ANGIOTENSIN II IN MECHANISMS OF HYPOTHALAMIC PRESSOR RESPONSES

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Electrical stimulation of certain zones of the hypothalamus can lead to elevation of the systemic arterial pressure and to changes in cardiac activity, respiration, and other somatovegetative parameters [1, 3, 4, 6, 14], although the neurophysiological and neurochemical mechanisms of formation of pressor responses of hypothalamic origin have not been adequately studied. As a result of the discovery of vasoactive neuropeptides, new data have been obtained on the mechanisms of formation of hypertensive states and the consequent origin of cardiovascular disturbances. It has been shown that injecting one of the vasoactive oligopeptides (angiotensin II) into the lateral cerebral ventricles induces a persistent rise of blood pressure (BP) together with somatovegetative changes similar to those arising in response to electrical stimulation of negative emotional centers in the hypothalamic region [2, 7, 12]. Formation of the pressor response under these circumstances depends on the integrity of many structures of the brain and, in particular, of the hypothalamus [10]. It has also been shown that the angiotensin II level in the hypothalamic region is the highest in all brain structures [8]. It has been shown that it is chiefly the hypothalamic neurosecretory cells whose activity is modified in response to intraventricular injection of angiotensin II and which respond in the opposite direction to injection of saralasin, a blocker of angiotensin II receptors [5]. Intraventricular injection of saralasin blocks pressor responses to central injection of angiotensin II and also of renin [11].

The aim of this investigation was to study the formation of pressor responses and changes in several autonomic parameters in response to stimulation of various hypothalamic zones in intact animals and in animals receiving a preliminary injection of the angiotensin II antagonist saralasin into the lateral ventricles.

EXPERIMENTAL METHOD

Experiments were carried out on 24 male chinchilla rabbits weighing 2-2.5 kg. Bipolar michrome electrodes (distance between the poles 0.4-0.5 mm) were implanted by means of a stereotaxic apparatus into the previously scalped animals. Electrical stimulation of the hypothalamic structures was applied in the form of square pulses of current (1 msec, 50 Hz, 100-250 μA). The strength of the current was chosen individually for each animal and was below the threshold of generation of a motor response. Saralasin (Serva, West Germany) was injected through a cannula inserted into the right lateral cerebral ventricle in doses of 1-1.5 μg in 10 μl of distilled water. In all the experimental animals BP, respiration, and the ECG in standard lead II were recorded by means of strain gauge and piezoelectric transducers, connected to a Mingograf-34 instrument (Siemens–Elema, Sweden). BP was measured by means of a catheter inserted into the femoral artery. At the beginning of each experiment basic values of BP, respiration, and the ECG were recorded. Changes in these parameters in response to stimulation of structures of the anterior, middle, and posterior hypothalamus were then studied. Saralasin was injected into the lateral ventricles and the time course of changes in the above parameters was analyzed for a period of 2 h. Against the background of the central action of saralasin, cardiovascular responses to stimulation of the hypothalamic structures were recorded every 10-15 min. The location of the electrodes was verified by a projection method on frozen brain sections cut every 180 μ.

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TABLE 1. Changes in Amplitude of Pressor Responses to Stimulation of Various Hypothalamic Structures and during Central Action of the Angiotensin II Receptor Blocker Saralasin (M ± m)

Hypothalamic structures	Amplitude of pressor responses, mm Hg	
	in intact animals	15 min after intraventricular injection of saralasin
Paraventricular nucleus	31 ± 0.9	10 ± 0.6
Supraoptic nucleus	24 ± 1.2	6 ± 0.4
Ventromedial nucleus	26 ± 1.1	16 ± 0.8
Supramammillary nucleus	21 ± 1.3	16 ± 0.7
Lateral hypothalamic field	16 ± 1.2	13 ± 0.5
Anterior hypothalamic field	18 ± 0.8	15 ± 0.4

EXPERIMENTAL RESULTS

Injection of saralasin into the lateral ventricles in doses of 1-1.5 μg led to a fall of BP in the rabbits by 9 ± 0.2 mm Hg with a latent period of 7 ± 0.3 min and with a duration of the hypotensive effect of 108 ± 2.4 min. The strongest hypotensive action of saralasin occured in animals with a high initial average level of BP (120-130 mm Hg); it was virtually absent in animals with a low average level of BP (80-90 mm Hg).

The subsequent morphological control showed that during the experiments the following hypothalamic zones were subjected to unilateral stimulation: the paraventricular, supraoptic, ventromedial, and supramammillary nuclei and the lateral and anterior hypothalamic fields. Electrical stimulation of the above-mentioned hypothalamic zones was applied for 3 sec; in intact animals it induced pressor and also pressor–depressor responses of BP and changes in respiration. As Table 1 shows, intraventricular injection of saralasin caused a decrease in amplitude of pressor responses to stimulation of the above-mentioned zones of the anterior, middle, and posterior hypothalamus. The amplitude of the depressor component of the cardiovascular responses remained unchanged under these circumstances. Saralasin had its strongest effect on pressor responses to stimulation of the paraventricular and supraoptic hypothalamic nuclei, which are known to contain neurosecretory cells. For instance, the amplitude of the pressor response to stimulation of the paraventricular nuclei against the background of the central action of saralasin was depressed on average by 68%, whereas the amplitude of the pressor response to stimulation of the supraoptic nucleus was depressed by 76% (Fig. 1). The amplitude of pressor responses to stimulation of hypothalamic structures not containing neurosecretory cells also was reduced during the central action of saralasin, but the degree of depression of the pressor response in this case was much lower. Thus, during the central action of saralasin, the pressor response to stimulation of the ventromedial nucleus was depressed by 39%, of the supramammillary nucleus by 24%, the lateral hypothalamic field by 17%, and the anterior hypothalamic field by 14%. The latent period of reduction of the amplitude of pressor responses to stimulation of the different hypothalamic zones against the background of the central action of saralasin was 11 ± 0.6 min, and the recovery period of the initial amplitude of the pressor responses was 115 ± 3.2 min. Intraventricular injection of saralasin caused no statistically significant change in the frequency and depth of respiration and in the amplitude of the principal ECG waves.

The experimental results show that intraventricular injection of saralasin, a specific blocker of angiotensin II receptors, reduces the amplitude of pressor responses to stimulation of various hypothalamic zones. This points to a role of the vasoactive oligopeptide angiotensin II in the mechanisms of formation of pressor responses to stimulation of hypothalamic structures. Electrical stimulation of these hypothalamic zones not only leads, evidently, to increased sympathetic tone, but it also activates certain neurochemical mechanisms and, in particular, it facilitates interaction between the endogenous vasoactive oligopeptide angiotensin II and receptor formations, resulting in elevation of the systemic

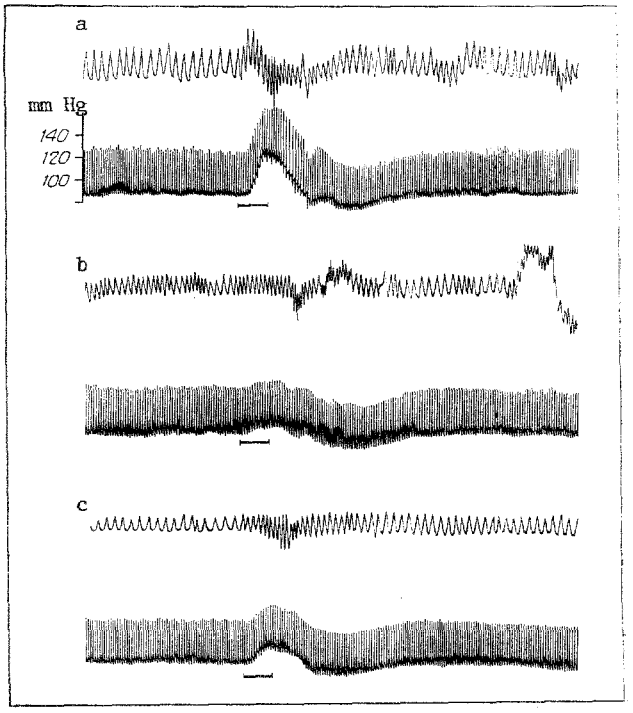

Fig. 1. Effect of stimulation of supraoptic hypothalamic nucleus on cardiovascular responses during central action of saralasin. From top to bottom: respiration, BP, marker of stimulation of supraoptic hypothalamic nucleus for 3 sec. a) Background trace; b, c) traces obtained 12 and 56 min after intraventricular injection of saralasin, respectively.

BP. The difference in the degree of depression of pressor responses to stimulation of structures in the anterior, middle, and posterior hypothalamus against the background of the central action of saralasin indicates differences in the level of participation of angiotensin II in the mechanisms of BP elevation in response to stimulation of the different hypothalamic formations. It can be concluded from the results that elevation of BP in response to stimulation of the supraoptic and paraventricular hypothalamic nuclei is based predominantly on a mechanism of interaction between endogenous angiotensin II and receptors in these structures, whereas the role of this mechanism in the formation of pressor responses to stimulation of the ventromedial and supramammillary nuclei and the lateral and anterior hypothalamic fields is relatively unimportant. Investigations [9, 13] have shown that the pressor response to intraventricular injection of angiotensin II is formed mainly through vasopressin release from the pituitary gland, and also through an increase of sympathetic tone in certain regions of the body besides those innevervated by the splanchnic, suprarenal, and renal nerves [15]. Vasopressin secretion is initiated by the activity of neurosecretory cells of the hypothalamus, and their activity is determined by the endogenous angiotensin II level. It can be tentatively suggested that the formation of pressor responses to electrical stimulation of hypothalamic structures is evidently the result of interaction of endogenous angiotensin II with the corresponding receptors of those structures, leading to the formation of vasopressin and its release into the blood stream and to an increase in peripheral resistance, and also of activation of the sympathetic nervous system, leading to constriction of peripheral vessels and to elevation of the plasma catecholamine levels The rise of BP in response to excitation of hypothalamic structures containing neurosecretory cells is evidently due mainly to the formation of vasopressin, whereas in response to excitation of other hypothalamic structures the pressor reponse is formed mainly through activation of the sympathetic nervous system.

LITERATURE CITED

1. A. V. Val'dman, M. M. Kozlovskaya, and V. A. Tsyrlin, Byull. Éksp. Biol. Med., No. 1, 3 (1968).

2. Zh. I. Deleva and N. A. Nikolov, Vasoactive Peptides [in Russian], Sofia (1980), p. 17.
3. K. V. Sudakov, Emotional Stress and Arterial Hypertension [in Russian], Moscow (1976).
4. A. V. Tonkikh, The Hypothalamo–Hypophyseal Region and Regulation of Physiological Functions [in Russian], Leningrad (1968).
5. T. Akaishi, H. Negoro, and S. Kobayashi, Brain Res., 188, 499 (1980).
6. M. H. Evans, Brain Res., 183, 329 (1980).
7. J. T. Fitzsimons, Rev. Physiol. Biochem. Pharmacol., 87, 117 (1980).
8. D. Ganten, K. Hermann, T. Unger, and R. E. Lang, Clin. Exp. Hypertens., 5A, 1099 (1983).
9. D. Haack and J. Möhring, Pflügers Arch., 373, 167 (1978).
10. A. K. Johnson, J. Buggy, G. D. Fink, and M. J. Brody, Brain Res., 205, 255 (1981).
11. I. A. Reid, Progr. Biochem. Pharmacol., 12, 117 (1976).
12. D. Ganten et al. (eds.), The Renin Angiotensin System in the Brain (Exp. Brain Res., Suppl. 4), Berlin (1982).
13. W. B. Severs and A. E. Daniels–Severs, Pharmacol. Rev., 25, 415 (1973).
14. G. Stock, U. Rupprecht, H. Stumpf, and K. H. Schlör, J. Autonom. Nerv. Syst., 3, 503 (1981).
15. T. Unger, W. Rascher, C. Schuster, et al., Eur. J. Pharmacol., 71, 33 (1981).

CATECHOLAMINE-CONTAINING SYMPATHETIC SPINAL NEURONS INNERVATING THE CAT HEART

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Intensive study of sympathetic preganglionic neurons in recent years [3-5, 8] has shown that besides the classical preganglionic neurons located in the intermediolateral nucleus of the gray matter of the spinal cord, other "untypical" neurons also exist. They may lie in the dorsomedial, lateral, and central part of the ventral horn [3-5]. Some of these cells have axons running to the heart through the stellate ganglion without interruption [3]. Reports widening our ideas on the neurotransmitters involved in the function of sympathetic preganglionic neurons have been published. They have revealed peptides (enkephalin, neurotensin, somatostatin, substance P) and serotonin [8, 9]. In the investigation described below the localization and neurotransmitter involvement of "untypical" sympathetic preganglionic neurons concerned with the regulation of cardiac activity were studied.

EXPERIMENTAL METHOD

Experiments were carried out on 28 noninbred cats weighing 2.5-3.5 kg. Under chloralose-pentobarbital anesthesia (50 and 10 mg/kg, respectively, intraperitoneally) the right stellate ganglion of the animals was exposed through an extrapleural approach. The localization of neurons whose axons are not interrupted in the stellate ganglion was determined by retrograde axonal transport of uranyl acetate (40% aqueous solution) through the caudal anastomosis of the stellate ganglion [2]. The presence of catecholamines in the cytoplasm of the neurons was established by the reaction with glyoxylic acid [6] and glutaraldehyde [1]. Fluorescence was observed in the Lyumam I-3 luminescence microscope. Resconstruction of the sections was carried out with the aid of the N-307 graph plotter.

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