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EFFECT OF ATRIOPEPTIN ON ADRENERGIC MECHANISM CONTROLLING VASCULAR TONE

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KEY WORDS: atriopeptin; smooth muscles; vascular tone.

The hypotensive effect of atriopeptin and some ways in which the peptide acts on smooth-muscle cells of blood vessels have been described in the literature [2-5].

The aim of this investigation was to study the effect of atriopeptin on one concrete mechanism of regulation of smooth muscle tone, namely the adrenergic mechanism. Considering the importance of the problem of the regional circulation, it was decided to investigate this problem on the vascular smooth muscle of several organs, differing in its initial functional properties.

EXPERIMENTAL METHOD

Contractile activity of smooth muscles of isolated preparations of cerebral and pancreatic arteries, the portal vein, and the aorta was recorded during constant-temperature perfusion with Krebs' solution, by means of mechanical to electrical transducers, under auxotonic conditions, by the method described previously [1]. The action of atriopeptin, noradrenalin, and other drugs aimed at modifying the initial functional state of the cell membranes was studied. A synthetic analog of atriopeptin of type I, II, and III, obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, was used.

EXPERIMENTAL RESULTS

Under the initial conditions, i.e., on the addition of atriopeptin (in a concentration of 10^{-10} to 10^{-7} M) to standard Krebs' solution, no changes in tone and spontaneous contractile activity took place in the smooth musculature of the blood vessels to the organs and the aorta (n = 27). Meanwhile the smooth muscles tested were activated sufficiently well by noradrenalin (10^{-6} M) and by a 40 M solution of potassium ions. If smooth muscle tone was first increased by means of these activators, atriopeptin caused relaxation in preparations of the aorta (10^{-7} M) and of the portal vein (10^{-10} M), but as before, it did not change smooth muscle tone in the basilar artery of the vein and the artery of the pancreas (Table 1, Fig. 1).

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TABLE 1. Comparison of Effects of Atriopeptin on Tone of Vascular Smooth Muscles

Experimental conditions	Aorta	Portal vein	Basilar artery of brain	Artery of pancreas
Direct effect of atriopeptin	No response	No response		No response
Effect of atriopeptin preceded by noradrenalin	Response of relaxation by 53.6% ($n = 11$)	Response of relaxation by 71.6% ($n = 17$)	The same ($n = 7$)	The same ($n = 9$)
p	$<0,001$	$<0,001$		
Effect of atriopeptin preceded by 40 M KCL solution	Response of relaxation by 72,7% ($n = 15$)	Response of relaxation by 89.9% ($n = 26$)	The same ($n = 7$)	The same ($n = 9$)
p	$<0,001$	$<0,001$		

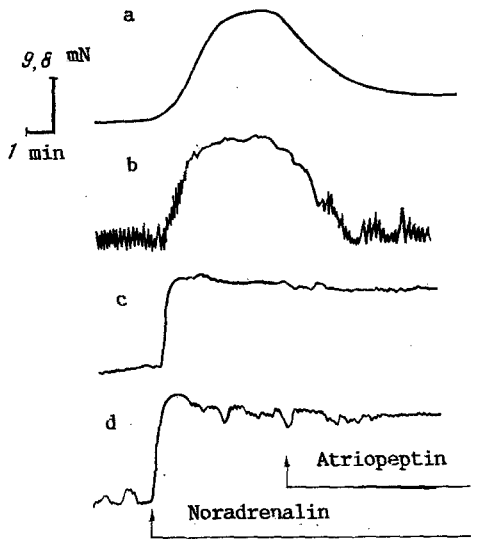

Fig. 1. Change in tone of smooth-muscle cells of aorta (a), portal vein (b), artery of pancreas (c), and basilar artery of brain (d), under the influence of atriopeptin after preliminary activation by noradrenalin.

The results demonstrated differences in manifestation of the effects of artriopeptin in different blood vessels and justified repetition of these experiments on arteries to the various organs, but in a different order.

As before, atriopeptin did not change the initial smooth muscle tone but induced a significant reduction in amplitude of contractile responses to noradrenalin (Fig. 2). The inhibitory effect of the peptide factor was particularly marked in arteries of the pancreas. In individual experiments the smooth muscles of these arteries completely lost their ability to respond to noradrenalin.

It will be clear that the smooth musculature of different vascular regions exhibits sensitivity to the atrial peptide, expressed as partial inhibition of noradrenalin effects in the large vessels (aorta and portal vein) and the formation of a refractory state to the adrenomimetic factor in arteries to individual organs.

To study the ionic mechanisms of the action of atriopeptin a series of experiments was carried out after preliminary modification of active transport of the surface membranes of the smooth muscle cells. These investigations were conducted on spontaneously active preparations of the portal vein, preactivated by noradrenalin.

The results showed (Fig. 3a) that when Na^+,K^+-ATPase was blocked by strophanthin K (10^{-6} g/ml) atriopeptin did not induce relaxation of the smooth muscles (n = 10). It can be concluded from these results that the action of atriopeptin is coupled with activity of the Na^+,K^+-pump of the surface membranes. However, experiments in which the ionic pump was blocked by strophanthin did not give the answer to the question of the character of the effect of atriopeptin on transport – whether activating or inhibitory.

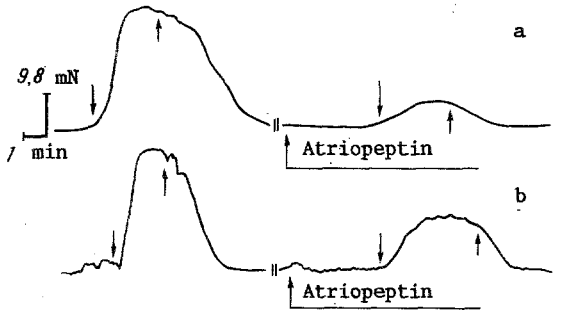

Fig. 2

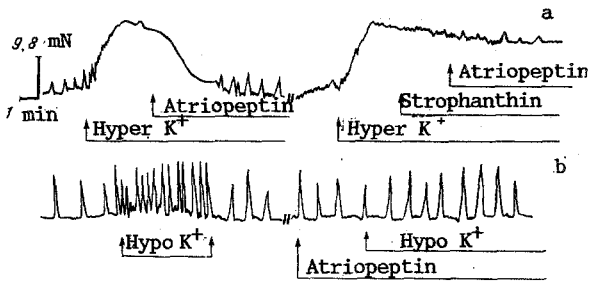

Fig. 3

Fig. 2. Effect of depression of noradrenalin-induced contractile responses of smooth muscles of pancreatic artery (a) and basilar artery (b) by atriopeptin. Arrow pointing downward – time of addition of noradrenalin; arrow pointing upward – end of action of noradrenalin.

Fig. 3. Action of strophanthin on effect of atriopeptin (a) and action of atriopeptin on hypopotassium effect in portal vein preparations (b).

To elucidate this problem another series of experiments was carried out with partial inhibition of Na^+,K^+-transport by a hypopotassium medium. Usually under those conditions, the frequency and amplitude of spontaneous contractions in strips of the portal vein were increased. After restoration of the K^+ ion concentration in the external solution the character of the spontaneous contractions returned to its initial state. When this test was carried out after addition of atriopeptin (10^{-7} M), the responses to the hypopotassium medium disappeared (n = 10; Fig. 3b).

The results suggest the following conclusion. If atriopeptin inhibited the transport mechanism of the membrane, its action on spontaneous contractile activity of cells of the portal vein would repeat the potentiating effect of a hypopotassium medium, and in the case of the combined action of hypopotassium solution and the peptide, this effect would be stronger. However, our results showed that the inhibitory effect of the hypopotassium medium on the pump was abolished by atriopeptin. It can accordingly be concluded that it is unlikely that atriopeptin has an inhibitory action on working of the pump. It must therefore be considered that atriopeptin activates the working of the membrane pump. This view is in agreement with those expressed by other workers [6], who obtained similar results in experiments on the aorta.

Atriopeptin was thus shown to have an inhibitory effect on noradrenalin-induced contractions in the smooth musculature of blood vessels. There is reason to consider that the regulatory role of the peptide in vivo can be reduced to activation of intracellular Na^+,K^+-ATPases. This activation limits the vasoconstrictor effect of catecholamines, or may, perhaps, actually block it completely in certain regional vessels, and it thus has a hypotensive action.

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