

THE EFFECT OF PARENTERAL ADMINISTRATION OF PAS ON UNCONDITIONED INTEROCEPTIVE REFLEXES

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PAS occupies an extremely important place among chemotherapeutic agents used successfully in the treatment of tuberculosis. The mechanism of its action, however, has as yet been inadequately investigated.

In the course of studies on the pharmacologic properties of PAS we had established [2] that PAS evoked, in the first phase of its action, stimulation of chemoreceptors on direct contact with them while in the second phase of its action it produced reversible functional "extinction" of chemoreceptors.

In the present communications, data are reported concerning the effect of PAS on interoceptive reflexes under conditions of resorptive action of the substance given intramuscularly.

METHODS

Experiments were carried out on cats under urethane anesthesia and also on decerebrate animals (a total of 64 experiments). Blood pressure and respiratory reflexes were studied.

In the first series of experiments, a study was made of the effect of PAS on reflexes from chemoreceptors of a segment of the small intestine humerally isolated and connected with the organism by nerves only.

At the start of an experiment, chemoreceptor reflex reactions to acetylcholine and carbonic acid in the perfused segment of intestine were established. PAS was then given intramuscularly (0.25-1 g per 1 kg body weight), following which reflexes arising on addition of the above-mentioned substances to the perfusate were tested every 15 minutes for an average of $1\frac{1}{2}$ hours.

RESULTS

The experiments showed that parenteral administration of PAS led, in the majority of cases, to diminution of blood pressure reflexes and partly of respiratory ones evoked by stimulation of the chemoreceptors in the perfused segment of small intestine. In a number of experiments the reflexes disappeared completely (Fig. 1). Enhancement of reflexes elicited by stimulation of chemoreceptors was observed only in those experiments in which acetylcholine in high concentration ($1 \cdot 10^{-3}$) was used as stimulus. Of 8 experiments in which acetylcholine in this concentration was used, complete suppression of blood pressure reflex was observed in one; in two, the initial reflex was diminished by 30-25%; and in 5 experiments administration of PAS was followed by increase in reflexes.

Of 13 experiments in which reaction to acetylcholine in concentration of $1 \cdot 10^{-4}$ was studied, in two the reflex disappeared completely; in 5 experiments considerable depression of the reflex was observed (by 32-41.6%). Least marked inhibition of the reflex was seen in 4 experiments (by 38-25.6%), and only in 2 experiments was the reflex enhanced following administration of PAS.

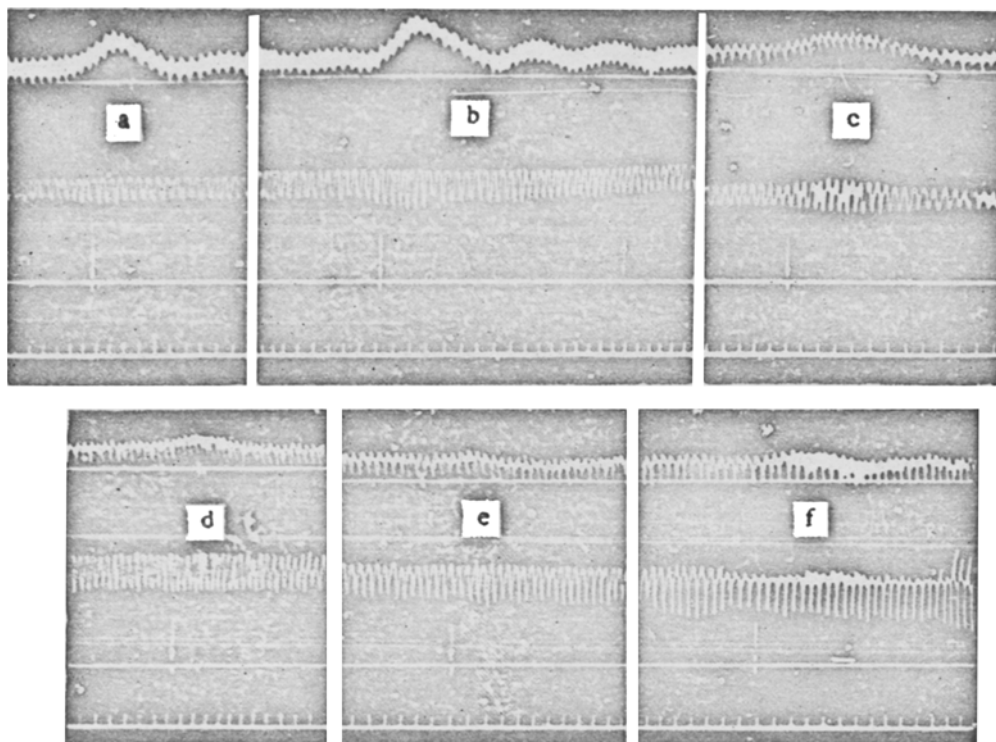


Fig. 1. Effect of intramuscular administration of PAS on reflexes from chemoreceptors in perfused segment of small intestine. a, b) Initial reflexes; c, d, e, f) reflexes after administration of PAS (0.5 g per 1 kg weight). Records from above down: blood pressure, respiration, stimulus marker, time marker (5 seconds). Arrow indicates time of PAS injection.

Of 4 experiments in which carbonic acid was used as chemoreceptor stimulant, in one the blood pressure reflex disappeared altogether; in two it was decreased by more than 50%; and in one — by 42.8%.

Since experimental conditions excluded the possibility of direct action by PAS on the chemoreceptors in the segment of intestine it could be assumed that the preparation, given intramuscularly, affected the central components of the interoceptive reflex arc. An attempt was made to localize more precisely the site of PAS action in the interoceptive reflex arc in the second series of experiments in which urinary bladder mechanoreceptors were subjected to excitation. This was achieved by distention of the bladder with air introduced into it under a pressure of 80-100 mm Hg. PAS was given intramuscularly in the dose of 0.5 g per 1 kg body weight.

The results of these experiments were as follows. PAS in the dose that consistently inhibited reflexes from chemoreceptors in the isolated loop of small intestine did not, as a rule, inhibit reflexes from bladder mechanoreceptors. In 5 out of 12 experiments, enhancement of blood pressure reflex was observed as soon as 15 minutes after injection of PAS. In 4 other experiments, enhancement of the reflex was preceded by its slight decrease over a period of 30 minutes to 1 hour; the reflex then gradually increased, finally exceeding the initial value. In 2 experiments the reflex remained unchanged, and in only one experiment was it diminished.

These experiments indicate that the vasomotor and respiratory centers, and the afferent pathways leading from them to blood vessels and heart, and also to respiratory musculature are not subject to the inhibitory effect of PAS, since otherwise the reflex from urinary bladder mechanoreceptors could not have been realized.

In order to confirm this conclusion, we staged a third series of experiments totalling 12, in which the effect of PAS on unconditioned reflexes arising from chemo- and mechanoreceptors was traced within the same experiment. Reflexes from small intestine chemoreceptors (to acetylcholine in concentration of $1 \cdot 10^{-3}$) and carbonic acid), from urinary bladder mechanoreceptors, and from receptors of the carotid sinus reflexogenic zone were studied at different times before and after injection of PAS. Observations in this series confirmed the findings

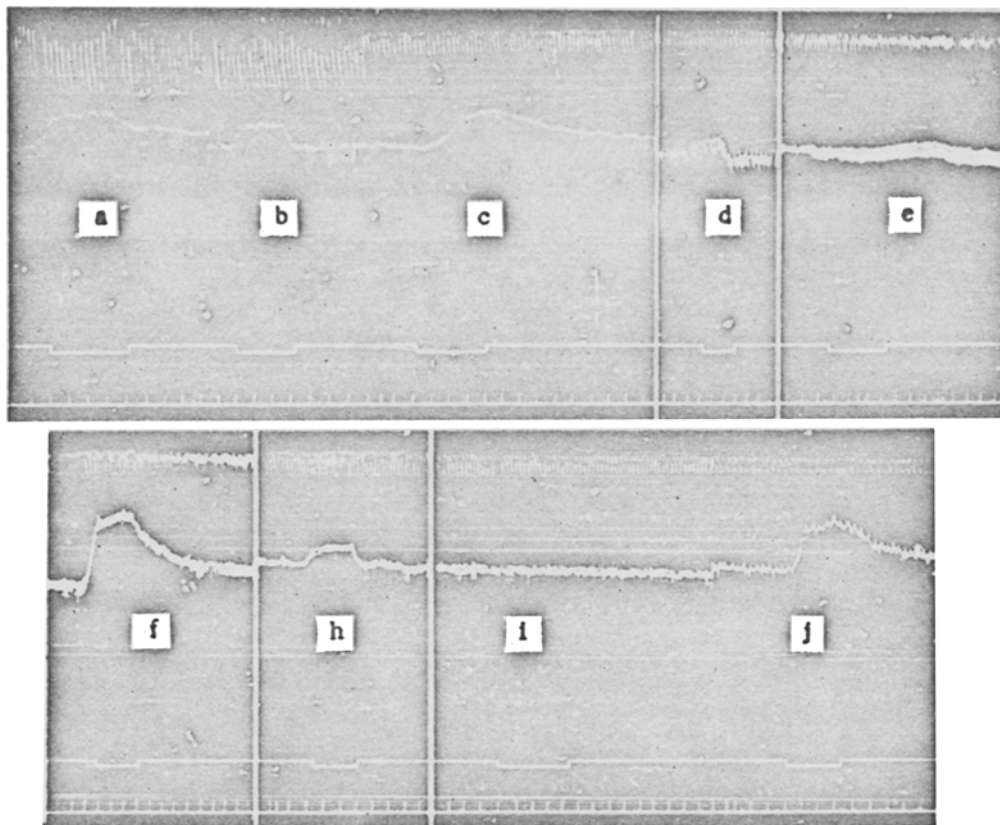


Fig. 2. Effect of PAS on reflexes from small intestine chemoreceptors, carotid sinus receptors and urinary bladder mechanoreceptors. a, b, c) Initial reflexes after injection of PAS (1 g per 1 kg weight); e) diminution; i) complete inhibition of reflexes from small intestine chemoreceptors; d, h) diminution of reflexes from carotid sinus receptors; f, j) enhancement of reflexes from urinary bladder mechanoreceptors. Records same as in Fig. 1.

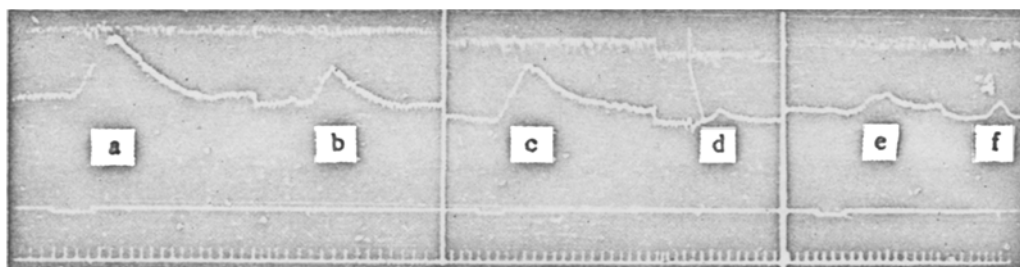


Fig. 3. Effect of PAS on reflexes from small intestine chemoreceptors in decerebrate cat. a, b) Initial reflexes; c, d, e) reflexes after injection of PAS (1 g per 1 kg weight). Records as Fig. 1.

obtained in the first and second series of experiments. Reflexes from the chemoreceptors of the isolated segment of small intestine in most cases were diminished. In 8 experiments, the blood pressure reflex diminished after PAS injection; it increased in 2 experiments.

Of 10 experiments in which reaction to carbonic acid was investigated, the blood pressure reflex disappeared completely in one, was decreased in eight, and slightly increased in one.

At the same time, reflexes from the urinary bladder mechanoreceptors were not only not depressed, but (in most cases) were enhanced. Such enhancement was observed in 7 out of 10 experiments, while slight diminution was seen in 3 experiments.

Reflexes from the carotid sinus zone receptors were, as a rule, inhibited (in this case we were concerned with a complex reflex determined by stimulation of chemo- and baroreceptors in the sinus). In 4 out of 9 experiments, considerable inhibition of the blood pressure reflex was noted; less marked inhibition occurred in 5 experiments. These data are presented in Fig. 2.

It was therefore established that PAS exerted different effects on various types of interoceptive reflexes. This was expressed in the fact that PAS predominantly inhibited reflexes which arose as the result of chemoreceptor stimulation.

The fourth series of experiments was concerned with attempts to localize more precisely the action of PAS in the efferent portion of the reflex arc, and consisted of studies on the effect of this preparation on reactions elicited by direct electric stimulation of the peripheral part of the vagus, transected in the neck, and the peripheral part of the splanchnic nerve. These experiments revealed that PAS inhibited, to some extent, transmission of excitation from the vagus to the heart. The preparation did not, however, exert any consistent effect on the peripheral part of the reflex arc innervating abdominal blood vessels and the adrenal gland.

These data on the distinctive features of the PAS effect on interoceptive reflexes obtained on parenteral administration of the preparation suggested the importance of determining in what part of the central nervous system was the blocking action of PAS on reflexes from chemoreceptors effected. With this aim in view, we undertook a fifth series of experiments, in which the influence of PAS on reflexes from chemo- and mechanoreceptors was studied on 9 decerebrate animals. It was found that in experiments without anesthesia but with transection at the collicular level, PAS (0.25-1 g per 1 kg body weight) given intramuscularly, in the majority of cases inhibited the reflexes (Fig. 3). In 5 experiments in which carbonic acid was used as chemoreceptor stimulant, the blood pressure reflex was diminished in four, and enhanced in one. Stimulation of the chemoreceptors by acetylcholine was performed in 7 experiments, in six of which administration of PAS led to diminution of the reflex, and in one of which the reflex was enhanced. Under similar experimental conditions, the reflexes arising from stimulation of the urinary bladder mechanoreceptors were not inhibited by administration of PAS.

Consequently, the predominantly inhibitory effect of PAS on reflexes elicited by stimulation of chemoreceptors can be realized in decerebrate animals also.

Results of the experiments on the action of intramuscular PAS on interoceptive reflexes lead to the conclusion that the selective inhibitory effect of this preparation on reflexes from chemoreceptors is achieved by direct action of PAS on the central elements of the chemoreceptive reflex arc. The preparation can be said to exert its action by predominant inhibition of the conducting part of the internal chemical analyzer.

SUMMARY

Studies of the effect of PAS on interoceptive reflexes have shown that intramuscular injections of PAS inhibit mostly reflexes elicited by stimulation of chemoreceptors. On the other hand, reflexes from mechanoreceptors were mostly enhanced. The inhibiting effect of PAS on chemoreceptors may also be elicited in the decerebrate animal.

LITERATURE CITED

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* In Russian.