The Hyperglycemia Syndrome in Extreme Conditions (Burn Trauma and Crush Syndrome): Major Aspects of Pathogenesis

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Using animal models of burn trauma and crush syndrome, the authors show that the main mechanism by which a hyperglycemia syndrome develops in these conditions is an altered interaction of insulin with its receptors in plasma membranes. As a result, the entry of glucose into cells is disrupted, hexokinase activity is lowered, and changes occur in the rates of enzymatic reactions involved in glucose transformations.

Key Words: *burn trauma; crush syndrome; insulin*

Extreme conditions such as burn trauma and crush syndrome remain one of the least studied areas of both theoretical and practical medicine, although their incidence rates have been rapidly rising in recent years [7,8].

It is now beyond doubt that tissue destruction in the lesion area in burn injuries and crush syndrome and the consequent traffic of nociceptive signals from that area to the central nervous system excite the hypothalamic neurons, which then begin to stimulate the hypophyseoadrenal system, resulting in a hormonal imbalance [1,4,5,12,15]. The hyper- or hyposecretion of a number of hormones, the increased production of many biologically active substances, and the entry of toxins from the affected area into the bloodstream combine to result in metabolic disturbances accompanied by endotoxicosis.

The state of stress in burn trauma and crush syndrome may be accompanied by a cascade-like development of adaptive and pathological reactions at the basis of which lie metabolic changes in organs and tissues and disturbances in morphological and functional properties of the cells [3].

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An important pathophysiological mechanism of the systemic response to burn trauma and crush syndrome is the development of hyperglycemia [6,9] and other abnormalities of carbohydrate metabolism. The hyperglycemia occurring in extreme conditions and stressful situations may result from altered insulin-binding activity (IBA) of blood cells, but this possibility has not been explored. It is known, however, that the insulin receptor, being an integral protein located in the lipid bilayer of the cell membrane, is subject to metabolic stresses and the effects of changes in the structural organization of the membrane [3].

In view of the foregoing, we have made an attempt to present an integral description of the metabolic and structural-functional disturbances developing in blood cells in burn trauma and crush syndrome and to propose a pathophysiological and pathochemical conception of how a hyperglycemia syndrome develops in these conditions.

MATERIALS AND METHODS

The experiments were carried out on 40 dogs and 200 rats. A third-degree burn involving 25-30% of the total body surface was caused by applying a burning

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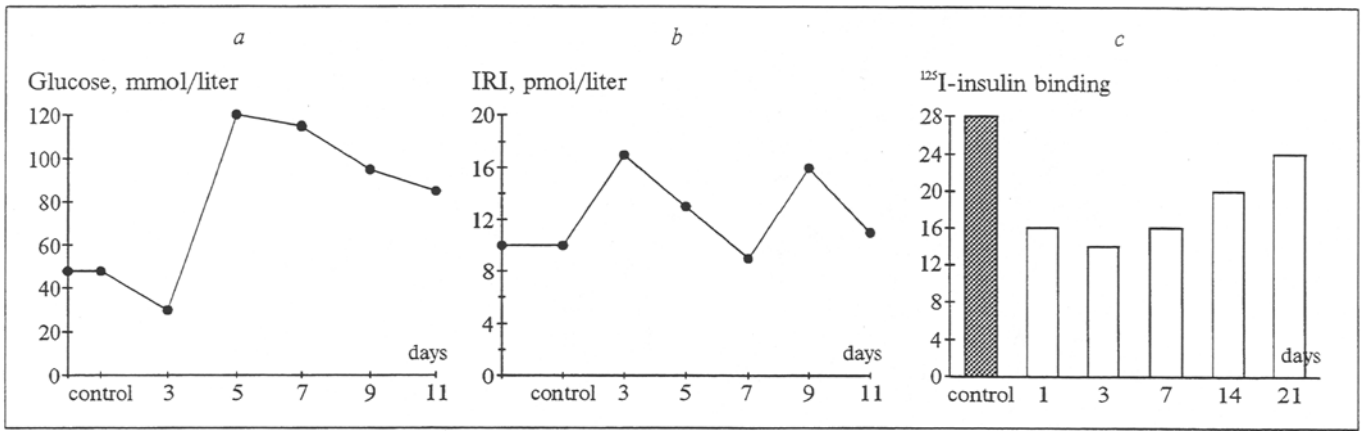

Fig. 1. Development of hyperglycemia syndrome. Variations in serum levels of immunoreactive insulin (IRI) (*a*) and glucose (*b*) and in specific ^{125}I–insulin binding to mononuclear cell receptors in rats after burn trauma.

alcohol-soaked cotton tampon to the epilated dorsal and lateral parts of the upper body. This resulted, within 50 sec, in the appearance of a burn surface that later became covered with a scab which in most animals came off without suppuration or liquefaction of the subjacent tissues. To prevent shock, the burn trauma was inflicted under ether anesthesia. The controls were 20 narcotized animals with a similar epilated skin area. A crush syndrome was produced by subjecting 3/4 of one thigh and 1/2 of one lower leg to a crushing pressure over 6 h by Kuzin's method [2].

Glycolytic breakdown of glucose was estimated by the glucose oxidase method using standard kits (Boehringer, Germany) which were also utilized to determine levels of lactate, lactate dehydrogenase (LDH) and glucose-6-phosphate dehydrogenase (G-6-PDH) activities, and the absolute and relative contents of ATP, ADP, and AMP. Hexokinase activity was estimated by noting increments in optical density at 340 nm as a result of NADH reduction in the reaction of coupled glucose oxidation with G-6-PDH. Fructose-1P-aldolase (F-1P-A) activity was measured with 2,4-dinitrophenylhydrazine by the method of Tovarnitskii and Valuiskaya in Sveshnikov's modification (1965). Levels of immunoreactive insulin (IRI) and cortisol were determined by radioimmunoassays using standard kits. The binding of ^{125}I-insulin to mononuclear cells, lymphocytes, and erythrocytes was estimated by the method of Roth and Cassell [13]. Insulin-receptor interaction in liver plasma membranes was studied by a method in which ^{125}I-insulin is displaced from its complex with receptors by incremental quantities of unlabeled insulin under equilibrium conditions [10]. For estimating the total number of insulin-binding sites and the affinity of receptors for insulin, Scatchard analysis [14] and Meyts and Roth's method [11] were applied. Cell sensitivity to insulin was estimated from the degree of glucose utilization by the cells. Finally, structural and functional properties of erythrocyte membranes were evaluated by alterations in their concentrations of malonic dialdehyde and hydroperoxides in their and antioxidant activity, as well as by measuring the microviscosity and hydrophobicity of these membranes with EPM spectroscopy using spin probes and an E-4 radiospectrometer (Varian, USA).

RESULTS

Both the burn trauma and crush syndrome were characterized, in addition to the clinical manifes-

TABLE 1. Activity of Glycolytic Enzymes in the Peripheral Blood and Liver of Rats with Burn Trauma. The Values are Means±SEM

Days postburn	Peripheral blood		Liver		
	LDH, U/liter	G-6-PDH, U/liter	F-1P-A, U/liter	HK, μmol/ NADPH/mg protein/h	LDH, μmol/ NADPH/mg protein/h
Control	2604.6±429.6	381.23±20.3	0.5±0.01	0.38±0.02	0.149±0.06
1	2061.5±272.0*	303.1±12.7*	2.72±0.03*	0.22±0.02*	0.153±0.006
3	2090.0±804.0	835.7±59.9*	1.7±0.025*	0.3±0.025*	0.20±0.021*
7	699.5±209.0*	374.3±71.0	3.5±0.049*	0.27±0.03*	0.178±0.02*
14	409.0±36.2*	725.0±20.1*	3.3±0.051*	0.51±0.04*	0.171±0.013
21	1170.0±325.0*	393.4±11.8	2.7±0.042*	0.47±0.01	0.165±0.16

Note. The asterisk denotes a significant difference from the control.

tations typical of such severe states as these, by hemoconcentration, erythrocytosis and pleiochromia, and by leukocytosis of the neutrophilia type, involving increased numbers of stab cells. In many animals, eosinopenia and lymphocytopenia were prominent. The main metabolic disorders were dysproteinemia with phasic changes in the protein spectrum of the blood; impaired integrity of lysosomal membranes with leakage of lysosomal enzymes including cathepsin D; and intensified hemolysis that increased toxic properties of the blood, which was manifested in a sharp rise in the leukocytic index of intoxication.

One important mechanism by which organs and tissues respond to the stress imposed by burn trauma and crush syndrome is the development of hyperglycemia [4,9] as a result of alterations in the IBA of blood cells and in the postreceptor regulation of insulin action.

During the first 24 h after the thermal burn, the serum level of corticosterone increased in rats 1.8-fold ($p<0.05$) while that of insulin decreased ($p<0.01$), as compared to controls. After day 3 postburn, serum insulin had risen more than 2-fold and remained high during the 3-week observation period (Fig. 1). Two peaks of hyperglycemia were observed, on days 1 and 14. The first peak resulted from the fall in insulin in consequence of its impaired biosynthesis and its decreased specific binding to cell receptors. The second peak, which occurred in the presence of hyperinsulinemia, was a reflection of the resistance to insulin due to the impaired IBA. During the first peak of hyperglycemia (day 1), the specific binding of ^{125}I-insulin to its receptors in mononuclear cells began to decrease and fell to low levels by day 3 (13.2±0.8% vs. 28.6±4.3% in the control group of rats; $p<0.01$). Subsequently, the IBA of mononuclears tended to return toward control values.

Thus, the observed reduction in the specific ^{125}I-insulin binding to mononuclear cell receptors during the hyperglycemia that followed the burn reflects the increased insulin resistance at the receptor level as a result of diminished receptor affinity for insulin.

During the first 24 h after the burn, there were reductions in both the basal ($p<0.05$) and insulin-stimulated ($p<0.05$) glucose uptake by mononuclear cells, i.e., these cells became less sensitive to insulin. As soon as day 3, however, a tendency toward normalization of basal glucose uptake was evident and uptake returned to normal by day 14 whereas insulin-stimulated glucose uptake did not stabilize before day 21.

Another contributor to the development of hyperglycemia was the impaired postreceptor regulation of glucose metabolism observed shortly after the burn trauma, as was indicated by elevated blood levels of lactate ($p<0.01$) and lowered ATP concentrations in the peripheral blood and liver ($p<0.05$). The elevation of lactate concentration in the liver is confirmed by the low concentration of hexokinase (HK) which enables mitochondrial ATP to be utilized for ensuring normal functioning of the insulin receptor in the plasma membranes.

A second limiting factor for glycolysis, as follows from Table 1, was G-6-PDH which is controlled by mechanisms of cellular and hormonal regulation. When the relationship between these mechanisms is disturbed in extreme conditions such as a severe thermal injury, this is bound to affect the activity of this enzyme and, consequently, the glycolytic process as a whole. The elevation of G-6-PDH activity by day 3 postburn ($p<0.05$) was followed by its poststress fall ($p<0.05$), i.e., as seen in the table, the activity of this enzyme was fluctuating.

LDH activity decreased in the peripheral blood ($p<0.05$) but increased in the liver ($p<0.05$), this being an adaptive response stimulating glycogenesis in that organ. The observed stability of P-1P-A activity is indicative of cytolytic changes in the liver consequent to the destabilization of cell membranes and dysfunction of the membrane-receptor complex in the cells, in particular as a result of impaired insulin-receptor interaction in the plasma membranes of hepatocytes. Indeed, the burn trauma was followed by a sharp fall in the IBA of hepatocytes in the early stress period - almost 3-fold by day 3 ($p<0.01$). Processing of the relevant data according to Scatchard showed that the reduced IBA of these cells was due to a decrease in the number of insulin-binding sites, but that the receptor affinity for insulin remained unchanged, as was indicated by the parallel courses of the curves.

Our experiments indicated that the pathogenesis of the burn trauma and the crush syndrome was not confined to the local injury to soft tissues or to the impaired activity of organs as a consequence of toxemia, for each of these represents just one link in a complicated chain of events that alter the regulation of metabolism and activity of a variety of physiological systems (Fig. 2). One of the mechanisms underlying the responses of organs to the trauma and to the dysfunction of their cells was found to be disorganization of carbohydrate metabolism and the development of a hyperglyce-

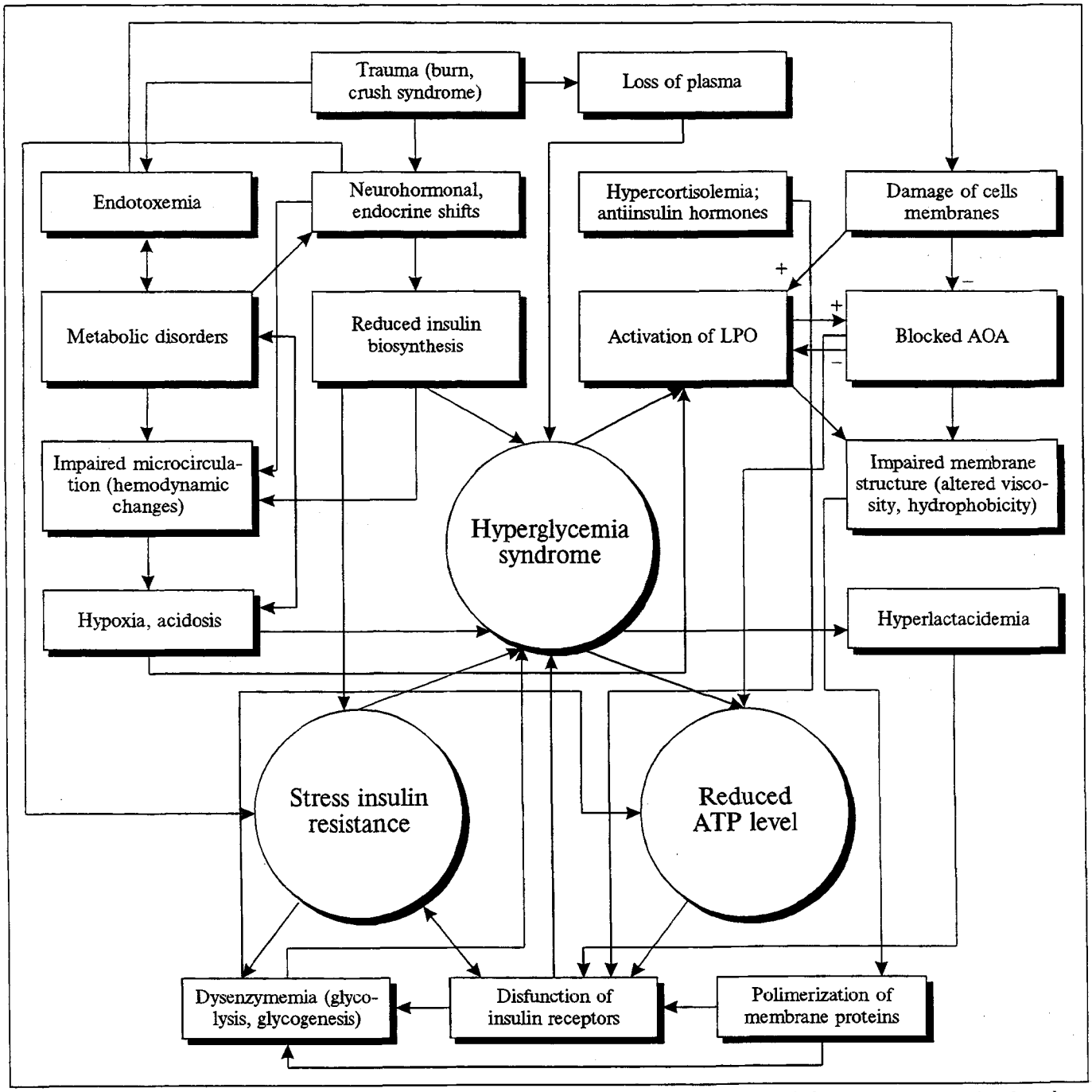

Fig. 2. Pathogenesis of the hyperglycemia syndrome in burn trauma and crush syndrome (schematic representation based on our own data). *Abbreviations*: AOA = Antioxidant activity; LPO = lipid peroxidation.

mia syndrome which depended on the IBA of blood and liver cells and on the state of enzymes involved in glycolysis.

Taken together, the results of our experiments indicate that the major mechanisms responsible for the hyperglycemia syndrome resulting from disturbances of carbohydrate metabolism and its regulation in a severe burn or crush injury are changes in all components of the interaction of insulin with plasma membrane receptors, which hinders glucose entry into the cells and reduces hexokinase activity in the liver, with resultant alterations in the activity of enzymes involved in glucose transformations (G-6-PDH, F-1P-aldolase, and LDH).

The insulin-binding activity of cells in severe thermal and crush injuries is associated not only with fluctuations of the insulin levels in the peripheral blood but also with metabolic disturbances in the cells, which results in a "stress insulin resistance" as a consequence of lessened cell sensi-

tivity to insulin at the receptor level and of reduced postreceptor action of this hormone.

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Spontaneous Activity and Evoked Potentials in the Caudal Trigeminal Nucleus, Ventrobasal Thalamus, and Cerebral Cortex of Rats with Neuropathic Trigeminal Neuralgia

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Incomplete compression of the infraorbital nerve in rats leads to spontaneous neuronal activity in the form of bursts in the caudal trigeminal nucleus and to epileptiform activity in the ventrobasal thalamus and cerebral cortex. From the latter, afterdischarges are also recorded.

Key Words: *evoked potentials; caudal trigeminal nucleus; ventrobasal thalamus; cerebral cortex, rats; neuropathic trigeminal neuralgia*

The experimental pain syndrome elicited by incomplete compression of the sciatic nerve has been found to be accompanied by a pathologically augmented activity in peripheral nerve fibers [8], dorsal horns of the spinal cord [12,13], and the ventrobasal thalamus [7]. These findings are consistent with the view [2] that at the basis of pain syndromes lies a pathological system composed of various structures pertaining to various levels of

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