mulation of several isoforms of proteins (hsp) with a molecular weight of 70 kD, which develop in cells under the influence of stress hormones, were found to play an important role in the mechanism of PASS. These proteins are known to exhibit the ability to disperse denaturation-destroyed proteins [14], to be bound to calmodulin receptors [15], as well as to suppress free-radical oxidation by activating antioxidation enzymes [7]. Due to these effects they stabilize the cell structures and contribute to PASS development during adaptation to repeated stress. With our use of adaptation to gradually exacerbated hypoxia, stress is reduced to the minimum, and hsp accumulation and PASS effects are little marked [12]. On the basis of this, we suggest that the cross antihypoxic effect of adaptation to stress is due to the development of PASS, i.e., to a direct increase of the resistance of cell structures to such factors as a high concentration of hydrogen ions, a reduced oxygen tension, deficiency of energy-rich phosphorus compounds, etc. During adaptation to hypoxia, PASS does not develop, and the protection is mainly associated with profound adaptive changes in the respiratory and circulatory function.

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# Responsiveness of Mesenteric Arterioles to Epinephrine in Metabolic Coma

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UDC 616.153.455.04:612.135.001.5

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 12, pp. 577-579, December, 1993
Original article submitted July 19, 1993

**Key Words**: *hypoglycemia; acetone; coma; microcirculation*

One critical state of the human body is the metabolic coma resulting from disruption of metabolic processes [5]. Its prominent causes are insulin-induced hypoglycemia and ketoacidosis. These frequently aggravate diabetes mellitus and are important considerations in insulin shock therapy and in acetone poisoning, respectively [3].

It is generally recognized that the major role in the establishment and maintenance of metabolic homeostasis of tissues in health and disease is

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0007-4888/93/0012-1471$12.50 

TABLE 1. Responsiveness of Mesenteric Arterioles to Epinephrine in Hypoglycemic Coma. The Values are Means±SEM

| Group | Arteriolar diameter, μ | Threshold epinephrine dose, μg | Arteriolar response to doubled threshold dose of epinephrine | | |
|---|---|---|---|---|---|
| | | | latency, sec | time taken to attain maximal response, sec | arteriolar narrowing, % |
| Control ($n$=12) | 32.0±2.9 | 0.003±0.0003 | 8.0±1.9 | 39.0±3.3 | 32.4±3.9 |
| Coma ($n$=11) | 36.7±4.1 | 0.004±0.0006 | 5.0±0.0 | 22.5±2.0** | 45.8±4.8* |

Note. Here and in Table 2: *$p$<0.05; **$p$<0.001

played by the microcirculatory bed [6,7]. Hence the great importance of studying the state of the terminal blood flow in metabolic coma.

The purpose of this study was to examine the responsiveness of mesenteric arterioles to epinephrine in rats with metabolic coma.

## MATERIALS AND METHODS

The study was conducted on random-bred sexually mature male rats weighing 160-220 g that were fed the standard diet. Two series of tests were run. In the first series, hypoglycemic coma was produced by an intramuscular injection of 20 units of insulin per kg body weight into rats that had fasted for 18 h. The comatose state of the animals was evaluated by recording its clinical manifestations and measuring blood sugar levels and rectal temperature at the height of coma and before insulin injection. In the second test series, acetone was injected intravenously in a 1:1.5 dilution (5.5 mmol/liter) to produce a comatose state induced by the resulting ketotoxicosis.

In both series, the test object was the mesoappendix. The rats were anesthetized with kalipsol (Hungary) injected intramuscularly at 200 mg/kg since kalipsol (ketamine) is the only anesthetic known to produce a surgical level of anesthesia when injected by this route [2]. After laparotomy, the cecum was removed, the mesoappendix was placed on the glass waveguide of a microscope stage, and vital microscopy of mesenteric vessels was performed using previously described procedures [1].

After the general state of the microcirculation had been assessed, the responses of arterioles 30-40 μ in diameter to epinephrine were investigated. Epinephrine solutions were applied in concentrations of $10^{-8}$ to $10^{-5}$ g/ml and the arteriolar sensitivity to epinephrine was assessed by noting its threshold dose that elicited a continuous response from the arterioles. The responsiveness of these to epinephrine was evaluated by the maximal response to its doubled threshold dose (by the degree of arteriolar narrowing expressed in percent of the initial diameter) and by temporal parameters of arteriolar responses - the latency period and the time taken to attain the maximal response. The responses were recorded by frame-by-frame microphotography at 5-second intervals (at a total magnification of ×169) and assessed by changes in arteriolar diameters on negatives subjected to micrometric processing on a Pentakta L 100 enlarger. The results were treated statistically using Student's $t$ test.

## RESULTS

In the first test series, rats developed a comatose state (2 h after insulin injection on average) marked by immobility, loss of pain sensitivity, increased tone of skeletal musculature, and (in most rats) tonic and clonic convulsions. Blood sugar levels fell to 0.61±0.09 mmol/liter and rectal temperature to 31.9±0.5°C ($p$<0.001).

Mesenteric biomicroscopy in the control group showed a rapid and uniform blood flow in all parts of the microcirculatory bed; the blood flow remained stable during the 2-hour observation period, without any signs of intra- or extravascular abnormalities. Rats in the state of hypoglycemic coma did not show visible differences from control rats in the picture of terminal blood flow. After the

TABLE 2. Responsiveness of Mesenteric Arterioles to Epinephrine in Acetonemic Coma. The Values are Means±SEM

| Group | Arteriolar diameter, μ | Threshold epinephrine dose, μg | Arteriolar response to doubled threshold dose of epinephrine | | |
|---|---|---|---|---|---|
| | | | latency, sec | time taken to attain maximal response, sec | arteriolar narrowing, % |
| Control ($n$=12) | 34.4±2.8 | 0.004±0.0005 | 6.0±0.7 | 35.0±1.3 | 41.6±5.6 |
| Coma ($n$=12) | 32.0±2.1 | 0.002±0.0002** | 5.0±0.0 | 17.0±1.6** | 64.2±4.1** |

threshold epinephrine dose (0.004±0.0006 μg), slight narrowing of arterioles, large numbers of plasma cells in some capillaries, and slowed blood flow in venules were observed. As in the control group, normal blood flow was reestablished without washing the mesentery. No statistically significant differences were detected between the test and control rats in threshold epinephrine doses or, accordingly, in arteriolar sensitivities to epinephrine (Table 1).

Arteriolar responses to the doubled threshold epinephrine dose were manifested, in all rats, in a marked vasoconstriction leading to emptying of capillaries and a jerky venular blood flow. After washing of the mesentery, however, the blood flow was completely restored. In these rats, as compared to those in the control group, the latent period tended to decrease, the time taken to attain maximal arteriolar constriction was 1.7 times shorter, and the constriction was more strongly marked (arteriolar diameters were narrowed by 41%). These features of the arteriolar responses suggested that the arterioles of rats in hypoglycemic coma were more responsive to epinephrine than were those of control rats.

It is currently believed that the insulin-induced hypoglycemic syndrome (IIHS) involves hemodynamic alterations in addition to endocrine disturbances, and that the systemic hemodynamics is altered only slightly in comparison to regional blood flows. However, the documentation on how the latter are affected in the IIHS is contradictory [8-10, 12], which may be due in part to variations in the severity and duration of this syndrome. The mechanism of blood flow redistribution involves catecholamines, notably epinephrine [9, 14] and insulin - both through direct vasodilation [12] and norepinephrine-mediated effects [14].

No information regarding intestinal blood flows in hypoglycemic coma could be found in the available literature. However, since blood flows in the splanchnic region have been reported to be increased in rats with IIHS [10] and in hypoglycemic stress [4], and since the mesenteric arterioles were found to have somewhat increased diameters in coma (Table 1), it is likely that the basal tonus of these vessels is lowered, and this probably explains why arteriolar contractility to applied epinephrine is increased. A contribution to the increased arteriolar responsiveness may also be made by the epinephrinemia-induced inhibition of the endothelial synthesis of prostacyclin and possibly also of other prostaglandins that modulate vasoconstrictor effects [13].

In rats of the second test series, the injection of acetone was followed by immobility, loss of pain sensitivity, and hyperventilation almost immediately postinjection. The arterioles of these rats were more sensitive to epinephrine than those of the control rats, as was indicated by the 2-fold decrease of its threshold dose (Table 2). Arteriolar responses to the double epinephrine dose were also stronger: arteriolar narrowing was 1.5-fold greater and occurred twice as rapidly as in the control rats. The mesenteric arterioles were thus more responsive to epinephrine in acetonemic coma, apparently because of the general toxicity of acetone [3]. Exposure of the brain to acetone may result in its dysfunction and impaired regulation of its vascular tone. It is probable that acetone elicits reactions typical of stressful situations, namely the release of epinephrine and corticosteroids followed by disturbances of peripheral blood flows. On the other hand, since acetone is eliminated from the body slowly, high concentrations of it in the blood are likely to be toxic for the endothelium. If so, then the arteriolar responsiveness to applied epinephrine would be enhanced as a result of the inhibited production by endothelial cells of vasodilators such as endothelium-dependent relaxation factor, $PGI_2$, and $PGE_1$, which modulate the effects of catecholamines and angiotensin II [11, 13].

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