MORPHOLOGY AND PATHOMORPHOLOGY

Effect of Behavioral Activation on Recovery of Resuscitated Rats

A. M. Gurvich, Yu. V. Zarzhetskii, E. A. Mutuskina, I. E. Trubina, M. Sh. Avrushchenko, and S. I. Pylova

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Exploratory behavior, level of anxiety, blood content of atherogenic risk factors, and morphological alterations in the brain were compared in rats survived after a 10-min cardiac arrest and maintained at different regimens after resuscitation. A positive role of active behavior and emotionally positive reinforcement in the postresuscitation recovery are demonstrated.

Key Words: *resuscitation; exploratory activity; neuron populations; atherogenesis*

New data obtained in resuscitation during the last decade show that the brain, which is most sensitive to ischemia and pathogenic factors of postresuscitation disease, not only passively, but also actively participates in the pathogenesis and compensatory and reparative processes [6]. It has been shown that electrical stimulation of the hypothalamic lateral preoptic nuclei responsible for emotionally positive reaction considerably accelerates postresuscitation recovery of the central nervous system (CNS) in rats resuscitated after cardiac arrest.

The aim of the present study was to evaluate the effect of long-term behavioral activity with emotionally positive reinforcement on functional and structural recovery of the brain during the postresuscitation period. Previously, we demonstrated a progressive (over 2-3 months) increase in blood content of atherogenic risk factors such as cholesterol, triglycerides, low and very low density lipoproteins [5]. In the present study we examined the effects of different behavioral postresuscitation regimens on the dynamics of atherogenesis.

Institute of General Resuscitation, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

The study was performed on 60 random-bred male rats weighing 150-200 g. Cardiac arrest (10 min) was induced by the 4-vessel occlusion [3]. The animals were resuscitated by indirect cardiac massage and air jet ventilation. Mortality during resuscitation was 30%. External neurological deficiency was assessed daily starting from day 1 postresuscitation using a 100-point scale [4] by the state of acoustic and visual analyzers, locomotor apparatus, reaction to pain, and some other parameters (eating, drinking, and neatness). According to this scale, 100 points corresponded to brain death and 0 corresponded to complete recovery. Three days postresuscitation the rats were divided into 2 groups (10 animals in each) so that each group comprised animals with neurological disturbances of the same severity. Group 1 rats were then maintained in a vivarium (passive resuscitated rats), while group 2 rats were trained the four-step food procuring conditioned reaction in a multialternative maze under conditions of free choice with positive reinforcement [7] starting from day 8 postresuscitation. Training sessions lasted 13 min and were repeated on the other days (20 times for each animal). In addition, group 2 rats were allowed to

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leave the home cage and to explore a "living room" with a chair, table, and shelves in it. Two groups of intact animals served as the control: passive intact rats (group 3, n=10) were kept in a vivarium, while active intact rats (group 4, n=10) were trained in the above-described paradigms. After completion of maze learning (2 months after resuscitation), animals of all groups passed functional tests in order to evaluate their anxiety (plus maze [1]) and exploratory activity (Rodeo-2 apparatus [2]), after which 5 animals from each group were selected for morphological examination of the brain. These were passive rats with maximum integral behavioral activity (IBA) and active rats with most active behavior in the maze judging from the number of correct responses. Morphological analysis was carried out as described previously [2]. The total density of neuron population was assessed in layer V of the sensorimotor cortex, CA4 region of the hippocampus, and Purkinje cells of the lateral cerebellar areas. In all animals, plasma contents of cholesterol, triglycerides, and low and very low density lipoproteins (LDL+VLDL) were measured in a Zond-1 fluorimeter using standard analytical kits [5]. The data were processed statistically using the Student and Wilcoxon—Mann—Whitney tests.

RESULTS

In the plus maze test, active resuscitated and intact animals showed a 4-fold higher frequency of hanging in comparison with the corresponding passive rats, which attests to a reduced anxiety in rats with active behavior (both intact and survived 10-min cardiac arrest). Testing in a Rodeo-2 apparatus revealed similar level of IBA in all groups except passive intact rats. Unlike passive resuscitated rats, in active resuscitated and intact rats this parameter did not decrease in repeated tests; IBA in passive intact animals remained at a low level and did not change during repeated tests (Table 1). Thus, reaction of active resuscitated rats to repeated testing in a Rodeo-2 apparatus became close to that of intact rats.

Morphological analysis showed that CA4 sector of the hippocampus was most sensitive to hypoxia. Functional disturbances and dystrophic changes in this brain area can be prevented by behavioral activation of resuscitated rats: in active resuscitated rats the neuron density was higher than in passive resuscitated rats by 29.9% and did not differ from that of intact active animals. Behavioral activation also increased, although to a lesser extent. The number of neurons in layer V of the sensorimotor cortex after resuscitation increased by 10.9% in active in comparison with passive resuscitated rats. The content and density of Purkinje cells in the lateral cerebellar areas was the same in active and passive rats (Table 1).

Biochemical analysis demonstrated a considerable rise of triglycerides and LDH+VLDL in the blood of resuscitated rats in comparison with intact controls. Active regimen promotes a decrease in both cholesterol and triglycerides. The content of cho-

TABLE 1. Effect of Behavioral Activation on Functional and Morphological Parameters of the Brain and Plasma Lipids ($M \pm m$)

Tests, parameters	Resuscitated		Intact	
	passive (group 1)	active (group 2)	passive (group 3)	active (group 4)
Functional				
Number of leanings	0.73±0.21	3.3±0.96*	0.8±0 44	4.3±0.95×
IBA, session 1	214.7±17.5×	212.0±13.20	147.2±11 57	258.2±19.28×
IBA, session 2	149.0±12.9+	174.9±19.90	154.7±22.25	215.2±12.27×
Morphological				
Total density of neurons, arb. units				
Cortex	54.9±0.7	60.9±1.0*	55.6±0.8	58.9±1.53
Hippocampus	146.8±10.01×	178.2±8.1*	174.9±5.8	171.5±8.02
Purkinje cells, arb. Units				
Cerebellum	14.7±0.5	13.9±0.7	14.3±0.4	16.2±0.77
Biochemical				
LDH+VLDL, mg/dl	246.3±17.5×	231.2±17.5°	160.0±14.7	148±7.8
Cholesterol, mmol/liter	5.0±0.25	3.7±0.29*	4.78±0.21	3.1±0.09×
Triglycerides, mmol/liter	3.90±0.21×	3.28±0.24*°	<0.90	<0.90

Note. p<0.05: *compared with group 1; ×compared with group 3; °compard with group 4; +compared with test 1 in the same group.

lesterol approximated that in intact animals, but the levels of triglycerides and LDL+VLDL in active resuscitated rats considerably surpassed those in intact controls (Table 1).

Thus, our findings suggest that behavioral activation with an emotionally positive component performed in resuscitated rats for 2 months after general neurological recovery reduces anxiety, restores exploratory activity to the control level (intact animals), prevents neuron depletion of layer V of the sensorimotor cortex and CA4 sector of the hippocampus, and reduces the content of some atherogenic components associated with premature aging.

It was reported that enriched environment and social interaction have a positive effect on the long-term impact of occlusion of the middle cerebral artery [9].

These data confirm the role of neurophysiological factors in mechanisms of recovery of CNS from global and regional ischemic pathology. However, the mechanisms of their action remain to be investigated as well as the possibility of differential use of these methods for different severities and stages of primary injury.

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