MECHANISM OF THE ACTION OF ADRENALINE ON BAROCEPTORS

THE ROLE OF GLUCOSE BLOOD LEVEL ON THE CHANGES OF BAROCEPTOR IMPULSES OBSERVED AFTER INTRAVENOUS ADMINISTRATION OF ADRENALINE

A. O. Navakatikyan

The Physiology Laboratory (Head of Laboratory: Full Member of the Acad. Med. Sci. USSR, Professor P. K. Anokhin) of the A. V. Vishnevsky Institute of Surgery (Director: Associate Member of the Acad. Med. Sci. USSR, Professor A. A. Vishnevsky)

(Received January 12, 1955. Submitted by Full Member of the Acad. Med. Sci. USSR P. K. Anokhin)

The work of Professor P. K. Anokhin and his collaborators has established that adrenaline, administered intravenously and intra-aortally, exerts a marked influence on the functional state of the baroceptors of the aortic and carotid sinus reflex zones. Small doses of adrenaline (0.1 g) enhance the excitability of the baroceptors, while large doses (0.5-1.5 g) lead to a reversible depression of baroceptor activity following an initial stage of increased excitability. These changes are explained by the chemical action of adrenaline on baroceptors [1, 6, 7, 8, 12].

Heymans and collaborators [13, 16, 17, 18, 19, 20, 21, 22] have shown that local application of adrenaline, noradrenaline and other sympathomimetic substances to the carotid sinus region produce reflex lowering of arterial pressure owing to increased excitation of baroceptors. The reason for this excitation, according to Heymans, is increased muscle tone of the carotid sinus. Vasodilator and sympathomimetic substances applied to the carotid sinus produce a reflex rise in blood pressure as a result of the relaxation of carotid sinus muscles caused, according to Heymans and others, by diminished stimulation of the baroceptors. The fundamental mechanism regulating the functional state of baroceptors is the muscle tone of blood vessels.

It is hardly possible to agree with the hypothesis postulated by Heymans and his co-workers.

It is well known that the carotid sinus is an artery of the elastic type [9]. Its wall contains relatively few muscle fibers, in spite of the fact that neighboring sections of the carotid arteries have a powerful muscular layer. The overwhelming majority of the baroceptors are found in the sinus adventitia.

It has been established that adrenaline causes contraction of the carotid sinus muscles and diminishes the circumference of the sinus [17, 18, 23].

Taking into account that the stimulation of baroceptors results not from changes of pressure but only from stretching [14, 15] it can be assumed that in experiments where adrenaline acted on the carotid sinus at constant pressure [4, 16] decreased stretching of the baroceptors could only occur as the result of their decreased stimulation. In fact, however, increased baroceptor stimulation was observed which consequently appeared, despite changes in the blood vessel muscle tone, as the result of the chemical action of adrenaline on these receptors [1].

A more complex situation is observed in experiments where adrenaline acts under conditions of changing pressure within the sinus. Landgren [23] demonstrated that adrenaline reduces the elasticity of the carotid sinus wall at a pressure of 0-100 mm of mercury, but increases it at a pressure of 100-200 mm. However, changes in elasticity cannot be the cause of enhanced excitation of baroceptors evoked by adrenaline. In the experiments of Heymans and co-workers [16, 17, 19, 20, 21, 22] this enhanced excitation persisted at blood pressures considerably lower than 100 mm of mercury, i.e., under conditions both of the magnitude of stretch and the degree of of elasticity below normal.

Small doses of acetylcholine increase the excitability of the carotid sinus baroceptors, while large doses depress it [24], i.e., its effect is analogous to that of adrenaline although these two substances affect arterial tonus differently.

In our opinion, Heymans and collaborators misinterpret the mechanism of the action of adrenaline on baroceptors, assigning the leading role to its action on the muscle tone of the vessels and completely ignoring the chemical effect of adrenaline on these receptors.

In our investigations of the effect of intravenous administration of adrenaline, the changes in the functional state of the baroceptors could have depended on the direct action of adrenaline on the baroceptors as well as on other changes associated with the administration of adrenaline (hyperglycemia, etc.).

In the experiments described below an attempt was made to elucidate the effect of changing blood glucose levels on the changes in the activity of the baroceptors evoked by adrenaline. Changes in blood glucose concentration could play a definite role in these experiments. This could be supposed on the grounds of the importance of carbohydrate metabolism in receptors as regards processes of their excitation [3, 11]; moreover, blood vessel receptors react to changes in glucose concentration [5, 10].

EXPERIMENTAL

Experiments were performed on rabbits under light urethane anesthesia (1 g per 1 kg body weight). Bioelectric potentials from the depressor nerve, reflecting the activity of the aortic arch baroceptors, were recorded oscillographically. The noise level of the oscillograph did not exceed 5μ v. The amplitude of the baroceptor volleys was 100-200μ v. The electrocardiogram was also recorded oscillographically. A simultaneous record of the blood pressure, measured by mercury and elastic manometers, was made on a kymograph. Records of blood pressure and of nerve impulses from the depressor were accurately synchronized.

RESULTS

Two series of experiments were carried out. In the first series the aim was to discover whether hyperglycemia could by itself affect the activity of baroceptors. In order to decide this question a study was made of the effect of intravenous administration of glucose on the depressor nerve impulses.

The rabbit was given from 2 to 10 ml of 10% glucose solution over a period of 15-30 seconds. This should have raised the blood glucose level by approximately 100-500 mg%.

Each of four rabbits was given glucose 3-4 times in different quantities at intervals of 30-40 minutes. The results of the experiments proved to be, on the whole, similar.

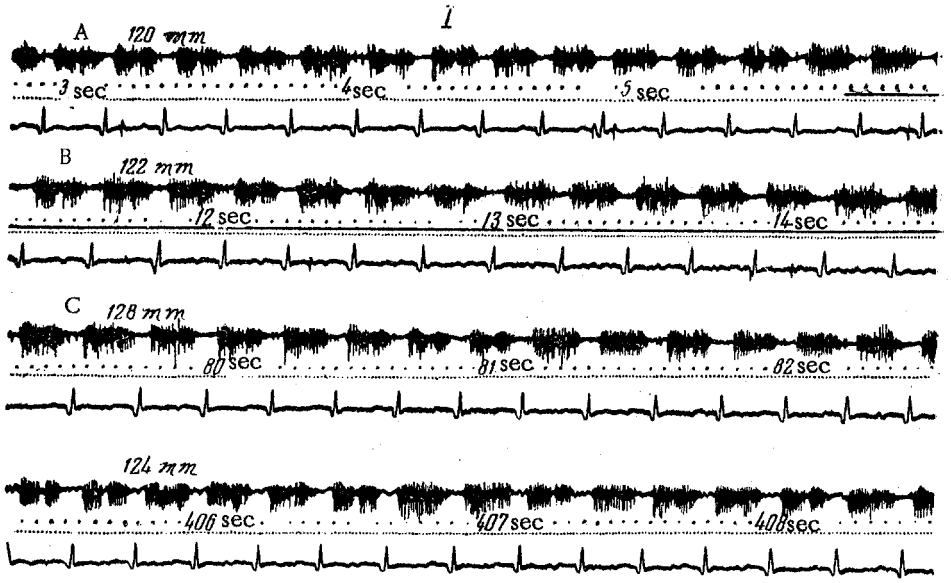
A slight rise in blood pressure (10 mm of mercury on an average) occurred during the administration of glucose; the blood pressure gradually returned to the original level in the course of 2-5 minutes (Fig. 1).

Some increase in the impulses from the depressor nerve was observed simultaneously with the rise in blood pressure (Fig. 1, B, C). Lowering of blood pressure was accompanied by a decrease in the depressor nerve impulses (Fig. 1, D).

Changes in nerve impulses in these experiments were not very pronounced. They were considerably less than those observed after the administration of adrenaline.

It follows from this that hyperglycemia which supervenes the administration of adrenaline cannot by itself play a significant part in the changes of baroceptor activity.

In the second series of experiments the effect of glucose after the administration of large doses of adrenaline was studied at the moment of adrenaline-induced depression of baroceptor activity (cessation of impulses at high blood pressure levels). It was supposed that intravenous administration of glucose at that moment might restore the baroceptor impulses, since Babsky and Kirillova [2] had demonstrated that small doses of adrenaline increased the excitability of the spinal cord whereas large ones depressed it. However, when adrenaline in large doses acted in solution rich in glucose it increased excitability instead of depressing it.



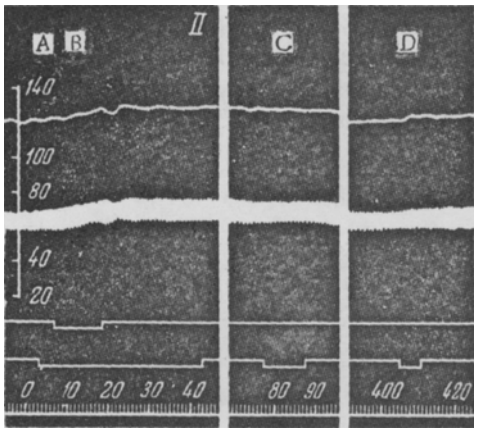


Fig. 1. The effect of intravenous administration of 5 cc 10% glucose solution (6-18 sec. of experiment) on the depressor nerve impulses (I) and blood pressure (II).

I) Records in each section (A, B, C, D) from above down: depressor nerve oscillogram; time in 0.05 and 0.01 sec. (dots); electrocardiogram. Figures refer to blood pressure levels and to time from the beginning of the experiment. Solid horizontal line denotes period during which glucose was administered;

II) Records from above down: mercury manometer record of blood pressure; elastic manometer record of blood pressure; record of glucose administration (depression in the line); record of period of oscillographic registrations (depression in the line); time in seconds. Scale of blood pressure levels in millimeters of mercury. Corresponding moments of the experiment are denoted by similar letters on the oscillogram and the kymogram.

In the present experiments adrenaline produced many of the same changes in the functional properties of the baroceptors as those observed by Babsky and Kirillova in the case of the spinal cord.

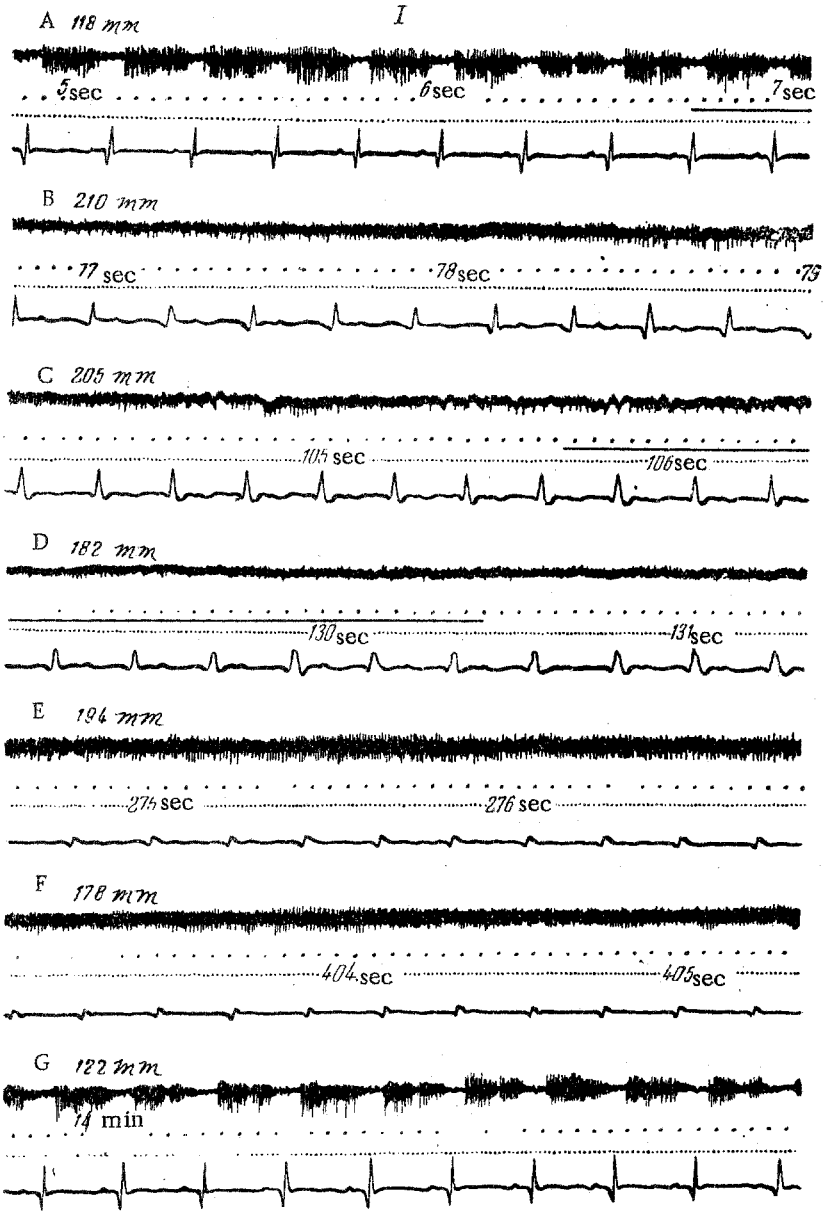
The similarity of the effect of adrenaline on baroceptors and on the cells of the spinal cord naturally suggested the possibility of a single mechanism for the action of adrenaline.

It was therefore decided to find out whether the depression of baroceptor activity (cessation of impulses at high blood pressure levels) depended on a deficiency of glucose.

To decide this question depression of baroceptor activity was evoked by large intravenous doses of adrenaline (0.8-1.2 mg) and during this time glucose was administered intravenously. If the depression of baroceptor activity were really related to glucose deficiency, it would be expected that the sharp rise in blood glucose level so produced would restore the baroceptor activity.

Experiments were performed on 5 rabbits who were given 5-20 ml of 10% glucose solution intravenously. Glucose was given 2-4 minutes after the injection of adrenaline, when depression of baroceptor activity took place.

One of such experiments is represented in Fig. 2, I and II. Intravenous injection of 1 mg adrenaline produced marked depression of baroceptor activity in the course of the first minute (Fig. 2, I and II, B). Despite a very high blood pressure level, the impulses were considerably weaker even during the first minute than before the administration of adrenaline. During the depression of baroceptor activity the impulses practically



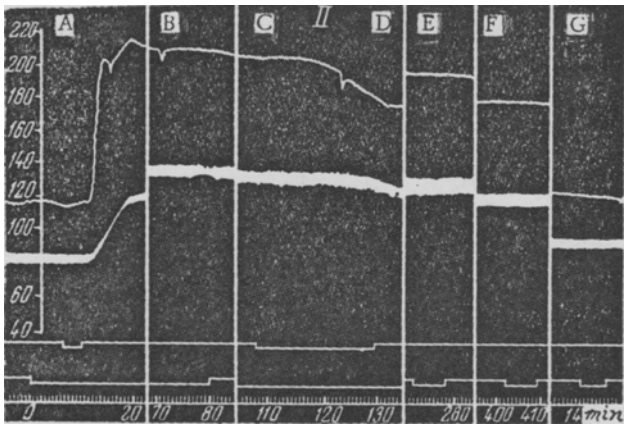


Fig. 2. The effect of intravenous administration of glucose (106-130 sec. of experiment) on the activity of aortic baroceptors depressed by administration of 1 mg adrenaline (I) and blood pressure (II).
Records from above downwards the same as in Fig. 1. In Fig. 2, II, the periods of administration of adrenaline (7-11 sec of experiment) and of glucose (106-130 sec of experiment) are marked by depressions in the third from the bottom horizontal line.

lost their volley character: the discharge during systole and ventricular diastole was of approximately equal strength.

Between 106 and 130 seconds of the experiment 10 ml of glucose solution was given (Fig. 2, I and II, C. D), which lowered the blood pressure by 20 mm of mercury. After 1.5 minutes, it again rose (Fig. 2, E).

Administration of glucose did not produce any marked changes in baroceptor activity.

During the administration of glucose the discharge continued to grow weaker and then began to increase slowly in strength. 1.5 minutes after the injection of glucose this increase was quite marked, but had not reached the original level (Fig. 2, I, E).

In this experiment, as in many of the others, considerable diminution of the electrocardiogram amplitude was observed after large doses of adrenaline (Fig. 2, I, E, F).

This did not, however, indicate diminished cardiac contractions, since during the same time the pulse pressure was not altered (Fig. 2, II, E, F).

Administration of glucose to four other rabbits also did not exert any appreciable effect on the depressed activity of the baroceptors.

The present experiments cannot in any way deny the possibility of a direct or indirect effect of adrenaline on carbohydrate metabolism in the baroceptors.

They do, however, indicate that adrenaline-induced depression of baroceptor activity is not dependent on depletion of glucose in the reflex zone.

Evidently the analogous effect of adrenaline on the cells of the spinal cord and on baroceptors is not determined by its influence on glucose consumption.

LITERATURE CITED

[1] P. K. Anokhin, Nervous Regulation of Circulation and Respiration * (Moscow, 1952), pp. 147-155.

[2] E. B. Babsky and A. A. Kirillova, Byull. Eksptl. Biol. i Med. 15, 6, 63-66 (1943).

[3] M. L. Belenky, Byull. Eksptl. Biol. i Med. 25, 2, 116-119 (1948).

[4] A. I. Kuznetsov, The Academician I. P. Pavlov Memorial Symposium * (1938), pp. 121-142.

[5] O. S. Merkulova, Izvest. Akad. Nauk SSSR, Ser. Biol. (1948), 4, 493-504.

[6] A. O. Navakatikyan, The Influence of Adrenaline and the Sympathetic Nervous System on the Functional State of Baroceptors in the Aortic and Carotid Sinus Reflex Zones. Thesis* (Moscow, 1952).

[7] A. O. Navakatikyan, Problems of Experimental Hypertension and Hypertensive Disease* (Moscow, 1953), third edition, pp. 136-156.

[8] A. O. Navakatikyan, Byull. Eksptl. Biol. i Med. 40, 10, 5-10 (1955).

[9] A. A. Smirnov, Carotid Reflex Zone* (Leningrad, 1945).

[10] V. A. Tychinin, Byull. Eksptl. Biol. i Med. 34, 6, 7-10 (1952).

[11] V. N. Chernigovsky, Fiziol. Zhur. SSSR 33, 1, 17-28 (1947).

[12] A. I. Shumilina, cited by P. K. Anokhin, supra [1].

[13] A. L. Delaunois and L. Martini, Arch. intern. pharmacodynamie 94, 4, 430-438 (1953).

[14] H. Harada, Japan, J. Med. Sci. IV Pharmacol. 12, 176-177 (1940).

[15] W. H. Hauss, H. Kreuziger, and H. Astroth, Z. Kreislaufforsch. 38, 28-33 (1949).

[16] C. Heymans, Acta Physiol. Scand. 29, 72-73 (1953).

* In Russian.

[17] C. Heymans and A. L. Delaunois, Science 114, 546-547 (1951).

[18] C. Heymans and A. L. Delaunois, Arch. intern. pharmacodynamie 96, 99-104 (1953).

[19] C. Heymans and G. Heuvel-Heymans, Arch. intern. pharmacodynamie 83, 520-528 (1950).

[20] C. Heymans and A. L. Delaunois, Arch. intern. pharmacodynamie 93, 95-104 (1953).

[21] C. Heymans and H. Mezzella, Arch, exptl. Pathol. Pharmakol. 215, 1-2, 100-102 (1952).

[22] C. Heymans, G. K. Vleeschhouwer, and G. Heuvel-Heymans, Arch. intern. pharmacodynamie 85, 1-2, 188-193 (1951).

[23] S. Landgren, Acta Physiol. Scand. 26, 35-56 (1952).

[24] S. Landgren, A. P. Skouby, and Y. Zotterman, Acta Physiol. Scand. 29, 381-388 (1953).