficient to be regularly detected in the thoracic duct lymph. In our original report on anaphylactic shock it was noted that in 2 of 9 cases of fatal shock we failed to find any activity in the thoracic duct lymph. These findings with histamine therefore afford circumstantial evidence of the validity of the histamine theory of anaphylactic shock in the dog.

8124 P

Muscle Atrophies. I. Water and Nitrogen Studies in Simple Disuse Atrophy.

HERMAN CHOR AND RALPH E. DOLKART. (Introduced by H. A. Davenport.)

From the Department of Nervous and Mental Diseases and the Department of Chemistry, Northwestern University Medical School.*

Histologic, chemical, and physiologic studies have been undertaken in various types of experimentally produced muscle atrophies in young *Macacus rhesus* monkeys. In a series of 6 animals, simple disuse atrophy was produced in the right leg of each animal by immobilizing it in a plaster cast. The left leg was used as the control in each case. The gastrocnemius and soleus muscles were completely removed by careful dissection from their proximal and distal attachments while the animals were under light ether anesthesia. The excised muscles (6 atrophied and 6 controls) were then weighed and split longitudinally, one-half being used in the preparation of

* This work was carried on with the assistance of a grant from the Council on Physical Therapy of the American Medical Association.