

ON THE MECHANISM OF THE ALLERGIC REACTION IN SKELETAL MUSCLE

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In previous investigations [1-10] we showed that the allergic reaction of skeletal muscle may be observed without its preliminary denervation [1, 11]. In experiments on guinea pigs and dogs, we succeeded in showing that in anaphylaxis, the activity of the neuro-muscular apparatus is altered. The activity of the muscle is especially depressed with direct administration of the resolving injection of anaphylactogen into the stream of the artery supplying the muscle under study; it was also established that depression of the muscle activity is not related to the drop in blood pressure.

It is known that an allergic reaction is accompanied by the liberation of a number of physiologically active substances (acetylcholine, histamine, serotonin, etc.). The following question arises: is the depression of muscle activity related to the secretion of these substances, particularly acetylcholine, during the allergic reaction, and to their action on the muscle?

We undertook a study of the effect of the curariform drug, diplacin [6], during anaphylaxis. It is known that diplacin, belonging to the drugs of the "pachycurare" group, causes a blockade of the neuro-muscular transmission which is of the competitive type, i.e., competes with acetylcholine for the cholinoreceptors. Thus, by comparing the effects of diplacin before and after injection of the resolving antigen dose, it is possible to evaluate changes in the competitive relationships between acetylcholine and diplacin for the cholinoreceptors in the skeletal muscle during anaphylaxis.

In our experiments, we did not use acetylcholine in studying the sensitivity of the skeletal muscle cholinoreceptors, although in experiments on isolated, smooth muscle organs by the method of Schultz-Dale, and in experiments with perfusion of various reflexogenic zones during the study of allergic reactions, acetylcholine testing is necessary. We did not use it because first of all, in contrast to smooth muscle, skeletal muscle is only minimally sensitive to acetylcholine if it is not first denervated, and secondly, the application of acetylcholine under conditions where the natural blood circulation was retained would cause a pronounced central effect; finally, and this is the fundamental reason, acetylcholine, just like histamine, when injected into preliminarily sensitized animals, causes their desensitization [12].

Thus, for the investigation of cholinoreceptor sensitivity in the skeletal muscle we chose another method — a study of the comparative effectiveness of diplacin blockade.

EXPERIMENTAL METHODS

The experiments were carried out on 21 dogs (sensitized and not sensitized). For sensitization, we used normal horse serum. The antigen was injected subcutaneously, using a dosage of 0.2 ml per kg of body weight, administered three times a day. Morphine-hexenal was used for narcosis. The contractions of the anterior tibial muscle were recorded during stimulation of the peripheral end of the transected peroneal nerve. The nerve was stimulated with rectilinear impulses at a frequency of 1 and 50 hertz, supplied by an electronic stimulator. The recording was made on a kymograph, using ink. At the time of resolution, the antigen (0.5 ml/kg) was injected into the stream of the artery supplying the subject muscle (femoral artery). Respiration was recorded via the trachea, and blood pressure in the majority of experiments with a Ludwig Manometer.

In orientating experiments, it was established that the most appropriate dose of diplacin was 0.2 mg/kg, using the intraarterial method of administration (into the femoral artery). This dose causes a brief blockade, the duration of which can be used to judge the curariform action of the substance [13].

EXPERIMENTAL RESULTS

Experiments on the non-sensitized animals. In order to elucidate the influence of normal horse serum on the effect of diplacin, experiments were carried out on 7 dogs. We compared the magnitude of the neuro-muscular transmission blockade caused by diplacin before and after injection of the anaphylactogen (normal horse serum). In these investigations, we did not note any definite changes in the magnitude of the curariform effect by diplacin following injection of the anaphylactogen: in 4 dogs the degree of the neuro-muscular blockade was identical; in 2 dogs we observed a minimal decrease in the effect of the diplacin, and in one dog the curariform effect was somewhat intensified (see table). In repeat injections of diplacin following the horse serum, the results were approximately the same, but for maximum validity we used only the results of the first injection of diplacin following administration of the horse serum.

Composite Table of the Experiments

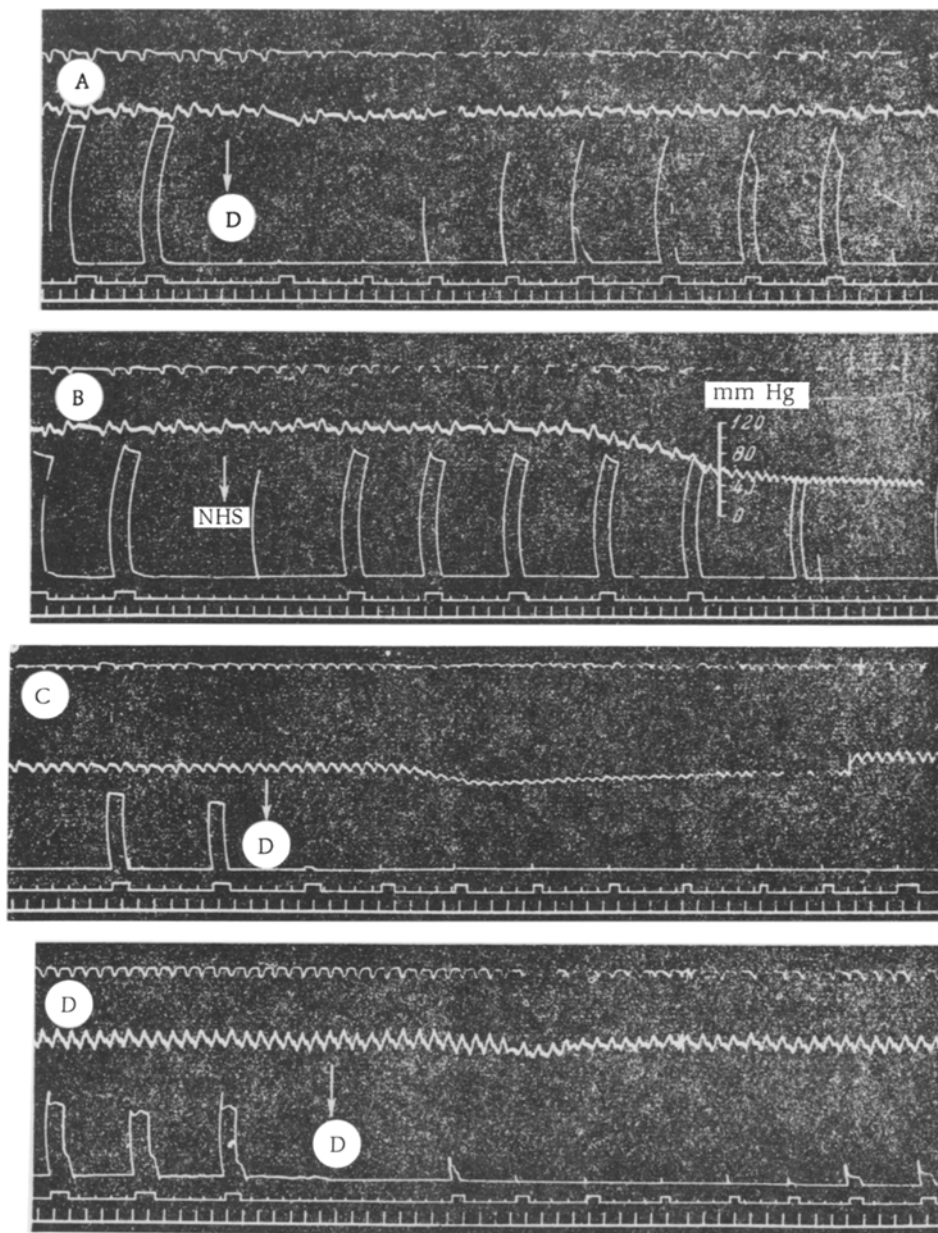
Animals	Number of animals in the experiment	Action of normal horse serum on the muscle contractions			Diplacin blockade following the injection of horse serum		
		depression	unchanged	intensification	depression	unchanged	intensification
		number of animals					
Not sensitized	7	2	5	—	2	4	1
Sensitized	14	9	2	3	4	—	10

Thus, the injection of normal horse serum into the nonsensitized dogs did not show any definite influence on the character of the skeletal muscle response to diplacin, and the effect of the latter did not change in the majority of the experiments, i.e., the sensitivity of the muscle cholinoreceptors of acetylcholine did not undergo particular changes.

Experiments on the sensitized animals. Experiments designed to study the effects of diplacin on the muscle during anaphylaxis were carried out on 14 dogs. The experimental conditions were the same as for the nonsensitized animals. The dogs were taken for the experiment on the 3rd-4th week of sensitization.

The curariform action of diplacin following the resolving injection of antigen changed in different ways. In 10 dogs the curariform action of diplacin was intensified, i.e., the effect of the diplacin action was prolonged in comparison with the original effect, prior to injection of the serum (see table and figure). In 4 animals, as a result of the action of the antigen, the effect of diplacin was less manifest. Analyzing these data, our attention was drawn to enhancement of the diplacin effect in those cases where it was injected against a background of depressed muscle activity following the resolving injection of antigen. It was shown earlier [8] that, in the majority of cases, injection of the resolving dose of antigen immediately causes depression of muscle activity; sometimes a certain intensification is initially observed, but there follows a gradual lowering of the height of the muscle contractions. The magnitude of the diplacin block decreased in those cases where diplacin was injected in the setting of an increase in the height of the contractions, i.e., intensified activity, which, as we have already indicated, is sometimes observed before subsequent depression of the activity. It must be noted that in 3 out of the 4 dogs the reaction of the organism to the resolving antigen dose was minimal in degree.

The decreased effect of diplacin in the setting of an initial intensification in muscle activity following administration of the resolving injection of antigen can be explained by a surplus of acetylcholine in the myoneural junction, and a shift in the competitive relationships between diplacin and acetylcholine for the muscle cholinoreceptors, favoring acetylcholine. It is possible that as a result of this shift there occurred a certain improvement in the activity of the muscle — elevation of the height of the contractions.



Diplocin blockade before and after the resolving injection of antigen. Sensitization interval of the dog was 21 days (experiment from March 10, 1960). Respiration, arterial pressure, muscle contraction, nerve stimulation marking, time markings. The vertical arrow signifies the moment of the arterial injection of the diplocin (D) and of the antigen, normal horse serum (NHS). A) Diplocin blockade before injection of the antigen; B) the same immediately after injection of the antigen; C) 15 min after the antigen injection; D) 45 min after the antigen injection.

When the diplocin was injected against the setting of depressed muscle activity following the resolving injection of antigen, its effect was intensified, i.e., the competitive relationships between acetylcholine and diplocin shifted in favor of the diplocin. If the depression of muscle activity occurred as a result of acetylcholine accumulation, then the effect of diplocin would have to be decreased, as was shown [10] in a special work with artificial elevation of the level of acetylcholine under conditions of cholinesterase blockade, using its phosphororganic inhibitor- armin [3]. This affords a basis for confirming that depression of muscle activity during anaphylaxis is nonacetylcholinic in nature.

According to the data in the literature [4], an anaphylactic reaction is accompanied by depression in the metabolic processes of the tissues; apparently, a depression in the processes of synthesis is also observed, and in the subsequent secretion of acetylcholine in the muscular tissue. Thus, the competitive relationships between acetylcholine and diplacin are shifted in favor of the diplacin.

The experimental data obtained are in agreement with the results of investigations performed in our laboratory [2, 5, et al.], in which it was also shown that the sensitivity of the vascular receptors to acetylcholine was decreased after an anaphylactic reaction.

Our experiments afford a basis for postulating that, in addition to other factors [14], a definite role in the pathogenesis of muscle injury of an allergic nature also may be played by a change in the sensitivity of the muscle cholinoreceptors to acetylcholine.

SUMMARY

In experiments on nonsensitized and sensitized dogs along with recording the contractions of the anterior tibial muscle during stimulation of the peroneal nerve the author studied the curare-like effect of diplacin before and after inoculation of an antigen (normal horse serum). Diplacin (0.2 mg/kg) and a resolving dose of the antigen (0.5 mg/kg) were introduced intra-arterially (femoral artery). In nonsensitized animals the extent of the curare-like effect of diplacin after inoculation of normal horse serum does not undergo any change. The effect of the diplacin before and after the resolving injection of the antigen to sensitized dogs was variable and depended upon the action of the resolving dose; viz: a) when the antigen administration caused an inhibition of muscular contractions (in most experiments), in indirect stimulation of the muscle the curare-like action of diplacin was more marked; b) when diplacin was introduced against the background of preliminary intensification of contraction prior to the inhibition, its effect was less pronounced.

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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.
