Parameters of Stress Response at Various Stages of Postresuscitation Period

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Transient circulatory arrest (10 min) was followed by changes in rat adrenals and thymus and a decrease in blood calcium and protein contents typical of stress response. Maintenance under unfavorable conditions for a long time also produced changes in stress-target organs accompanied by a considerable shift in functional state of the central nervous system manifested in enhanced behavioral response to exogenous stimulation.

Key Words: *postresuscitation period; circulatory arrest; stress response; environmental factors*

Our previous studies showed that resuscitated rats display enhanced behavioral response to stimulation, changes in the functional state of the central nervous system (CNS), and decreased adaptive capacities under conditions of prolonged psychophysiological load [1, 2]. These data suggest that sustained postresuscitation changes in the brain and other tissues increase the sensitivity to stress, which leads to the development of neurotic disorders accompanied by specific and nonspecific changes in organs and systems [5]. Here we studied changes in rat thymus and adrenals (main target organs in nonspecific stress reaction), blood levels of calcium and protein (parameters of homeostasis reflecting the severity of stress and undergoing considerable changes during reperfusion after experimental brain ischemia and under critical conditions [4,6]), and behavioral activity (integral functional characteristic of CNS) at various stages of the postresuscitation period.

MATERIALS AND METHODS

Experiments were performed on male outbred albino rats weighing 180-220 g. The rats were exposed to 10-min circulatory arrest [3]. Intact rats served as the control.

In series I we studied the effects of transient circulatory arrest (stress) on the total plasma contents of calcium and protein and relative weights of the thymus (RWT) and adrenals (RWA). RWT and RWA were estimated 4, 7, 14, and 30 days after resuscitation. Plasma calcium and protein contents were measured on a Cobas Mira Plus device 7 days after resuscitation. The animals were kept in a vivarium under standard conditions.

In series II, the effects of prolonged exposure to environmental factors on test parameters were studied. Intact and resuscitated rats were kept under various conditions for 2 months. Group 1 rats (14 intact and 15 resuscitated rats) were kept in 40×30× 15-cm standard cages (SC) under sensory deficient conditions. Group 2 animals (10 intact and 10 resuscitated rats) were kept under sensory enriched conditions in 65× 65×45-cm chambers (living room, LR). The chamber included double-decker houses, dark compartments allowing animals to avoid conflict situations, swing, inclined surfaces, and various periodically renewed objects for realization of locomotor and exploratory activities. Intact (n=10) and resuscitated animals (n=10) were maintained in different LR. Group 1 was divided into 2 subgroups: subgroup 1 included 10 resuscitated and 10 intact

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TABLE 1. RWT, RWA, and Biochemical Blood Parameters in Intact and Resuscitated Rats 1 Month after 10-Min Circulatory Arrest (*M*±*m*)

Parameter	Intact (*n*=10)	Postresuscitation period, days			
		4 (*n*=6)	7 (*n*=6)	14 (*n*=7)	30 (*n*=7)
RWT, mg/g	1.140±0.063	0.637±0.031*	0.713±0.10*	1.152±0.071^{+}	1.503±0.074*
RWA, mg/g	0.199±0.007	0.246±0.021*	0.295±0.0.033*	0.225±0.035^{+}	0.182±0.012
Calcium, mmol/liter	2.980±0.075	—	2.720±0.043*	—	—
Protein, g/liter	63.36±1.51	—	57.4±0.72*	—	—

Note. *p<0.01 compared to intact rats, ^{+}p<0.05 compared to day 7 (U test).

rats living in two SC (10 animals in each). Subgroup 2 rats (n=9) were maintained in 2 SC. Intact and resuscitated animals were kept separately. RWT, RWA, and biochemical parameters of the blood were measured after 2 months.

In series III, intact (n=13) and resuscitated rats (n=17) were kept in SC for 4 months.

The effects of 2- and 4-month life in SC on the functional state of CNS were evaluated by total behavioral activity (TBA, total count of behavioral reactions) of rats in the open-field test. Behavioral tests were performed using a RODEO-2 device (non-stress variant) under conditions of suppressed exploratory activity [1] and minimal exogenous stimulation.

The results were analyzed by Student's t test, Mann—Whitney U test, and ANOVA.

RESULTS

RWT decreased, while RWA increased 4 and 7 days after resuscitation (p<0.01, Table 1). These changes are typical of stress response. RWT and RWA returned to normal 14 days after resuscitation. It should be emphasized that RWT surpassed the control on day 30 of the experiment (p<0.01, Table 1). Seven days after resuscitation plasma calcium and protein contents were below the control (Table 1).

In series II, no differences were found between intact and resuscitated rats of group 1 kept under various conditions (10 or 5 animals in each cage). Therefore, we combined data on intact and resuscitated animals in different subgroups. RWT in intact and resuscitated rats kept in SC for 2 months was lower compared to animals maintained in LR (Table 2). Biochemical parameters of the blood in intact rats did not depend on environmental conditions. However, test parameters in resuscitated rats living in SC were lower than in animals kept in LR. The relative weights of internal organs and biochemical parameters of the blood in resuscitated rats maintained in LR did not differ from the control (Table 2). It should be emphasized that resuscitated rats displayed more pronounced reactions to SC conditions than intact animals. Resuscitated rats living in SC had higher RWA and lower plasma calcium content than intact animals (Table 2).

Two months after resuscitation TBA of rats maintained in SC did not differ from that on days 9 and 10 postresuscitation and was similar to that in intact animals (Fig. 1, *a*). However, TBA of resuscitated rats kept in SC for 4 months was higher than 2 months after resuscitation and surpassed that in intact animals (Fig. 1, *b*). We found no differences between TBA of rats in 2 consecutive open-field

TABLE 2. RWT, RWA, and Biochemical Parameters of the Blood in Intact and Resuscitated Rats Kept for 2 Months after Resuscitation under Various Environmental Conditions (*M*±*m*)

Parameter	Intact		Resuscitated	
	SC (*n*=14)	LR (*n*=10)	SC (*n*=15)	LR (*n*=10)
RWT, mg/g	0.896±0.053*	1.206±0.084	0.792±0.052*	1.137±0.086
RWA, mg/g	0.147±0.014	0.153±0.008	0.180±0.006^{+}	0.166±0.011
Calcium, mmol/liter	3.29±0.08	3.32±0.03	2.92±0.02*$^{+}$	3.33±0.06
Protein, g/liter	70.9±0.58	72.8±1.35	70.2±0.76*	73.6±0.76

Note. p<0.05: *compared to LR; $^{+}$compared to intact rats kept under similar conditions.

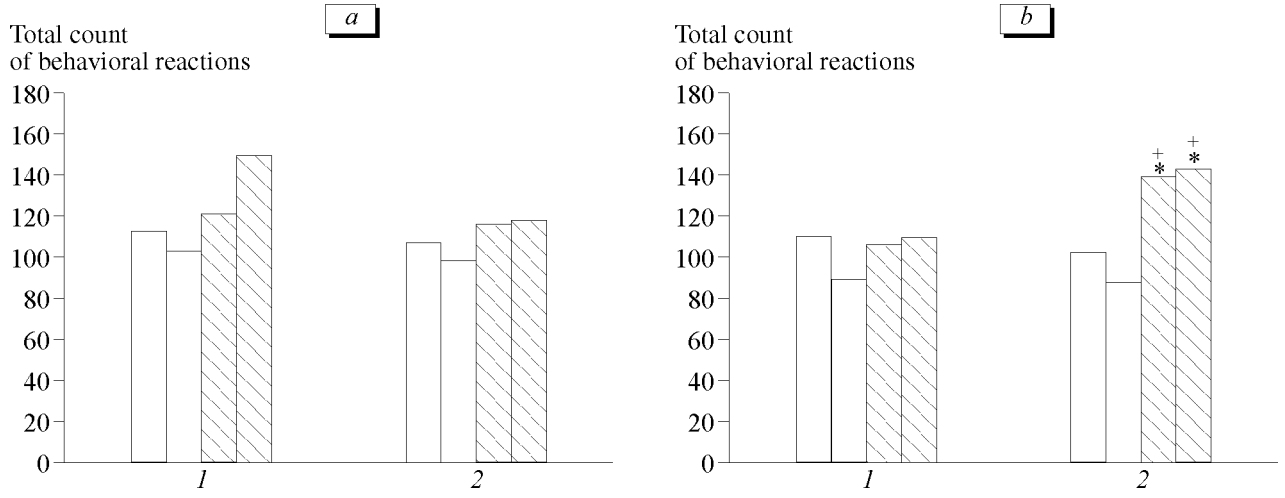

Fig. 1. Changes in open-field total behavioral activity of intact (*1*) and resuscitated rats (*2*) kept in standard cages. $p<0.02$: *compared to intact rats in the same open-field test; +compared to rats of the same group 9 and 10 days after resuscitation. Light bars: 2 consecutive open-field tests 9 and 10 days after resuscitation. Shaded bars: 2 consecutive open-field tests 2 (*a*) and 4 months (*b*) after resuscitation.

tests 4 months after resuscitation. Therefore, the increase in TBA is associated with changes in functional state of CNS, but not with forgetting.

Our results indicate that changes in internal organs and biochemical parameters of the blood induced by transient circulatory arrest disappeared 2 weeks after resuscitation, but repeatedly developed in rats kept in SC for 2 months. Intact animals displayed similar, but less pronounced reactions to environmental factors. Functional state of CNS was similar in intact and resuscitated rats and did not differ from that observed in the early postresuscitation period. Stress-induced changes in internal organs and blood parameters were less pronounced in resuscitated and intact rats kept in LR (compared to SC). As differentiated form intact rats, prolongation of living of resuscitated animals in SC to 4 months was accompanied by a decrease in their resistance to stress (psychophysiological load) [1] and changes in functional state of CNS (prevalence of excitation over inhibition). Therefore, delayed postresuscitation encephalopathies are manifested in the development of neurotic disturbances. Our results indicate that resuscitated rats are more sensitive to chronic stress than intact animals. During recovery after circulatory arrest environmental conditions determine functional state of CNS and other organs and can promote or prevent the development of delayed postresuscitation encephalopathies.

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