Reprinted from THE JOURNAL OF IMMUNOLOGY
Vol. 37, No. 5, November, 1939

RÔLE OF „AUTO-ANTIGENS" IN THE PATHOGENESIS OF PHYSICAL ALLERGY

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Received for publication July 27, 1939

Frequent objections have been raised to the use of the term „allergy" in referring to the so-called physical allergies due to exposure to cold, heat, ultraviolet irradiation, etc. There has been as yet no evidence of an immunologic basis for these diseases. However, from the investigations of Roth and Horton (1, 2) it has been shown that in these conditions, in common with other allergic states, histamine is liberated from the cells and this leads to local and often systemic reactions.

Apparently in the case of physical allergy it is not necessary to assume cell injury due to the antigen-antibody reaction, because the damaging agents themselves are capable of injuring the cells sufficiently to release histamine, particularly in individuals whose cells have a low resistance against such physical damaging agents. Furthermore it is very difficult to imagine an ordinary stimulus of a physical nature which can have anything to do with antigens, or with antibody production.

We felt that this generally accepted explanation concerning the pathogenesis of physical allergy, i. e., that the release of histamine is due directly to the physical injury of the cells, was not completely satisfactory. The present experiments are an attempt to determine whether these allergies due to physical factors may in some way be explained on an immunologic basis (3).

EXPERIMENTS

1. Blood was taken from normal guinea pigs and allowed to clot. The serum was separated, half of the amount was exposed to heat by being kept at a temperature of 56°C. for 1½ minutes. The other half was exposed to cold by placing it in an ice-salt mixture at a temperature of —5°C. for 1½ minutes. The samples of serum were allowed to come to room temperature and seven guinea pigs (all males weighing 200—250 grams) were injected intraäbdominally with 3 ml. of serum treated with cold and another 7 guinea pigs with 3 ml. of serum treated with heat. These injections were followed by no symptoms. Two weeks later guinea-pig serum was treated in the same way as before. Five guinea pigs exposed to cold received intraäbdominally 2 ml. of serum treated with cold, and 5 guinea pigs previously treated with serum exposed to heat received 2 ml. of serum treated with heat. Two guinea pigs from each group were used for crossexperiments, that is, 2 guinea pigs which on the first occasion were given serum exposed to cold, received serum exposed to heat and vice versa.

As a result of the injections in 4 to 5 minutes marked anaphylaxis developed in all except those 4 guinea pigs in which the reinjection was crossed. The anaphylaxis reached its maximum in 10 minutes after the reinjection (itchiness of the nose, scratching of the nose, milling movements with the mouth, ruffling of the fur, excitement, trembling, gradually increasing dyspnea, convulsions, etc.). The body-temperature showed a drop of 2 to 3°C. 10 minutes after the reinjection. In the 4 „crossed" guinea pigs there was no change in the temperature, and no symptoms. At necropsy pulmonary emphysema was observed in the animals which had shown anaphylactic shock.

The results of this experiment show very definitely that the serum of the guinea pigs by exposing to some physical agent such as cold or heat, undergoes certain changes which cause it to acquire antigenic properties. But the exposure

was carried out in test tubes and *in vitro* experiments do not always reproduce processes happening in the living organism.

2. In the next series of experiments instead of the guinea-pig serum, the guinea pigs themselves were exposed to cold and heat. Ten guinea pigs were exposed to each physical stimulus, by means of immersing the hind limbs in hot water (58°C.) or in cold icesalt mixture (—5°C.) for two minutes. These exposures were not followed by any noticeable symptoms apart from the pain in the hind limbs. After two weeks, the animals were reinjected intraäbdominally with 2 ml. of previously treated serum (serumpretreatment was carried out in the same manner as in the previous experiment). In all guinea pigs, anaphylactic shock with thermal drop (2 to 3°C.) developed within the first five minutes. Three guinea pigs (2 from the group exposed to heat and 1 from that exposed to cold) died 15 to 20 minutes after the injection was given; the other guinea pigs recovered slowly in ½ to 1 hour, but they still showed obvious emphysema at necropsy carried out at the end of that time.

3. In the last experiment 12 guinea pigs were exposed to cold and 12 to heat in the same manner as in the previous experiments. However, instead of injecting serum to produce shock, the animals were re-exposed to cold, or to heat. In 2 guinea pigs from each group the re-exposure was crossed (the heat-pretreated animals were exposed to cold and the cold-pretreated group to heat).

In the 20 animals who received exposure corresponding to the pretreatment, signs of anaphylactic shock appeared 5 minutes after the re-exposure. Six animals (4 from the cold-pretreated and 2 from the heat-pretreated group) died of very severe shock 20 to 25 minutes after the re-exposure, the other animals began to recover from the shock in 30 minutes. They were killed at that time and necropsy revealed marked emphysema of the lungs.

In marked contrast to these results, the 4 animals sensitized to heat or cold and treated with the opposite exposure did not develop anaphylactic shock; they showed normal

behavior throughout the whole experiment. There was no sign of emphysema at necropsy. Temperatures were not taken in this series of experiments since the exposure made it difficult to carry it out.

DISCUSSION

The present experiments are based on the assumption that the exposure of the organism to a physical stimulus might lead to chemical structural changes in the protein of the plasma or cells sufficient to cause denaturation of the protein of the organism, making it in effect a foreign protein for that organism. The denatured protein so produced might act as an antigen, and this might then lead to antibody-formation. When the next exposure to the same physical stimulus occurs, the conditions for the formation of the same antigens („auto-antigens") are again present. Just as the first exposure to the physical damage corresponded to the sensitizing injection, the second exposure corresponds to the reinjcetion of a foreign protein. There is consequently a combinig of the immune bodies, cell-injury, release of histamine, and local or systemic reactions characteristic of allergy.

The evidence of the present experiments indicates that this assumption is correct and that „auto-antigens" may be formed in the organism itself by the physical stimulus. The results show that the procedures used in the experiment were sufficient to produce „auto-antigens" from the protein of the guinea pig's own organism and that the re-exposure of the animals to the same stimulus elicited very marked symptoms of anaphylactic shock with a fall of body temperature and the development of pulmonary emphysema.

Advantage may be taken of the presence of such auto-antigens in the diagnosis and treatment of physical allergies. The desensitization of patients with cold-or heat-hypersensitivity by frequent immersion of hands and feet in hot or cold baths (1, 2) may be explained on the basis of auto-antigens. The frequent exposure to conditions producing the antigenic substance is comparable to the frequent injection of the offending proteins in other types of allergies, such as hay-fever and food allergies.

This new evidence, does not, of course, indicate that all cases belonging to the group of physical allergy have the same mechanism. Among them are undoubtedly cases that lack any immunologic basis. These are due simply to hypersensitiveness to some physical stimulus and the symptoms are elicited by release of histamine from the cells, this release being directly due to the injury as such. But from our experiments one might suppose that there are, at least, some cases with a real immunologic basis, with the same mechanism as described in the above experiments. These cases would form the group of physical allergy to which the term of allergy as originally applied by Pirquet and Schick may rightly be applied. It may be assumed that there is some difference in the resistance of the proteins of different individuals which may be a predisposing factor, that is, some individuals have a tendency to physical allergy because their body protein undergoes a chemical change more easily under the influence of physical stimuli than does that of „normal" individuals.

The conception that under purely physical influences, the organism's own protein can be changed in its structure in such a way that it becomes foreign for the organism and acquires antigenic property (in our terminology, te possibility of developing „auto-antigens") is new and not only has theoretical interest and importance, but its possible practical significance may stimulate further research in finding a new treatment for the diseases belonging to the group of physical allergy.

SUMMARY

1. Guinea-pig serum was exposed to cold (—5°C.) or to heat (56°C.) for 1½ minutes, and injected into a group of normal guinea pigs. Three weeks later reinjection of similarly treated serum caused an anaphylactic shock when the serum injected had been exposed to the same physical condition, but no anaphylaxis resulted when the serum injected had been exposed to the opposite physical condition.

2. Exposure of guinea pig's hind legs to cold (—5°C.) or heat (56°C.) followed three weeks later by injection of serum

treated with cold or heat resulted in anaphylactic shock in the correspondingly treated group but not in the cross-treated group.

3. Similar exposure of the guinea pig's hind limbs followed by re-exposure three weeks later to the same stimulus also resulted in anaphylactic shock. Cross experiments were again negative.

The present experiments seem to indicate a new mechanism in the production of physical allergies by which the organism's own protein can be changed by various physical agents, such as heat an cold, so that it acquires antigenic properties and becomes in our terminology an „auto-antigen".

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