EXPERIMENTAL DATA ON THE THERAPEUTIC EFFECT OF PARA-AMINO-SALICYLIC ACID (PAS)

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Although PAS is widely used for tubercular diseases, the mechanism of its effect has not been sufficiently studied. More particularly, the question of PAS's effect on the nervous system and the importance of this effect to the mechanism of the preparation's therapeutic action has only been touched upon. With this in mind, we decided to study the effect of PAS on the interoceptive reflexes.

In previous works conducted on healthy cats[6, 7], we established that PAS causes stimulation of the chemoreceptors by indirect contact with them. In the second phase of its action, the preparation causes a reversible functional interruption or a considerable decrease in chemoreceptor excitability. It was also established that PAS injected intramuscularly inhibits reflexes from the chemoreceptors, while increasingthe reflexes from the mechanoreceptors in a majority of experiments.

In this work, we present results obtained in experiments studying the effect of PAS (0.25-1.0 per 1 kg of weight) on reflexes caused by stimulating the chemoreceptors of the small intestine, the receptors of the carotid sinus reflexogenic zone and the bladder mechanoreceptors in animals suffering from tuberculosis.

EXPERIMENTAL METHODS

A total of 19 animals were infected with an emulsion of bovine tuberculosis microbes (K-2 strain). The culture was injected into the femoral vein in a dose of 0.025-0.02 mg per 1 kg of weight.

The animals were used in the experiment 10-25 days after the infection, after which they were subjected to careful pathologico-anatomical examination. Tuberculosis was observed in all of the animals beginning the 14th day after infection, and becoming most strongly expressed on the 20th-25th day after infection.

The arterial pressure and respiratory reflexes from the chemoreceptors of the small intestine were examined under conditions of perfusion of the organ, which was isolated from circulation. We used acetylcholine in a concentration of $1 \cdot 10^{-4}$ (1 ml) or carbon dioxide as a stimulant. The reflexes from the carotid sinus reflexogenic zone were elicited by pressure on the common carotid artery for a period of 15 seconds, and the reflexes from the bladder mechanoreceptors, by air expansion of the bladder walls with a pressure of 80-100 mm of mercury.

EXPERIMENTAL RESULTS

In the majority of experiments conducted, PAS caused the reflexes from the chemoreceptors of the small intestine to decrease by 25-75%. In several experiments, the reflexes from the chemoreceptors became inhibited as soon as 15-20 minutes after the PAS injection (Fig. 1).

The reflexes from the receptors of the carotid sinus reflexogenic zone were completely inhibited. In this series of experiments, as opposed to the experiments on healthy animals, the reflexes from the bladder mechano receptors were also inhibited. Only in 3 out of 11 experiments were the reflexes observed to increase. In 6 experiments, the reflexes decreased (Fig. 2), and, in 2 experiments, the reflex remained practically the same. The PAS injection also inhibited the respiratory reflexes in the majority of experiments.

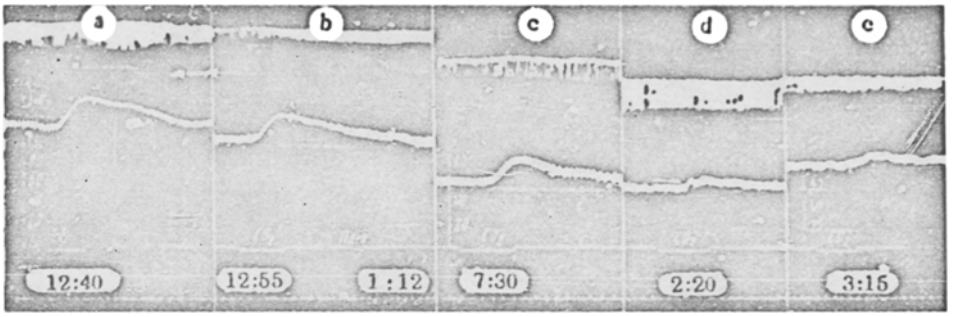

Fig.1. Decrease in reflexes from the chemoreceptors of the small intestine in an animal with tuberculosis after intramuscular injection of PAS (0.5 g per 1 kg of weight).
a, b) initial reflexes; c, d, e) reflexes after PAS injection. Curves from top to bottom signify: respiration, blood pressure, indication of stimulation, indication of time (in 5 second marks).

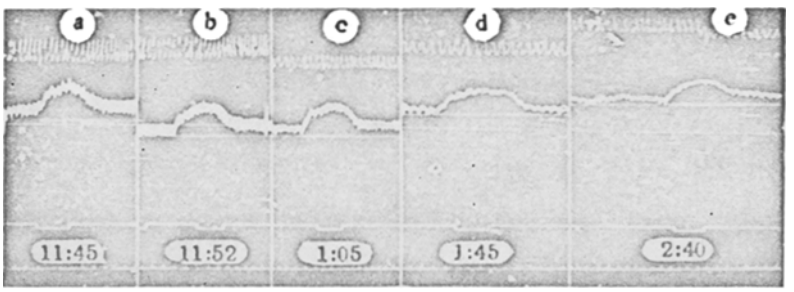

Fig. 2. Decrease in reflexes from bladder mechanoreceptors in an animal with tuberculosis after PAS injection. PAS injected at 12:32 PM.
a, b) initial reflexes; c, d, e) reflexes after PAS injection. Curves mean the same as in Fig. 1.

Having established that PAS, parenterally injected, has a primarily inhibitory effect both in healthy and in tubercular animals on the reflexes from the chemoreceptors, we went on to determine what effect PAS had when inadequate stimulants, causing pathological reactions, were used. We used post-transfusion shock for this study.

It has recently been established [2, 9 and others] that the reflexes from the vascular chemoreceptors, which occur due to the stimulation of these chemoreceptors by heterogeneous blood and by the secondary products resulting from the reaction of the host's blood with the transfused blood, play an important part in the development mechanism of post-transfusion shock.

We caused shock to develop by infusing 10 ml of preserved donor's blood into a femoral vein. The experiments were done on 18 cats. The animals were matched in pairs according to sex and weight and then separated into a control and an experimental group. The animals were intramuscularly injected with PAS in a dose of 0.5-1 g per 1 kg of animal weight 45 minutes to 1 hour, 25 minutes before the experiment.

In all of the control experiments, the infusion of 10 ml of preserved blood into the femoral vein caused

monotypic and rather pronounced disturbances in circulation and respiration. The change in circulation consisted of an abrupt drop of the arterial pressure level, occurring in most cases 20-60 seconds after the foreign blood infusion. In these experiments, arterial pressure fell 39-112 mm, an average of 69 mm of mercury. In the majority of experiments, the lowered blood pressure gradually (over a period of 2-3 or more minutes) returned to the original level.

Respiratory changes were observed simultaneously with the circulatory disturbances. These changes were manifested by a complete inhibition of respiratory movements, interrupted occasionally by single inhalations.

The latent period was 25-60 seconds, and the respiratory movements were inhibited for a period of 20-30 seconds.

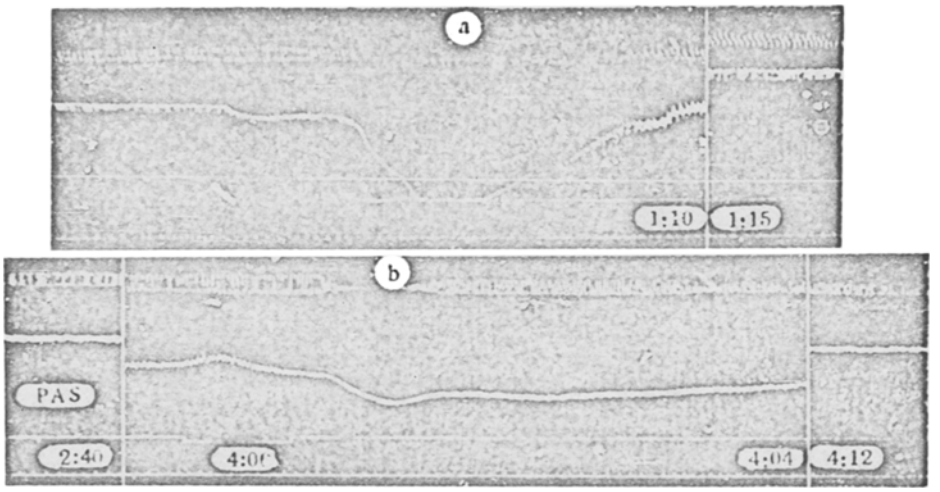

Fig. 3. Effect of PAS on post-transfusion shock.
Results of both the experiment and the control given in the figure: a) control, b) 10 ml of preserved donor's blood infused into the femoral vein 1 hour and 20 minutes after the intramuscular injection of 20 ml of a 10% solution of PAS. The curves are the same as in Fig. 1.

The results obtained from the experiments with the animals given a preliminary injection of PAS 45 minutes to 1 hour and 25 minutes before the transfusion of donor's blood were quite different. Although blood pressure and respiration changes were also observed in these experiments, they were much less expressed than in the control. Arterial pressure decreased less in the experimental animals than in the control animals, which had not been injected with the preparation. In 7 out of 8 experiments, for example, it fell 10-69 mm of mercury, and, in the other experiment, it remained unchanged. In these experiments, arterial pressure fell an average of 46 mm of mercury, or 66.6% of the average arterial pressure fall in the control experiments.

As far as the respiratory reaction was concerned, the complete inhibition of respiration so typical of heterotransfusion shock was absent in 3 out of 8 experiments. Respiration was inhibited in the other 5 experiments, but less than in the control.

Upon comparison of the arterial pressure and respiration reactions caused by the heterogeneous blood transfusion which occurred in the experiment with those which occurred in the control, it is evident that the preliminary injection of PAS reduced the post-transfusion shock in 5 out of 8 experiments (Fig. 3).

From the results of our observations, one can conclude that PAS weakens one phase of post-transfusion shock, which phase may possibly be connected genetically with the participation of the chemoreceptors.

We know from the literature that overstimulation of the interoceptors, and of the chemoreceptors particularly, plays an important role in the development of pathological processes in the body [1, 4, 9 and others]. As has recently been established, in a tuberculosis infection, overstimulation of the chemoreceptors by the activity and decomposition products of the tuberculosis microbacteria as well as by pathological exchange products which form in great quantities at the focus of specific inflammation, is observed [3, 5, 8 and others].

Since PAS inhibits the reflexes from the chemoreceptors, judging from our observations, it must thereby prevent this overstimulation and, therefore, also the appearance of a series of complex reflex phenomena, which are very important to the pathogenesis of the tuberculosis infection and its clinical manifestations.

It is possible that the rapid symptomatic effect obtained from the therapeutic use of PAS in tuberculosis, which usually occurs before positive changes can develop in the anatomical picture of the disease, is due to these established pharmacological properties of PAS.

SUMMARY

Experiments on animals infected with tuberculosis bacilli have shown that parenteral injections of PAS inhibit reflexes from chemoreceptors. The same effect of PAS on interoceptors has been elicited in cases of pathologic reflexes originating from chemoreceptors. The instantaneous symptomatic reaction of tuberculosis patients treated by PAS is possibly due to its inhibitory effect on reflexes from chemoreceptors.

LITERATURE CITED

[1] V. A. Alekseev, Byull. Eksptl. Biol. i Med., 1954, Vol. 38, No. 9, pp 15-18.

[2] P. N. Veselkin, and M. N. Kuznetosovskaya, Sov. Khir., 1934, Vol. 7, No. 2-3, pp.442-446

[3] I. E. Gaber, Summary of the Proceedings at the Scientific Session of the Leningrad Institute for Tuberculosis Research (in Russian), Leningrad, 1955, pp.66-67.

[4] P. P. Goncharov, On Cardiac Tamponade (in Russian), Leningrad, 1936.

[5] F. A. Levtova, in the book: Concerning the Role of the Nervous System in the Pathogenesis and Therapy of Tuberculosis (in Russian), Moscow, 1954, pp.42-50.

[6] N. V. Netudykhata, Summary of the Proceedings at the Scientific Session of the Leningrad Institute for Tuberculosis Research (in Russian), Leningrad, 1955, pp.80-81.

[7] N. V. Netudykhata, Byull. Eksptl. Biol. i Med., 1957, Vol. 44, N . 7, pp.69-73.

[8] K. A. Poletaeva, in the book: Concerning the Role of the Nervous System in the Pathogenesis and Therapy of Tuberculosis (in Russian), Moscow, 1954, p. 60.

[9] I. I. Fedorov, in the book: Pathophysiological Principles of Blood Transfusion (in Russian), Kiev, 1951.