THE MECHANISMS OF CHEMORECEPTION

Communication I. Relationship Between the Acetylcholine Concentration and the Reflex Production in Cholinergic Receptors

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The elucidation of the mechanism of chemoreception is of practical and theoretical interest. The literature on this subject comprises a considerable number of papers. Many aspects of the physiology of chemoreception are still, however, inadequately studied. Very little attention has been paid to the quantitative aspects of the relationship between the chemical agent and the chemoreceptors; in particular there is no information on the relationship between the acetylcholine concentration and the reflexes arising from cholinergic receptors.

Acetylcholine, being a powerful stimulator of chemoreceptors, evidently has a general reflex influence in addition to a local action at the moment of its secretion.

It has been shown [4, 8] that the effectiveness of the action of acetylcholine on the cholinergic receptors of heart muscle is dependent on the acetylcholine concentration. These investigation, however, were carried out on cold-blooded animals (frogs). Moreover, these authors were not concerned with reflexes from cholinergic receptors. Meanwhile,the work of V.N. Chernigovskii and his coworkers and of other authors has shown convincingly that reflexes from the chemoreceptors of any organ have an action on the function of nearly every organ and system of the body.

Acetylcholine has two quite opposite effects on the vasomotor system. The pressor action of acetylcholine, for instance, when applied to the chemoreceptors of normal organs isolated from the circulation of the blood, is well known. Conversely, when acetylcholine penetrates into the general circulation of the blood [3] or is injected intravenously [1], it has a depressor effect. In either case a connection is observed between the concentration of acetylcholine and the degree of intensify of the vascular reaction. Attention to this was first drawn by V.N. Chernigovskii, who carried out experiments to study the relationship between the reflex response and the strength of the interoceptove stimulation [7].

The importance of a detailed explanation of this relationship is perfectly clear; however, we found no other reports of research into this problem in the literature and we decided to make a more detailed study of these aspects.

EXPERIMENTAL METHOD

One of the indices of the function of the chemoreceptors is the reflex from them on any organ. As an indicator of the activity of the cholinergic receptors, we therefore selected the reflex on the arterial pressure. Investigation of the reflexes from the chemoreceptors was carried out in acute experiments on 20 cats under urethane anesthesia, by the well-known method of V.N. Chernigovskii [6]. The depth of the anesthesia was adjusted to give disappearance of the corneal reflex. A segment of small intestine 20 cm in length, isolated from the circulation of the blood but preserving its nerve connections, was perfused with oxygenated Tyrode solution at a temperature of 37-39°. For the investigation we chose a caudal segment of the ileum. The arterial pressure was recorded on a chymograph with a mercury manometer, connected to the carotid artery. Solutions of acetylcholine were prepared in the same Tyrode solution in concentrations of: 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} g/ml. The cholinergic receptors were stimulated by 1 ml of acetylcholine solution of required concentration, injected into the flow of perfusion fluid next to the arterial cannula. The magnitude of the reflex was calculated from the level of the arterial pressure before application of the stimulus. The order of use of the different concentrations was deliberately varied.

EXPERIMENTAL RESULTS

In the course of the investigations a clear relationship was observed between the changes in the arterial pressure level in response to stimulation of the cholinergic receptors with different concentrations of acetylcholine.

In one of the experiments, for example, stimulation of the receptors with acetylcholine solution in a dilution of 10^{-3} caused an increase in the arterial pressure of 44 mm Hg; a solution in a concentration of 10^{-4} raised the arterial pressure by 32 mm Hg; the pressor effect from a solution in a concentration of 10^{-5} was 18 mm Hg, 10^{-6}–10 mm and 10^{-7}–only 4 mm; a concentration of 10^{-8} had hardly any effect on the arterial presssure, i.e., it was the threshold value.

These experimental results indicate that the magnitude of the reflex is directly dependent on the acetylcholine concentration. The disproportion noted in individual cases between the acetylcholine concentration and the reflex which it caused could be entirely attributed to possible experimental error: The acetylcholine solution, when injected into the flow of perfusion fluid, underwent further dilution, but not always to the same degree.

Not all the animals showed the same sensitivity to acetylcholine. The threshold concentration of acetylcholine for some animals was 10^{-7}, for others 10^{-6}, and in a few, 10^{-5}. The higher concentrations behaved in a similar way. A concentration of 10^{-3} in one animal caued an increase of 56 mm Hg in the arterial pressure, whereas in some animals this concentration increased the arterial pressure by only 20 mm Hg. In all cases, however, the magnitude of the reflexes was more or less directly dependent on the concentration of the stimulus.

From the results of experiments on 20 animals we obtained the following mean values of the magnitude of the reflexes for each concentration of acetylcholine:

Acetylcholine concentration (in g/ml)	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
Respective magnitude of reflex rise in arterial pressure (in mm Hg)	31.6	17.2	7.7	4.0	2.0	0

These results are shown graphically in Figs. 1 and 2. The graph of the reflexes in Fig. 1 is in the form of a parabola, and the logarithmic graph (see Fig. 2) is in the form of a straight line, which indicates a direct, but not directly proportional, relationship between the value of the reflex and the acetylcholine concentration. This relationship may be expressed by the formula:

$$H_2 = H_1 \cdot 2^{\lg \frac{C_2}{C_1}},$$

where C_1 is the first concentration of acetylcholine; C_2, the second concentration of the drug; H_1, the magnitude of the reflex in response to C_1; and H_2, that in response to C_2.

It may be concluded from these investigations that the intensity of the reflexes from the cholinergic receptors of the vessels of the small intestine in the cat corresponds strictly to the concentration of the stimulus.

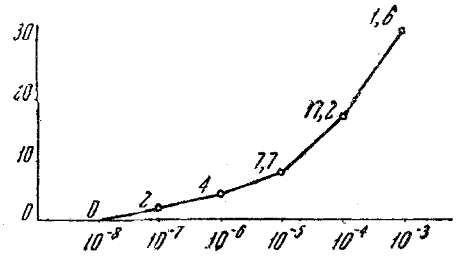

Fig. 1. Relationship of magnitude of reflex to acetylcholine concentration. On abscissae: concentration of acetylcholine (in grams/ml); on ordinates: magnitude of reflex (in mm Hg).

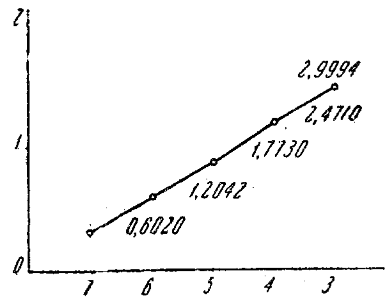

Fig. 2. Logarithmic graph of the magnitudes presented in Fig. 1.

Deviations from this relationship do not exceed 3-7%, and may be attributed to the margin of experimental error.

The quantitative relationships between the acetylcholine concentration and the intensity of the reflexes from the receptors are distinctive in character. From the existing work [7] it might have been expected that a twofold change in the magnitude of the reflex would require a twofold change in the acetylcholine concentration, which could be expressed by the formula:

$$H_2 = \frac{C_2 H_1}{C_1}.$$

Our results showed, however, that a twofold change in the intensity of the reflex called for a tenfold change in the acetylcholine concentration (see the figures cited above), as expressed by the formula which we deduced. If this finding is a regular feature for any chemical compound, it merits particular attention.

As a result of the experiments it was found that an increase in the acetylcholine concentration from 10^{-3} to 10^{-2} was not accompanied by a twofold increase in the intensity of the reflex. The reflex was increased, but not twofold–in fact, much less. This phenomenon was due either to the fact that an acetylcholine concentration of 10^{-3} constitutes almost a full load for the cholinergic receptors, or to the fact that the reaction of the vasomotor system to stimulation of these receptors by a concentration of 10^{-3} has reached almost its maximum limit.

Since the threshold concentration of acetylcholine for the intestinal vessels of the cat is on the average 10^{-8} g/ml (1 γ%), it is obvious that such a concentration of acetylcholine is already present in these vessels, reaching them as a result of the continuous functioning of tissue structures. The application of a solution in this concentration to the cholinergic receptors does not, therefore, cause any change in the existing concentration of acetylcholine in the vessels or in the function of the receptors. Hence it may be accepted that the normal concentration of acetylcholine in the vessels of the small intestine is 1 γ%; in indivual cases it may vary between 0.1 and 10.0 γ%. In this respect the results of our experiments are reasonably close to the data in the literature concerning the acetylcholine content of the rabbit's blood [2], namely 10^{-9}-10^{-8} g/ml, and the acetylcholine content of the rectus femoris muscle [5] of the adult rabbit (0.12 γ/g muscle).

SUMMARY

The author has established a direct, but not proportional relationship between the concentration of acetylcholine and the intensity of the reflexes from cholinergic receptors expressed by the formula:

$$H_2 = H_1 \cdot 2^{\lg \frac{C_2}{C_1}}$$

where C_1 is the first and C_2 – the second concentration of acetylcholine; H_1 – the value of the reflex in response to C_2 and H_2 – in response to C_2.

The threshold concentration of acetylcholine cholinergic receptors of the small intestine is 10^{-8} g/ml. Hence the author considers the acetylcholine content in the small intestine vessels of cats to average normally 1α%.

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