MECHANISM OF CHANGES IN VASCULAR CHEMORECEPTORS ON ADAPTATION OF REFLEXES

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 51,
No. 1, pp. 8-13, January, 1961
Original article submitted January 4, 1960

Research on the nature of reflex reactions with change in receptor metabolism is attracting the interest of investigators as a possible way of revealing the mechanisms of reception and the nature of the processes underlying excitation. This accounts for the attention being devoted to these investigations by several leading schools of physiology (V. N. Chernigovskii and colleagues, C. F. Anichkov and colleagues, Heymans and colleagues).

An important result of studies in this direction has been the demonstration of the relation between reception and the course of carbohydrate-phosphorus metabolism, oxidation–reduction processes, and the activity of sulfhydryl groups in sensitive nerve endings. Attention has been centered particularly on the changes in metabolism of the chemoreceptors under the action of acetylcholine and cyanide compounds, i.e., the two most universal stimuli of vascular receptors [1-11, 14].

A study of the mechanism of the changes occurring in the receptors in the case of prolonged action of stimuli and adaptation of reflexes is of considerable interest. The value of such an approach becomes clear when we consider that, firstly, prolonged action of a stimulus on a vessel wall occurs very often in natural conditions of existence of the organism; secondly, changes in the receptor metabolism occurring on excitation can be more easily detected with prolonged action of stimuli; and, thirdly, a study of the restoration of the function of receptors after their adaptation can bring us nearer to discovering the main metabolic link of their excitation.

Experimental Method

The experiments were conducted on 24 rabbits and 12 cats under chloral hydrate or urethane narcosis. We registered the changes in blood pressure (mercury and membrane manometers) and respiration (Marey's capsule connected to tracheal cannula) following stimulation of the vascular chemoreceptors in the isolated rabbit ear, in a loop of the small intestine, and in the carotid sinus of the rabbit and cat. The vessels of these regions were perfused with Ringer-Locke solution under pressure and at constant temperature. The pressure in the perfusion system was below the threshold of excitability of the vascular baroreceptors.

For exciting or depressing the activity of the chemoreceptors, we added the following substances to the Ringer-Locke solution without altering the pressure in the perfusion system: acetylcholine ($1 \cdot 10^{-5}$ to $1 \cdot 10^{-4}$ – 32 experiments), adrenalin ($1 \cdot 10^{-6}$ – 24 experiments), cysteine ($1 \cdot 10^{-4}$ – 21 experiments), ATP ($1 \cdot 10^{-4}$ – 12 experiments), sodium fluoride ($6.6 \cdot 10^{-3}$ – 14 experiments), cadmium chloride ($2 \cdot 10^{-4}$ – 18 experiments), and proserine (neostigmine) ($1 \cdot 10^{-5}$ to $1 \cdot 10^{-6}$ – 6 experiments).

*Deceased.

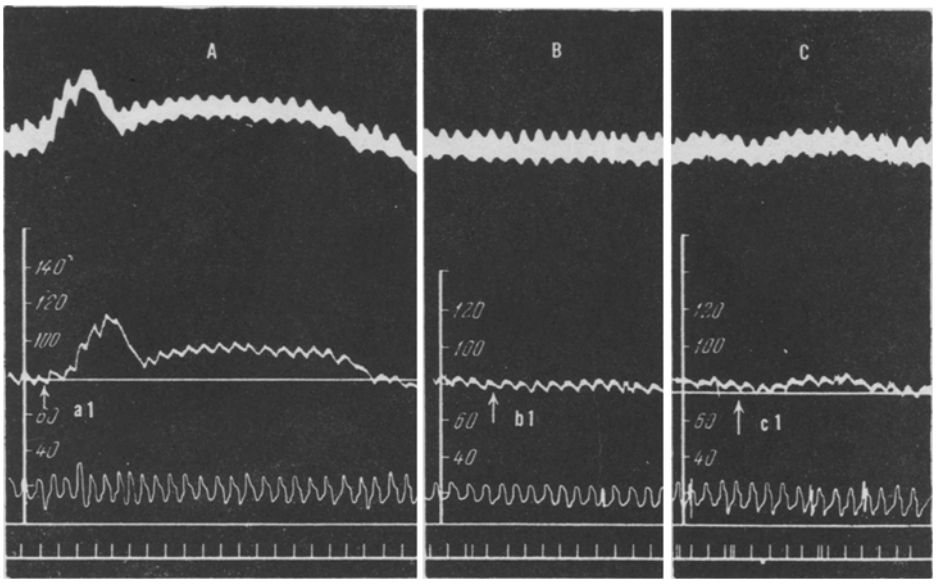

Fig. 1. Effect of cadmium chloride on degree and time of adaptation of reflexes in stimulation of cat carotid sinus receptors by acetylcholine. Meaning of curves (top to bottom): pressure in common carotid artery (membrane manometer); the same (mercury manometer); initial pressure level; respiration trace; zero line; time marks (5 sec): a) change in blood pressure on perfusion with acetycholine ($1 \cdot 10^{-4}$); b) the same on perfusion with calcium chloride solution ($2 \cdot 10^{-4}$); c) the same on repeat perfusion with acetylcholine ($1 \cdot 10^{-4}$). Arrows indicate start of action of stimulus. a1) Acetylcholine $1 \cdot 10^{-4}$; b1) $CaCl_2$ $2 \cdot 10^{-4}$; c1) acetylcholine $1 \cdot 10^{-4}$.

Experimental Results

When the vascular region of the isolated rabbit ear (18 experiments), the vessels of an isolated loop of the small intestine and of the carotid sinus of the rabbit (24 experiments), and cat (12 experiments) were perfused with acetylcholine ($1 \cdot 10^{-4}$), and adrenaline ($1 \cdot 10^{-6}$) solutions we noted reflex changes in the blood pressure and in the rhythm and depth of respiration. With prolonged action of these stimuli, despite the continuing perfusion, a restoration of the initial level of blood pressure and respiration was recorded – adaptation of the reflexes occurred. A fundamentally similar effect was observed by M. L. Belen'kii [6] on perfusion of the carotid sinus by potassium cyanide solutions.

It should be noted that the changes in blood pressure on stimulation of the chemoreceptors of different vascular regions were not of the same nature. For instance, on stimulation of the vascular receptors of the intestine and carotid sinus with acetylcholine, we observed a pressor reaction, while on stimulation of the receptors of the ear vessels we often observed a fall in blood pressure.

A prior perfusion of the vascular regions with a solution of cadmium chloride which, as we know, binds sulfhydryl groups, led either to a complete disappearance of the reflexes when the receptors were stimulated by acetylcholine or adrenalin, or to a pronounced reduction in the time of adaptation of these reflexes (Fig. 1).

The time for adaptation of the reflexes in the case of acetylcholine and adrenalin changed when the carbohydrate-phosphorus metabolism was destroyed by the introduction of sodium fluoride ($6.6 \cdot 10^{-3}$). We should note that sodium fluoride had a different effect on adaptation of reflexes induced by different stimuli: the reflexes due to adrenalin (8 experiments) were first to disappear, then those due to acetylcholine, and, last of all, those due to stimulation of the vascular mechanoreceptors. Within a definite period of action of sodium fluoride acetylcholine still caused a response, but adaptation very soon set in (5 experiments).

The time for adaptation of the reflexes on stimulation by acetylcholine varied considerably when cysteine ($1 \cdot 10^{-4}$), a donor of sulfhydryl groups, was added to the perfusate. In this case, the time for adaptation of the reflex in 12 out of 18 experiments was $1\frac{1}{2}$-2 times longer than usual. We should point out that cysteine itself did not cause any appreciable change in blood pressure or respiration.

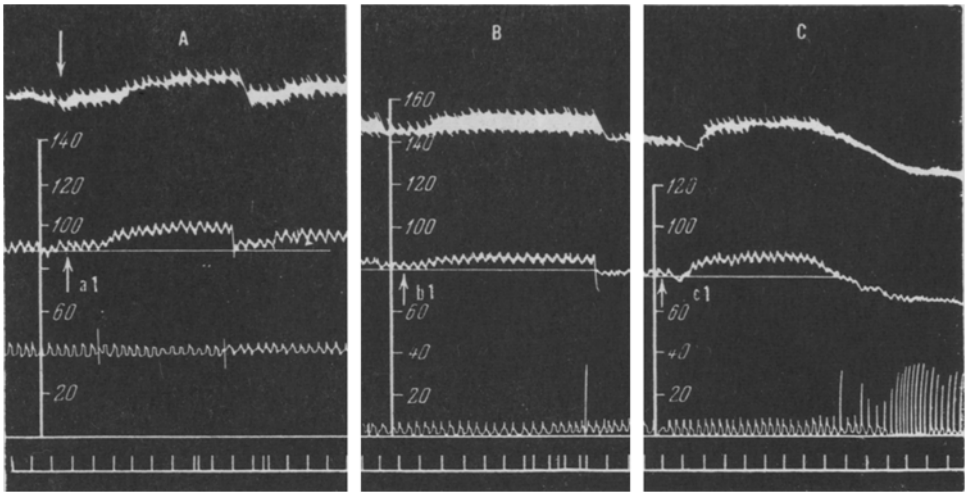

Fig. 2. Effect of ATP and cysteine on restoration of reaction after adaptation of reflex following prolonged action of acetylcholine on vascular chemoreceptors of small intestine of cat. Meaning of curves (top to bottom): pressure in common carotid artery (membrane manometer); the same (mercury manometer); initial pressure levels; respiration trace; zero line; time marks (5 sec); a) action of acetylcholine; b) action of acetylcholine after previous perfusion of vessels with ATP ($1 \cdot 10^{-4}$); c) action of acetylcholine after previous perfusion of vessels with cysteine ($1 \cdot 10^{-4}$). Arrows indicate start of action of stimulus. a1, b1, c1) Acetylcholine, $1 \cdot 10^{-4}$.

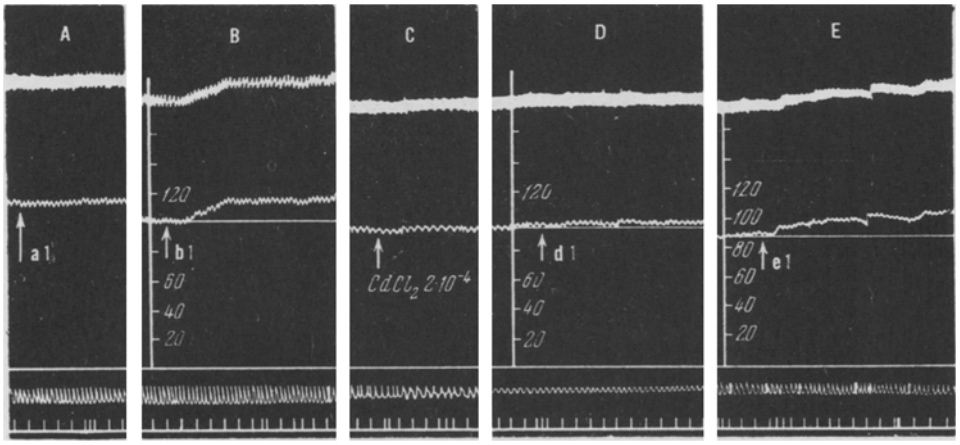

Fig. 3. Restorative effect of cysteine on reflex reaction following stimulation of vascular chemoreceptors of small intestine of cat by adrenalin. Meaning of curves (top to bottom): pressure in common carotid artery (membrane manometer); the same (mercury manometer); initial pressure level (b, d, and e); zero line; respiracion trace; time marks (5 sec): a) action of cysteine ($1 \cdot 10^{-4}$); b) action of adrenalin ($1 \cdot 10^{-6}$); c) action of cadmium chloride ($2 \cdot 10^{-4}$); d) action of adrenalin ($1 \cdot 10^{-6}$) after cadmium chloride; e) action of cysteine ($1 \cdot 10^{-4}$). Arrows denote start of action of stimulus. a1, e1) Cysteine, $1 \cdot 10^{-4}$; b1, d1) adrenalin, $1 \cdot 10^{-6}$.

In a considerable number of experiments, after the attainment of adaptation of the reflexes due to acetylcholine and adrenalin, we added to the perfusate substances selectively activating different sides of the metabolism in the sensitive nerve endings. We found that we could again evoke the corresponding reflex reaction by interfering with the metabolism in the receptors. This restorative effect was manifested in varying degree in the stimulation of different receptive fields, and was least expressed in the case of stimulation of the carotid sinus receptors.

Different substances possessed a different restorative effect on the vascular receptors. After adaptation of the reflexes due to acetylcholine, a brief perfusion of the vascular region with ATP or cysteine restored the initial reaction to acetylcholine. The restorative effect of cysteine, however, was much greater (Fig. 2).

In these experiments, acetylcholine was again added to the perfusion liquid 1-1½ min after the action of cysteine or ATP. In control experiments, there was no restoration of the reflexes due to acetylcholine during this time. On stimulation of the receptors by adrenalin, the restorative effect following the action of ATP was more pronounced. The restorative effect of ATP after adaptation of the reflexes due to acetylcholine was considerably enhanced in the case of a previous perfusion with acetylcholine and cysteine simultaneously. For instance, addition of ATP to the perfusion liquid in seven experiments on vessels of the cat intestine after adaptation of the reflex due to acetylcholine led to a 20-55% restoration of the reaction, judging from the change in blood pressure. The addition of ATP after adaptation of the reflexes following perfusion with acetylcholine and cysteine simultaneously led to a 40-80% restoration of the reaction.

In several cases, the introduction of cysteine after adaptation of the reflexes due to acetylcholine and adrenalin, or after removal of the effect by cadmium chloride produced the effect characteristic of adrenalin or acetylcholine. In other words, cysteine appeared to repeat the effect of the previously acting stimulus (i.e., acetylcholine or adrenalin).

As the curve shows (Fig. 3), the passage of cysteine through the vessels of the small intestine produced no change in the blood pressure or respiration (Fig. 3a). Perfusion with adrenalin led to a pronounced pressor effect (Fig. 3b), and cadmium chloride removed the effect of adrenalin (Figs. 3c,d). Subsequent perfusion with cysteine again produced a pressor effect (Fig. 3e).

The addition of a mixture of acetylcholine and proserine to the perfusion liquid did not significantly alter the time of adaptation of the reflexes.

The most general result of our investigation is the conclusion that significant changes occur in the metabolism of vascular receptors on adaptation of the reflexes. When the action of the stimuli is prolonged, changes occur in the carbohydrate phosphorus metabolism, the metabolism of sulfhydryl compounds, in the sensitive nerve endings. The decisive role of these metabolic processes in maintaining prolonged excitation is indicated by the pronounced reduction in the time of adaptation after the action of cadmium chloride or sodium fluoride on the receptors. The energy potential of the carbohydrate-phosphorus metabolism is obviously of particular importance for maintaining prolonged excitation.

An interesting approach toward an understanding of the nature of metabolic transformations in the adaptation of reflexes is revealed by attempts to restore the initial magnitude of the responses by directed interference with the receptor metabolism.

The adaptation of reflexes on prolonged action of acetylcholine cannot be attributed to inactivation of acetylcholine, by the action of cholinesterase, for instance. This was indicated by the experiments in which proserine was added to the perfusion liquid without altering the course of adaptation of the reflexes. Cysteine had a considerable restorative action, sometimes more pronounced than that of ATP. It is obvious that the individual links of the complex chain of metabolic transformations causing excitation in the receptors are unequally affected on adaptation. First of all, there is a reduction in the activity of sulfhydryl enzymes, which play an important role, particularly in processes of carbohydrate-phosphorus metabolism.

The change in the activity of this link "guards," as it were, against the exhaustion of the energy potentials of the nerve elements, their high-energy phosphorus compounds. We showed that, if prolonged excitation of receptors is maintained in conditions where the activity of sulfhydryl compounds is not reduced (simultaneous perfusion with acetylcholine and cysteine), the subsequent links of metabolism assume decisive importance in adaptation. In these cases, the restorative effect of ATP is more pronounced. We should point out that, in the case of adaptation of reflexes on perfusion with an adrenalin solution, such a sequence could not be detected.

In subsequent investigations, it will be important to discover the role of relations between the changes in the individual links of the reflex arc for the development of adaptation of reflexes. The changes occurring in the nerve centers [12,14], effectors, and receptors on adaptation of reflexes indicate the extreme complexity and variety of mechanisms governing the phenomenon under investigation.

SUMMARY

The authors studied the changes in the arterial blood pressure and respiration occurring on perfusion of the vessels of the rabbit ear, and of the small intestine and carotid sinus in cat and rabbit with acetylcholine and adrenalin solutions. Administration of cadmium chloride and sodium fluoride has markedly reduced the time of adaptation of these reflexes. The reflex reaction after its adaptation was restored, in a number of cases, by the addition of cysteine and adenosine triphosphate to the perfusate. This effect of cysteine was more pronounced after the adaptation of the reflexes to acetylcholine. The changes occurring in various metabolic links in the receptors during reflex adaptation are discussed.

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