MECHANISM OF INHIBITION OF ANAPHYLACTIC REACTION BY NARCOSIS*

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(Presented by Active Member AMN SSSR N. N. Zhukov-Berezhnikov)
Translated from Byulleten' Éksperimental' noi Biologii i Meditsiny, Vol. 51, No. 5, pp. 81-85,
Original article submitted June 3, 1960

About 60 years have passed since Richet's classical experiments (1902), which led to the formulation of the main views on anaphylaxis. These were concerned more with the phenomenological aspect of the problem. Yet there is still no satisfactory explanation of the mechanisms of anaphylaxis. The vast literature on this question indicates the great difficulties encountered in its solution.

One of the lines of research on the mechanisms of anaphylaxis is an investigation of the role of the nervous system in the pathogenesis of the anaphylactic reaction. This problem has been investigated by several experimental methods—by pharmacological alteration of the functional state of the central nervous system, mainly by narcosis; by extirpation of various parts of the central nervous system, by intradural injection of the anaphylactogen, and by conditioned-reflex reproduction of the anaphylactic reaction.

The greatest number of experiments, however, have been devoted to a study of the effect of narcosis on anaphylactic shock. A. M. Bezredka [4] was the first to show that narcosis inhibits anaphylactic shock. These initial data have been confirmed several times, and in recent years have been supplemented by a study of the effect of narcosis on other allergic reactions—the Arthus-Sakharov phenomenon, the Schwartzmann phenomenon, tubercular allergy, and brucellar allergy [3, 5, 10, 11].

But narcotic substances are known to act not only on the nervous system, but also on other organs and tissues of the organism, and to produce changes in metabolism, permeability, and several other tissue changes which have some bearing on allergic reactions [8]. Hence, several immunologists believe that the mechanism of the observed inhibition of the allergic process is obscure and that the role of the nervous system in this phenomenon has not been proved, since narcosis may have a toxic effect on the smooth musculature.

The aim of this work was to investigate the mechanism of the inhibition of the allergic reaction by narcotics.

METHOD

To resolve this question we combined the method of pharmacological alteration of the functional state of the central nervous system with the classical Dale-Schultz method of investigating the tissue sensitivity of an isolated organ. We called this combined method of investigation the cross-checking method. It consists in a determination of the role of the narcotic state in the course of the anaphylactic reaction in the intact organism and a subsequent study of the tissue sensitivity to the anaphylactogen in an isolated organ—the uterus of the same animal—by means of the Dale-Schultz method [12] (A. T. Kravchenko and N. V. Galanova [1948]).

* I consider it my duty to express my sincere thanks to Corresponding Member AN SSSR Kh. S. Koshtoyants for kindly providing the facilities for the conduction of this work.

TABLE 1

Comparative Study of Sensitivity of Isolated Uterine Horn to Horse Serum, Histamine, and Acetylcholine After Injection of Shocking Dose of Protein Into Narcotized Animals

No. of experiments	Horse serum			Histamine			Acetylcholine		
	dilution	exposure (in min)	reaction	dilution	exposure (in min)	reaction	dilution	exposure (in min)	reaction
3	$1:10^{-5}$	1—5	—	$1:10^{-8}$	1—5	— (1+)	$1:10^{-7}$	1—5	— (1+)
10	$1:10^{-4}$	1—5	—	$1:10^{-6}$	1—2	+	$1:10^{-5}$	1—2	+
5	$1:10^{-3}$	1—5	— (1+)	$1:10^{-7}$	1—5	— (2+)	$1:10^{-6}$	1—2	+
2	$1:10^{-2}$	1—5	— (1+)	$1:10^{-5}$	1—2	+	$1:10^{-4}$	1—2	+

Symbols: Absence of muscular contraction; + presence of muscular contraction. Figure in brackets denotes number of experiments in which a positive reaction was obtained.

The experiments were performed with 50 guinea pigs, weighing 300-420 g, which were divided into five groups (two experimental and three control, ten animals in each). All the animals were sensitized by a single subcutaneous injection of 0.1 ml of horse serum and 18-22 days later were taken for the experiment.

Narcosis was produced by the intraperitoneal injection of urethan, 1 g per kg of body weight, and lasted for 2-7 hr. The animals of the first experimental group were given a shocking dose (0.4 to 0.8 ml) of horse serum, intraperitoneally or subcutaneously, $1\frac{1}{2}$-$2\frac{1}{2}$ hr after the onset of deep narcosis.

The same dose of horse serum was injected into the ten pigs of the first control group. All the control animals reacted to the injection of the shocking dose of protein by severe and lethal shock.

In the animals of the first experimental group (first series of experiments) the shock was considerably weakened or completely inhibited by narcosis. After 24-36 hr we investigated the specific tissue sensitivity to horse serum on the isolated uterus of these animals in the experiment in vitro.

In the second experimental group (second series of experiments) the sensitized animals were decapitated $1\frac{1}{2}$-2 hr after the onset of narcosis and the reaction to specific protein was investigated on the isolated uterus in the experiment in vitro.

In only two out of the ten narcotized animals of the second control group did we observe a pronounced anaphylactic reaction after the injection of the shocking dose of protein. In the other animals the shock was greatly weakened or completely suppressed.

The experiments in vitro were carried out in the following way. The two uterine horns were separated by the usual method and put into the dishes (capacity 50 ml) containing Ringer-Locke solution at 37.5° on the Dale-Schultz apparatus. Oxygen was passed through the Ringer-Locke solution (50-60 bubbles per minute). The contractions of the smooth muscle of the isolated uterus were recorded on a kymograph by light scribes. After the uterine horns were placed in the dishes they were kept there for 15-35 min to acquire their initial tonus. The scribes were brought against the smoked tape immediately before the start of the experiment. Parallel records of the responses of the two horns were made. Normal sera in the following concentrations were used: horse serum—$1 \cdot 10^{-5}$, $1 \cdot 10^{-4}$, and $1 \cdot 10^{-3}$, nonspecific ram serum—$1 \cdot 10^{-4}$ and $1 \cdot 10^{-3}$. In addition, nerve mediators were used—acetylcholine in concentrations $1 \cdot 10^{-7}$, $1 \cdot 10^{-6}$, $1 \cdot 10^{-5}$, and $1 \cdot 10^{-4}$, and histamine in concentrations $1 \cdot 10^{-8}$, $1 \cdot 10^{-7}$, $1 \cdot 10^{-6}$, and $1 \cdot 10^{-5}$. These concentrations of substances were final, i.e. their dilution by the liquid in the dish was taken into account.

The duration of action of each stimulus was decided by the aim of the experiment. The preparations were washed for 5 to 25 min after the action of the stimuli.

TABLE 2

Comparative Study of Sensitivity of Isolated Uterine Horn to Horse Serum, Histamine, and Acetylcholine $1\frac{1}{2}$-3 Hr After Onset of Narcosis in Animals

No. of experiments	Horse serum			Histamine			Acetylcholine		
	dilution	exposure (in min)	reaction	dilution	exposure (in min)	reaction	dilution	exposure (in min)	reaction
10	$1:10^{-4}$	1—2	+	$1:10^{-6}$	1	+	$1:10^{-6}$	1	+
5	$1:10^{-3}$	1	+	$1:10^{-7}$	1	+	$1:10^{-7}$	1—2	+
5	$1:10^{-2}$	1	+	$1:10^{-8}$	1—2	+ (2—)	$1:10^{-5}$	1	+

Note. Symbols as in Table 1.

RESULTS OF EXPERIMENTS

In proceeding to the discussion of the experimental results we must mention that the threshold doses, determined in special experiments, were as follows: horse serum $1 \cdot 10^{-5}-1 \cdot 10^{-4}$, histamine $1 \cdot 10^{-8}-1 \cdot 10^{-7}$, acetylcholine $1 \cdot 10^{-7}-1 \cdot 10^{-6}$.

The threshold doses depended on the individuality of the animal and the time spent by the isolated preparation in the experiment.

Table 1 shows that animals under narcosis became desensitized after the injection of a shocking dose of protein, despite the absence of external symptoms of anaphylactic shock. Yet, it is quite obvious that combination of the antigen and antibody took place. The evidence for this was the onset of desensitization in all the experimental animals, and the isolated uterine preparation did not respond by muscular contraction to known supraliminal doses of protein.

As an illustration of this we show the kymograph trace of the responses of the uterine horn of experimental pig No. 7 (Fig. 1).

In this connection, it is important to recall that the onset of a state of antianaphylaxis after the injection of a shocking dose of protein into narcotized animals was first noted by A. M. Bezredka [1907], and then by A. T. Kravchenko and N. V. Galanova [9].

Yet, such an experimental procedure did not enable us to draw a definite conclusion about the mechanisms of the inhibition of anaphylaxis by narcosis, or to indicate its nature, nervous or tissue, since it is possible that narcosis, by altering the metabolic processes of the organ tissues, lowers their general reactivity. Indeed, for removal of this objection we used another two stimuli, histamine and acetylcholine, in the experiments, but this was indirect information. The experiments showed that tissue sensitivity to histamine and acetylcholine persisted in the desensitized animals. There was only a slight rise in the threshold of response. On the basis of these results, we can postulate different biochemical pathways for the action of the protein, on one hand, and histamine and acetylcholine, on the other.

For direct experimental evidence of the nervous nature of the inhibition of anaphylaxis by narcosis a second series of experiments was undertaken. The sensitized animals were narcotized and then decapitated $1\frac{1}{2}$ hr after the onset of deep narcosis. Both uterine horns were used in the experiment in vitro, and the presence of sensitivity to protein, histamine, and acetylcholine was investigated. The results obtained are given in Table 2.

Table 2 shows that the tissues of a narcotized animal did not lose their sensitivity to a specific protein stimulus. The threshold of response of the isolated preparation to histamine and acetylcholine remained the same or was even a little lower. As an illustration of this fact we show a kymograph trace of the functional activity of the muscle in response to the action of specific protein for experimental guinea pig No. 15 (Fig. 2).

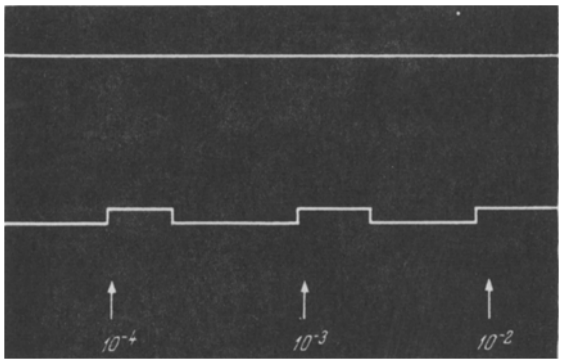

Fig. 1. Onset of desensitization in animal after inhibition of anaphylactic reaction by narcosis. Meaning of curves (top to bottom): trace of functional activity of uterine horn in vitro; stimulation marks. Vertical arrows denote moment of injection of horse serum. Serum concentration is indicated.

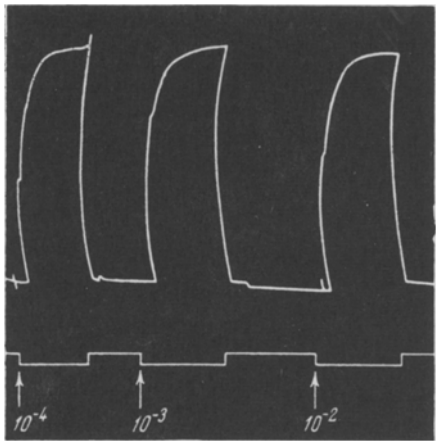

Fig. 2. Persistence of tissue sensitivity to specific protein $1\frac{1}{2}$-3 hr after onset of narcosis. Meanings as in Fig. 1.

To verify the specificity of the reaction of the animal tissue to serum antigen we investigated the reaction to ram serum in dilutions $1 \cdot 10^{-4}$ and $1 \cdot 10^{-3}$ in ten experiments with five guinea pigs. The experiments showed that the organ taken from a narcotized animal did not contract in response to the action of the nonspecific ram serum.

The effect of narcosis itself on the reaction of an isolated preparation of a nonsensitized animal was also tested in ten experiments with five guinea pigs. There was no specific reaction to horse serum in these conditions—the organ did not contract.

An examination of the results of these experiments suggests that in such a multistructural reaction as the anaphylactic reaction there are two interconnected and interdependent phases: an immunochemical (or specific) phase, and a physiological (or nonspecific) phase.

The underlying feature of the immunochemical, or specific, phase is the immunological mechanism proper, the antigen-antibody reaction. The physiological, or nonspecific, phase of the anaphylactic reaction involves many systems and organs of the organism, primarily the smooth musculature, the level of functional activity of which can be altered by a great variety of factors, including antigenic factors, and this accounts for the nonspecificity of this phase of anaphylaxis.

The results of the two series of experiments, particularly the second series, and of the various control experiments have shown that the physiological phase of the anaphylactic reaction is blocked by interference with the functional state of the central nervous system, by the resultant inhibitory state, and not by poisoning of the tissues of the internal organs. From these experiments we can subscribe to M. Bezredka's opinion that the inhibition of anaphylaxis by narcosis is of a nervous nature, and also to the idea of the leading role of the central nervous system in the anaphylactic reaction [1, 2, 6] or, more precisely, in its physiological phase.

At the same time our experiments, and also the published information [4, 9, 13], require that the part played by nervous mechanisms in the course of such a complex, generalized reaction as the anaphylactic reaction must be defined and demarcated. Such a problem has been made possible by the differentiated approach to the clarification of the mechanisms of induction and development of the anaphylactic reaction and its separation into two phases—the immunochemical and physiological. From our experimental data, and also the data in the literature, we can conclude that the employed methods of investigation do not demonstrate a leading role for the nervous system in the realization of the immunochemical phase, since the combination of antibody with antigen (cause of desensitization) occurs even when the nervous apparatus is excluded. Here, however, we must mention the existence of trophic nervous effects, which can determine the degree of reaction between tissue substrate and antigenic stimulus and thus alter the intensity of the anaphylactic reaction, as some of our experiments indicate.

The decisive influence of the neurodynamics of the cortical-subcortical system is clearly demonstrated in the occurrence of the physiological phase of the anaphylactic reaction. Alteration of the established intercentral relations by the mechanisms of the cortical dynamic stereotype and induction relations [7] can lead to a pronounced weakening or complete inhibition of the physiological phase of the anaphylactic reaction.

SUMMARY

The mechanisms involved in the arrest of anaphylactic reaction by anesthesia were analyzed. As demonstrated, inhibition of anaphylactic reaction occurs at the expense of the changes in tissue sensitivity resulting not from the tissue poisoning by anesthetics, but from altered functional condition of the central nervous system. A suggestion is made that in such a complicated polystructural reaction as the anaphylaxis, there are two interconnected and interrelated phases: immunochemical and physiological or specific and nonspecific. The author's own data and that derived from the literature show that realization of the specific phase of anaphylactic reaction may be effected without the nervous system playing a leading part in it, whereas the nonspecific phase of this reaction occurs with the participation of the neuro-reflex control, as a decisive factor.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
