Praca oryginalna *Original paper*

Influence of bradykinin and ACE inhibitors on selected biochemical markers of oxidative stress in rats with induced ischemia-reperfusion syndrome

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Summary

Cessation of blood flow in tissues leads to depletion of energetic resources of cells, disturbances in the activity of enzymes of the oxidative chain and electrolyte disorders, as well as to the production of reactive oxygen species. A great deal of attention has been paid to those problems since they are responsible for most of the complications in the ischemia-reperfusion (I/R) syndrome.

Understanding the antioxidative mechanisms involved in I/R syndrome provides us with the potential to correct at least some of the resulting disturbances. One of the potentially beneficial factors is insulin. This observation directed our attention to the insulin-like factors, kinins (especially bradykinin), the activation of which was detected in I/R syndrome. The effect of bradykinin is modified by concurrent administration of the specific antagonists of bradykinin receptors, B1 and B2. The aim of the current study was to assess the role of bradykinin. In the study, the employed agents included the angiotensin converting enzyme inhibitor, which prevents the degradation of endogenous kinins, and blockers of bradykinin receptors, which abolish the influence of kinins. We observed that after 4 hours of ischemia followed by reperfusion, levels of free radicals in tissues as well as levels of peroxides in plasma increased significantly. Administration of bradykinin, captopril or enalapril resulted in the decline of these free radical levels. The application of B2 receptor antagonist decreased the beneficial influence of bradykinin, whereas B1 receptor antagonist revealed no significant effect. Activities of antioxidative enzymes (superoxide dismutase, catalase, and glutathione peroxidase) were measured. After 4 hours of ischemia and consecutive steps of reperfusion, a statistically significant increase in their activities was observed when bradykinin or ACE inhibitors were administered. Application of B2 receptor blockers reduced the effect of bradykinin, whereas the effect of B1 receptor antagonists was minute.

Keywords: bradykinin, ischemia-reperfusion syndrome, ACE inhibitors

Cessation of blood flow to tissues leads to the depletion of the energetic resources of cells, disturbances in the enzyme activity of the oxidative chain and electrolyte disorders as well as to the production of reactive oxygen species. The latter are not only toxic to tissues affected by ischemia but also may be deleterious to the entire organism. Great attention has been paid to these problems since they are responsible for most of the complications in the ischemia-reperfusion (I/R) syndrome.

Understanding the antioxidative mechanisms involved in the ischemia-reperfusion syndrome would provide us with the potential to correct at least some of the resulting disturbances. In our earlier experiments the beneficial influence of insulin has been noticed (11, 18). This observation directed our attention to the insulin-like factors, i.e. kinins, the activation of which was detected in I/R syndrome. Results of recent studies indicate that bradykinin administrated in low doses reduces I/R damage (7, 9).

As previously published, the effect of bradykinin is modified by concurrent administration of specific antagonists of bradykinin receptors, B1 and B2 (12, 26).

Since the reports have been inconclusive, we have decided to verify the published results in our work.

The aim of the current study was to assess the role of bradykinin. Angiotensin converting enzyme inhibitors, which prevent the degradation of endogenous kinins, and blockers of bradykinin receptors, which abolish the influence of kinins, were employed in this study.

Materials and methods

In the experiment adult, male Wistar rats, weighing 256 g ± 32 g, were used. The animals were housed in room conditions of neutral temperature 18 ± 1°C, a photoperiod of 12 hrs, with the free access to water and food (LSM standard laboratory diet). Experiments were always performed at the same time of the day. Pharmaceuticals were administered intraperitoneally in the following doses: ketamin – 90 mg/kg body weight, xylazin – 10 mg/kg body weight, bradykinin ([Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg] acetate) – 320 µg/kg body weight, captopril ([2S]-1-[3-mercapto-2-methyl--propionyl]-L-proline) – 3 mg/kg body weight, enalapril ([2S]--1-[N-(1-ethoxycarbonyl)-3-phenylpropyl]-L-proline) – 2 mg/kg body weight, HOE 140 (D-Arg-[Hyp^3-Thi^5-D-Tic^7-Oic^8]--bradykinin) – B2 receptor antagonist – 200 µg/kg body weight, desArg^9[Leu^8]-bradykinin ([Arg-Pro-Pro-Gly-Phe-Ser--Pro-Leu]acetate) – B1 receptor antagonist – 250 µg/kg body weight.

The animals formed three experimental groups. Each group was subdivided into six subgroups.

Group I included control rats, with the normal blood supply. Group II comprised the animals subjected to ischemia and Group III was formed by the animals subjected to ischemia followed by reperfusion. In subgroup 1 the animals were treated with an injection of 1 ml 0.9% NaCl, sixty minutes before sampling, in subgroup 2 the rats were treated with bradykinin sixty minutes before sampling, in subgroup 3 the rats received captopril sixty minutes before sampling, in subgroup 4 the rats were given enalapril sixty minutes before sampling, in subgroup 5 the rats were treated with both bradykinin and bradykinin B1 receptors antagonists sixty minutes before sampling and in subgroup 6 the rats received bradykinin and bradykinin B2 receptor antagonist sixty minutes before sampling.

Ischemia of the lower hindlimb was produced by placing a pneumatic tourniquet around the left thigh and inflating the cuff to 200 to 210 mm Hg, which was almost twofold higher than the resting systolic blood pressure. The procedure produced complete ischemia as is determined by the blanching of the skin of the leg and a decline in the interstitial temperature of the foot. The foot temperature was monitored by a temperature probe inserted into the tissue just before the inflation of the pneumatic cuff. The temperature was monitored throughout the ischemic period and during reperfusion. During ischemia the foot temperature was 28° ± 1°C, compared with a temperature of 34° ± 1°C before the inflation of the cuff. The tourniquet was applied for 4 hrs and then the garrot was released and reperfusion induced for 30, 60 or 120 minutes.

Twenty three hours after the beginning of the experiments the animals belonging to particular groups were treated with kallikrein-kinin system modifiers (bradykinin, captopril, enalapril and bradykinin receptor blockers) or 0.9% NaCl (control), respectively. Fifty minutes later the rats were anesthetized by an intraperitoneal application of ketamin and xylazine. After the subsequent 10 min the thorax and abdominal cavities were opened. Blood samples were collected on heparin by puncturing the right ventricle. Samples of skeletal muscle were collected in the third and tenth minute of reperfusion, each time from the same part of the muscle. One part of each muscle sample was placed in liquid nitrogen (sample 1) and the other in a container with ice (sample 2).

Free radical levels were determined in sample 1, employing paramagnetic electron resonance. Activities of superoxide dismutase, catalase and glutathione peroxidase were determined in sample 2. The tissue was homogenized for 30 s in a teflon homogenizer in 10 volumes of 50 mM Tris - 0.1 mM EDTA (pH 7.6) at 4°C. The homogenates were centrifuged at 12 000 × g for 20 minutes at 4°C in the Janetzki K-24 centrifuge to remove the tissue debris. The activity of catalase was measured in the supernatant. Activities of superoxide dismutase and glutathione peroxidase were measured in a cytosolic fraction obtained as the supernatant after subsequent centrifugation at 105 000 × g for 20 min. Activity of SOD was measured in the cytosolic fraction by the technique described by Misra and Fridovich and was expressed in units per mg of protein (U/mg) (20). Activity of catalase in the skeletal muscle was measured with the technique described by Beers et al. It was expressed in Bergmeyer units per 1 gram of protein. Activity of glutathione peroxidase in the skeletal muscle was measured by the technique of Little and O'Brien and expressed in units per gram of protein (U/g) (13). Concentration of malonyldialdehyde (MDA) in homogenates of skeletal muscle was measured as described by Ohkawa et al. (23). Plasma levels of superoxides were measured with Bioxytech H_2O_2 – 560 Test (Oxis, USA). Protein concentrations in subcellular fractions were measured according to Lowry (14).

After applying the Q-Dixon test for uncertain results, mean arithmetic values and standard deviations were calculated. The statistical significance was determined using the t-Student test for unrelated values. The differences were considered statistically significant when $p < 0.05$.

The project was approved by The Local Ethical Commission for Experiments on Animals in Poznań (assessment no. 99/2001).

Results and discussion

It was observed that after 4 hours of ischemia followed by reperfusion levels of free radicals in tissues as well as levels of peroxides in blood plasma increased significantly. The administration of bradykinin, captopril or enalapril resulted in a decline of the free radical levels. The application of B2 receptor antagonist decreased the beneficial influence of bradykinin, whereas the B1 receptor antagonist revealed no significant effect. The increased concentration of malonyldialdehyde in skeletal muscle and blood was detected during ischemia followed by reperfusion. Again the administration of bradykinin and/or ACE inhibitors resulted in a statistically significant decrease in concentration of this compound during both ischemia and reperfusion, as compared to the reference group of animals. The data are presented in tab. 1.

Activities of antioxidative enzymes (superoxide dismutase, catalase and glutathione peroxidase) were measured. After 4 hours of ischemia and consecutive steps of reperfusion, a statistically significant increase

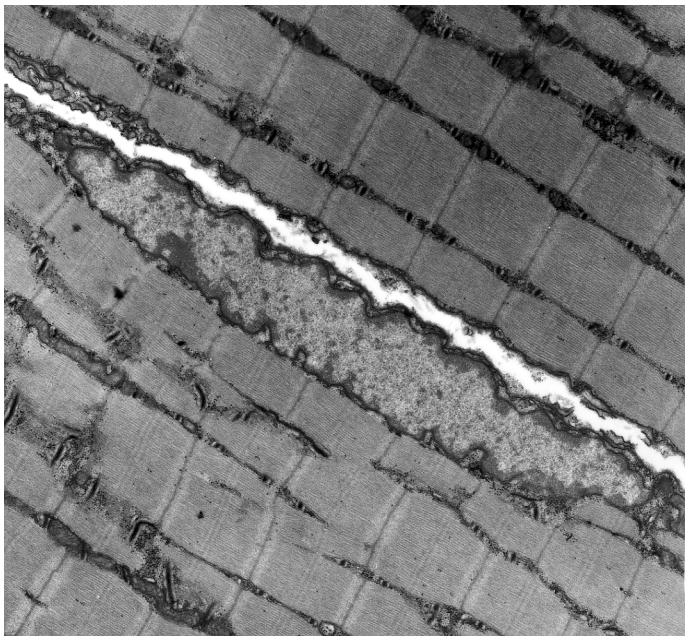

Fig. 1.

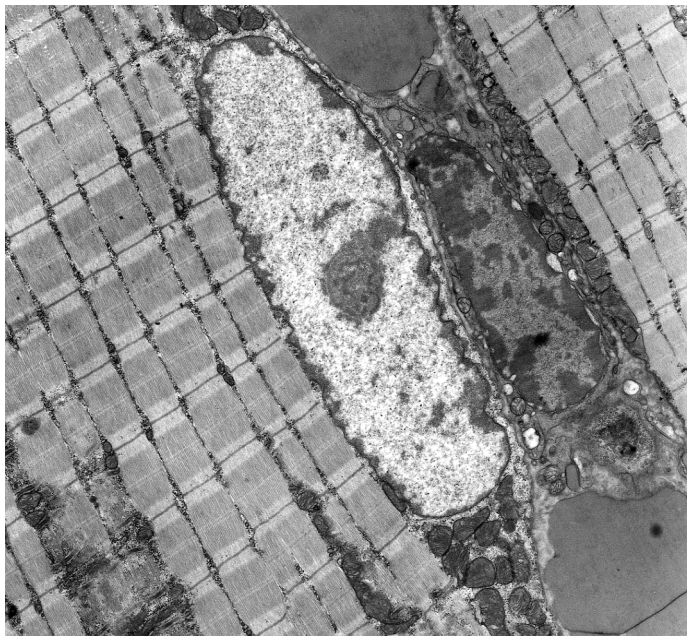

Fig. 2.

in their activities was observed when bradykinin or ACE inhibitors were administered. Some increase in the activities resulted from the administration of B1 receptor antagonist. The application of B2 receptor antagonist decreased the effect of bradykinin (tab. 2).

Kinins prevent excessive accumulation of ATP decay products, which may result in lower levels of free radicals observed during reperfusion. This claim is indirectly also confirmed by the data on the stimulatory effect of ATP decay products on tissue kinin synthesis (4). The studies of Needleman (22) proved that the kalikrein-kinin system in the heart and skeletal muscles was activated in response to a local imbalance in the demand for oxygen and its supply. The purpose of this activation was to restore both proper oxygen supply and levels of high-energy compounds (7). The results of this study have confirmed this observation. The decrease of free radical levels in animals which have been treated with bradykinin, captopril or enalapril prove the protective role of kinins on ischemic tissues (5). It was assumed that application of the kinase II inhibitors, captopril and enelapril, should beneficially influence the mechanisms protecting cells against damage caused by ischemia followed by reperfusion.

The data presented by Fenoy (7) suggested that kinin vasodilatory effect was independent of the renin-angiotensin system, and that it was linked to the stimulation of nitrous oxide releases by vascular endothelium (28). The reaction of NO with superoxide radical involves one of the main ways to eliminate nitrous oxide. Sweeping of the superoxide radicals by thiol compounds such as captopril increases the half-life of NO, enhancing its vaso-dilatory effect. Another mechanism contributing to the more effective action of nitrous oxide after captopril administration may result from the synthesis of more stable nitrosotrioles. The results presented by van Gilst (28) demonstrate the influence of ACE inhibitors on prostacyclin synthesis. Prostacyclins are known to decrease free radicals production in tissues. They also modulate the free radical reactions in granulocytes, and lower the production of catecholamins, being a significant source of free radicals in ischemic muscle (28). However, our results show a decrease of free radicals levels in the analyzed tissues after administration of exogenous bradykinin. It still remains to be elucidated whether the observed phenomenon has resulted from the modulated production of free radicals or rather from the changed efficacy of antioxidant systems. These studies have revealed an increase of SOD and GSH-Px activities after administration of ACE inhibitors. Increased activity of glutathione peroxidase was also detected in erythrocytes of patients receiving captopril (8). Perhaps this may result from intensified glucose metabolism, leading to an increased level of NADPH, which affects the activity of GSH-Px (24). The assumption that bradykinin moderates the course of I/R syndrome, including the effect on antioxidative enzyme activities, is supported by results obtained in the group of rats receiving antagonists of bradykinin receptors B1 and B2. It should be stated here that B2 receptors are constitutively present on the surface of various cell types, whereas the number of B1 receptors is regulated by inflammatory factors and by the activation of B2 receptors.

The effects of the activation of B1 and B2 receptors differ significantly. The activation of B2 receptors results in beneficial decrease in free radicals production and vasodilatation while the activation of B1 receptors leads, among other, to unfavorable effects, such as increased levels of inflammatory factors and enhanced permeability of vessels (16, 25). The data from literature suggest that the effects of bradykinin, and the antagonists of bradykinin receptors, are strongly affected by the doses applied. This may be the reason why the results from various labs differ significantly (15, 26). In our studies we have found no significant influence of

Tab. 1. Levels of free radicals in skeletal muscle, levels of malonyldialdehyde in skeletal muscle and levels of superoxides in plasma of rats treated with bradykinin, captopril, enalapril or bradykinin receptor blockers (mean ± SD)

Group	Reference group	Bradykinin – BK	Captopril	Enalapril	BK + B1 blocker	BK + B2 blocker
Levels of free radicals (10^{18} of unpaired spines/1 g tissue)						
Control	0.59 ± 0.13	0.53 ± 0.11	0.53 ± 0.11	0.50 ± 0.18	0.60 ± 0.12	0.52 ± 0.17
4-hours of acute ischemia	1.68^{a} ± 0.10	1.27^{ab} ± 0.17	1.21^{ab} ± 0.24	1.19^{ab} ± 0.27	1.46^{a} ± 0.14	1.73^{ac} ± 0.15
30rd minute of reperfusion	2.68^{a} ± 0.13	2.01^{ab} ± 0.11	1.84^{ab} ± 0.26	1.78^{ab} ± 0.22	2.15^{a} ± 0.18	2.74^{ac} ± 0.20
60th minute of reperfusion	2.94^{a} ± 0.14	2.18^{ab} ± 0.19	2.03^{ab} ± 0.23	1.98^{ab} ± 0.27	2.31^{a} ± 0.17	2.87^{ac} ± 0.17
120th minute of reperfusion	3.32^{a} ± 0.11	2.87^{ab} ± 0.23	2.38^{ab} ± 0.29	2.41^{ab} ± 0.29	2.91^{a} ± 0.28	3.55^{ac} ± 0.25
Levels of malonyldialdehyde (nM/1 g tissue)						
Control	25.15 ± 1.33	23.05 ± 1.27	20.95± 1.12	21.02 ± 1.31	22.59 ± 1.41	25.86 ± 1.25
4-hours of acute ischemia	38.71^{a} ± 2.57	32.58^{ab} ± 1.85	28.76^{ab} ± 1.41	27.61^{ab} ± 1.57	32.92^{a} ± 1.61	40.25^{ac} ± 1.41
30rd minute of reperfusion	44.57^{a} ± 2.11	40.87^{ab} ± 1.96	38.52^{ab} ± 1.72	36.93^{ab} ± 1.37	38.96^{a} ± 1.88	45.88^{ac} ± 1.55
60th minute of reperfusion	43.15^{a} ± 2.45	39.07^{ab} ± 1.83	38.54^{ab} ± 1.61	37.15^{ab} ± 1.41	39.74^{a} ± 1.77	44.52^{ac} ± 1.61
120th minute of reperfusion	44.65^{a} ± 2.62	38.16^{ab} ± 2.18	37.17^{ab} ± 1.79	36.58^{ab} ± 1.69	39.78^{a} ± 2.96	45.16^{ac} ± 1.54
Levels of superoxides (μM H_2O_2/1 ml)						
Control	1.52 ± 0.24	1.87 ± 0.28	1.24 ± 0.21	1.76 ± 0.18	1.74 ± 0.25	1.99 ± 0.23
4-hours of acute ischemia	6.30^{a} ± 0.23	3.72^{ab} ± 0.24	3.52^{ab} ± 0.32	3.81^{ab} ± 0.45	4.12^{a} ± 0.21	7.25^{ac} ± 0.35
30rd minute of reperfusion	12.41^{a} ± 0.32	6.72^{ab} ± 0.32	6.18^{ab} ± 0.52	7.55^{ab} ± 0.56	7.22^{ac} ± 0.37	11.82^{a} ± 0.25
60th minute of reperfusion	8.39^{a} ± 4.11	6.45^{ab} ± 4.57	6.05^{ab} ± 3.92	7.15^{ab} ± 4.52	6.97^{a} ± 4.57	7.83^{ac} ± 4.25
120th minute of reperfusion	9.31^{a} ± 0.43	5.93^{ab} ± 0.51	5.75^{ab} ± 0.32	7.95^{ab} ± 0.45	6.31^{a} ± 0.41	8.89^{ac} ± 0.47

Explanations: means significantly different ($p < 0.05$) compared to: a) control group, b) group with reperfusion, c) group with bradykinin blocker and the group with bradykinin

Tab. 2. Activities of superoxide dismutase, catalase and glutathione peroxidase in skeletal muscle of rats treated with bradykinin, captopril, enalapril, or bradykinin with bradykinin receptors blockers (mean ± SD)

Group	Reference group	Bradykinin – BK	Captopril	Enalapril	BK + B1 blocker	BK + B2 blocker
Activity of superoxide dismutase (SOD) (U/1 mg protein)						
Control	5.86 ± 0.42	6.74 ± 0.31	7.01 ± 0.28	6.86 ± 0.25	6.26 ± 0.49	5.49 ± 0.47
4-hours of acute ischemia	8.32^{a} ± 0.35	9.36^{ab} ± 0.65	9.23^{a} ± 0.81	9.27^{a} ± 0.61	8.96^{a} ± 0.69	8.15 ± 0.52
30rd minute of reperfusion	8.66^{a} ± 0.57	9.73^{ab} ± 0.51	9.67^{ab} ± 0.57	9.74^{ab} ± 0.43	10.05^{ab} ± 0.92	8.11 ± 0.74
60th minute of reperfusion	8.87^{a} ± 0.55	9.34^{a} ± 0.65	9.79^{ab} ± 0.45	9.87^{ab} ± 0.65	9.06^{a} ± 0.75	8.24 ± 0.63
120th minute of reperfusion	10.24^{a} ± 0.84	12.14^{ab} ± 0.75	13.05^{ab} ± 0.61	12.59^{ab} ± 0.79	11.88^{a} ± 0.68	9.68 ± 0.85
Activity of catalase (CAT) (U/1 mg protein)						
Control	0.42 ± 0.04	0.51 ± 0.05	0.58 ± 0.03	0.56 ± 0.04	0.47 ± 0.10	0.41 ± 0.03
4-hours of acute ischemia	0.83^{a} ± 0.05	0.98^{ab} ± 0.16	0.99^{ab} ± 0.09	0.97 ± 0.08	1.15^{ab} ± 0.12	0.77^{a} ± 0.09
30rd minute of reperfusion	0.88^{a} ± 0.11	0.97^{a} ± 0.09	1.08^{ab} ± 0.08	1.09^{ab} ± 0.07	0.91^{a} ± 0.08	0.82^{a} ± 0.11
60th minute of reperfusion	0.89^{a} ± 0.12	1.67^{ab} ± 0.09	1.47^{ab} ± 0.13	1.78^{ab} ± 0.09	1.46^{ab} ± 0.35	0.81^{ac} ± 0.21
120th minute of reperfusion	1.79^{a} ± 0.19	2.16^{ab} ± 0.21	2.07 ± 0.17	2.46^{ab} ± 0.32	2.33^{ab} ± 0.19	1.65^{ac} ± 0.31
Activity of glutathione peroxidase (GSH-Px) (U/1 mg protein)						
Control	5.23 ± 0.43	6.10 ± 0.45	6.80 ± 0.55	6.37 ± 0.52	5.58 ± 0.84	5.17 ± 0.23
4-hours of acute ischemia	8.32^{a} ± 0.75	9.94^{ab} ± 0.69	9.93^{ab} ± 0.68	9.63^{ab} ± 0.51	9.07^{a} ± 0.39	7.27^{c} ± 0.43
30rd minute of reperfusion	9.59^{a} ± 0.56	11.13^{ab} ± 0.71	10.85^{ab} ± 0.65	10.94^{a} ± 0.82	10.88^{ac} ± 0.58	9.07^{c} ± 0.79
60th minute of reperfusion	10.63^{a} ± 0.72	12.34^{ab} ± 0.82	12.17^{ab} ± 0.75	12.08^{ab} ± 0.61	11.67 ± 0.82	9.44 ± 0.71
120th minute of reperfusion	12.52^{a} ± 0.75	14.74^{ab} ± 0.72	15.37^{ab} ± 0.36	14.25^{ab} ± 0.49	15.55^{a} ± 0.61	11.37^{c} ± 0.59

Explanations: as in tab.1.

B1 receptor blockers on the activity of the assayed enzymes. The kinin-induced intensification of amino acid transport and protein synthesis was suggested to represent another mechanism explaining increased activity of antioxidant enzymes in the skeletal muscle. The influence of bradykinin on protein synthesis was proven *in vitro* as well as in patients during the postoperative period (6, 10). Another possibility to consider is the activation of enzymes indirectly through transmitter system II or directly – by bradykinin (17). We have observed the effects of kinins occurring less than an hour after their administration. This is possible due to the relatively short time needed for internalization of the receptor-bradykinin complex. Within 30-40 min 80% of receptor-bound bradykinin is translocated into the cell and released. Bradykinin remains within the cell for another 120 min (21). We have noticed reduced levels of free radicals that inactivate antioxidative enzymes. This is consistent with the data presented by Zieden (29), that have proven an inhibitory effect of captopril on oxidation of lipoproteins. Also Mira et al. (19) found that ACE inhibitors swept off free radicals generated by xantine dehydrogenase-oxidase system. The switch from dehydrogenase to oxidase activity can be blocked by ACE inhibitors which blocks the endothelin and vasopressin mediated release of calcium ions from their intracellular pool (27). Calcium-dependent calpain protease, which converts xantine dehydrogenase into oxidase, is not active if cellular concentration of Ca^{2+} is insufficient (3).

Another reason for reduced generation of free radicals caused by kininogenesis modifiers can include improved vascular flow resulting from activation of the endogenous bradykinin-nitrous oxide-prostacycline system, leading to an improved supply of oxygen (1). This effect can also result from the inhibitory influence of ACE inhibitors on neutrophile chemotaxis in tissues subjected to I/R syndrome, as suggested by Clapperton (2). Perhaps the suppression of interleukin 1, detected by Schindler (25), may also be responsible for this phenomenon. Our current knowledge does not allow us to pinpoint the mechanisms that play the pivotal role. It should, however, be kept in mind that activity of antioxidative enzymes is controlled by the combined effect of all mentioned factors.

Conclusions

The kinin degradation inhibitors captopril and enalapril, as well as exogenous bradykinin, exert an inhibitory effect on oxidative stress generated during the course of I/R syndrome in rats. Bradykinin inhibits oxidative enzymes and, at the same time, increases the activity of antioxidative ones. Application of B2 receptor blockers reduced the effect of bradykinin, whereas the effect of B1 receptor antagonists was minute.

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