THE INFLUENCE OF INHIBITORS OF THE GLYCOLYTIC CYCLE AND THE C_3 ACID CYCLE ON THE CHEMICAL SENSITIVITY OF THE CAROTID SINUS AND INTESTINAL REFLEXOGENIC ZONES

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It may now be considered established that the mechanism of chemoreception in the carotid sinus and intestinal reflexogenic zones is closely connected with the carbohydrate metabolism in the tissue of the receptors [1, 2, 4, 5, 6]. However, the role of the C_3 acid cycle in the mechanisms of chemoreception has not yet been explained. It was shown in a previous communication [3] that disturbance of the glycolytic cycle by sodium fluoride, or of the C_3 acid cycle by hydroxylamine leads to a decrease in the sensitivity of the intestinal receptors to acetylcholine. The depressing action of sodium fluoride on reflexes caused by acetylcholine may be abolished by the addition to the perfusate of the end product of glycolysis, namely pyruvic acid, but the depressing action of hydroxylamine is not abolished by this acid. In this connection it has been postulated that the role of the various links in the chain of tissue metabolism in the mechanisms of chemical stimulation of the intestinal receptors is not identical, and that in fact the C_3 acid cycle is more closely connected with the mechanism of reception of acetylcholine than is the glycolytic cycle.

It was considered of interest to investigate whether similar relationships also applied to the chemical stimulation of the receptors of the carotid sinus reflexogenic zone.

EXPERIMENTAL METHOD

In 29 cats under urethane anesthesia the isolated carotid sinus was perfused with oxygenated Ringer-Locke's solution. All vessels leading from the carotid bifurcation were ligated with the exception of the external and common carotid arteries into which were inserted efferent and afferent cannulas, and the carotid sinus nerve was preserved intact. As stimulus we used acetylcholine in a dilution of 10^{-4} g/ml, which was injected into the perfusion fluid with a syringe in a volume of 0.5 ml. The reflex changes in arterial pressure and respiration were recorded by the usual methods.

It must be pointed out that when the receptors of the carotid sinus were exposed to the action of acetylcholine, besides a deepening of respiration we often observed an increase in the arterial pressure in some experiments and a decrease in others. Since a control injection of 0.5 ml of Ringer-Locke's solution did not cause such a fall in the blood pressure, the depression caused by the acetylcholine could not be associated with the increased pressure within the sinus itself as a result of injection of the acetylcholine solution. It must also be mentioned that after division of the carotid sinus nerve, acetylcholine in the same dose did not cause changes in the respiration and blood pressure, which undoubtedly suggests that the depressor reaction was reflex in nature.

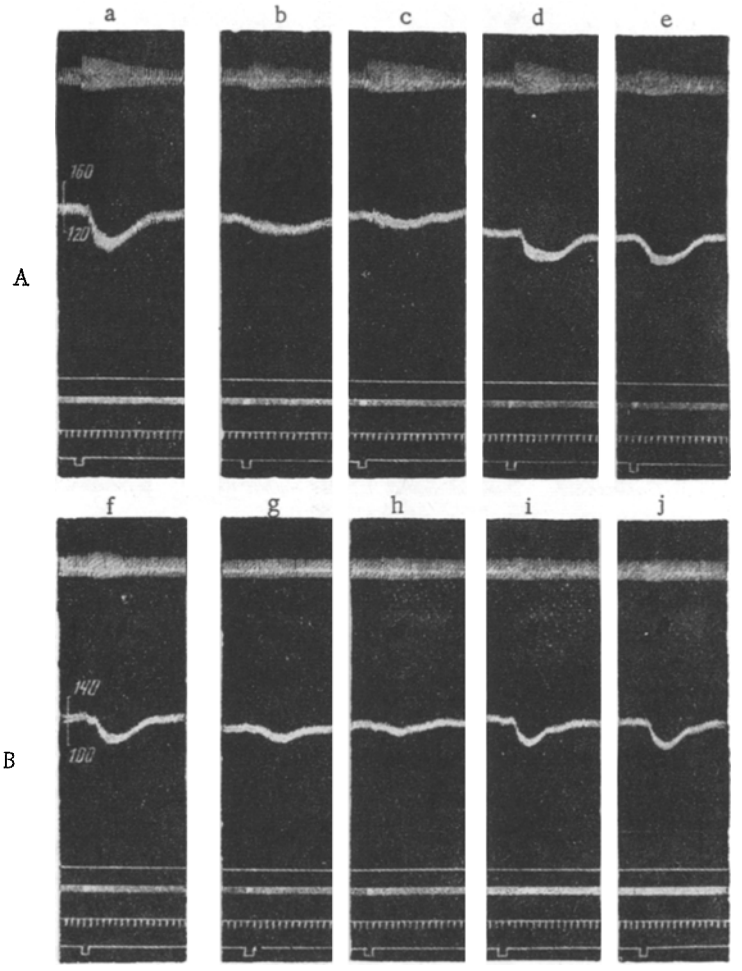

Fig. 1. Reaction of the circulation and respiration to stimulation of the carotid sinus receptors of a cat with acetylcholine (0.5 ml, 10^{-4} g/ml). A) Perfusion of the carotid sinus with Ringer-Locke's solution without sodium pyruvate. Reflex to actylcholine: a) 5 minutes before injection of sodium fluoride; b, c, d, e) 5, 15, 40 and 50 minutes after injection of sodium fluoride into perfusion fluid (1 ml 10^{-2} g/ml). B) Perfusion of carotid sinus with Ringer-Locke's solution containing sodium pyruvate in a concentration of 10^{-4} g/ml. Reflex to acetylcholine: f) 5 minutes before injection of sodium fluoride; g, h, i, j) 5, 15, 40 and 50 minutes after injection of sodium fluoride (1 ml 10^{-2} g/ml). Significance of curves (from above down): respiration; arterial pressure; zero line; velocity of perfusion; time marker (5 seconds); stimulation marker.

EXPERIMENTAL RESULTS

Identical results were obtained in eight experiments, as shown in Fig. 1.

It will be seen from Fig. 1, a-e that the reflexes to acetylcholine were at first depressed by the action of sodium fluoride, and were subsequently restored 40-50 minutes after injection of sodium fluoride. After the reflexes had been restored the carotid sinus was perfused with Ringer-Locke's solution containing the sodium salt of pyruvic acid in a concentration of 10^{-4} g/ml. Against this background sodium fluoride was again injected, and at various intervals of time after the injection the magnitude of the reflexes was determined. It is clear from Fig. 1, f-j that the respiratory reflex was not restored at all under these conditions, but the depressor reflex was restored after the same period of time as in the absence of pyruvic acid.

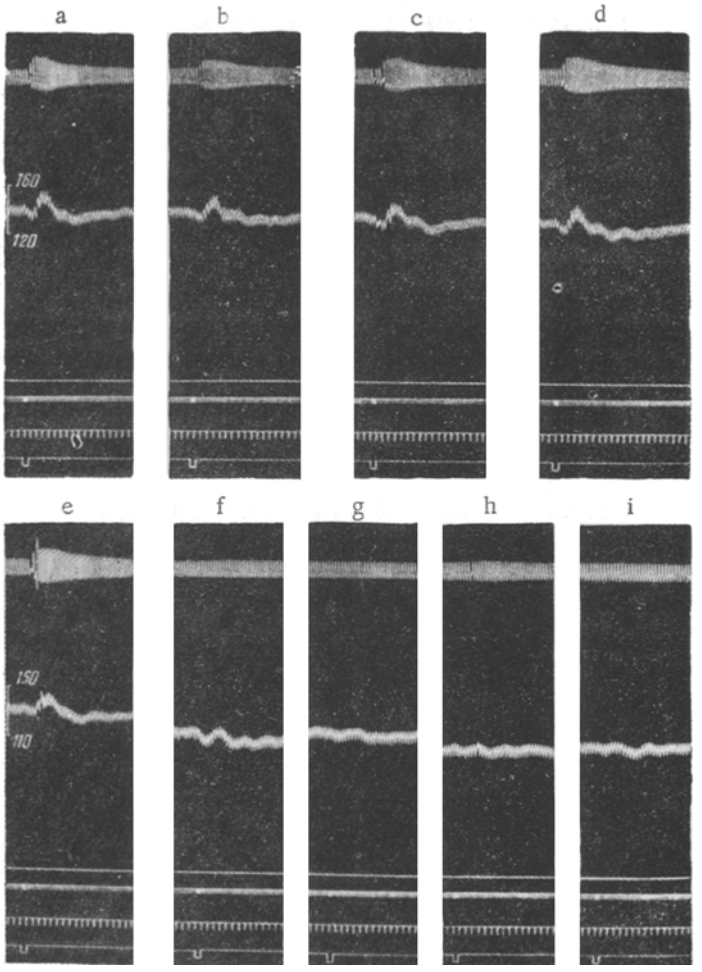

Fig. 2. Reaction of the circulation and respiration to stimulation of the carotid receptors of the cat with acetylcholine 0.5 ml 10^{-4} g/ml). a) Reflex to acetylcholine 5 minutes before injection of hydroxylamine; b, c, d) 5, 10 and 30 minutes after injection of hydroxylamine (1 ml 10^{-2} g/ml); e) reflex to acetylcholine 5 minutes before injection of sodium fluoride; f, g, h, i) 5, 10, 45 and 55 minutes after injection of sodium fluoride into the perfusion fluid (1 ml 10^{-2} g/ml). Significance of the curves as in Fig. 1.

In other experiments in which, at the very beginning of the experiment, the isolated carotid sinus was perfused with Ringer-Locke's solution containing sodium pyruvate, we also failed to observe any hastening of the restoration of the reflexes to acetylcholine after their inhibition by sodium fluoride. In this way a significant difference was found in the mechanisms of reception of acetylcholine between the carotid sinus and intestinal reflexogenic zones.

According to our hypothesis, the influence of pyruvic acid on reflexes from the intestine inhibited by sodium fluoride is that this acid promotes the C_3 acid cycle when glycolysis is disturbed. The fact that pyruvic acid does not have this action during perfusion of the carotid sinus indicates that a normal C_3 acid cycle, in which pyruvic acid is the substrate, evidently does not play an important part in the preservation of the reception of acetylcholine in this zone.

In eight experiments we introduced hydroxylamine solution (1-3 ml of 10^{-2} g/ml), which inhibits the C_3 acid cycle [5], into the perfusion fluid entering the carotid sinus, and in contrast to the experiments on the intestine we observed no essential change in the excitability of the receptors in this region. By comparison with the reflex produced by acetylcholine before the injection of hydroxylamine (Fig. 2a), the reflexes 5, 10 and 30 minutes after injection of hydroxylamine showed practically no decrease in magnitude (Fig. 2, b, c, d).

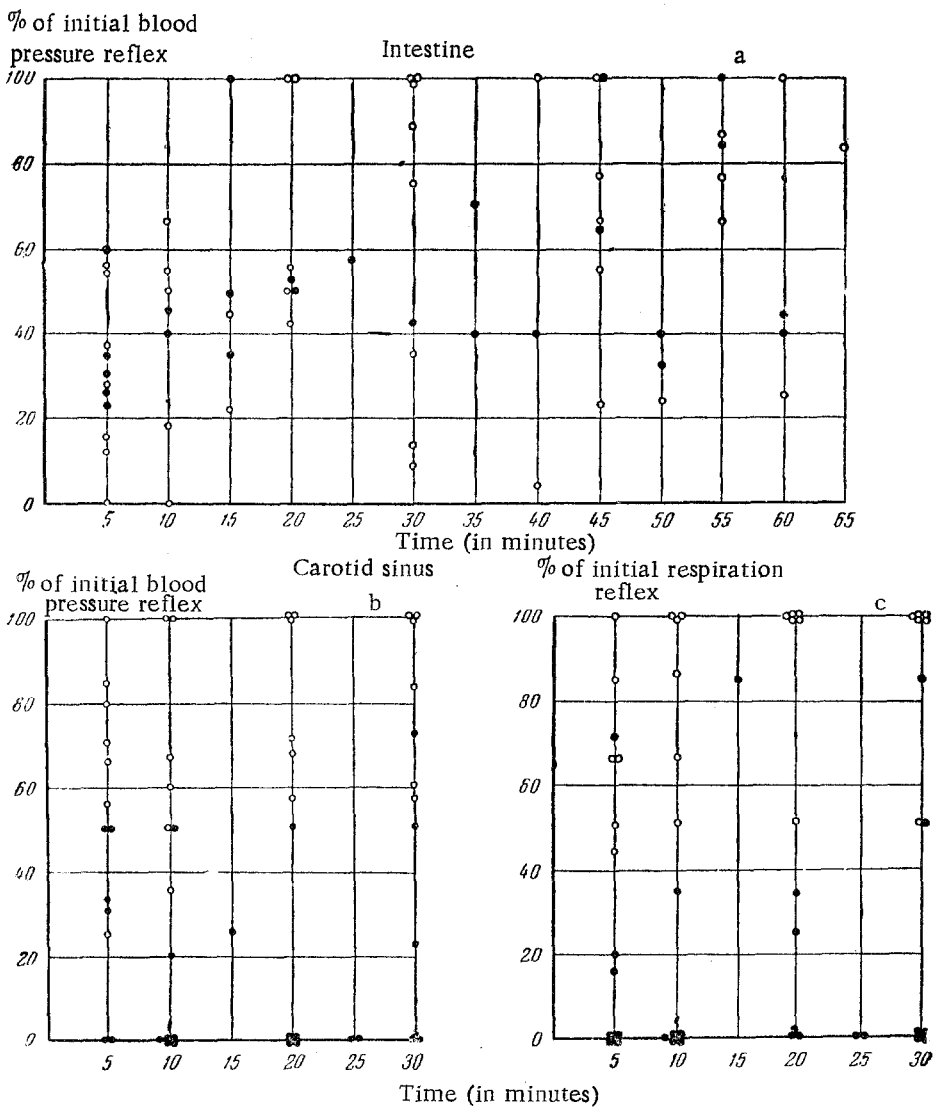

Fig. 3. The effect of sodium fluoride and hydroxylamine on the chemoreflexes from the intestine and carotid sinus. a) Intestinal perfusion experiments; b, c) carotid sinus perfusion experiments. Conventional signs: points – reflexes to acetylcholine after injection of sodium fluoride; circles – reflexes to acetylcholine after injection of hydroxylamine.

We thought it of interest to compare the effect of sodium fluoride and hydroxylamine in the same dose on the receptors of the carotid sinus on the one hand, and the intestinal receptors on the other. After injection of sodium fluoride (1 ml 10^{-2} g/ml) the reflexes to acetylcholine almost failed to appear (Fig. 2, e-i). This fact suggests that the receptors of the carotid sinus are more sensitive to sodium fluoride as a glycolytic inhibitor than to hydroxylamine, inhibiting the C_3 acid cycle.

In order to compare the depressing action of hydroxylamine and sodium fluoride in the same dose on the sensitivity of the carotid sinus and the intestinal reflexogenic zones to acetylcholine, in 12 experiments we perfused a loop of intestine and in 13 experiments the carotid sinus. The results of these experiments are shown in Fig. 3, in which the magnitudes of the reflexes are given as percentages of the initial reflex of blood pressure and respiration, at different intervals of time after injection of hydroxylamine and sodium fluoride into the perfused organ. The dose of hydroxylamine and sodium fluoride solutions injected in these experiments was the same (5 ml 10^{-2} g/ml of solution into the loop of intestine and 1 ml 10^{-2} g/ml of solution into the sinus). Figure 3,a shows that only hydroxylamine caused a sharp decrease to 20% in the magnitude of the reflexes. Both hydroxylamine and sodium fluoride had a weaker influence on this magnitude, and moreover both enzyme poisons had approximately equal depressing actions.

A quite different picture is seen in Fig. 3, b and c, which shows the results of experiments to perfuse the carotid sinus. Here hydroxylamine caused only a comparatively weak depression, not as a rule exceeding 50%. Sodium fluoride, on the other hand, caused a depression of the reflexes which, in the majority of the experiments, considerably exceeded 50% and in some experiments reached 100%.

The results obtained thus suggest that, in contrast to the intestinal receptors, the sensitivity of the carotid sinus to acetylcholine is more closely connected with the glycolytic cycle of tissue metabolism. Bearing in mind the specific sensitivity of the carotid sinus zone to anoxia, the facts described above may be of definite importance to the understanding of the changes in the function of this zone in different conditions.

SUMMARY

Acute experiments were performed on cats with perfusion of the isolated sinocarotid zone, whose nervous connections with the body were left intact. As demonstrated, the inhibitor of glycolysis (sodium fluoride) markedly depresses the reflexes from the sinocarotid receptors provoked by acetylcholine, whereas the tricarbonic acid cycle inhibitor (hydroxylamine) exerted a mild and brief depressing effect on carotid receptors. Addition of the tricarbonic acid cycle (pyruvic acid) into the perfusate of the substrate did not accelerate the restoration of the reflexes deranged by sodium fluoride.

In comparing the data thus obtained with the results of altered intestinal sensitivity during the action of poisons of the tricarbonic acid and glycolytic cycles a conclusion was drawn that as distinct from the intestinal receptors, chemoreception of the sinocarotid zone is to a much greater extent associated with the glycolytic cycle of tissue metabolism.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
