EFFECT OF EXERCISE ON RENIN, KALLIKREIN, AND ANGIOTENSIN-CONVERTING ENZYME IN MAN

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The grounds for undertaking this investigation were as follows: the kallikrein–kinin system of the blood and kidneys plays an active part in the regulation of arterial pressure both at rest and during short-term or long-term physical exertion [2, 3, 8]. The plasma renin level rises considerably during exercise, making possible the formation of increased quantities of pressor angiotensins [7, 9, 15]. There is solid evidence for several biochemical links in the chain of functional interaction between the kallikrein–kinin and renin–angiotensin systems. This interaction is effected through angiotensin-converting enzyme (ACE) and the recently discovered role of kallikrein as a direct activator of the blood plasma renin [11, 16, 17].

It was accordingly decided to study parameters of the blood renin–angiotensin and kallikrein–kinin systems that are connected with changes in hemodynamic parameters of healthy subjects during exercise.

EXPERIMENTAL METHOD

The subjects of the investigation were 21 healthy men, not engaged in regular athletics, and with a mean age of 33.1 ± 0.8 years. The subjects did measured and gradually increasing exercise on a bicycle ergometer with a power of 25 W, which subsequently increased by 25 W every 5 min. The maximal load was 100-125 W. The work was done in recumbency with the upper half of the trunk raised through 30°. Blood for the biochemical tests was taken from the cubital vein before and immediately after the end of the exercise.

Renin activity in the blood was determined by a radioimmunologic method using standard kits from CEA-IRE-Sorin (France). ACE activity was determined [5] in the serum, using hippuryl-histidyl-leucine as the substrate, and kallikrein activity and the prekallikrein level also were determined [6].

The following hemodynamic parameters were studied at the same time: the systolic and diastolic blood pressure by Korotkov's auscultative method, the heart rate from the ECG, the stroke volume of the heart by ultrasonic echocardiography on an "Ekoline-20A" apparatus (Smith Kline Instruments, USA). These parameters were used to determine the cardiac and stroke indices and also the specific peripheral resistance, which were calculated by the usual equations.

The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The data in Table 1 show that exercise was accompanied by changes in the levels of all biochemical parameters tested. The functional trend of these changes points to activation of humoral systems, regulating the arterial pressure level and acting in opposite directions. An increase in plasma renin activity by 41.1% was accompanied by an increase in the kallikrein level by 95.5% and a corresponding decrease in the prekallikrein level. It will be

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TABLE 1. Changes in Activity of Blood Renin–Angiotensin and Kallikrein–Kinin Systems before and after Exercise in Man

Parameter	At rest	After exercise
Renin	1,40±0,12	1,98±0,16* (+41,4)
ACE	7,94±0,55	6,83±0,81 (—13,9)
Prekallikrein	394,0±17,6	318,0±18,5* (—19,3)
Kallikrein	22,4±2,1	43,8±4,4** (+95,5)
Renin/ACE	0,17	0,30
Kallikrein/renin	16,0	27,0
Kallikrein/ACE	2,8	6,4

Legend. Enzyme activity for renin — in ng/ml/h, for ACE in nanomoles histidyl-leucine/ml/min, for kallikrein and prekallikrein in milliunits/ml serum. *P < 0.05, **P < 0.001. Here and in Table 2 difference in percent shown in parentheses.

TABLE 2. Changes in Hemodynamic Parameters in Healthy Subjects as a Result of Exercise

Parameter	At rest	After exercise
Blood pressure, mm Hg		
systolic	118,8±2,2	162,4±4,8*(+36,7)
diastolic	78,4±1,9	80,0±2,1
Heart rate, beats/min	67,0±1,9	139,2±3,6*(+107,8)
Stroke index, ml/m^2	42,0±2,3	41,3±5,4
Cardiac index, liters/min/m^2	2,83±0,13	5,65±0,51*(+99,6)
Specific peripheral resistance, dynes·sec·cm^{-5}·m^{-2}	2598±65	1521±97*(—41,4)

*P < 0.001.

noted that blood ACE activity (a factor converting angiotensin I into the more effective pressor form — angiotensin II) did not change significantly; moreover there was a tendency for ACE activity to fall during exercise.

These changes were accompanied by marked shifts in the hemodynamic indices (Table 2), and particular attention is drawn to the increase of 107.8% in the heart rate without any significant change in the stroke index of the heart and the diastolic pressure. These changes in the hemodynamic parameters are typical of submaximal physical exertion in healthy individuals and they indicate that the necessary increase in cardiac output and in the blood flow to working skeletal muscles are maintained by sympathetic inotropic influences on the heart, accompanied by a simultaneous decrease in the resistance of the vascular system through activation of dilator mechanisms of peripheral regulation of the circulation [4].

When relations between the biochemical components of the renin-angiotensin and kallikrein–kinin systems involved in regulation of the arterial pressure are defined, the polyfunctional nature of the lines joining them must be noted. Kallikrein, through bradykinin formation, participates in the regulation of the raised arterial pressure and, at the same time, it facilitates the cardic ejection and increases the venous return of blood to the right heart [1]. Meanwhile kallikrein itself (both renal and plasma) may play an essential role in the conversion of renin into its active form [16, 17]. The function of ACE, the key enzyme linking the angiotensin and kallikrein–kinin systems, likewise may vary. The "usual" function of ACE is to convert angiotensin I formed by the action of renin into the more active form, which helps to maintain the tonic activity of the blood vessels. At the same time, a reciprocal relationship evidently exists between ACE and renin: an increase in renin activity is inhibited by converting enzyme, as investigations using ACE inhibitors during exercise

[15] or in patients with essential hypertension [13, 14] have shown. The absence of any increase in ACE activity in the present investigation or even a tendency for it to decrease can thus be interpreted as a mechanism maintaining the functions of the pressor factors (renin) at the given stage of the response of the body to moderate physical exertion. At the same time, however, a depressor controlling factor is activated, in the form of a considerable (by 95.5%) increase in kallikrein activity. The renin/ACE, kallikrein/renin, and kallikrein/ACE ratios given in Table 1 indicate a change in the relations between pressor and pressor-limiting tendencies during physical exertion. The increase in renin activity was considerably greater than the increase in kallikrein activity, and for that reason the values of the ratios during exertion shift in favor of kallikrein.

It must be supposed that plasma ACE activity is stable under normal conditions. Conversion of angiotensin II probably is achieved on account of a tissue peptidyl-dipeptidase, located mainly in the endothelium of the lungs and kidneys. On the whole this analysis indicates that the relations between the various humoral factors involved in arterial pressure control during exercise may be represented as follows: activation of the sympathetic component (with the participation of catecholamines of the adrenals and heart), activation of the renin–angiotensin system as supporting component, activation of the kallikrein–kinin system as a factor controlling the level of both hemodynamic and biochemical control systems.

Probably there is every right also to include the prostaglandin system in this scheme [10] also because the realization of any hemodynamic response at the level both of the blood vessels and of the heart itself invariably requires their participation.

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