ing from lumbosacral osteochondrosis pain accompanied by ischialgia, although the anesthetic does not reach the pertinent sections of the spinal column or roots. It may be assumed that in these cases the therapeutic effect has to do with disengagement of the intraosseous receptors and, consequently, with limitation of afferent influences, alleviating the excitation process which is associated with root compression, muscle spasms, etc. Osteochondrous root syndromes are accompamied by changes of the bone tissue regional hemodynamics and an increase of the intraosseous pressure [4], which, as has been shown in this study, may promote a drop of the afferent reaction threshold for stimulation of nerve trunks and hence intensification of the pain syndrome.

REFERENCES

1. D. P. Bilibin, O. A. Shevelev, N. A. Khodorovich, and S. S. Usanov, *Byull. Eksp. Biol.*, № 11. 523-525 (1987).
2. R. A. Durinyan, *Central Structure of Afferent Systems* [in Russian], Moscow (1965).
3. L. V. Kolyuzhnyi, *Physiological Mechanisms of Pain Sensitivity Regulation* [in Russian], Moscow (1984).
4. E. L. Sokov, *Zh. Neuropathol. Psikhiatr.*, № 4, 57-61 (1988).
5. G. A. Yankovskii, *Osteoreception* [in Russian], Riga (1982).
6. *Textbook of Pain*, Ed. by P. D. Wall and R. Melzack, Edinburg (1989).

Cardiac Output and Regional Blood Flow Changes in Alert Rats with Acute Streptozotocin-Induced Diabetes

L. V. Kuznetsova, N. A. Medvedeva, and O. S. Medvedev

UDC 612.13:616.379—0.08.64

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 6, pp. 589—592, June, 1993
Original article submitted January 5, 1993.

Key Words: *regional blood flow; vascular resistance; diabetic ketonuria*

Microangiopathy is known to be the main cause of death and disability among patients suffering from diabetes mellitus. In the eighties several groups of investigators put forward the hypothesis that the trigger factor causing microcirculatory disturbances in diabetes might be changes in the regional blood flow [9,12,15]. According to this hypothesis, the early increase in blood flow and capillary pressure in some vascular regions results in the development of microvascular sclerosis followed by a decrease in blood flow and weakened autoregulation.

It should be noted that the early changes in blood flow observed in experimental diabetes mellitus are likely to be related to a rise in the blood sugar level, since the injection of insulin to rats 40 to 50 hours after streptozotocin (STZ) injection normalized the blood sugar level and hemodynamic indexes [10].

Streptozotocine injection to rats was previuosly shown by us to result in marked changes in the systemic blood flow as early as 24 hours post-injection: the total peripheral resistance dropped and the cardiac index rose [1]

The aim of this study was to investigate the regional blood flow changes in alert rats 24 hours after STZ injection. The diabetic syndrome, manifested in a blood sugar level rise 24 hours following STZ injection, was referred to as acute streptozotocine-induced diabetes.

MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 300 to 400 g. Cardiac output and blood flow in 10 organs were determined by the

Department of Human and Animal Physiology, Biology Department of M. V. Lomonosov University, Laboratory of Experimental Pharmacology, Institute of Experimental Cardiology, Cardiology Research Center, Moscow. (Presented by I. P. Ashmarin, Member of the Russian Academy of Medical Sciences)

0007-4888/93/0006-0653$12.50

method of labeled microspheres, described in detail earlier [2]. Under light ether anesthesia catheters were implanted into the left ventricle of the heart (through the right carotid artery) for microsphere infusion, into the abdominal cavity (through the right femoral artery) for arterial pressure (AP) measurement and blood sampling, and into the right jugular vein for STZ injection. The rats were then placed in separate cages for 48 hours to recover. After recovery the animals were weighed and the baseline indexes of the systemic and regional blood flow were measured. The procedure was as follows: about 100,000 microspheres (with an average diameter of 15 μ, NEN, USA, volume 0.15 ml) were slowly infused into the left ventricle of the heart (over 25 to 30 sec). Blood sampling through the femoral catheter was started 5 sec before the infusion and was continued 60 sec after the infusion at the rate of 0.6 ml/min.

Twenty-four hours after the first blood flow measurement, STZ dissolved in 0.9% NaCl solution was injected through the venous catheter in a dose of 60 mg/kg.

Twenty-four hours following the injection all the animals were divided into two groups (with and without ketonuria) according to the results of urine testing for ketone bodies with the use of Multistix reagent strips (Ames, Great Britain), whereupon the animals were weighed and the systemic and regional blood flow indexes were recorded.

The blood sugar concentration was measured at the end of the experiment with a glucometer (Miles, USA).

Upon completion of the experiment the animals were sacrificed using a high dose of nembutal; the organs and tissues in which blood flow had been measured were weighed and placed in disposable test tubes. All the measurements of the number of microspheres were done with a Compugamma 1282 gamma counter (LKB-Wallac, Finland).

Cardiac output and regional blood flow values were calculated using the standard formulas [6]. The cardiac index was expressed as the cardiac output per 100 g body weight. In addition, the following indexes were measured:

TPVR-AP/CI, where TPVR=total peripheral vascular resistance (mm Hg/ml/min per 100 g), AP=mean arterial pressure (mm Hg), and CI=cardiac index (ml/min/100 g), and RVR=AP/RBF, where RVR=regional vascular resistance (mm Hg/ml/g) and RBF=regional blood flow (ml/min/g); SO=CO/HR, where SO=systolic output (ml), CO=cardiac output (ml/min), and HR=heart rate (beats/min). The data are presented as $M\pm m$. For statistical analysis of the results Student's t test was used. The differences were considered to be significant with $p<0.05$.

RESULTS

Twenty-four hours after STZ injection all the animals (n=13) exhibited glucosuria. Six animals showed ketone bodies in the urine (the group with ketonuria). In addition, all the animals showed pronounced hyperglycemia, the glucose concentration being the same in both experimental groups: in rats with ketonuria 408±15 mg/100 ml, in rats without ketonuria 421±16 mg/ml.

The systemic and regional blood flow indexes in alert rats with and without ketonuria before and 24 hours after STZ injection are presented in Table 1.

Twenty-four hours after STZ injection all the animals showed a significant drop of the AP and TPVR and a marked increase in the CI as a result of a rise of SO. In addition, both groups showed a significant rise of the blood flow in the small intestine, as well as of the cardiac, cerebral, and renal blood flow.

Changes in the RVR in rats with and without ketonuria 24 hours after STZ injection in comparison to the baseline values are presented in Fig. 1. The factors implicated in the decrease of TPVR observed 24 hours following STZ injection include: 1) a nonspecific decrease in the contractility of the vascular smooth muscle cells due to intracellular impairment of glucose metabolism [8,13] and plasma hyperosmolarity

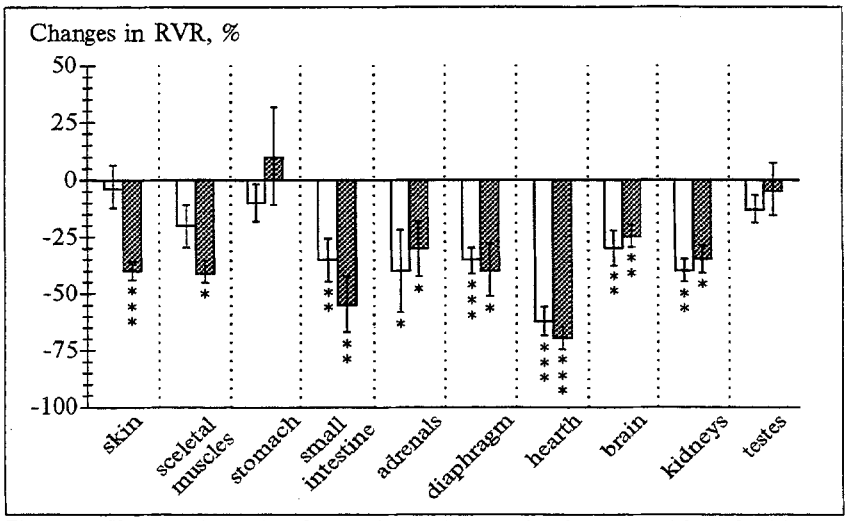

Fig. 1. Changes in regional vascular resistance in alert rats with and without ketonuria 24 hours after streptozotocin injection in comparison with baseline values. * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$ in comparison with baseline values (Students's t test).

[4,7]; 2) an increase in the plasma level of endogenous vasodilative substances in rats with STZ-induced short-term diabetes (such as glucagon, prostacycline) [6,10,14]; 3) a decrease in the vascular sympathetic tone [1].

The observed increase in the CI in rats with acute experimental diabetes is believed to be the consequence of increased sympathetic inotropic action on the heart [1].

It should be noted that the severity of the hemodynamic changes depends on the degree of metabolic disturbances caused by STZ injection. Thus, the presence of ketone bodies in the urine suggests a more serious impairment in the metabolism and the development of diabetic ketoacidosis. The data presented in Table 1 show that rats with ketonuria showed a greater increase in CI (102±18% versus 41±8% in rats without ketonuria, $p<0.05$) and in SO (105±19% versus 32±10% in rats without ketonuria, $p<0.05$) and a greater decrease in TPVR (57±6% versus 38±4% in rats without ketonuria, $p<0.05$) The most significant differences in the blood flow and RVR were found in the skin and skeletal muscles: in rats with ketonuria the blood flow in these regions was significantly higher (in the skin by 0.076±0.019 ml/min/g, and in the muscles by 0.056±0.020 ml/min/g, $p<0.05$) and the vascular resistance was found to be lower, whereas in rats without ketonuria these indexes did not change (see Table 1 and Fig. 1).

Thus, the data obtained suggest that alert rats with acute 24-hour-long STZ-induced diabetes developed a hyperkinetic type of circulation, manifested in an increase of CI and decrease of TPVR along with increased blood flow in some vascular regions. Diabetic rats with ketoacidosis showed a higher plasma osmolarity level in comparison with the diabetic animals without ketoacidosis [5]. The significantly more marked differences in the hemodynamic indexes in the animals with ketonuria could be accounted for by the higher plasma osmolarity in diabetic ketoacidosis.

According to the concept of the hemodynamic genesis of diabetic microangiopathy [9,12,15], the initial hyperkinetic circulation could eventually result in morphological alterations in the microvessels, causing vasoconstriction and hence an increase in vascular resistance and depression of the blood flow in some vascular regions.

In light of this, we thought it of interest to compare the data presented in this paper with earlier-obtained indexes of the systemic and regional blood flow in alert rats with 13-week-long chronic STZ-induced diabetes [3].

Just as in acute diabetes, rats with chronic STZ-induced diabetes showed hypotension, systemic vasodilation, and a raised CI. However, despite the persisting hyperkinetic circulation, the regional blood flow in chronic diabetes is markedly different from that in acute diabetes. While in acute diabetes (24 hours after STZ injection) alert rats showed decreased vascular resistance and increased blood flow in many organs (Table 1, Fig. 1), in chronic diabetes of 13 weeks duration the increased blood flow and decreased vascular resistance were observed only in the skeletal muscles; in the kidneys and testes the blood flow was found to be significantly lower, whereas the vascular resistance was increased, suggesting the development of microangiopathy; in the rest of the organs the blood flow and vascular resistance were no different from the control values.

The data presented suggest that the development of microvascular lesions varies with the organ affected. According to the hypothesis of a hemodynamic genesis of diabetic microangiopathy, the major factor responsible for morphological alterations in the vessels is decreased vascular resistance of resistive arterioles and increased blood flow. The effect of hyperperfusion for different organs may be different depending on the vascular bed architectonics [11]. Thus, in the skeletal muscles decreased resistance of resistive arterioles may lead to additional capillaries becoming active again and changes in the capillary pressure will not be marked. In this case the development of microvascular changes will be more gradual than in the kidneys, where virtually all the capillaries are permanently active and where the increased resistance of resistive arterioles observed at the initial stages of experimental diabetes (Fig.1) results in a marked increase in the capillary (glomerular) pressure, hyperfiltration, and hence in a more rapid development of morphological microvascular alterations and decreased blood flow.

Thus, the findings show that a hyperkinetic type of circulation is found at the early stages of streptozotocin-induced diabetes and it is dependent on the metabolic disturbances developing in experimental animals after STZ injection. As the disease progresses, these functional impairments are likely to result in structural microvascular alterations and the development of microangiopathy.

REFERENCES

1. L. V. Kuznetsova, N. A. Medvedeva, and O. S. Medvedev, *Byull. Eksp. Biol.*, **113**, № 2, 250-252 (1992).
2. O. S. Medvedev, A. N. Murashev, F. E. Meertsuk, and S. F. Dugin, *Fiziol. Zh. SSSR*, **72**, № 2, 253-256 (1986).
3. N. A. Medvedeva, L. V. Kuznetsova, and O. S. Medvedev, *Ibid*, **38**, № 2, 25-29 (1992).
4. R. A. Brace and D. K. Anderson, *J. Appl. Physiol.*, **35**, 90-94 (1973).

5. J. A. Charlton, C. J. Thompson, and P. H. Baylis, *J. Endocr.*, **116**, 343-348 (1988).
6. P. A. Craven, M. A. Caines, and F. R. DeRubertis, *Metabolism*, **36**, 95-103 (1987).
7. J. J. Friedman, *Amer. J. Physiol.*, **256**, H1134-H1138 (1989).
8. T.-S. Lee, K. A. Saltsman, H. Ohashi, and G. L. King, *Proc. Nat. Acad. Sci. USA*, **86**, 5141-5145 (1989).
9. H.-H. Parving, G. S. Vibertu, H. Keen, *et al.*, *Metabolism*, **32**, 943-949 (1983).
10. A. A. Quyymi, P. Iaffaldano, J. L. Guerrero, *et al.*, *Diabetes*, **38**, 1585-1594 (1989).
11. R. G. Tilton, K. Chang, *et al.*, *Ibid*, pp. 1258-1270.
12. J. E. Tooke, *Clin. Sci.*, **70**, 119-125 (1986).
13. B. A. Wolf, J. R. Williamson, R. A. Easom, *et al.*, *J. Clin. Invest.*, **87**, 31-38 (1991).
14. L. F. Yrle, J. K. Smith, J. N. Benoit, *et al.*, *Amer. J. Physiol.*, **255**, G542-G546 (1988).
15. R. Zatz and B. M. Brenner, *Amer. J. Med.*, **80**, 443-453 (1986).

Impact of Acute Hypoxia on the Fatty-Acid Composition and Lipid Peroxidation in Liver Microsomal Membranes and Blood Plasma of Rats with Low and High Resistance to Oxygen Deficiency

V. I. Sharapov, Yu. V. Nacharov, O. R. Grek, and G. S. Yakobson

UDC 616.36-018.1:576.314]-008.939.15-39-092:612.273.2]-092.9

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 115, № 6, pp. 592-594, June, 1993
Original article submitted December 18, 1992.

Key Words: *individual resistance to hypoxia; fatty acids; lipid peroxidation; liver microsomes*

Within populations of animals there exist intraspecific differences in the resistance to hypoxia that are determined by the totality of genotypic and phenotypic properties possessed by the organism [4,15]. These differences manifest themselves at the organismic and organic as well as tissue levels [5,11]. The importance of research into the mechanisms by which a high resistance to oxygen deficiency is assured stems from the fact that hypoxia is a major factor in the pathogenesis of all pulmonary and cardiovascular diseases and is usually the immediate cause of death under extremely adverse conditions.

Novosibirsk Medical Institute, Institute of Physiology, and Institute of Clinical and Experimental Lymphology, Siberian Branch of the Russian Academy of Medical Sciences, Novosibirsk.

The purpose of this study was to examine how acute hypoxia affects the fattyacid composition and lipid peroxidation (LPO) in liver microsomal membranes and blood plasma of animals differing in their resistance to oxygen deficiency.

MATERIALS AND METHODS

The experiments were conducted on 120 male Wistar rats weighing 190-220 g. Their resistance to hypoxia was assessed by noting the time at which the first agonal inspiration occurred during elevation to an "altitude" of 11,500 m at a rate of 50 m/sec in a pressure chamber [4]. The animals were then divided into four groups: group 1 comprised low-resistance intact animals (LR control); group 2, high-resistance intact animals (HR

0007-4888/93/0006-0656$12.50