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Duration of Protection by Antihistaminics in Anaphylactic Shock

Traina and Aleksandrowicz reported recently[1] that, in contrast to the findings of Pasteur, Vallery-Radot, Halpern and Holtzer[2], guinea pigs which survived a previous exposure to anaphylactic shock during antihistaminic treatment were protected against a second challenging injection of the sensitizing agent given one day later. These experiments were carried out on thirteen guinea pigs, of which two were used for control. The implication of such a result might become extremely broad from the point of view of the mechanism of action of antihistaminic drugs.

We thought it worth while, therefore, to report the results of routine experiments carried out over a period of three years, which included most of the known antihistaminics in clinical use. The number of guinea pigs used in these experiments amounts to about eight hundred. The sensitization consisted in two injections of 0·1 c.c. horse serum, given subcutaneously or intraperitoneally, 48 hr. apart. After eighteen days the animals so sensitized were re-injected intravenously (saphenous vein) with 0·5 c.c. serum. With this technique, 80–85 per cent of the guinea pigs used for control died from anaphylactic shock, while all animals given 5–10 mgm./kgm. of the various antihistaminics tested ('Diatrin', 'Antergan', 'Neo-antergan', 'Benadryl', 'Pyribenzamine', etc.) survived. The re-injection with the sensitizing agent of the treated animals which survived the first shocking dose, one day later, produced fatal shock in the same percentage of guinea pigs as in the untreated control group.

Our findings do not agree with those of Traina and Aleksandrowicz, who used the same animal as we did (guinea pig); but are parallel to those of Vallery-Radot, Halpern and Holtzer, though they used a different animal (rabbit). Our conclusion based on this study is that the protection against anaphylactic shock lasts for the same length of time as the presence of the antihistaminic drug in the organism. On the basis of these relatively simple experiments we do not feel justified, however, in making any statement as to the relationship of the antihistaminic drug to the antigen–antibody reaction or, more generally, to the mechanism of action.

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Influence of some Inhibitors of Animal Hexokinase on Yeast Hexokinase

The observations of Colowick *et al.*[1] that the hexokinase activity of extracts of brain or muscles from normal animals may be inhibited by the addition of some anterior pituitary extracts in the presence of adrenal cortex extract, and that this inhibitory effect is prevented by insulin, has been confirmed by Reid, Smith and Young[2].

Broh-Kahn and Mirsky[3], and more recently Smith[4] and Stadie and Hangaard[5], have been unable to confirm the second observation of Colowick *et al.*, that extracts of muscles of alloxan-diabetic rats show an alteration of the hexokinase activity when compared to normal controls, which may be reversed by insulin.

Besides the action of anterior pituitary extracts on the hexokinase activity, extracts of spleen (Broh-Kahn and Mirsky[3]) and meningococcal endotoxin (Kun[6]) have been found to exert on muscle hexokinase an inhibitory effect which is reversed by insulin.

In the present investigation, the inhibitory activity of anterior pituitary extract and of the meningococcal endotoxin on yeast hexokinase has been investigated. Of the various extracts prepared by Colowick *et al.*, the aluminium hydroxide adsorbate (procedure 2) has been used. The meningococcal endotoxin was prepared according to Kun[7] from a strain of *Neisseria meningitidis* (Type 1, Jordan) kindly supplied by the Central Public Health Laboratory. The hexokinase was prepared from acetone-dried yeast or fresh yeast, ground with quartz sand and water, and centrifuged in an ordinary centrifuge. The supernatant was then spun in the high-speed head at 15–16,000 rev. per min. The assays of hexokinase activity were made as described by Colowick *et al.* The composition of the reaction mixture is given in Table 1.

Table 1. Effect of anterior pituitary extract on yeast hexokinase in absence or presence of insulin.
The main compartment of the Warburg vessels contains: 0·5 ml. of 0·04 *M* $MgCl_2$, 0·12 *M* $NaHCO_3$; crystalline insulin (Boots) 200 μgm. in 0·10 ml. *M*/300 HCl or 0·10 ml. *M*/300 HCl; eucortone (Allen and Hanbury) 0·10 ml.; enzyme solution. One side-bulb contains: 0·25 ml. of 0·4 per cent glucose, 0·54 *M* NaF, 0·03 *M* $NaHCO_3$; 0·25 ml. of 0·04 *M* adenosine triphosphate; the other one contains: 0·40 ml. of anterior pituitary extract or 0·40 of 0·1 *M* Na_2HPO_4. Total volume: 2·35; gas, nitrogen + carbon dioxide (5 per cent). Incubation, 10 min. at 30°

Glucose (μgm.) utilized per 2·35 ml. reaction mixture				
With anterior pituitary extract		Control with insulin	Differences in glucose utilization in % of *A*	
No insulin *A*	With insulin *B*	*C*	(*A* − *B*)	(*A* − *C*)
520	529	445	− 1·73	+14·2
339	339	385	0	−13·5
326	333	347	− 2·15	− 6·43
439	401	384	+ 8·65	+12·5
185	185	199	0	− 7·5
409	417	413	− 1·95	− 0·98
347	285	361	+19·3	− 4·0
429	429	425	0	+ 0·93
530	498	534	+ 6·0	− 0·75
458	465	469	− 1·53	− 2·4

Neither the anterior pituitary extracts nor the meningococcal endotoxin in various concentrations from 1 to 3 mgm. dry weight showed any inhibitory effect on yeast hexokinase activity, and, consequently, any influence of insulin could not be demonstrated. The results are summarized in Tables 1 and 2.