Slow Cascade Adaptation Drift under the Action of Extreme Factors

V. P. Shakhov

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A study is made of the slow cascade drifting mechanism of adaptation, which is involved in hyperplasia of the hemopoietic tissue under the action of extreme factors of various genesis on the organism. Being universal in nature, the main vector of this mechanism is shown to pass sequentially through the nervous, endocrine, T-cell, macrophagal, and hemopoietic systems.

Key Words: *central nervous system; T lymphocyte; macrophage; stress; blood loss*

Extreme factors acting on the organism are known to trigger mechanisms boosting the work of the cell to a higher functional level, which manifests itself in the resistance phase of the stress reaction, the phenomenon of adaptive stabilization of structures, hyperplasia, and hypertrophy of tissues and organs. The mechanisms lying at the root of these phenomena are still unclear [3,5,7,8].

The aim of the present study was to investigate how the central nervous system (CNS), and the glucocorticoid, T-cell, macrophagal, erythropoietic, and hemopoietic systems interact in the organism exposed to extreme factors.

MATERIALS AND METHODS

The experiments were carried out on male mice, (CBA×C57Bl/6) F_1 hybrids, weighing 18-21 g. The animals were subjected to a 10-hour immobilization in the supine position, a 20% acute blood loss, and intraperitoneal injection of 1 ml meat-peptone broth for the induction of aseptic inflammation [1]. Intraperitoneal injections were performed as follows: for the blockade of the CNS with droperidol (0.69 mg/kg), for the blockade of the T-cell system with monoclonal anti-Thy-1.1 antibodies (ISN) in a dose of 0.5 ml/mouse (titer 1:256), and for the blockade of the macrophagal system with carrageenan (Sigma) in a dose of 50 mg/kg [1,5]. Some experiments were performed on preliminarily (1-1.5 months before the study) adrenalectomized or thymectomized mice, which were injected at different times with dexamethasone (0.05 mg/kg, i.p., Sigma) or thymocytes of intact mice in a dose of 10^7 cells per mouse, respectively [5]. In the experimental mice the following parameters were determined: the cellularity and weight of the thymus and spleen, in the peripheral blood the number of erythrocytes, leukocytes, and reticulocytes and the leukocytic formula, and in the bone marrow of the femur the total number of myelokaryocytes, the myelogram, hemopoietic islets (isolated with collagenase, Serva), and erythroid or granulocytic colony-forming units (CFU-E and CFU-GM). CFU-E and CFU-GM were studied by culturing nonadhering mononuclear cells from the bone marrow in 0.8% methyl cellulose medium (Sigma) supplemented with 10% fetal calf serum (Serva), 280 ml/liter L-glutamine (Sigma), 90% IMDM medium (Iscove's Modified Dulbecco's Medium, Flow), and 40 μg/ml gentamicin (Serva) and containing 0.5 U/ml erythropoietin (Serva) or 150 U/ml granulocyte-macrophage colony-stimulating factor (GM-CSF, Sigma), respectively [1,6]. The blood glucocorticoid level was assayed fluoro-

Laboratory of Biochemistry and Biotechnology, Research Institute of Cardiology, Tomsk Research Center, Siberian Division of the Russian Academy of Medical Sciences

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metrically [12]. The content of Thy-1.1 cells in the bone marrow was determined by the cytotoxic test using complement (*Virion*, Russia), trypan blue (Serva), and Thy-1.1 monoclonal antibodies [1,6]. Production of erythropoietin and GM-CSF in supernatants of a 1-day culture of adhering cells from the bone marrow was bioassayed *in vitro* [1,6]. The tolerance of a physical load (the duration of swimming with a load equal to 1% of the body weight) and hypoxic hypoxia [5], and the 50% survival time after injection of cycloheximide (250 mg/kg) or irradiation in a dose of 7.5 Gy were determined [1,5]. The data were processed statistially using the Wilcoxon—Mann—Whitney nonparametric test [4].

RESULTS

The experiments revealed that immobilization, acute blood loss, or inflammation leads to hyperplasia of the bone marrow on days 4-6 after the intervention (Tables 1 and 2), which manifests itself in an increased number of myelokaryocytes, hemopoietic islets, and CFU-E and CFU-GM, which form an integral part of the hemopoietic tissue. In all cases we observed an increased level of 11-corticosterone, the presence of Thy-1.1 cells in the bone marrow, local hyperproduction of GM-CSF and erythropoietin by myelokaryocytes, enhanced output of hemopoietic islets, CFU-E and CFU-GM, and hyperplasia of the bone marrow, which coincide with the resistance phase of the general adaptation syndrome (Tables 1 and 2). The direction of the cascade mechanism was found to drift depending on the nature of the extreme factor. Thus, inflammation primarily stimulates leukopoiesis, while acute blood loss mainly activates erythropoiesis; immobilization is an intermediate factor. The development of the above phenomenon can be abolished by a droperidol blockade of the CNS (1-24 h), adreno- or thymectomy, suppression of T lymphocytes with anti-Thy-1.1 monoclonal antibodies (2-3 days), or a carrageenan blockade of the macrophagal system (3-4 days, Table 1). However, bone marrow hyperplasia and resistance to a physical load, hypoxic hypoxia, irradiation, and cycloheximide treatment developed in the stressed adrenalectomized mice if glucocorticoid insufficiency was corrected with dexamethasone, and in thymectomized immobilized animals which received an injection of viable thymocytes. Evidently, a sequence of commands is relayed from one regulatory system to another and to effector organs as follows: CNS (1-24 h)>glucocorticoid system (1-3 days)>T-cell system (2-5 days)>macrophagal system (3-5 days)>bone marrow (4-7 days). The general principles of structural adaptation of the bone marrow observed by us are in good agreement

TABLE 1. Possible Development of Bone Marrow Hyperplasia and Resistance to Extreme Factors in Mice (CBA×C57Bl/6) F_1 against the Background of Treatment with Droperidol, Thy-1.1 Monoclonal Antibodies, Carrageenan, Dexamethasone (in Adrenalectomized Animals) and Thymocytes (in Thymectomized Animals) after a 10-Hour Immobilization

Type of influence	Time of injection, days					Development of phenomenon	
	1	2	3	4	5	hyperplasia	resistance to extreme factor
Droperidol	*					-	-
		*				±	±
			*			+	+
Adrenalectomy+dexamethasone	*	*	*			+	+
		*	*	*		±	±
			*	*	*	-	-
Thy-1.1 monoclonal antibodies	*	*				±	±
		*	*	*		-	-
				*	*	+	+
Thymectomy+thymocytes	*					-	-
		*				+	±
			*			+	+
Carrageenan	*	*				±	±
		*	*	*		-	-
			*	*	*	+	+

Note. *Indicates the time of injection; +(-) indicates reliable development (abolishment) and ± partial development of bone marrow hyperplasia or resistance to extreme factors.

TABLE 2. Studied Indexes in Mice Subjected to 10-Hour Immobilization, 20% Acute Blood Loss, and Inflammation

Index	Time, days								
	0	1	2	3	4	5	6	7	8
Immobilization									
11-hydroxycorticosteroids, mmol/liter	33	89*	63*	55*	38	34	29	37	34
Leukocytes, $\times 10^9$	8.1	14.5*	7.5	8.7	8.2	8.9	9.5	11.4*	8.9
Erythrocytes, $\times 10^{12}$	6.7	5.9	4.5	3.7	4.7	7.3	6.2	4.5	6.9
Reticulocytes, ‰	12	36*	18	15	44*	33*	18	13	10.9
Cellularity of thymus, $\times 10^6$	118.2	78.3	30.1*	39.5*	77.4*	63.7*	96.6	103	110
Cellularity of bone marrow, $\times 10^6$	17.8	21.3*	16.1	19.2	18.5	19.9	25.9*	28.7*	20.5
Hemopoietic islets, $\times 10^3$	39	47*	29	36	48*	59*	49*	42	35
CFU-E, $\times 10^5$	0.3	1.2*	0.1	0.9	2.5*	2.2*	0.5	0.3	0.9
CFU-GM, $\times 10^5$	0.5	1.9*	0.3	1.1*	3.9*	2.7*	0.8	0.3	0.5
Erythropoietin, arb. units	0.3	2.1*	0.3	1.1*	1.6*	0.9*	0.7	1.1*	0.9*
GM-CSF, arb. units	0.2	1.9*	0.3	0.7*	1.9*	0.8*	0.9*	1.5*	1.1*
Acute blood loss									
11-hydroxycorticosteroids, mmol/liter	33	92*	48*	38	33	31	36	30	36
Leukocytes, $\times 10^9$	8.1	12.9*	10.3	7.4	11.3*	12.8*	16.7*	12.5*	10.7
Erythrocytes, $\times 10^{12}$	6.7	6.1	5.1	4.9	5.3	4.5	5.1	5.3	7.1
Reticulocytes, ‰	12	42*	54*	87*	112*	130*	61*	30*	31.8
Cellularity of thymus, $\times 10^6$	118.2	56.9	34.9*	40.1*	68.8*	78.3*	101	98.9	106
Cellularity of bone marrow, $\times 10^6$	17.8	16.1	15.4	20.7	21.9	24.7*	29.5*	26.2*	17.8
Hemopoietic islets, $\times 10^3$	39	55*	41	44*	56*	45*	51*	47	43
CFU-E, $\times 10^5$	0.3	1.7*	0.3	1.2*	4.7*	3.9*	1.2*	0.5	1.1
CFU-GM, $\times 10^5$	0.5	0.8	0.6	0.7	1.8*	1.1*	0.7	0.9	0.7
Erythropoietin, arb. units	0.3	3.4*	0.9*	2.9*	2.2*	1.8*	1.9*	0.9*	0.2
GM-CSF, arb. units	0.2	0.5	0.2	0.5	0.6	0.4	0.3	0.7	0.7
Inflammation									
11-hydroxycorticosteroids, mmol/liter	33	65*	42*	39	29	32	31	27	30
Leukocytes, $\times 10^9$	8.1	10.7	6.9	7.7	7.5	8.4	9.1	10.2	7.6
Erythrocytes, $\times 10^{12}$	6.7	5.4	6.3	5.8	6.1	5.5	6.1	5.8	5.5
Reticulocytes, ‰	12	24*	18	24*	20*	14	11	14	14
Cellularity of thymus, $\times 10^6$	118.2	80.1	60.5*	55.7*	91.2	101.4	97.4	105	121
Cellularity of bone marrow, $\times 10^6$	17.8	18.2	15.9	21.3	23.6*	26.4*	27.7*	22.1*	18.9
Hemopoietic islets, $\times 10^3$	39	43*	37	39	46*	64*	55*	49	40
CFU-E, $\times 10^5$	0.3	0.7	0.2	0.4	1.1*	0.7	0.3	0.6	0.1
CFU-GM, $\times 10^5$	0.5	1.1*	0.3	2.9*	4.9*	3.8*	2.5*	1.5*	1.9*
Erythropoietin, arb. units	0.3	0.5	0.1	0.8	0.3	0.3	0.5	0.3	0.6
GM-CSF, arb. units	0.2	2.9*	1.0*	3.1*	3.0*	1.1*	2.9*	1.0*	0.9*

Note. *$p<.05$.

with the data reported by other authorities [3,5,7,8]. However, this interpretation of our experimental data is by no means the only possible mechanism of adaptation, which ignores the contribution of other systems of the organism in this process. For instance, migration of T lymphocytes, the regulators of hemopoiesis in the bone marrow, may be modulated through opioid peptides, which affect glucocorticoid secretion [10,12], while administration of ganglioblockers, α- and β-adrenolytics, or mimetics makes it possible to abolish or to alter the time or pattern of bone marrow hyperplasia in stress [2,9].

Thus, our findings attest to the presence of a slow cascade mechanism of adaptation which drifts toward augmented erythro- or myelopoiesis depending on the nature of the extreme factor. Inhibition

of either of these systems during its peak activity (critical period) abolishes the adaptation cascade.

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