

# MECHANISM OF THE ACTION OF STAPHYLOCOCCUS ENTEROTOXIN ON THE ANIMAL BODY

## COMMUNICATION 2. THE EFFECT OF STAPHYLOCOCCUS ENTEROTOXIN ON CIRCULATION

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In Communication 1 results of our experiments on the effect of staphylococcus enterotoxin on the motor function of the stomach and intestine of animals were presented. These experiments showed that the cholinergic effect of staphylococcus enterotoxin played an important part in the mechanism of its action on the digestive organs.

The presence of vagotropic action shown by staphylococcus enterotoxin with respect to the intestine gave immediate grounds for supposing that it would have an active effect on the circulatory apparatus.

Further reactions occurring in the body under the influence of enterotoxin filtrates from staphylococci on the circulatory apparatus were investigated. The experiments were performed on 71 cats. Our investigations were confined to an attempt to solve a limited problem within the complex of reactions occurring under these conditions; this limited problem posed the question whether the circulatory apparatus was affected in staphylococcus enterotoxin poisoning and what were the basic mechanisms of such involvement.

This problem had not received experimental investigation.

### EXPERIMENTAL METHODS

The first series of experiments was concerned with the effect of staphylococcus enterotoxin on the arterial blood pressure of intact animals. A total of 22 experiments on 17 cats was carried out.

The experimental method consisted of recording arterial blood pressure in cats, under urethane anesthesia, before and after intravenous administration of staphylococcal enterotoxin filtrates. The pressure in the common carotid artery was recorded by a spring manometer, and in 6 cases by a mercury manometer. Respiration was recorded by means of a Marey's tambour.

Staphylococcal enterotoxin filtrates were introduced (in doses of 2 ml/kg) into the jugular vein which, like the common carotid artery, was exposed prior to the experiment.

The filtrates tested were of those staphylococcal strains which produced food poisoning and enterotoxic syndromes when tested on kittens and pups. Sterile nutrient medium and filtrate of staphylococcal strain which did not possess enterotoxic properties were used as controls.

### EXPERIMENTAL RESULTS

A definite arterial blood pressure reaction was observed upon intravenous administration of staphylococcal enterotoxin filtrates in doses of 2 to 6 ml.

Immediately after injection of the enterotoxin filtrates there was a considerable drop in blood pressure, lasting up to 24 minutes and followed by a subsequent levelling out. In some experiments, mainly when large doses of the filtrates were given, a second fall in blood pressure occurred and in many cases resulted in the animal's death. The average fall of systolic pressure was 43 mm Hg, of diastolic pressure — 36 mm. The rate of cardiac contractions was increased in the majority of the experiments. Duration of the drop in blood pressure was, in some cases, over one hour. The blood pressure did not return to the original level in any of the experiments (Fig. 1).

In addition to a fall in blood pressure and acceleration of the cardiac rhythm changes in respiration were observed in most of the experiments. The respiratory excursions increased in frequency with a simultaneous diminution in amplitude; this occurred most frequently immediately after injection of the enterotoxin filtrates. The amplitude of respiratory movements began to increase towards the end of the experiments.

Seven control experiments showed that sterile nutrient medium, used for growing the staphylococcal enterotoxin, and filtrates of staphylococcal strains without enterotoxic properties produced a rise of arterial blood pressure in the experimental animals.

The fact that intravenous injection of sterile nutrient medium caused a rise of arterial pressure lends further support to the conclusion that the observed drop in blood pressure was undoubtedly associated with the action of staphylococcal enterotoxin filtrates.

It is known from clinical observations that facial pallor and lowering of blood pressure are associated with cases of food poisoning of staphylococcal origin. The vasomotor reaction and fall of blood pressure in these patients are evidently connected with the action of staphylococcal enterotoxin on the circulatory apparatus. This is fully confirmed by our experimental studies of this question. However, this does not provide a definite answer as to the mechanism of the reaction since it could arise from: 1) impairment of central regulation of blood circulation (collapse), 2) involvement of peripheral blood vessels (by analogy with the action of arsenic) and 3) impairment of cardiac activity.

Experiments on cats following administration of adrenalin, atropine and papaverine were carried out in order to elucidate the mechanism of blood pressure lowering caused by staphylococcal enterotoxin filtrates. In all the experiments the blood pressure was recorded by means of a mercury manometer.

Six experiments were staged against the background of adrenalin action. 1 ml/kg adrenalin in concentration 1:10,000 was given intravenously and the reaction obtained was similar to that observed in intact animals: fall of blood pressure and acceleration of the cardiac contraction rate.

The response to enterotoxin filtrates against the background of adrenalin action, which produced enhanced sensitivity of organs and tissues to adrenergic reactions, was thus similar to that obtained in the preceding series of experiments on intact animals. Had the staphylococcal enterotoxin filtrates affected adrenergic reactions inversion of the response could have been expected.

The next 6 experiments were performed on atropinized cats. Atropine was given intravenously in the dose of 0.0005 g per 1 kg body weight in the form of a 0.1% solution of atropine sulfate (0.5 ml/kg). As in the preceding experiments, a fall in blood pressure and acceleration of the rate of cardiac contractions were observed.

It should be noted that, in comparing the blood pressure values, in two cases there was even an increase (experiments Nos. 5 and 6), while in the remaining experiments, except No. 1, there was a slight lowering of blood pressure averaging 30 mm Hg, i. e., less than in the experiments with adrenalin cited above (46-39 mm Hg).

The experiments in which adrenalin and atropine were used pointed to a definite relation between blood pressure and the activity of the central sections of the autonomic nervous system. The results of these experiments thus do not contradict the proposed hypothesis but do not provide direct proof of it. Four more experiments were therefore carried out, with administration of papaverine as a myotropic agent.

Intravenous administration of staphylococcal enterotoxin filtrate against the background of papaverine action was followed by appreciable fall in blood pressure. The systolic pressure fell by an average of 40 mm Hg, the diastolic — by 31 mm; in experiments with adrenalin the systolic pressure fell by an average of 46 mm, diastolic — by 39 mm, and in those with atropine the former fell by 30 mm on the average.



Fig. 1. Changes in blood pressure under the influence of staphylococcal enterotoxin filtrate. Kymogram of experiment No. 50. Records from above down: 1) respiration; 2) blood pressure; 3) blood pressure base line; 4) time marker (20 seconds); | — enterotoxin injection.

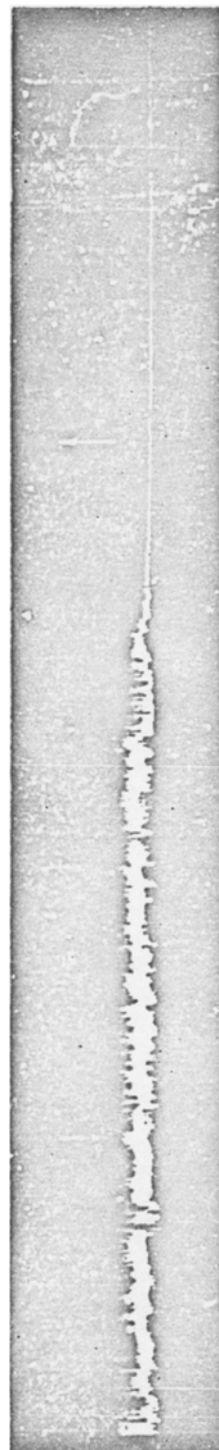


Fig. 2. Changes in blood pressure under the influence of staphylococcal enterotoxin filtrate on the isolated heart. Kymogram of experiment No. 7; | — enterotoxin injection, | — washing.

In subsequent experiments the influence of enterotoxin filtrates on the arterial blood pressure of cats was determined after preliminary transection of the spinal cord.

In all 4 experiments the staphylococcal enterotoxin filtrates produced lowering of blood pressure but to a lesser extent than in experiments on animals with intact spinal cord.

These data not only do not contradict but definitely support the working hypothesis of vagotonic influence of these filtrates.

It is known that parasympathetic impulses are excitatory with respect to hollow smooth-muscle viscera of the gastro-intestinal tract and inhibitory with respect to the smooth muscle elements of the vascular wall.

The series of experiments on animals pretreated by various autonomic poisons (atropine, adrenalin, papaverine) prior to administration of staphylococcal enterotoxin filtrates thus showed that the latter maintained their characteristic action under these conditions, causing hypotension in the experimental animals.

As already mentioned, the extent of blood pressure lowering was least marked in the atropinized animals. These findings suggested that preservation of the animal's reaction to administration of enterotoxic filtrates after treatment with autonomic poisons could depend on the ability of the organism to mobilize its compensatory adaptation.

Since the administration of autonomic poisons could be associated with changes in the function of some organs leading to changes in the activity of others, it was decided to stage the experiments under more "pure" conditions, using the classic isolated heart method.

The experiments were performed on hearts isolated by the Kravkov technic. The animals used were adult cats. Following isolation, the heart was perfused for 15-25 minutes with Ringer-Locke solution warmed to 37°. When a stable background of activity was established, the heart was switched to perfusion with staphylococcal enterotoxin filtrates in dilutions of 1:50-1:100. A total of 14 isolated heart experiments was carried out.

It was found that perfusion of the isolated cat heart with a solution of staphylococcal enterotoxin filtrate led to rapid cardiac arrest in diastole. Such arrest occurred in 11 of the 14 experiments, while bradycardia accompanied by diminished strength of cardiac contractions was observed in 2 experiments.

Subsequent washing of the heart with nutrient medium failed to restore its activity in 6 cases and led to transient resumption of activity in 4 cases. No washing was performed in 4 cases (Fig. 2). In 6 of the 7 control experiments the amplitude of cardiac contractions showed some increase under the influence of sterile nutrient medium. The rate of cardiac contractions increased in 5 cases.

The staphylococcal enterotoxin is thus characterized by marked toxicity with respect to the isolated heart, causing its arrest in high dilution in Ringer-Locke solution.

Consequently, the hypotensive action of staphylococcal enterotoxin may be attributed to the depressive effect of the enterotoxin both on the vasomotor centers and the heart muscle.

#### SUMMARY

The effect of staphylococcus enterotoxin on the circulatory apparatus was investigated. Experiments were conducted on cats. It was established that there is a fall in the blood pressure in intravenous injection of staphylococcus enterotoxin. Experiments which were carried out on animals in which atropine, adrenalin and papaverine were previously administered showed that in these conditions enterotoxin, likewise, causes hypotonia.

It was also demonstrated that the isolated heart is arrested in the diastolic phase under the effect of staphylococcus enterotoxin.

The results of these experiments allow us to conclude that the effect of staphylococcus enterotoxin is mostly manifested by way of the elements of the parasympathetic portion of the nervous system.

#### LITERATURE CITED

A. I. Stolmakova. Byull. Eksptl. Biol. i Med., 43, No. 8, 58-62, 1957.\*

\* Original Russian pagination. See C.B. Translation.