CHANGES IN ACTIVITY OF LUNG ANGIOTENSIN-CONVERTING ENZYME AND SYSTEMATIC HEMODYNAMICS IN SPONTANEOUSLY HYPERTENSIVE RATS UNDER GALVANIC STIMULATION

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An important function of the pulmonary microvessels is inactivation of the depressor peptide, bradykinin (Bk) – and conversion of angiotensin I (ANG-I) into a powerful pressor factor, angiotensin II (ANG-II). These coupled processes are effected with the participation of an angiotensin-converting enzyme (ACE; EC 3.4.15.1), which is localized in the membrane of the endothelial cells [10, 12]. ACE is ascribed an essential role in the regulation of the arterial blood pressure (BP) and in the pathogenesis of arterial hypertension [7, 9]. The development of spontaneous hypertension in Okamoto-Aoki rats is accompanied by changes in activity not only of the ACE of the lungs [1, 2, 4], but also of ACE of the brain, kidneys, and blood serum [4, 5, 14]. The use of pharmacological inhibitors of ACE (teprotide, captopril, etc.) in vivo does not enable the role of regional changes in ACE activity in the genesis of hypertension to be evaluated, for irrespective of how they are administered, these inhibitors are quickly distributed in the blood stream and exert a systemic action [8]. It was shown previously that local depression of ACE function in the lungs can be achieved in normotensive rats (NTR) by the action of a galvanic current (GC) on the chest [6]. The aim of this investigation was to compare changes in the systemic hemodynamics and in ACE activity in the lungs during stimulation of the chest by GC in spontaneously hypertensive rats (SHR) and NTR.

EXPERIMENTAL METHOD

Experiments were carried out on female SHR of the Okamoto-Aoki (n = 65) and NTR of the Wistar-Kyoto lines (n = 20), ages 6 months and weighing 260-300 g. The mean value of BP was measured in the femoral artery by a direct method ("Barovar" instrument, strain gauge transducer); other parameters of the systemic hemodynamics were determined by tetrapolar rheography [3]. Physiological ACE activity in the lungs was assessed by comparing doses of BK ("Reanal," Hungary) and ANG-I ("Sigma," USA) which, when injected into the ventricles of the heart, induced a standard change of average BP [1]. Biochemical ACE activity in the lung tissue and blood serum (substrate – hippuryl-histidyl-leucine) ("Serva," West Germany) – was determined by the method described previously [4]. The source of GC was an AGP-33 apparatus. The area of the hydrophilic pads, soaked in physiological saline, was 5 cm^2. When GC was applied to the projection region of the lungs the electrodes were located bilaterally, on epilated areas of thoracic skin; when GC was applied to other regions than the lungs, they were located bilaterally, on the skin of the upper third of the surface of the thigh. The dose for a single exposure to GC was 0.2 mA/cm^2 for 30 min. This procedure was carried out daily for 10 days on the conscious animals. During this period their systolic BP level was measured in the artery at the base of the tail by an indirect method, using a piezoelectric replacement transducer and biopotentials amplifier. The animals were anesthetized with urethane (1.5 g/kg, subcutaneously) 48-96 h after the end of galvanic stimulation and parameters of the systemic hemodynamics and ACE activity were studied. SHR and NTR not subjected to galvanic stimulation served as the control. The significance of changes was assessed by Student's test.

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TABLE 1. Change in Parameters of Systemic Hemodynamics of SHR and NTR under the Influence of GC

Parameter	GC applied to chest		GC applied outside the projection region of the lungs of SHR (n = 10)
	SHR (n = 10)	NTR (n = 10)	
Average BP in femoral artery, mm Hg	105,0±1,7 (142,6±1,7) $p_1<0,001$ $p_2<0,001$	92,5±2,0 (99,5±2,4)	147,5±3,1
Heart rate, beats/min	267±12 (390±12) $p_2<0,001$	357±10 (362±10)	386±17
Stroke index, ml/kg	0,860±0,024 (0,502±0,022) $p_1<0,001$ $p_2<0,001$	0,558±0,016 (0,570±0,021)	0,611±0,021
Cardiac index, ml/min/kg	227±6 (195±9) $p_1<0,01$	198±3 (204±4)	233±4
Specific peripheral vascular resistance, mm Hg/ml/min/kg	0,464±0,01 (0,774±0,033) $p_1<0,001$ $p_2<0,001$	0,462±0,013 (0,488±0,013)	0,635±0,015

Legend. Data for SHR and NTR not subjected to GC given in parentheses. p_1) Significance of differences between experimental and control animals, p_2) significance of difference between SHR subjected to the action of GC on the chest and outside the projection region of the lungs.

EXPERIMENTAL RESULTS

Under the influence of GC applied to the chest of SHR the mean BP level fell, the heart rate was reduced, and the stroke index and cardiac index increased (Table 1, Fig. 1). Application of GC to the chest of NTR had no significant effect on BP, cardiac output, and peripheral vascular resistance. When GC was applied outside the projection region of the lungs (to the skin of the thighs) the SHR did not develop a hypotensive effect. In the animals of this group, however, an increase was observed in the stroke index and cardiac index (by 21.7 and 19.4% respectively, $p < 0.01$) and the peripheral vascular resistance decreased (by 17.9%, $p < 0.01$) although the decrease was less marked than when GC was applied to the chest of SHR.

Parameters of ACE activity differed signficantly in the experimental and control SHR (Table 2). The development of vasodilator and hypotensive effects in response to application of GC to the chest of SHR was accompanied by a considerable decrease (by 2.3 times) in kinase activity of ACE in the lungs. ANG-I-converting activity was unchanged. The results of direct biochemical determination of ACE activity (as reflected in hydrolysis of hippuryl-histidyl-leucine) in the lung tissue and blood serum are, at first glance, paradoxical. Activity in the lung tissue of the experimental SHR was increased by 1.5 times, whereas in the blood serum it was considerably reduced (by 2.5 times) compared with the control SHR, in which the hypotensive effect was absent.

Where the decrease in serum ACE activity explains the hypotensive effect of galvanization, the increase in ACE activity in the lungs contradicts this fact. However, it must be recalled that the angiotensin-converting function of the lungs was unchanged in SHR of the experimental group, and its level was much lower than that in intact NTR of the same age and weight [2]. Consequently, the increase in ACE activity in the lungs after exposure to GC is of no functional importance for ANG-II formation. More probably the fall in systemic BP taking place under the influence of GC was connected with a change in BK metabolism. In the experimental SHR BK metabolism was depressed by more than half compared with that in the control group of animals.

Thus the decrease in ACE activity in the blood, while angiotensin conversion was unchanged, and the simultaneous reduction of the kinin-degrading function of the lungs are factors leading to a fall of pressure under the influence of GC.

When the results are examined, attention must be paid to the similarity of the changes in the hemodynamics and ACE activity arising under the influence of GC applied to the chest of SHR, and under the influence of synthetic ACE inhibitors (captopril). Long term adminis-

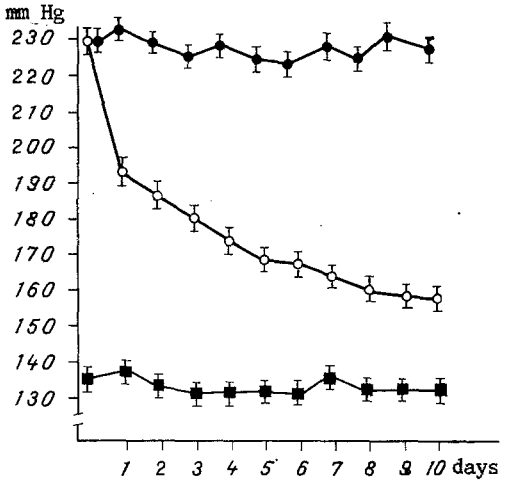

Fig. 1. Dynamics of systolic BP (in mm Hg) of rats under the influence of daily exposure to GC (0.2 mA/cm^2). Empty circles – GC applied to chest of SHR (n = 15), filled circles – GC applied to SHR outside projection region of lungs (n = 15), filled squares – GC applied to chest of NTR (n = 10).

TABLE 2. Changes in Parameters of ACE Activity during Application of GC to the Chest of SHR

Parameter	Experiment (n = 15)	Control (n = 15)	p
Kinase function of lung ACE: coefficient of BK metabolism in lungs	23,3±4,4	53,6±5,9	<0,001
ANG-I-converting function of lung ACE: coefficient of ANG-I metabolism in lungs	0,3±0,2	0,3±0,1	
ACE activity based on hydrolysis of hippuryl-histidine-leucine:			
in lungs, nmoles His-Leu/min/mg protein of supernatant of lung tissue homogenate	46,7±3,9	31,4±1,1	<0,01
in blood serum, nmoles His-Leu/min/mg protein	0,13±0,01	0,34±0,01	<0,001

Legend. Coefficient of metabolism expressed in hemodynamically active units, destroyed or formed in the lungs. For BK, dose difference RV – LV/dose in LV; for ANG-I, dose difference LV – RV/dose in RV (LV – left ventricle, RV – right ventricle). Doses of BK and ANG-I, when injected into ventricles of the heart, induce a standard hemodynamic response of the average BP of ±15-20 Hg within the linear range [3].

tration of captopril to SHR also leads to a fall of the systemic BP due to a decrease of the peripheral vascular resistance, and the developing vasodilatation is accompanied by an increase in cardiac ejection [8, 13]. Meanwhile, during chronic inhibition of ACE by captopril, the activity of this enzyme (based on hydrolysis of hippuryl-histidyl-leucine) increases in the lung tissue but decreases in the blood serum, whereas according to the results of physiological testing, conversion of ANG-I into ANG-II in the vascular bed is considerably reduced. The absence of a parallel between determination of ACE activity in vitro and in vivo can be interpreted as the result of induction of ACE synthesis under conditions of continuous binding of the enzyme with the specific inhibitor [11, 15]. Without discussing this hypothesis, it is important to note that a similar principle was discovered in the case of local action by GC on ACE in the lungs.

Thus during local application of GC to ACE in the lungs changes in the hemodynamics and in the biochemical and physiological parameters of ACE activity develop and are similar to those observed under the influence of specific ACE inhibitors.

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EEG CHANGES AND MANIFESTATIONS OF PARKINSONISM FOLLOWING INTRACAUDATE INJECTION OF DOPAMINE ANTIBODIES

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The syndrome of parkinsonism has been shown [1, 3] to be connected with the formation of a generator of pathologically enhanced excitation (GPEE) [3] in the caudate nuclei (CN). GPEE formation may be the result of insufficiency of dopaminergic inhibitory control, leading to disinhibition of the cholinergic neurons of CN, or it may be an expression of primary hyperactivity of these neurons [1, 3, 4]. Insufficiency of the dopaminergic nigrostriatal system may be the result of injury to the dopaminergic neurons of the substantia nigra [15] or of a disturbance of dopamine (DA) secretion by the nerve endings of these neurons in CN [1, 3]. We know that antibodies to neurotransmitters can selectively bind the corresponding transmitters in the body and change the functional state of systems and organs [7, 10].

The aim of this investigation was to study the possibility of GPEE formation in CN and of thereby reproducing the basic symptoms of the syndrome of parkinsonism (oligokinesia, rigidity, tremor) by binding DA with antibodies in these nuclei.

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