

THE INFLUENCE OF THE FUNCTIONAL STATE OF THE
CENTRAL NERVOUS SYSTEM UPON THE PENICILLIN THERAPY OF
EXPERIMENTAL STAPHYLOCOCCIC INFECTIONS

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Experimental investigations devoted to a study of the role played by disturbances of the functional state of the central nervous system in the treatment of infections by antibiotics are still rather few [5, 8].

The present communication is devoted to a comparison and an analysis of the results of penicillin therapy of staphylococcic infections produced experimentally in normal animals and in animals with experimental neurones.

EXPERIMENTAL METHOD

The experiments were conducted on 48 white male rats weighing 100-115 g. All the animals developed conditioned reflexes after the food-shock technique of L.I. Kotliarevskii.

All the animals developed stable stereotypes of the conditioned reflexes (two positive reflex responses to sound and light stimuli and a differentiation to a sound of another strength) and were then divided into four groups of 12 rats each.

Inflammation was produced by introducing into the muscle of the right rear foot pad a 20-hour culture of Staphylococcus aureus (strain No. 75) in a dose of about 2 billion microbes per 200 g weight of animal. The animals of the first group were not injected.

Animals of the second group began receiving penicillin four hours after being infected. The sodium salt of penicillin, dissolved in a 1% solution of pyramidon, was injected into the muscle of the left rear foot pad morning and night for three days. Each dose consisted of 40,000 units so that the total of each course was 200,000* units of the antibiotic.

In animals of the third group the activity of the higher nervous system was severely disrupted. The rats were placed in a special chamber with a floor of metal sheeting. In this chamber the feeding apparatus was set up as in the L.I. Kotliarevskii chamber. At the time of the conditioned stimulus, when the animal would run to the feeder, it would receive a 30-volt shock.

In each experiment there were 5-6 such combinations. At the same time each day the stereotype of the conditioned reflexes was checked. The inflammation in this group of rats was produced after the damage to the activity of the higher nervous system. The rats of the fourth group were infected at the same time as the rats of

*As in original – Publisher's note.

the third group.

The therapy of the third and fourth groups was conducted using ekmonovotsillin,* the scheme of treatment being the same as with penicillin.

The effectiveness of the penicillin therapy was judged by: alterations at the site of injecting the staphylococcus (extent of inflammatory infiltration, extent of inflammatory contracture), by the general condition of the animals and by changes in the state of the conditioned reflex activity. In animals of the third and fourth groups before and during the course of the experimental therapy the phagocytic activity was tested repeatedly by the method of N.V. Puchkov and S.M. Titova. In addition, the blood penicillin concentration was followed (1 hour thirty minutes, 2 hours, 3 hours 30 minutes after commencing therapy). The animals were sacrificed 12-42 days after being infected and after the experiments had been completed.

All the animals were autopsied and both rear foot pads were studied microscopically. The histologic sections were stained with hematoxylin-eosin, by the methods of Van Gieson and Gram-Weigert (for microbes in the tissues).

Beginning with the second day after inoculation, all the animals of the first group developed marked alterations in their conditioned reflex activity, a diffuse cortical inhibition setting in. In rare cases single conditioned reflexes remained. Later, there occurred a temporary and incomplete restoration of the conditioned reflexes with phasic manifestations (leveling and paradoxical phases), lengthening of the latent period and diminution in the vigor of the conditioned reflexes. For the 42 days of the study a full restoration of conditioned reflex activity was not observed. At the same time there was observed an alteration in the general state and behavior of the animals: dyspnea, loss of weight, and torpor. At the site of inoculation of the staphylococcus in the first days inflammatory swelling and infiltration was seen. The extremity swelled to 2-2½ times its usual size. Later, abscesses formed. As a rule, the abscess broke spontaneously 12-30 days after the injection of the staphylococcus. In rats sacrificed 12 days after the beginning of the experiment, pus foci demarcated from the surrounding tissues by a loose capsule of immature connective tissue were noted. In the tissues of the inflammatory foci, staphylococcal accumulations were noted.

In rats of the second group (treated with penicillin), the general and local manifestations were much less evident. Two to three days after the inoculation there was observed only slight induration at the site of the injection. By the 12th day after inoculation, local indurations averaging 0.3 x 0.5 cm were found in only five of the twelve rats. In this period (6-12 days after the beginning of the experiment) all the animals normalized their conditioned reflex activity. In animals sacrificed on the 12th day of the experiment there was seen only residual inflammation in the form of a connective tissue scar which, in some instances, still contained a little pus. Examination of sections of these areas failed to reveal any staphylococci.

In the rats of the third group, 4-7 days after beginning the use of electric shock, there occurred a complete disruption of higher nervous activity. A complete inhibition of all conditioned reflexes and a very considerable alteration in the behavior of the animals were observed. There was a sharp diminution in all reflexes naturally associated with eating, defense and posture. The animals were apathetic, sleepy and untidy. The rats lost much weight. The animals were infected 17 days after development of the described symptoms. A study of conditioned reflex activity showed that the introduction of the staphylococcus against a background of disruption of higher nervous activity (both in the treated and untreated animals) led to profound and long-continued inhibition not only of artificial but also natural conditioned reflexes. In all the animals, in spite of treatment with ekmonovotsillin, the clinical manifestations were very severe. Three rats died within the first day after inoculation. In all the animals the course of the disease was severe. The inflammatory swelling spread to the entire right rear extremity, the groin and the abdomen, and dystrophic manifestations such as loss of hair were noted. In the region of the infection there was widespread tissue necrosis - something that was not observed in the first two groups. The majority of the animals developed staphylococcemia.

In rats of the fourth group, not subjected to the preliminary disruption of higher nervous activity, treatment with ekmonovotsillin produced a rapid clearing of both the local and generalized manifestations of the staphylococcal infection. By the 6-8th day there was normalization of the higher nervous activity of these animals. By this time, the survivors of the third group displayed severe nervous system alterations. These animals

* Transliteration of Russian - Publisher's note.

were sacrificed 12 days after inoculation.

Blood penicillin levels were adequate in the animals of the third and fourth groups: 3.84 units per ml 2 hours after beginning treatment and 0.96 units per ml 3 hours after beginning of treatment.

During therapy with ekmonovotsillin, the leucocytes of the rats in the fourth group displayed a marked rise in their phagocytic capacity. Rats with disruption of higher nervous activity had a depression of leucocytic activity.

Therapy with ekmonovotsillin under such conditions failed to improve phagocytosis; the phagocytic activity remained low in the period of therapy during the subsequent period of observation.

The data obtained demonstrate that staphylococcal inflammation leads to definite depression of conditioned reflex activity.

The results of our experiments correspond with the findings reported in the literature as to the state of nervous activity on the highest levels during staphylococcal intoxication [1, 2, 4]. Early penicillin therapy leads to rapid clinical recovery with normalization of the higher nervous activity. It may be supposed that the success of the therapy depends not only on the direct effect of the penicillin upon the staphylococcus which is sensitive to the antibiotic but also of the influence exerted by the antibiotic upon conditioned reflex activity.

Our previous studies [6] had shown that penicillin injections in normal animals shortened the latent period of the conditioned reflexes and re-enforced the process of stimulation of the central nervous system. U.G. Gasanov [3] showed that injection of penicillin markedly improved the process of internal inhibition.

The material presented above permits us to come to the conclusion that the effectiveness of the penicillin treatment of various foci of infection depends primarily on the state of the central nervous system. The weak effect of penicillin therapy against a background of disruption of higher nervous activity may be presumed to be due to a lowering of the activity of the various defensive immunological mechanisms, the one studied by us being phagocytosis.

SUMMARY

In experiments on rats, it was established that treatment of focal staphylococcal infection by penicillin brings about quick recovery and normalization of higher nervous activity if the latter had no additional disturbance. However, if function of the higher nervous activity was seriously disrupted penicillin therapy of staphylococcal infection was almost ineffective.

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