DEPENDENCE OF TONE OF THE INTERNAL CAROTID ARTERY ON CYCLIC AMP

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The smooth muscle tone of blood vessels depends mainly on biogenic amines and peptides. The effect of these substances is in all probability realized with the aid of cyclic AMP [2, 5], which is formed in the plasma membrane of muscle cells and, under the influence of the enzyme adenyl cyclase, which is found there, it acts on intracellular processes of contraction and relaxation of smooth muscles, and then is quickly broken down by another enzyme, phosphodiesterase [1]. The role of cyclic AMP in the formation of the tone of the internal carotid arteries is particularly interesting because these arteries participate through an active vascular mechanism in the regulation of the cerebral circulation and in the development of arterial spasm [3].

The object of this investigation was to study the role of endogenous cyclic AMP in the formation of tone of the internal carotid artery by acting on the enzyme systems responsible for its synthesis (adenyl cyclase) or destruction (phosphodiesterase) in the vessel wall.

EXPERIMENTAL METHOD

Experiments were carried out on the internal carotid artery of dogs (21 animals, isolated from the rest of the circulation). The artery, which remained *in situ* with its innervation intact, was perfused continuously by means of a constant output pump with oxygenated Ringer–Krebs bicarbonate solution with glucose at 37°C at the rate of 12-18 ml/min [3]. Changes in perfusion pressure reflected changes in the tone of the internal carotid artery. The test substances — cyclic AMP and also activators and inhibitors of the enzymes forming or destroying cyclic AMP (the doses are stated below) — were injected under standard conditions into the perfusion fluid flowing through the artery. To study the effect of one substance on another (for example, of A on B), they were injected successively (B_1, A, B_2) or during continuous infusion of the second substance (B_1, infusion of A, B_2); the effect of the first injection (B_1) served as the control (100%). The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

After injection of cyclic AMP into the internal carotid artery (1-2 mg into the perfusion fluid flowing along the vessel) a fall in tone of its wall took place (Fig. 1A). A similar effect was observed after injection of adenosine (1-2 mg), which activates adenyl cyclase in the vessel wall and increases endogenous cyclic AMP production, into the perfusion fluid. However, the effect of adenosine on the internal carotid artery was on average 57% greater ($0.01 > P > 0.001$) and lasted for 44% longer ($P < 0.001$) than the effect of similar doses of cyclic AMP in the same experiments, a result which can evidently be explained by the low permeability of the cell membranes of the vessel wall for cyclic AMP.

The dilator effect of cyclic AMP and adenosine were more marked when the tone of the wall of the internal carotid artery was first increased by continuous injection of serotonin (0.001-0.01 μg/ml) into the perfusion fluid or after an increase in the K^+ concentration in the perfusion fluid to 10-15 mM (at the expense of a corresponding decrease in the Na^+ concentration). The same dilator effects of cyclic AMP were noted after injection of prosta-

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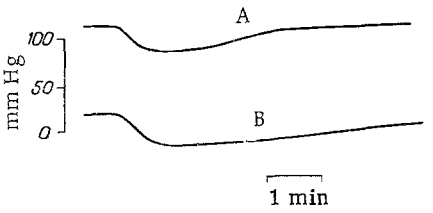

Fig. 1

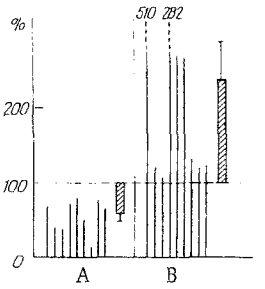

Fig. 2

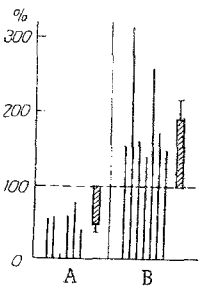

Fig. 3

Fig. 1. Lowering of perfusion pressure, evidence of a decrease in tone of wall of internal carotid artery, isolated from remainder of dog's circulation, under influence of cyclic AMP. A) Intraarterial injection of 2 mg cyclic AMP; B) injection of 2 mg adenosine, causing formation of cyclic AMP in vessel wall through activation of endogenous adenyl cyclase.

Fig. 2. Dependence of constrictor effect of PGE_2 on endogenous adenyl cyclase activity promoting cyclic AMP synthesis in vascular wall. A) Activation of adenyl cyclase by adenosine, B) inhibition of adenyl cyclase by β-adrenoblocker propranolol. Here and in Fig. 3, shaded columns represent mean values of change in effect of PGE_2 (in % of effect in control, taken as 100).

Fig. 3. Dependence of constrictor effect of PGE_2 on activity of endogenous phosphodiesterase, destroying cyclic AMP in vessel wall. A) Inhibition of phosphodiesterase by theophylline; B) activation of phosphodiesterase by imidazole.

glandin E_2 (PGE_2) into the artery, causing its constriction [4]. Intraarterial injection of cyclic AMP (1-2 mg) caused a marked decrease in the constrictor effect of PGE_2 (0.1-1 μg), and this effect was reduced on average by 52 ± 4.8%.

The magnitude of the constrictor effect of PGE_2 (0.1-1 μg) on the internal carotid artery depended on the activity of enzymes responsible for synthesis (adenyl cyclase) or destruction (phosphodiesterase) of cyclic AMP in the vessel wall. Activation of endogenous adenyl cyclase in the vessel wall by means of adenosine [8], injected into the perfusion fluid (5-20 μg/min), regularly caused a decrease in the constrictor effect of PGE_2 on the internal carotid artery (Fig. 2A). Conversely, after inhibition of endogenous adenyl cyclase in the vessel wall by the β-adrenoblocker [7] propranolol (1-2 mg into the perfusion fluid) an increase in constriction of the artery by PGE_2 developed (Fig. 2B).

As a result of inhibition of endogenous phosphodiesterase in the vessel wall by means of theophylline [9], injected into the perfusion fluid (0.1-0.25 μg/min), a decrease in the constrictor effect of PGE_2 was regularly observed (Fig. 3A). Conversely, when the phosphodiesterase in the vessel wall was activated by injection of imidazole [6] (0.1-0.5 mg/min) into the perfusion fluid the constrictor effect of PGE_2 was increased (Fig. 3B).

When activation of adenyl cyclase (by adenosine) took place simultaneously with inhibition of phosphodiesterase (by theophylline) the effect was additive; the tone of the vessel wall was approximately doubled compared with the control.

Hence, when the concentration of endogenous cyclic AMP in the vessel wall was increased through activation of adenyl cyclase or through inhibition of phosphodiesterase, the constrictor effects of PGE_2 on the internal carotid artery were reduced. Conversely, during inhibition of adenyl cyclase or activation of phosphodiesterase, leading to a decrease in the cyclic AMP content in the arterial wall, the constrictor effects of PGE_2 were regularly increased. This is evidence that the cyclic AMP content in the vessel wall, which depends on the activity of adenyl cyclase and phosphodiesterase, is a factor determining the tone of the internal carotid artery under natural conditions. The antagonistic relations found in these experiments between the cyclic AMP content in the vessel wall and the constrictor effect of PGE_2 on the internal carotid artery also indicate that the endogenous cyclic AMP level in the smooth-muscle coat of the vessel may determine the magnitude of vasoconstrictor influences on the artery during regulation of its lumen. Finally, it can be accepted, as some workers have suggested, that PGE_2 exerts its effect through its influence on enzyme systems responsible for the synthesis (adenyl cyclase) and destruction (phosphodiesterase) of cyclic AMP in the vessel wall.

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STUDY OF DIFFERENT TYPES OF ADRENERGIC SYSTEMS IN MAN

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Investigations of sensitivity to hormonal and cyclic nucleotide control are no less important than determination of concentrations of hormones and cyclic nucleotides. This approach is particularly important when studying the biochemistry and physiology of catecholamines under normal and pathological conditions. However, an obstacle to its use is the lack of methods of evaluating the state of adrenergic systems in man.

A change in the response to catecholamines is not necessarily the result of changes in adrenoreactivity. In fact, any response to catecholamines involves the sensory component – the adrenergic system (the adrenoreceptors themselves and subsequent elements) and the effector component, such as the contractile system of blood vessels. Clearly, changes may take place not only in the sensory, but also in the effector component, especially in disease.

Before reliable conclusions can be drawn on the location of changes in the first component, it is essential to study at least two parameters with respect to which the first component is identical but the second differs. If, under these circumstances, changes in the response to adrenomimetics (AM) are identical, it can be concluded that the disturbances are in the adrenergic system. The use of parameters which differ only in the first component, such as the response of the blood pressure to isoprenaline and histamine (or acetylcholine), is noteworthy.

Another feature which distinguishes our approach is that it takes into account the presence of different types of adrenoreceptors, namely α and β, and also the presence of subtypes β_1 and β_2 among the latter [3, 9, 10, 13]. The first type was stimulated by the relatively specific α-AM phenylephrine [9], β_1- and β_2-receptors were stimulated by the specific β-AM isoprenaline [3, 10, 13].

EXPERIMENTAL METHOD

Tests were carried out on 13 healthy adults aged 19-22 years and 22 healthy children aged 10-14 years. Phenylephrine was injected subcutaneously in a dose of 10 mg into the adults and 9 mg into the children, and isoprenaline was given in doses of 7.5 and 6.2 mg (sublingual-

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