of pain and of its protopathic component. The results confirm the view [1, 2] that integral perception and adequate response to nociceptive stimulation depend on the mutual balance between activity of the specific and nonspecific systems of the brain.

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MODULATING EFFECT OF ANGIOTENSIN II AND BRADYKININ ON NEUROTRANSMITTER SENSITIVITY OF CENTRAL NEURONS

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KEY WORDS: neuron; angiotensin II; bradykinin; neuromodulators; neurotransmitters.

Much attention has been paid in recent years to the study of the participation and functional role of biologically active compounds, especially those of peptide nature, in the molecular processes of integrative activity of the brain and single neurons [1, 2]. A characteristic feature of endogenous neuropeptides, such as angiotensin II and bradykinin, is their marked polyfunctional properties: They induce many diverse peripheral and central effects and influence learning and memory processes, motivations, neuronal electrogenesis, and synaptic transmission [3, 7, 8]. However, the concrete cellular and molecular mechanisms of the central action of many neuropeptides remain inadequately studied and have been investigated mainly in whole brain structures, after systemic and intraventricular injection.

The aim of this investigation was to study the effects of endogenous neuropeptides — angiotensin II and bradykinin — on chemical sensitivity of cerebral cortical neurons to the neurotransmitters acetylcholine and noradrenalin.

EXPERIMENTAL METHOD

Experiments were carried out on sensomotor cortical neurons of unanesthetized male rabbits weighing 2.5-3 kg, immobilized with muscle relaxants, and lightly fixed in a frame. After trephining, a miniature micromanipulator, in which the microelectrode was placed, was fixed to the animal's skull by means of quick-hardening plastic (Noracryl). Electrical activity was recorded extracellularly and the test substances applied microiontophoretically by

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TABLE 1. Response of Cortical Neurons to Neuropeptides and Neurotransmitters

Substance	Character of neuronal resp.						Total number of sensitive cells	
	activation		inhibition		phasic response			
	abs.	%	abs.	%	abs.	%	abs.	%
Angiotensin II	50	71	16	23	5	6	71	100
Bradykinin	58	83	12	17	—	—	70	100
Acetylcholine	56	82	10	15	2	3	68	100
Noradrenalin	4	6	51	83	7	11	62	100

means of 4-5-barreled glass microelectrodes, with glass fiber capillary tubes, with total diameter of the tip of 4-6 μ. The recording channel of the microelectrode was filled with 2.5 M NaCl and the remaining channels with aqueous solutions of angiotensin II (2.5 mM, pH 4.5), bradykinin triacetate (2 mM, pH 4.5), saralasin (2.5 mM, pH 5.0) (all from Serva, West Germany), acetylcholine hydrochloride (0.5 M, pH 5.5), and noradrenalin bitartrate (0.5 M, pH 6.5) (from Sigma, USA), made up immediately before the experiments. A 0.9% solution of NaCl was used as the control. The substances were applied to the zone of the cell to be recorded either consecutively or simultaneously, by means of a programmed microphoresis apparatus (WP Instruments, USA), by cationic currents of 10-80 nA, from 10 sec to 3 min in duration. The derived potentials were amplified by an MEZ 8101 microelectrode amplifier (Nihon Kohden, Japan) and a VC-9 dual-beam oscilloscope (from the same firm), after which they were standardized by means of a driven multivibrator into square pulses with a duration of 3 msec, which were recorded on an N327/5 high-speed automatic ink-writer. The following frequency of the pulses was transformed at the same time into an analog voltage and recorded as an integral curve. The criterion of response of the neurons to application of the substances was a change (increase or decrease) in firing rate of not less than 30% compared with the initial value, and the stability of the response patterns of the neurons to repeated application of the substances. The results were subjected to statistical analysis on the EMG-666 computer (Hungary) and the significance of differences was determined by Pearson's chi-square test.

EXPERIMENTAL RESULTS

Data showing the response of 82 rabbit sensomotor cortical neurons to microiontophoretic applications of angiotensin II, bradykinin, acetylcholine, and noradrenalin are summarized in Table 1.

As the results show, angiotensin II, bradykinin, and acetylcholine had a mainly excitatory influence on unit activity, whereas noradrenalin reduced the discharge frequency of the nerve cells significantly more often ($P < 0.05$). Investigation of the effect of angiotensin II on the response of the cells to acetylcholine showed that in 94% of cases (67 of all neurons sensitive to angiotensin II) the neuropeptide modified these responses; in 52 (77%) cells angiotensin II potentiated responses to this neurotransmitter, as was shown by an increase in amplitude of the responses and in the duration of the after-effect, as well as by shortening of their latent periods ($P < 0.05$). In the remaining nerve cells angiotensin II weakened responses to acetylcholine. Angiotensin II similarly increased the amplitude of responses of 48 (76%) of 65 neurons to microiontophoretic application of noradrenalin ($P < 0.05$), and in 17 cells of 65 neurons to microiontophoretic application of noradrenalin ($P < 0.05$), and in 17 cells weakening of responses to the neurotransmitter was observed. Potentiation of the original response of the neuron to noradrenalin after microiontophoretic application of angiotensin II is illustrated in Fig. 1.

The study of interaction of bradykinin with acetylcholine on cortical neurons (60 cells) showed that in 93% of cases (56 neurons) bradykinin modified responses to microiontophoretic application of acetylcholine. In 44 cells initial responses to acetylcholine were potentiated (Fig. 2), whereas in 12 neurons bradykinin weakened responses to this neurotransmitter. Differences in effects of bradykinin on cortical unit responses to microiontophoretic application of acetylcholine were statistically significant ($P < 0.05$). No significant predominant trend of the effect of microiontophoretic applications of bradykinin on neuronal responses to noradrenalin was found: Potentiation was observed in 20 neurons, weakening in 16, and reversal or appearance of previously absent responses in 14.

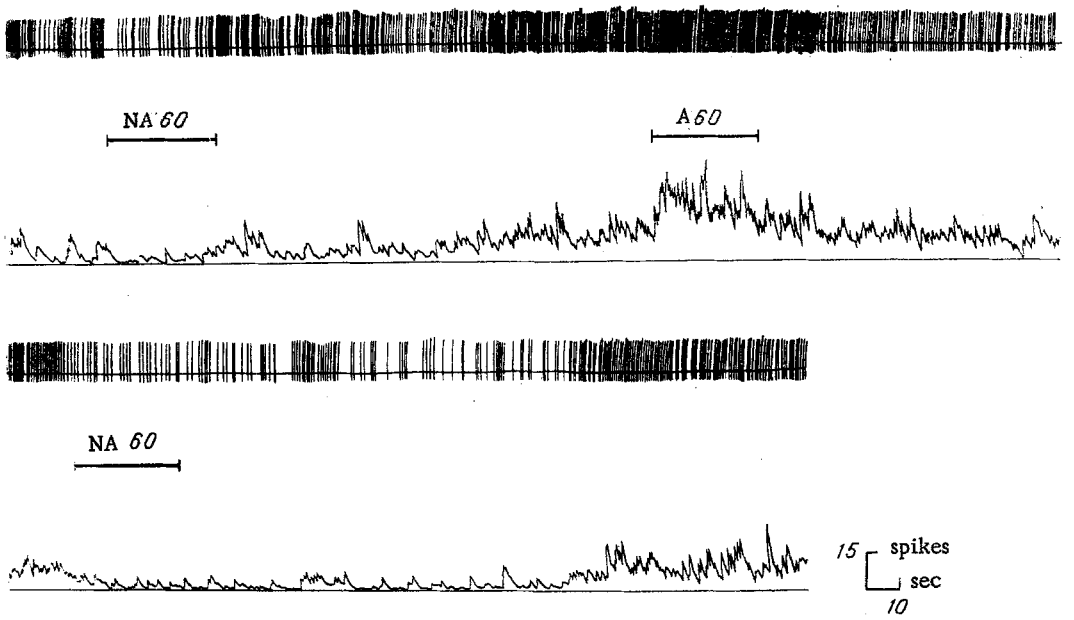

Fig. 1. Potentiation of response of a cortical neuron to microiontophoretic application of noradrenalin by angiotensin II. Above, standardized traces of spike discharge of nerve cell; below, analog curve corresponding to changes in frequency of spike discharges. A) Angiotensin II; NA) noradrenalin. Times of application of substances indicated by bold horizontal lines. Numbers show values of electrophoretic current (in nA).

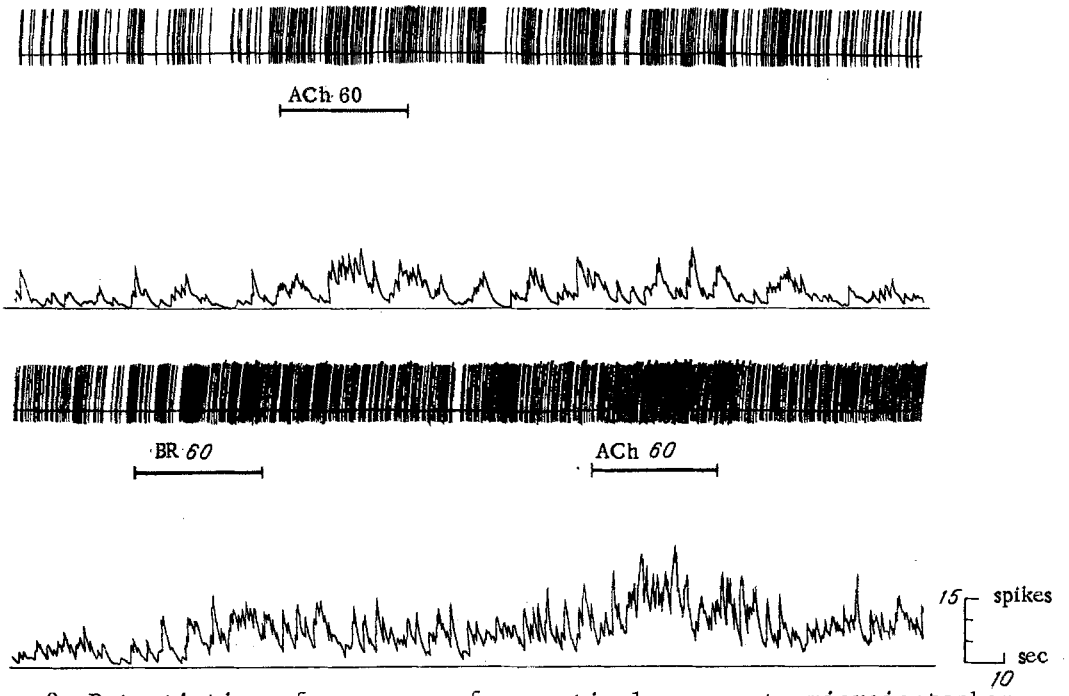

Fig. 2. Potentiation of response of a cortical neuron to microiontophoretic application of acetylcholine by bradykinin. BR) Bradykinin; ACh) acetylcholine. Remainder of legend the same as to Fig. 1.

In a study of the specificity of the neuronal effects of angiotensin II, conducted on 52 cortical neurons, saralasin (Sar^1-Ala^8-angiotensin II), a competitive blocker of its receptors with a weak inhibitory effect on unit activity, was used. It was found that in 67% of neurons saralasin completely blocked responses to angiotensin II, in 28% of cases it weakened them, and in 5% it did not affect these responses. At the same time it was found that saralasin had no effect on 65% of neurons, or potentiated responses to acetylcholine very slightly, whereas in 14% of neurons it completely blocked the response to this neurotransmitter, and in 21% of cortical neurons it induced a varied degree of inhibition of responses to acetylcholine,

possible evidence that the effect of angiotensin II on cortical unit activity may be mediated to some degree through central neurotransmitter systems, cholinergic in particular.

The results are evidence that at the central neuron level, marked functional interaction of angiotensin II and bradykinin with the neurotransmitters acetylcholine and noradrenalin takes place, and it is characterized by the fact that the neuropeptides mainly potentiate and prolong the responses of the neurons to these mediators. This effect can be explained, in particular, by data showing that microinjections of angiotensin II into the cat cerebral cortex lead to increased release of acetylcholine from nerve endings, but without any effect on acetylcholinesterase activity [4]. It has also been shown that angiotensin II stimulates noradrenalin secretion by nerve endings and inhibits its reuptake [11]. It can be tentatively suggested that angiotensin II not only has a direct specific effect on cortical unit activity, mediated by heterogeneous receptors [9], but it also acts on adrenergic and cholinergic brain structures and increases neurotransmitter release from nerve endings which, in turn, excite or inhibit activity of target cells. This is confirmed, in particular, by our own experiments and data obtained by other workers who studied neurons of the preoptic region [5]. There is also evidence in the literature on the molecular effect of bradykinin on various neurotransmitter processes in certain brain structures [6, 10]. It seems likely that endogenous neuropeptides angiotensin II and bradykinin may be synaptic polymediator neuromodulators at the central neuron level.

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REGULATION OF HUMAN RESPIRATION UNDER EXCESSIVE INTRAPULMONARY PRESSURE

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Respiration under excessive intrapulmonary pressure (EIPP) is used in clinical practice to present the development of pulmonary atelectasis, to improve gas exchange in the lungs, to reduce the strain on the inspiratory muscles [4, 15], and also in aviation medicine to maintain the pilot's oxygen supply at high altitudes [1, 2]. However, under these circumstances EIPP induces a number of unfavorable responses, mainly affecting respiration and the circulation, which limit the usefulness of this method. In particular, EIPP creates increased resistance to expiration, which has effects similar to those of the elastic resistance to respiration [12]. The fundamental physiological mechanisms of the action of EIPP on the respiratory system have been studied mainly in experiments on anesthetized animals [5, 7]. The predominant role of reflexes from the lung mechanoreceptors in the formation of the response of respiration to the action of EIPP has been demonstrated. Meanwhile the mechanisms of regulation of respiration in the conscious subject have been inadequately studied.

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