THE USE OF CYSTEINE TO NORMALIZE INTEROCEPTIVE REFLEXES ALTERED BY THE ACTION OF TOXIC SUBSTANCES OF ASCARIDES*

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny
Vol. 49, No. 5, pp. 83-86, May, 1960
Original article submitted May 18, 1959

In articles published earlier [1, 2, 3], we showed that the action of toxic substances of ascarides on the intestinal chemoreceptors causes change in the excitability of the afferent nerve endings. As a result, the vascular and respiratory reflexes from these receptors in response to the customary stimuli (acid, alkali, acetylcholine) are replaced by biphasic pressor-depressor, or solely depressor, reactions on the part of the blood pressure and by inhibition on the part of the respiration. The changes in the reflexes were rather stable; prolonged perfusion with Locke-Ringer's solution for more than two hours did not restore the normal reactions.

We set ourselves the task of finding agents which would normalize reflexes disturbed under conditions of ascariasis. On the basis of the literary data and on the material from our own investigations, cysteine was used under different experimental conditions for this purpose. The experimental results are presented in this article.

EXPERIMENTAL METHOD

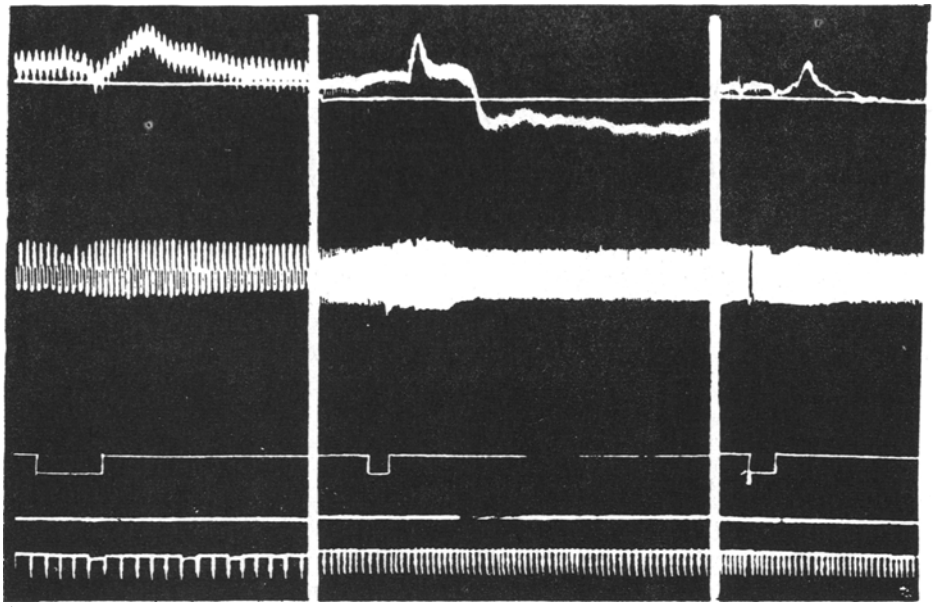
The experiments were performed on cats under intravenous urethan anesthesia (a total of 49 experiments were performed). We studied the vascular and respiratory reflexes from the chemoreceptors of a humorally isolated intestine before and after the action of ascarides toxic substances and then after the use of a solution of cysteine. We used acetic acid (0.5-1 ml of a 1% solution), sodium bicarbonate (1-2 ml of a 1.5 % solution) and acetylcholine (0.5-1 ml of a $1 \cdot 10^{-4}$ solution) to stimulate the receptors. As material containing toxic substances of the ascaris, we used water extracts of Ascaris suum, prepared according to E. N. Pavlovskii's method, in part of the experiments and the products of the vital activity of Ascaris suum, obtained by the usual method, in the rest of the experiments. We took into account the fact that the water extracts of the parasites and their metabolites produced in vitro which we used in the experiments were not in themselves equivalent to the helminthotoxins. However, the extracts are assumed to correspond to a specific degree to the endotoxins released in the intestine of the host upon its digestion of the parasite's body, while the products of their vital activity in vitro are assumed to correspond to the exotoxins of the helminths. V. N. Chernigovskii's well-known method was used to isolate the small intestine.

EXPERIMENTAL RESULTS

Since ascarides are usually localized in the small intestine, in the first series of experiments, we introduced the material containing the toxic substances of the parasites into the lumen of the isolated intestine. Under the influence of the helminthotoxins, the reflexes ordinarily elicited by our experimental stimulants (acid, alkali, acetylcholine), i.e., increased arterial pressure and respiratory stimulation, were supplanted by biphasic pressor-depressor or solely depressor blood pressure reactions, and , often, by respiratory inhibition . It should be mentioned that the larger doses of the toxic material caused the greatest changes in chemoreception. We had previously [1] established thar prolonged perfusion with a Locke-Ringer's solution for over two hours does not restore the normal reflexes. To normalize chemoreception in these experiments, we used a solution of cysteine, which we introduced into the vascular system of the isolated intestine through the perfusion course 40-60 min after the administration of the helminthotoxins. It was found that cysteine restored the normal vascular and respiratory reflexes in a large majority of cases.

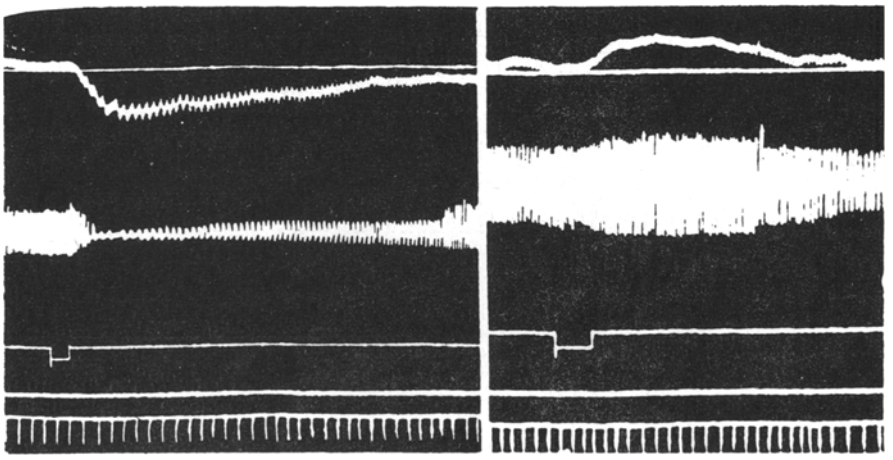
It is known that interoception can be studied by another method, in which the active principle is supplied to the nerve endings through the vascular system of a humorally isolated organ. The reactions observed with the use of this method should be regarded as the sum total of the reactions from the vascular receptors and the tissue elements of the actual organs. Another experimental series was performed according to this method: The ascarides toxic material was introduced into the vessels of the isolated intestine, and chemoreception was examined before and after the action of the helmin-

* Presented at the meeting of the Visiting Session of the Department of Sciences of the Academy of Sciences of the Byelorussian Soviet Republic, December, 1958 (Vitebsk).



a b c

Fig. 1. Vascular and respiratory reflexes from intestinal chemoreceptors to 1 ml of a 2% $NaHCO_3$ solution before (a) and after (b) the influence of ascarides toxic substances and after the use of cysteine (c). Experiment Dec. 14, 1957. Curves show (from top to bottom): blood pressure (mercury manometer); original blood pressure level; respiration; indication of stimulation; zero level of manometer; time (in 5 sec marks).



a b

Fig. 2. Vascular and respiratory reflexes from the intestinal chemoreceptors of a cat to 1.5 ml of a 1.5% $NaHCO_3$ solution with natural ascariasis (a) and after the use of cysteine (b). Experiment Jan. 13, 1959. Curves the same as in Fig. 1.

thotoxins and the use of cysteine. The results of these experiments were essentially the same as those of the first series of experiments. In the second series, as in the first, the character of the vascular and respiratory reflexes changed under the influence of the helminthotoxins. Normalization of the reactions by cysteine succeeded to the same degree.

Analysis of all the experimental results shows that, regardless of the type of toxic material used (extract or products of the vital activity), the contact of the intestinal chemoreceptors with these ascarides toxic products was attended by the disturbance of chemoreception and the distortion of the vascular and respiratory reflexes to the usual stimulants. The use of cysteine, however,

Vascular and Respiratory Reflexes from Intestinal Chemoreceptors before and after the Influence of Ascarides Toxic Substances and then after the Use of Cysteine

Expt. date	Experimental conditions	Time (in hours and minutes)	Stimulant and dose	Change in arterial pressure*(in millimeters of mercury)	Reaction duration (in seconds)	Change in respiration
Dec. 14, 1957	Before administration of ascarides toxic material	11.57	1 ml of 2% $NaHCO_3$ solution	+ 14	45	Mild stimulation
	After administration of ascarides toxic material	12.59	The same	+ 14; − 14	290	Mild inhibition
	After administration of cysteine . . .	13.50	The same	+ 12	40	Mild stimulation
Sept. 19, 1958	Before administration of ascarides toxic material	11.23	1 ml of 1% acetic acid solution	+ 4	20	None
	After administration of ascarides toxic material	12.25	The same	+ 10; − 2	37	None
		12.29	The same	+ 4 ; − 2	155	None
		12.59	The same	+6 ; −6	145	None
	After administration of cysteine	13.07	The same	+ 2	15	None
Sept. 19, 1958	Before administration of ascarides toxic material	11.59	1 ml of $1\ 10^{-4}$ acetyl-choline	+8	110	Mild stimulation
	After administration of ascarides toxic material	12.49	The same	+ 14; − 36	295	Stimulation—acute inhibition
	After administration of cysteine	13.21	The same	+ 5	40	Mild stimulation
Jan. 20, 1959	With natural ascariasis	11.40	1 ml of $1 \cdot 10^{-4}$ acetyl-choline	+ 2; − 30	Not restored after 20 minutes	None
	After administration of cysteine	12.52	The same	− 3	50	Mild stimulation
		13.39	The same	+ 3	25	Inhibition

* Plus = rise, minus = fall of arterial pressure.

caused the stable normalization of chemoreception disturbed under the influence of experimental ascariasis. One can therefore propose that blockade by the toxins of the sulfhydryl groups of the active protein complexes, or enzymes, plays an essential role in the action mechanism of ascarides toxic substances. This process is reversible; saturation by substances rich in SH groups (cysteine) effects the restoration of the former reflexes, i.e., normalizes the reflexes (Fig. 1).

Our experiments studying chermoreception under conditions of natural ascariasis were of particular interest. During the acute experiments with humoral isolation of the small intestine, we occasionally discovered natural ascariasis in the cats. This material was of course extremely useful to our research. First of all, we established that, with pronounced ascariasis, chemoreception was altered in a way similar to that which we observed with experimental ascariasis intoxication, i.e. the vascular and respiratory reflexes from the chemoreceptors of the isolated intestine in response to the customary stimulants (acid, alkali and acetylcholine) were distorted, the reactions of the arterial blood pressure becoming pressor-depressor or solely depressor and the respiration usually becoming inhibited. After establishing these changes in chemoreception, we used the cysteine solution to normalize the reflexes. The experiments showed that chemoreception altered under the influence of natural ascariasis can be normalized with the aid of cysteine (Fig. 2). The results of the experiments examining chemoreception in cats with natural ascariasis confirmed the changes we established in the character and duration of interoceptive reflexes under the influence of ascarides toxic substances. The theory that blockade by these toxins of the sulfhydryl groups plays an important part in the action mechanism of ascarotoxins was also confirmed.

The data from 4 experiments are included by way of illustration (see table).

Therefore, the changes in chemoreception caused by ascariasis are evidently connected with biochemical shifts in the receptor field which occur under these conditions. This was also indicated to a certain degree by the change we established in special investigations (14 experiments) in the pH of the perfusate flowing out of the vein of the intestine after the action of the ascarides toxic substances. In these experiments, we usually observed the concentration of hydrogen ions in the perfusate to increase considerably, up to as much as pH = 0.46; in the control experiments, however, the maximal change in the pH during the experiment was 0.06.

Our next project was to determine whether cysteine had a detoxicating effect under conditions of general ascariasis. We conducted acute experiments with the use of cysteine under conditions of experimental ascariasis induced by administering the toxic material into a non-isolated intestine or into the animal's general blood stream. These investigations established that intravenous injections of the cysteine solution decreased or completely prevented disturbances in circulation and respiration caused by the action of ascarides toxic substances. These investigations will be continued under conditions of chronic experiments.

SUMMARY

In acute experiments on cats under urethane anesthesia the author studied the change of the vascular and respiratory reflexes from the chemoceptors of a humorally isolated intestine following the action of ascarides toxic substances (Ascaris suum water extracts or the metabolites of these parasites produced in vitro), as well as the normalizing effect of cysteine. As established, the vascular and respiratory reflexes, altered as a result of the toxic products of ascarides, become normalized after the administration of cysteine. In the presence of marked ascariasis in cats, the interoceptive reflexes from the chemoceptors of the isolated intestine are similarly changed; cysteine administration also normalizes the reflexes in natural Ascaris infestation.

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† Original Russian pagination. See C. B. translation.