

INHIBITION OF THE ANAPHYLACTIC REACTION BY THE  
CREATION OF A DYNAMIC STEREOTYPE

V. I. Luk'yanenko

Division of Immunobiology (Head — Active Member AMN SSSR N. N. Zhukov-Verezhnikov), Institute of Experimental Biology (Dir. — Prof. I. N. Maiskii), AMN SSSR; Division of Experimental Biology and Pathology (Head — Prof. I. K. Esipova), Institute of Experimental Biology and Medicine (Dir. — Prof. E. N. Meshalkin), Siberian Branch, AN SSSR, Moscow  
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The study of the defensive and regulatory activity of the central nervous system in immunological and allergic processes is one of immense importance to the elucidation of the physiological mechanisms of reactions in response to antigenic stimuli. Investigations by Soviet physiologists and immunologists [3, 6, 7, 8, 10] have established the presence of a connection between the functional state of the central nervous system and the activity of the apparatus of immunogenesis.

The regulation of the course of allergic reactions by the higher divisions of the brain, representing as it were the reverse side of immunological phenomena, has been inadequately studied from the point of view of the significance of these problems in the theory and practice of immunity. It would be of great interest to discover the role of a cortical dynamic stereotype, as a complex system of conditioned reflexes, in the reaction of the body to an antigenic stimulus.

The development of our knowledge of the patterns of activity and the functional properties of the higher divisions of the brain has led physiologists to regard the cortex as having a powerful influence on the realization of unconditioned acts. It has been shown, in particular [2, 5], that the reaction to unconditioned stimuli depends not only on the physiological properties of the actual stimulus but also on the general neurodynamic background, on the combination of excitation and inhibition to be found in the central nervous formations.

The importance of the initial neurodynamic background to the reactivity of the animal body was shown especially clearly by the work of Dolin and his collaborators during the study of the systemic character of the work of the brain, which was a further development of ideas put forward by Pavlov's school.

The formation of a dynamic stereotype in the activity of the brain is based on its ability to form and consolidate the functional integration of the centers when these are systematically bombarded with nervous impulses from the periphery. The source of the impulses for these centers is provided by the action on the body of an external stereotype of stimuli which, when applied repeatedly and uniformly, is fixed in the cerebral cortex, as a result of which a dynamic stereotype is produced. The characteristic properties of the stereotype are its inertia, its resistance to change and its ability to overcome "new situations and new stimuli."

It has now been established [1, 4, 5, 9, 11] that, after the production of a stable stereotype of conditioned reflexes, cortical influences may distort the reactions to different unconditioned stimuli of a chemical, physical and antigenic nature.

In the light of the foregoing remarks it appeared possible and necessary to make an experimental study of the physiological mechanisms of the participation of the cerebral cortex in the regulation of allergic reactions, using the anaphylactic reaction as an example.

## EXPERIMENTAL METHOD

Experiments were carried out on 51 guinea pigs in the course of 1958-60.

On each successive day the experimental animals were fixed in a special stand, where, in identical experimental conditions and in a strictly constant time and order of stereotype, they were systematically injected subcutaneously with isotonic sodium chloride solution, and then 15-30 minutes later food reinforcement (carrot) was given. All these manipulations were carried out by the same experimenter.

The animals were thus subjected to the action of an external stereotype of stimuli, incorporating a complex group of moderately strong tactile, visual, auditory, proprioceptive and chemical stimuli, accompanying the injection of sodium chloride and preceding the food reinforcement.

The daily stereotyped injections of physiological saline under constant experimental conditions lead to the formation and consolidation of conditioned reflex connections not only to the injection of physiological saline but also to the whole complex experimental situation. With such a stereotype of external stimuli there is created a functional integration of the excited and inhibited nervous centers, which is brought about by the formation of a dynamic structure of interconnected, complex physiological processes in the body as a whole.

The animals were sensitized by means of crude horse serum in dilutions of 1:1000 or 1:100, in a volume of 1 ml, given subcutaneously. The assaulting dose (1 ml) of protein stimulus was given in the form of a 40-80% solution of horse serum. The number of daily stereotyped injections of 1 ml of physiological saline varied from 28 to 40, and sensitizing dose of protein was given after 9-15 daily injections of physiological saline, while the assaulting dose was given after a further 18-25 days.

The degree of severity of the anaphylactic shock and the intensity of the reaction were noted as follows: ++++ lethal shock; +++ severe shock; ++ moderate shock; + slight shock; - general and marked inhibition.

## EXPERIMENTAL RESULTS

In the first experiments, carried out on 11 guinea pigs to study the influence of systemic factors in the activity of the brain on the realization of the action of the antigenic stimulus, a dynamic stereotype was formed as described above. On the 28th day after the beginning of formation of the stereotype, the deliberate alteration of the leading component of the external stereotype of stimuli - replacement of physiological saline by an assaulting dose of protein (horse serum in a volume of 1 ml of a 40% solution) - led to the marked inhibition or weakening of the response reaction of the animal to the protein stimulus.

Of the five experimental animals (Nos. 1-5) only two (Nos. 3 and 4) developed anaphylactic shock in a mild or moderately severe form (Fig. 1a). The other three guinea pigs (Nos. 1, 2 and 5) reacted to the injection of horse serum by a state of general inhibition, accompanied by adynamia and by the loss of several unconditioned reflexes (feeding and orientational).

Of the six control animals, four (Nos. 7, 8, 9 and 11) developed a severe form of shock after injection of the assaulting dose of protein, and guinea pig No. 11 died from shock. Only two animals (Nos. 6 and 10) developed a mild or moderately severe form of anaphylactic shock after injection of horse serum (see Fig. 1a). It could be provisionally concluded from these pilot experiments that, by actively creating a definite trend in the course of the fundamental nervous processes by modifying the external stereotype of stimuli, the sensitivity of the animal to the protein stimulus could be significantly altered.

The further development of these experiments was connected with the necessity of studying the effect of systemic factors on both the process of development of sensitization and the efficacy of action of the assaulting dose. It was thus necessary to discover what dose of protein - sensitizing or assaulting - loses its specific action. We accordingly carried out a second series of experiments in two variants on 15 guinea pigs.

In one variant of the experiments (guinea pigs Nos. 12-16), before the establishment of a dynamic stereotype, the animals received an injection of the sensitizing dose of protein (1 ml in a dilution of 1:1000), after which we proceeded with the formation and consolidation of the cortical stereotype.

The subcutaneous injection of the assaulting dose of protein (1 ml of a 40% solution of horse serum) given on the 27th day after the daily stereotyped injections of physiological saline, did not lead to the obvious

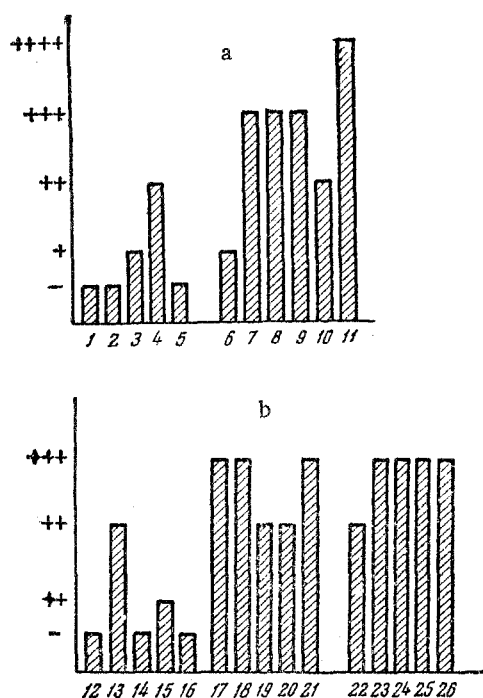


Fig. 1. The influence of systemic mechanisms in the activity of the brain on the realization of an antigenic stimulus in guinea pigs.

under these conditions all the guinea pigs developed anaphylactic shock in a moderately severe or severe form. In the control group of animals all the guinea pigs (Nos. 22-26) reacted to the injection of horse serum in the same dilution by the development of a severe or moderately severe form of anaphylactic shock.

The facts obtained from this series of experiments provided further evidence that the threshold of sensitivity of an animal to a protein stimulus may be essentially changed by a conditioned reflex method. At the same time it was found that it is easier to inhibit the reaction to the assaulting dose of protein than the reaction to the sensitizing dose of protein by means of the mechanisms of a dynamic stereotype. A similar conclusion emerges from an analysis of the available literature on the inhibition of the anaphylactic reaction by various types of agents [12, 13, 14]. Meanwhile the analysis of our own findings does not permit a final conclusion to be drawn. Other variants of experiments are required, and it is hoped to continue with these in the future.

The further analysis of this problem which we are considering led to the necessity of carrying out a series of experiments to study the stability and the physiological strength of the systemic mechanisms when they exerted their inhibitory influence on the mechanisms of the anaphylactic reaction. For this purpose we both increased the total number of stereotyped injections of physiological saline to 40 (instead of 26-28 in the previous experiments) and increased the intensity of the antigenic stimulus and the sensitizing dose (for sensitization we used serum in a dilution of 1:100; for the assaulting injection we gave 1 ml of a 40-80% solution of serum). The experiments were carried out on 15 guinea pigs. As controls we used two groups of guinea pigs (10 animals).

In the experimental animals we produced a stable stereotype of reactions to the subcutaneous injection of physiological saline (40 injections altogether), which was then replaced by the protein stimulus (the subcutaneous injection of 1 ml of a 40-80% solution of horse serum). The guinea pigs of the first control group were injected with horse serum in the same dilution. The guinea pigs of the second control group were given daily subcutaneous injections of physiological saline in a volume of 1 ml, but the experimental conditions were varied; the injections were given in different places, in different parts of the body and at different times and in a different order. By means of this modification of the experiments we were able to show experimentally how the variation of the conditions affects the formation of the stereotype and that physiological saline itself has no nonspecific desensitizing action.

appearance of anaphylactic shock (Fig. 1b). It is evident that in guinea pigs Nos. 12, 14 and 16 anaphylactic shock did not develop at all, whereas in guinea pigs Nos. 13 and 15 a mild and moderately severe form of shock developed in response to the injection of horse serum. The results of this variant of the experiments were in good agreement with our original findings that it is possible in principle to inhibit an anaphylactic reaction by means of systemic mechanisms.

In the other variant of the experiments (animals Nos. 17-21) the sensitizing dose was injected, not before the formation and consolidation of the cortical stereotype as in the previous experiment, but after, which would enable us to investigate the problem of the arresting of the process of sensitization by means of systemic mechanisms in the activity of the brain.

In this series of experiments, after the formation of the dynamic stereotype, on the 27th day after daily stereotyped injections of physiological saline, the latter solution was deliberately replaced by 1 ml of sensitizing dose of protein in a dilution of 1:1000, and immediately afterwards the experiments were interrupted for 18 days. After this time had elapsed in the conditions of the stereotyped injections of physiological saline, the animals received a subcutaneous injection of 1 ml of a 40% solution of horse serum. The experiments showed that

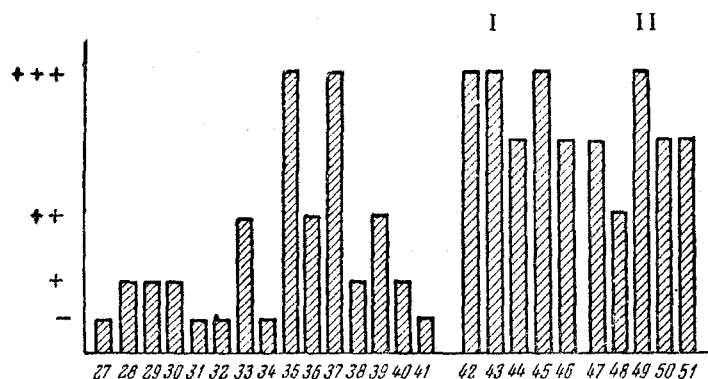


Fig. 2. Inhibition of the anaphylactic reaction by the mechanisms of a dynamic stereotype.

As shown in Fig. 2, experimental guinea pigs Nos. 27, 31, 32, 34 and 41 reacted to the subcutaneous injection of an assaulting dose of protein by a severe general inhibition, extending also the subcortical formations, manifesting itself as the loss of orientational and feeding unconditioned reflexes.

Guinea pigs Nos. 28, 29, 30, 38 and 40 developed a mild form of anaphylactic shock. Three guinea pigs (Nos. 33, 36 and 39) reacted to the injection of protein by anaphylactic shock of a moderate degree of severity. Only in guinea pigs Nos. 19 and 21 did a severe form of shock terminate in death.

In both control groups the injection of horse serum in the same dilution was followed by the development of severe manifestations of shock, terminating in individual cases in death.

It follows from the experiments described that the effect of inhibition of the anaphylactic reaction by the mechanisms of a dynamic stereotype is a function of two variables: the stability of the induced stereotype and the strength of the antigenic impulse. The depth of inhibition of the anaphylactic reaction increases with an increase in the stability of the stereotype and decreases with an increase in the strength of the antigenic impulse. Furthermore it is essential to have strict observance of the technical conditions of formation of the stereotype, as is illustrated by the results of the experiments on the animals of the second control group of the last series. It is important in principle to emphasize that the role of a dynamic stereotype in the modification of immunobiological reactivity is effective only when the animal is subjected to the action of threshold, i.e., of relatively weak, shock-producing doses of protein, and when the strength of the antigenic pathological stimulus is increased, the physiological mechanism of defense of which we consider the functional manifestation to be the dynamic stereotype becomes less effective.

It may be postulated that in all these experiments we are concerned with the formation of a complex conditioned reflex to the internal state of the animal, characterized by the pattern of the unconditioned reactions and of their underlying metabolic processes, themselves caused by the particular system of stereotyped stimuli, the first of which become conditioned stimuli setting in motion the chain of subsequent unconditioned reflex reactions.

This dynamic pattern of unconditioned processes, incorporating the reactions of many systems of the body and caused by a complex conditioned stimulus and increasing the resistance of the animal to pathogenic agents, may be designated a complex conditioned "reflex of nonspecific resistance."

By means of this method it is possible to judge the role of the normally functioning cerebral cortex in the course of immunological and allergic processes, and to ascertain the character of the cortical influence, its duration and its strength.

#### SUMMARY

It was established by experiments carried out on guinea pigs that it is possible to change the sensitivity of the body to antigenic stimulation by creating dynamic stereotype in the brain hemispheres. It was shown that it was possible to inhibit, to invert or to considerably diminish the anaphylactic shock by the systemic mechanisms. The extent of anaphylactic shock inhibition by the systemic mechanisms depends on the stability of dynamic

stereotype and the strength of the antigenic impulse. The mechanisms of dynamic stereotype are effective only in the action upon the organism of the threshold (i.e., the relatively weak) shock doses of the protein stimulus. In analyzing our own material and the data of other authors a suggestion is made that the dynamic sterotype is a functional manifestation of the physiological preventive measure against pathological actions.

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