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ROLE OF ADRENERGIC MECHANISMS IN REGULATION OF VENULAR PERMEABILITY DURING SHORT- AND LONG-TERM IMMOBILIZATION

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KEY WORDS: venular permeability; microcirculation; mast cells; adrenergic regulation; immobilization.

Immobilization leads to phasic disturbances of vascular permeability in various organs [1, 2, 5]. The writer's previous investigations [3] showed that catecholamines can play different (depending on the duration of immobilization) roles in the regulation of venular permeability. At the same time, there is evidence that β-agonists are able to reduce venular permeability when disturbed by histamine, bradykinin, and prostaglandins [10, 12, 14], i.e., by biologically active subtances which accumulate in excess in the tissues during stress.

The aim of this investigation was to study the role of α- and β-adrenergic mechanisms in the regulation of venular permeability during short- and long-term immobilization.

EXPERIMENTAL METHOD

Experiments were carried out on 169 male Wistar rats weighing 200-250 g. The animals were immobilized in the supine position for 30 min (short-term immobilization) or 24 h (long-term immobilization).

Quantitative evaluation of venular permeability in the rate mesentery was carried out by contact luminescence biomicroscopy (CLB) based on the LYUMAM KF-1 microscope (Leningrad Optical-Mechanical Combine). Rabbit globulin labeled with fluorescein isothiocyanate (FITC) was used as indicator of disturbances of venular permeability.

Biomicroscopic evaluation of the state of the microcirculation conducted on an apparatus based on the "Docuval" microscope (Carl Zeiss, East Germany).

The morphological and functional state of the mesenteric mast cells (MC) was determined after fixation of the tissue with 96° alcohol and staining with 0.5% toluidine blue.

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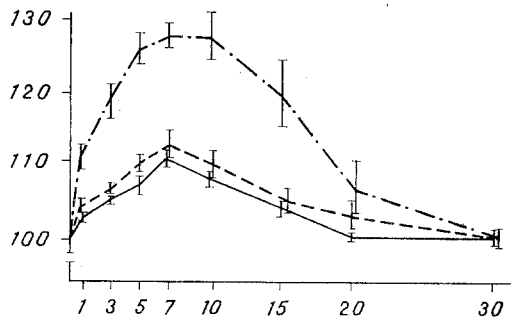

Fig. 1

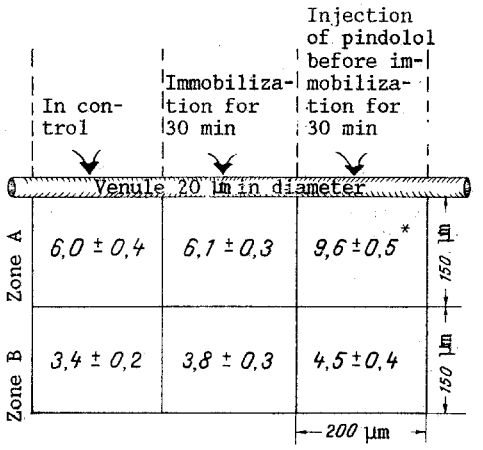

Fig. 2

Fig. 1. Permeability of mesenteric venules of rats for globulin-FITC in the case of short-term immobilization and under the same conditions but after prophylactic injection of the β-adrenoblocker pindolol (CLB method). Abscissa, time after injection of permeability indicator (in min); ordinate, increase in intensity of luminescence (in %), 100% denotes initial background luminescence. Continuous line – contol, broken line – immobilization for 30 min, line of dots and dashed – pindolol + immobilization for 30 min.

Fig. 2. Mean number of mast cells in perivenular regions of mesentery in rats subjected to short-term immobilization with or without preliminary injection of the β-adrenoblocker pindolol (scheme). Zone A denotes region of mesentery immediately adjacent to a venule 20 µm in diameter. Zone B denotes region of the mesentery lying 150 µm from the venule. Dimensions of regions in which mast cells were counted 200 × 150 µm.

The following drugs were used: the α-adrenoblocker phentolamine in a dose of 1 mg/kg (subcutaneously), the β-adrenoblocker pindolol (Visken) in a dose of 0.1 mg/kg (intramuscular), and the β-adrenoceptor agonist terbutaline in a dose of 2.5 mg/kg (intramuscularly). In the case of short-term immobilization the drugs were injected in a single dose 1 h before the procedure, whereas in the case of long-term immobilization they were given in two doses, the first 1 h before immobilization and the second after immobilization for 12 h (phentolamine or pindolol) or for 19 h (terbutaline). The experimental results were subjected to statistical analysis with calculation of the error of the arithmetic mean by Peters' method, using Moldenhauer's factor C [4].

EXPERIMENTAL RESULTS

The study of venular permeability by the CLB method showed that immobilization for 30 min does not increase the passage of globulin-FITC through the wall of the venules. Administration of the α-adrenoblocker phentolamine before short-term immobilization did not affect the state of venular permeability, whereas prophylactic injection of the β-adrenoblocker pindolol increased the passage of globulin-FITC through the all of the venules 1-15 min after injection of the indicator (Fig. 1).

Intravital study of the microcirculation showed that immobilization for 30 min causes no disturbances compared with the control, and prophylactic injection of phentolamine likewise was not reflected in the character of the terminal blood flow. In 50% of rats receiving pindolol before short-term immobilization, a phenomenon of pavementing of leukocytes in the venules was found, whereas in animals not receiving pindolol it was observed in only 20% of cases.

The study of the morphological and functional state of MC in the experiments with short-term immobilization of animals receiving or not receiving prophylactic phentolamine showed that the total number of MC and the degree of their degranulation were identical with those in the control. Meanwhile preliminary injection of pindolol into animal subjected to short-term immobilization increased the number of MC in the perivenular regions of the mesentery (Fig. 2).

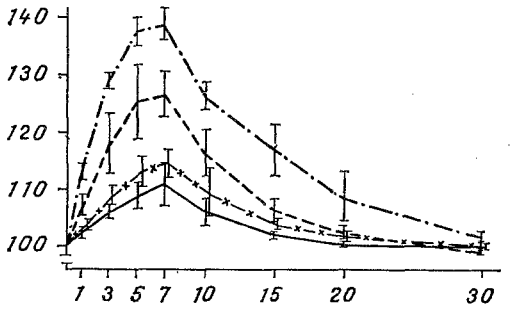

Fig. 3. Permeability of mesenteric venules of rats for globulin-FITC during long-term immobilization, preceded or not by injection of the β-adrenoblocker pindolol or the β-agonist terbutaline (CLB method). Abscissa, time after injection of permeability indicator (in min); ordinate, increase in intensity of luminescence (in %), 100% denotes initial background luminescence. Continuous line – control, broken line – immobilization for 24 h, line of dots and dashes – pindolol + immobilization for 24 h, line of dashes and crosses – terbutaline + immobilization for 24 h.

The next series of experiments conducted by the CLB method showed that immobilization for 24 h is accompanied by increased permeability, expressed as an increase in passage of globulin-FITC through the wall of the venules 1-15 min after injection of the indicator.

The study of venular permeability during long-term immobilization preceded by injection of phentolamine showed that the drug had no significant effect on passage of globulin-FITC. Meanwhile an increase in its passage from the venules was observed during long-term immobilization preceded by injection of pindolol, and reduced passage was observed after injection of the β-agonist terbutaline (Fig. 3). Injection of terbutaline during long-term immobilization accelerated the terminal blood flow in the venules and reduced the intensity of erythrocytic aggregation in 40% of cases.

MC in rats subjected to long-term immobilization preceded by injection of pindolol and terbutaline were more numerous than in animals not receiving the drugs (4.5 ± 0.04, 4.5 ± 0.4, and 3.7 ± 0.1 per field of vision). Injection of terbutaline under these circumstances reduced the degree of degranulation of MC to 5.0 ± 0.4% compared with animals not receiving terbutaline (12.0 ± 0.7%, $p < 0.001$).

The results indicated that regulation of permeability by catecholamines under conditions of short-term and long-term immobilization is effected through the β-adrenoceptor apparatus of the endothelial and mast cells.

These data agree with results obtained by Svensjö and co-workers [10, 12-14], who used a method of intravital luminescence microscopy of the mucous membrane of the hamster retrobuccal pouch and showed that β-agonists participate in the regulation of venular permeability when disturbed by histamine, bradykinin, prostaglandins, and other mediators of inflammation.

Our own results, indicating acceleration of the terminal blood flow, leading to reduction of the intensity of erythrocytic aggregation in the case of prophylactic injection of terbutaline into animals subjected to long-term immobilization, agree with data obtained previously by other workers [10, 11].

The increase in the number of MC in the perivenular regions in the case of short-term immobilization preceded by injection of pindolol, together with the increased intensity of pavementing of leukocytes in the venules may be due to the outflow of basophilic leukocytes through the wall of the venules at sites of increased permeability.

The same mechanism of an increase in the number of MC may perhaps also apply in the case of long-term immobilization coupled with administration of pindolol.

Experimental results showing that terbutaline can reduce degranulation of MC under conditions of immobilization for 24 h are in agreement with data showing that β-agonists depress the secretory activity of MC under normal conditions [6-9].

The increase in the number of MC during long-term immobilization preceded by injection of terbutaline may perhaps be connected with reduction of the degranulation of these cells, which may also be one of the mechanisms of reduction of venular permeability.

It was thus shown that during short-term and long-term immobilization, regulation of venular permeability by catecholamines is effected mainly through β-adrenoceptors of the venular endothelium and of the mast cells.

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CARNOSINE PREVENTS ACTIVATION OF FREE-RADICAL LIPID OXIDATION DURING STRESS

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Carnosine (β-alanyl-L-histidine), a dipeptide contained in muscle tissue in millimolar concentrations, is currently attracting ever-increasing attention of investigators. One reason for the increased interest in the study of the properties of carnosine is the fact that data have recently been obtained on new properties (immunoregulatory, antineoplastic, etc.) of this dipeptide which are of clinical importance. The discovery of the antioxidative activity of carnosine in systems in vitro [9], and also of the unique property of this dipeptide of lowering the concentration of free-radical oxidation (FRO) products through direct interaction with them [3], appears to be very important.

Antioxidants are known to possess an adaptogenic action, which is due to prevention of activation of FRO caused by stress-inducing factors [7]. On the basis of data on the effective antioxidative action of carnosine in vitro, and considering the extremely low toxicity of this dipeptide, it was logical to suggest that carnosine, administered in vivo, would possess marked stress-protective properties.

The aim of this investigation was to study changes in parameters of FRO in the brain and blood and also in the lipid composition of the brain of rats subjected to stress induced by painful electrical stimulation with or without previous administration of carnosine.

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