PHARMACOLOGY

THE EFFECT OF EPHEDRINE ON CAROTID CHEMORECEPTORS

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Studies of the effect of various chemical agents on the isolated carotid sinus helped to elucidate the important part played by the latter in regulating the organism's activity (C. Heymans, S. V. Anichkov, G. Liljestrand and others).

Among other substances, sympathomimetic agents have also been used.

Thus, S. V. Anichkov, V. V. Zakusov, A. I. Kuznetsov and N. G. Polyakov (1936) noted the excitatory action of adrenalin on respiration mediated by carotid sinus chemoreceptors.

A. I. Kuznetsov (1938) noted that on perfusion of the isolated carotid sinus with a 1 : 100,000 solution of adrenalin, there was stimulation of respiration and lowering of blood pressure. Similar action has been exhibited by sympatol (1 : 1000).

C. Heymans and D. Cordier (1940) point out respiratory changes which occur under the influence of adrenalin and which are mediated by reflexes from the carotid sinus zone.

C. Heymans (1953) studied the effect of adrenalin and noradrenalin on blood pressure from the point of view of the carotid sinus zone. S. V. Anichkov (1951) studied the effect of adrenalin on the carotid sinus chemoreceptors and referred to it as a feebly acting agent.

A. I. Kuznetsov, studying the effect of ephedrine on the isolated carotid sinus, noted stimulation of respiration during perfusion with ephedrine in 1 : 100,000 dilution. He considers that ephedrine, like other sympathetic poisons, exerts a weak action on carotid chemoreceptors.

C. Heymans (1953) observed changes in blood pressure under the action of ephedrine on the carotid sinus.

Although some data are available concerning the action of ephedrine on the carotid body, its effect on the sensitivity of carotid body cells to various chemical substances has not been studied at all. Changes in sensitivity of carotid chemoreceptors are of no mean importance to reflex regulation of vegetative functions of the organism.

It is well known that ephedrine increases the sensitivity of adrenalin-reactive systems to adrenalin. Our investigations (A. I. Mitrofanov, 1956) have shown that ephedrine abolishes the blocking effect of ganglion-blocking substances on n-choline -reactive systems of ganglia which have common pharmacologic features with those of the carotid bodies.

METHODS

An investigation (on 31 cats) was made of the effect of ephedrine on the sensitivity of carotid body chemoreceptors to acetylcholine and to sodium cyanide.

Isolated carotid sinus (Moiseev-Heymans-Anichkov technique) was used. Respiration served as test reaction.

RESULTS

Perfusion with ephedrine solutions of various concentrations (1 : 16,666; 1 : 50,000 and 1 : 500,000) did not produce any definite changes in respiration. These data differed from those of A. I. Kuznetsov (1938) who observed stimulation of respiration under the influence of ephedrine in 1 : 100,000 dilution.

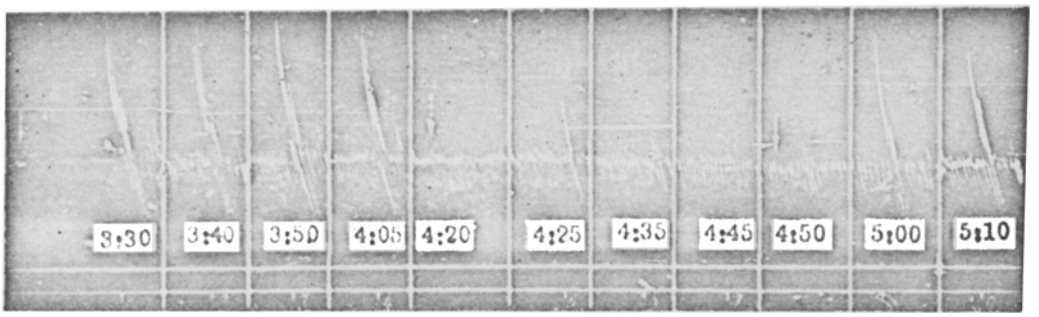

Fig. 1. Effect of ephedrine on carotid chemoreceptors. Perfusion of carotid sinus by the Moiseev-Heymans-Anichkov technique. Records from above down: respiration, time marker ½ introduction of Ringer-Locke solution; introduction of ephedrine solution 1 : 16,666; 1, 2, 3, 4, 5, 6, 7, 8, 9) introduction of acetylcholine solution 0.4 ml 1 : 25,000. Experiment: March 2, 1955. Decerebrate cat, 3.6 kg.

At the same time our experiments showed that the sensitivity of the carotid body to acetylcholine (0.4 ml 1 : 25,000) was lowered under the influence of ephedrine (in various concentrations); the degree of lowering was related to dilution of ephedrine. Reactivity of the carotid body was restored on washing with Ringer-Locke solution.

Figure 1 demonstrates that the respiratory reaction to the first and to repeated administration of acetylcholine during perfusion with Ringer-Locke solution is practically identical. The reaction to acetylcholine is diminished when perfusion with ephedrine solution (1 : 16,666) is begun, and by the 15th minute of such perfusion it virtually disappears. During washing with Ringer-Locke solution, the respiratory reaction to acetylcholine is restored, but does not reach the initial value even by the 20th minute.

Fig. 2. Effect of ephedrine on carotid chemoreceptors. Perfusion of carotid sinus by the Moiseev-Heymans-Anichkov technique. Records: similar to Fig. 1. ½ introduction of Ringer-Locke solution; ½ introduction of ephedrine solution 1 : 50,000; 1, 2) introduction of sodium cyanide solution 0.2 ml 1 : 1000. Experiment March 18, 1955. Decerebrate cat, 2.8 kg.

Changes in sensitivity of the carotid body to acetylcholine under the influence of ephedrine could develop as a consequence of vasoconstriction in the carotid body with resultant hindrance of acetylcholine access to its chemoreceptors. To check this, we staged experiments in which sodium cyanide – the anoxic poison being studied – was introduced into the inlet tube during perfusion with ephedrine. If diminution of reaction to acetylcholine were due to vasoconstriction, there should also be diminution of reaction to cyanide, all other conditions being similar. Since 1 : 50,000 concentration of ephedrine was found experimentally to give a clear, but not extremely pronounced effect, it was this concentration which was used in subsequent experiments.

Sodium cyanide in amounts of 0.2 ml (1 : 1000) increased respiratory reaction when given during perfusion with ephedrine (1 : 50,000).

Figure 2 shows that ephedrine (1 : 50,000) not only does not weaken the carotid body reaction to cyanide, but, on the contrary, evokes certain enhancement of this reaction (judged by stimulation of respiration) as compared to the original.

The experiments thus demonstrated that vasoconstriction in the carotid body during perfusion with ephedrine was hardly likely to play a part in the diminished reaction to acetylcholine.

It was essential to check that sensitivity of the carotid body to acetylcholine was diminished, and its sensitivity to sodium cyanide increased, during perfusion with ephedrine under identical conditions (on the same animal). Into the inlet tube was introduced 0.4 ml acetylcholine solution (1 : 25,000) and 0.2 ml sodium cyanide solution (1 : 10,000). Lower concentration of sodium cyanide than in the previous experiments was taken intentionally, in order to evoke a smaller change in respiration than that produced by acetylcholine. Acetylcholine was introduced first, followed by cyanide after 5-10 minutes. This was prompted by the fact that preliminary introduction of acetylcholine did not alter the action of sodium cyanide. Changes in respiration obtained under these experimental conditions are presented in Fig. 3, which shows that normally sodium cyanide (0.2 ml 1 : 10,000) alters respiration much less markedly than acetylcholine (0.4 ml 1 : 25,000). During perfusion with ephedrine,

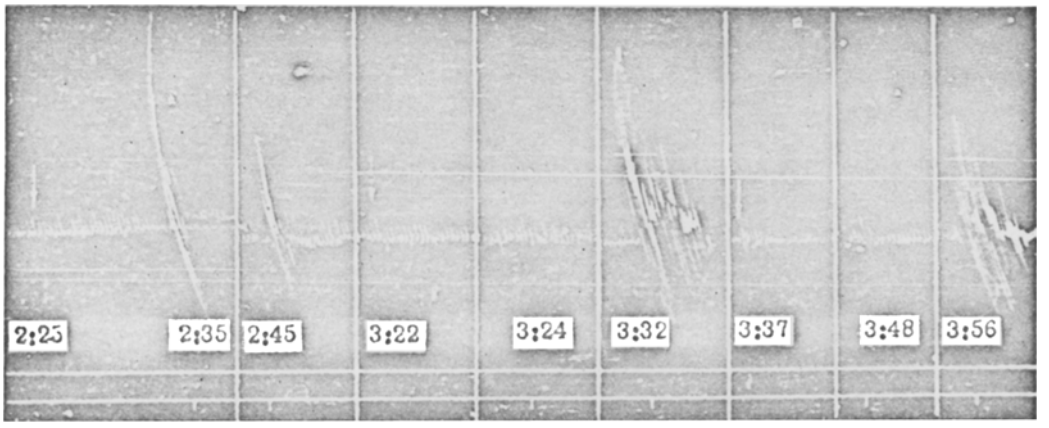

Fig. 3. Effect of ephedrine on carotid chemoreceptors. Perfusion of carotid sinus by the Moiseev-Heymans-Anichkov technique. Records: similar to Fig. 1. ↓ introduction of Ringer-Locke solution; ↓ introduction of ephedrine solution 1 : 50,000; 1, 3, 5) introduction of sodium cyanide solution 0.2 ml 1 : 10,000. Experiment March 28, 1955. Decerebrate cat, 3 kg.

the carotid body sensitivity to acetylcholine drops sharply, while sensitivity to sodium cyanide increases significantly (judging by stimulation of respiration). When ephedrine is washed away with Ringer-Locke solution its sensitivity to acetylcholine begins to increase slightly and its sensitivity to cyanide begins to decrease.

These experiments show that ephedrine causes some biochemical shifts to occur in the carotid body, which lead to changes in its reaction to acetylcholine and cyanide.

It is known that carotid body chemoreceptors in some respects approach the n-choline-reactive systems of ganglia, as witnessed by the selective action of ganglion poisons both on the carotid body and the sympathetic ganglion (S. V. Anichkov and collaborators, 1936; S. V. Anichkov, 1945, 1947).

Taking into account the results obtained, it was essential to discover whether the antagonism between ephedrine and anticholinergic substances would not become apparent in their action on the choline-receptors of the carotid body. This investigation was of theoretical as well as practical interest, considering the physiological role of the carotid body.

Paramion* was used as an anti-n-choline agent; it is a curare-like substance. It is known that curare blocks carotid chemoreceptors; the effect of paramion on the carotid sinus had not been studied up to the present.

No significant changes in respiration were noted during perfusion of the isolated carotid sinus with paramion in concentrations of 1 : 10,000 and 1 : 5000; carotid body sensitivity to acetylcholine was lowered, indicating blocking of n-choline-reactive systems in the carotid body. Washing with Ringer-Locke solution led to restoration of this sensitivity, which was fairly rapid (by the 3rd minute).

Paramion did not alter carotid body sensitivity to sodium cyanide (0.2 ml 1 : 1000 in inlet tube).

It is known that curare, too, does not exert any effect on carotid body sensitivity to anoxic poisons, in particular the cyanides (S. V. Anichkov, 1949, 1953).

Paramion thus exerts the same effect on the carotid body as curare.

Having established the changes in sensitivity of the carotid body under the influence of ephedrine alone, and paramion alone, we undertook the study of their combined effect.

Perfusion with a solution containing a mixture of ephedrine (1 : 50,000) and paramion (1 : 5000) was associated with marked weakening of the respiratory reaction, indicating blocking of the carotid body n-choline-reactive systems.

Restoration of carotid body sensitivity to acetylcholine after washing with Ringer-Locke solution was delayed as compared to such restoration after perfusion with ephedrine or paramion, separately, and subsequent washing with Ringer-Locke solution.

No antagonistic action of ephedrine and paramion on the carotid body chemoreceptors was therefore found in our experiments. These results did not agree with data from experiments on n-choline-reactive systems of autonomic ganglia where antagonism between ephedrine and anticholinergic agents, with a competitive type of action, was found to exist (A. I. Mitrofanov, 1956).

At the same time, the present experiments showed that ephedrine enhanced carotid body sensitivity to cyanides. Evidently, ephedrine increases carotid body sensitivity to oxygen deficiency, i. e., enhances its participation in regulation of oxygen content in the blood.

SUMMARY

The carotid sinus was isolated by the method of Moiseev-Heymans-Anichkov, respiration serving as a test. Perfusion of 1 : 50,000 solution of ephedrine caused respiration to be lowered by acetylcholine and enhanced by the sodium cyanide. Thus, it has been shown that ephedrine accelerates sensitivity of the carotid body to the cyanides.

Cyanides are anoxic poisons, their effect being like that of oxygen insufficiency. Hence, ephedrine enhances the sensitivity of the carotid body to oxygen insufficiency accelerating its participation in the control of blood oxygen.

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