

MICROBIOLOGY AND IMMUNITY

THE COMPETITION OF ALLERGIC PROCESSES

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The role of interaction between antigens, and in particular of competition between them in the process of the immunological reorganization of the body, has been the subject of fairly extensive literature. This problem was investigated in a most profound and detailed manner by P. F. Zdrodovskii and his co-workers [3], who were studying the possibility, the conditions, and the laws of inhibition of the immunological activity of the body. There are indications of the inhibitory effect of sensitization of the body on the production of antibodies – agglutinins and antitoxins [5, 7, 1].

The role of interaction between allergens in the development of a state of increased sensitivity of the body has received far less study. In this problem, which is of theoretical and practical importance, the only aspect which has been investigated is the possibility of increasing allergy by the influence of nonspecific sensitization, mainly during infectious diseases.

The possibility of suppression of development of increased sensitivity of the body as a result of competition between allergic processes has been almost completely ignored. The literature on this subject is extremely limited. Lewis [8], for instance, showed that it was possible to inhibit the development of sensitization to one protein by the simultaneous or subsequent (24 hours after sensitization) injection of a large dose of another protein. However, experiments by A. M. Gardash'ian [2] showed the possibility of development of anaphylaxis to both allergens after sensitization of guinea pigs with a mixture of horse and rabbit sera in the most widely different proportions (from 1:100 to 1:20,000).

The aim of the present investigation was to ascertain the possibility of and the conditions for inhibition of the development of the allergic reorganization of the body as a result of competition between the allergens.

EXPERIMENTAL METHOD AND RESULTS

The experiments were performed on that classic and thoroughly studied model – anaphylactic shock in guinea pigs (initial weight 250 - 280 g), sensitized by a single subcutaneous injection of different doses of horse and ox serum, either simultaneously or by injection of the allergens at different intervals of time. From 21-24 days after injection of the second allergen, an assaulting injection of ox or horse serum was given (0.25-1 ml, intracardiac injection). Under these conditions the main criterion of the degree of allergic reorganization of the animal was the depth of the anaphylactic shock. As is known, the anaphylactic shock resulting from the use of this method is generally fatal.

In the first experiment simultaneous sensitization of the animals with both allergens in different doses was carried out (Table 1).

As the results given in Table 1 show, the simultaneous sensitization with two antigens, in which one is greatly in excess of the other, leads to a less profound allergic reorganization in respect to the second allergen (in 3 of 6 guinea pigs, after an assaulting injection of 0.25 ml of ox serum only slight manifestations of anaphylactic shock were observed). The results obtained confirm the experimental findings of V. I. Ioffe and his

TABLE 1

Development of Anaphylaxis to Ox Serum After Simultaneous Sensitization with Two Allergens

Guinea pigs	No. of animals	Sensitizing dose of serum		No. surviving shock
		horse	ox	
Experimental	6	0,01	0,01	0
	6	0,1	0,01	0
	6	1,0	0,01	3
Control	3	0,01	—	0
	3	1,0	—	0
	3	—	0,01	0

ried out. The assaulting injection of ox serum was given 21-24 days after sensitization with the second allergen. The results of the experiments are shown in Table 2.

From these experimental results it can be concluded that suppression of the development of sensitization to ox serum is observed when the sensitizing dose of this serum is injected at the height of the allergic reorganization of the animal to the other antigen (from 7-14 days after sensitization).

It must be pointed out that of the 6 guinea pigs sensitized to ox serum 7 days after the injection of horse serum, and not developing fatal shock after the assaulting injection of ox serum, in three animals the manifestations of shock were extremely slight. After sensitization of the animal with equal doses of each allergen at intervals of 7 days, some degree of weakening in the intensity of the allergic reorganization to the second allergen was also observed.

Animals surviving an assaulting injection of one of the allergens (usually ox serum) were given an assaulting injection of the second allergen. It was shown in this way that the animals which had survived anaphylactic shock appeared to be desensitized to injection of the second allergen if it was injected within a few hours after survival from shock. Under these conditions the degree of desensitization was inversely proportional to the severity of the shock which the animal had survived. Twenty-four hours afterwards the sensitization was usually completely restored.

It can thus be concluded from the results obtained that at the height of development of sensitization the animal is observed to be relatively refractory to the injection of a nonspecific allergen. This refractoriness is not, however, found in all animals by the method which we used, and is less marked than in inhibition of

co-workers [4], who demonstrated the possibility of suppression of the development of sensitization to one of the components of a combined allergen when the other was present in considerable excess.

In the next experiments we studied the development of sensitization after injection of allergens at different intervals. In these experiments sensitization to the second allergen (ox serum) was produced both at the onset of the allergic reorganization (after 72 hours) and at its height (after 7-14 days).

The guinea pigs were sensitized by the subcutaneous injection of 0.01-1.0 ml of horse serum. After 3-7 or 14 days, sensitization of the experimental animals with 0.01 ml of ox serum was carried out.

TABLE 2

The Development of Anaphylaxis After Successive Sensitization by Two Allergens After Different Intervals of Time

Guinea pigs	No. of animals	Intervals between sensitizations	Sensitizing dose of serum		No. surviving shock
			horse	ox	
Experimental	5	72 hrs.	1,0	0,01	0
	10	7 days	1,0	0,01	6
	5	7 »	0,01	0,01	2
	5	14 »	1,0	0,01	3
Control	5	—	1,0	—	0
	5	—	—	0,01	0

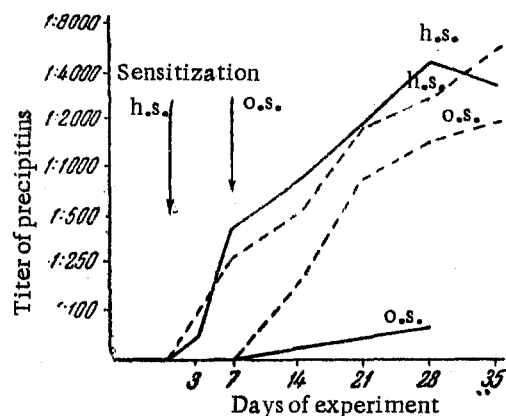


Fig. 1. Average titers of precipitins to horse and ox protein.
— experimental group; --- control groups; h. s. — horse serum; o. s. — ox serum.

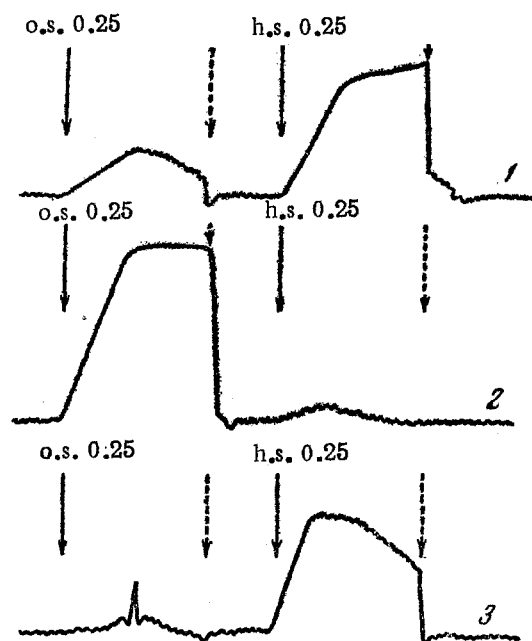


Fig. 2. Reaction of the isolated intestine of sensitized guinea pigs (experiment 30 days after sensitization).

Experimental group: 1 — sensitization to 1.0 ml of horse and 0.01 ml of ox sera at intervals of 7 days. Control group: 2 — sensitization to 0.01 ml of ox serum; 3 — sensitization to 1.0 ml of horse serum; h. s. — horse serum; o. s. — ox serum;
↓ rinsing with Ringer-Locke solution.

musculature. In the literature no investigations of this sort have been reported. The experiments were carried out on an isolated segment of intestine, from 24-30 days after sensitization to the second allergen, by the generally accepted method of Schultz and Dale [6].

antibody formation. This is probably due to the greater sensitivity of the guinea pig to an anaphylactic reaction.

The development of serum anaphylaxis is known to be accompanied by the production of precipitins to the allergen injected. It was considered to be of interest to investigate whether inhibition of antibody formation is observed under these conditions. For this purpose blood was taken from all the experimental animals (20 guinea pigs) 3, 7, 14, 21 and 28 days after the first sensitization, and the titer of the precipitins in the serum was determined.

It was found that 3 days after sensitization the titer of the precipitins to horse serum varied from 0 to 1:100, 7 days after — from 1:100 to 1:800, increasing on the 21st-28th day to 1:1000-1:8000. The injection of the second allergen did not affect the precipitin titer. The antibody titer of the control animals also increased in a similar manner.

The precipitin titer to the second allergen — ox serum, injected into the experimental animals 7 and 14 days after sensitization to horse serum — altered in a different manner. In this case, 21 days after the injection of ox serum in not one of the 20 animals did the precipitin titer exceed 1:100, and in 4 guinea pigs precipitins were found only in titers less than 1:10. In control animals, receiving only 0.01 ml of ox serum (5 animals) the antibody titers at this time varied from 1:800 to 1:2000 (Fig. 1).

From the results obtained it may be concluded that inhibition of the allergic reorganization of the animal is accompanied also by inhibition of immunogenesis, and also that this latter is more marked and is observed in all the experimental animals. No direct quantitative relationship between the degree of sensitivity of the animal and the precipitin titer in the blood of the animal could be observed.

In the pathogenesis of the anaphylactic reaction, spasm of smooth musculature plays a highly important part [11 and others], and the sensitivity of this tissue to the allergen increases sharply in the process of sensitization [8, 10]. This change in the sensitivity of the smooth musculature is specific for the allergic reorganization.

Experiments were carried out to ascertain the effect of competition between allergens on the development of increased reactivity of the smooth

It was shown by these experiments that after sensitization to the allergens at an interval of 7 days, the reaction of the smooth musculature was considerably more marked to the first allergen — horse serum (Fig. 2), whereas in a comparison of the kymograms from the corresponding control animals this difference was not observed. However, the reaction of the isolated intestine to the second allergen was nevertheless somewhat more marked than in unsensitized animals, which suggests only a reduction in, rather than a complete absence of, allergic reorganization of the smooth musculature to the second allergen.

Altogether 19 guinea pigs and corresponding controls took part in the experiment.

Thus the results obtained demonstrate that the laws of excitation and inhibition, discovered by N. E. Vvedenskii and I. P. Pavlov for nervous processes, and confirmed by P. F. Zdrodovskii and his co-workers for the immunological reactivity of the animal body (antibody formation), are also true for the allergic reorganization of the body (anaphylaxis). In this case also, at the height of the allergic reorganization the animal is relatively refractory to the action of other stimuli. This refractoriness also extends to the function of antibody formation (precipitins), which emphasizes once more the close interconnection between these processes. Investigations carried out on isolated organs (segments of the small intestine) have shown that the reduction in the degree of allergic reorganization is also accompanied by a reduction in the reaction of the smooth musculature to the corresponding allergen, a feature which was observed in all the experiments carried out.

The results obtained call for a fresh reappraisal of the special features of the course of secondary infections, developing in association with an underlying disease, always accompanied by an allergic reorganization of the body.

It is essential to bear these findings in mind when composing rational schemes of combined immunization, since the allergic reorganization of the body plays an essential role in the vaccinal process.

SUMMARY

This work was conducted on guinea pigs sensitized by various doses of horse and ox sera simultaneously or at various intervals between the administration of the allergens (on the 3rd, 7th, 14th and 21st day). The allergic reorganization was judged by the death of the animals in injecting the booster dose of one of the allergens, the value of the antibodies — precipitins for them, as well as the reaction of the isolated intestinal portion to the allergens. It was demonstrated that at the peak of the allergic reorganization (in 7-14 days) the body is relatively refractory to the sensitization by other allergens, which is demonstrated by the survival of more than 50% of the animals injected with a booster dose (with the 100% mortality rate of the control animals), by the considerable depression in the production of precipitins, and decreased reaction of the smooth muscles to the second allergen.

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