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Mechanism of the Effect of Postresuscitation Changes in the Brain on the Dynamics of Extinction of Orientation and Exploratory Response in Rats

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The type of open-field behavior (determined in preliminary tests) was preserved after 10-min circulatory arrest. Postresuscitation changes in the bran modified orientation and exploratory activity under conditions of its partial extinction before clinical death. High behavioral activity of rats in the first open-field session after resuscitation was related to the impairment of memory traces, while that in the follow-up period was associated with the formation of a pathological self-maintaining system between components of orientation and exploratory behavior.

Key Words: *orientation and exploratory activity; postresuscitation period*

Previous studies showed that rats subjected to 10-min circulatory arrest exhibit increased behavioral response to novelty in the open-field test in the postresuscitation period [2]. Experiments with primary extinction of orientation and exploratory activity before modeling of clinical death were performed to evaluate the effect of postresuscitation changes in the brain on behavioral activity of rats not associated with high reactivity to stimulation. This approach characterized the influence of clinical death on preservation of typological behavioral characteristics that play a role in brain recovery [5].

Here we studied whether the behavioral pattern is preserved after severe global ischemia. In addition, we evaluated the effect of ischemic brain damage on functional recovery of the central nervous system (CNS).

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MATERIALS AND METHODS

Experiments were performed on 123 male outbred albino rats weighing 180-230 g. Systemic circulatory arrest in 53 ether-anesthetized animals was modeled by 10-min intrathoracic ligation of the major vessels [3] and followed by closed-chest cardiac massage and artificial ventilation. The control group included intact rats.

Orientation and exploratory activity of rats was studied using the open field test. The number of vertical rearing postures (VRP), explored holes (EH) in the chamber's floor, and horizontal locomotor activity were recorded automatically on a RODEO-2 device. Total behavioral activity (TBA) was calculated as the sum of parameters recorded over 3 min. A total of 8 open-field sessions were carried out; the first 4 sessions were performed 10-14 days before modeling of clinical death.

The effect of circulatory arrest on preservation of behavioral characteristics was estimated by the overall coefficient of correlation (r) between TBA before and 3 (session 5), 4 (session 6), 9 (session 7) and 10 days

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after resuscitation (session 8). The partial coefficient (r) was calculated to evaluate the relationship between behavioral parameters in the open field. This approach allowed us to exclude the influence of one parameter on another.

RESULTS

The coefficient of correlation (r) between TBA in the 3rd and following sessions was high in control rats ($p<0.01$). The highest coefficient of correlation (r) was revealed between TBA in sessions 4 and 5-8 (Table 1). The effect of circulatory arrest on preservation of the behavioral pattern in rats after circulatory arrest was evaluated relative to TBA in session 4. Resuscitated rats differed from control animals by low coefficient of correlation between TBA in sessions 4 and 5, as well as in sessions 4 and 8 (Table 1). It should be noted that TBA of control and resuscitated rats differed in sessions 5 and 8 (Table 2).

The existence of a strict correlation between TBA of rats before and 4 (session 6) or 9 days after resuscitation (session 7) reflected preservation of the behavioral pattern. However, postresuscitation changes in the brain altered behavioral activity of animals 3 and 10 days after resuscitation (sessions 5 and 8, respectively).

High behavioral activity of resuscitated rats in session 5 (first session after resuscitation) was associated with partial forgetting, which resulted from memory dysfunction. This conclusion was derived from the decrease in TBA during session 6 to the control level. However, it could not explain further increase in TBA of resuscitated animals during session 8. Resuscitated rats exhibited a higher number of VRP (11.5±0.9 *vs*. 7.1±0.8 in the control, $p<0.01$) and EH (11.1±1.0 *vs*. 7.9±1.1 in the control, $p<0.05$).

Each behavioral parameter reflects the end or intermediate result of functional systems that have a specific organization of constituting elements. Hence, novelty led to the appearance of new functional systems to realize various behavioral reactions in the form of horizontal locomotor activity, VRP, and hole exploration. It was hypothesized that horizontal locomotor activity also serves as a constituent of other functional systems.

The correlations between behavioral parameters were studied to evaluate the relationship between functional systems. Strong correlations were revealed between horizontal locomotor activity and other behavioral parameters of rats in sessions 1 and 4 (before modeling of clinical death, Table 3). These data show that horizontal locomotor activity play a role in the realization of behavioral reactions (VRP and hole exploration). Extinction of orientation and exploratory activity was accompanied by the appearance of a positive correlation between the number of VRP and EH (Table 3). A correlation between these parameters is associated with the involvement of horizontal locomotor activity in the performance of VRP and hole exploration. Partial coefficient of correlation between the number of VRP and EH in session 4 approached zero (r=-0.2), when the parameter of horizontal locomotor activity was eliminated.

A negative partial correlation (r=-0.23, $p<0.05$) was found between the number of VRP and EH in session 1 (elimination of horizontal locomotor activity). Our findings suggest the existence of reciprocal relations between functional systems for behavioral reactions in rats with high orientation and exploratory activity. To test this hypothesis, we formed 2 subgroups of animals whose TBA in session 1 was above (group 1, n=52) or below the mean value (group 2,

TABLE 1. Correlations between TBA of Control (n=32) and Resuscitated Rats (n=32) in the Open Field

Session	Session						
	2	3	4	5	6	7	8
Control							
1	+0.49*	+0.32	+0.23	+0.08	+0.07	+0.08	+0.13
2	+1.0	+0.64*	+0.61*	+0.49*	+0.33	+0.23	+0.37
3		+1.0	+0.77*	+0.54*	+0.55*	+0.54*	+0.62*
4			+1.0	+0.66*	+0.77*	+0.58*	+0.77*
Resuscitation							
1	+50*	+0.22	+0.20	+0.01	+0.02	+0.17	+0.03
2	+1.0	+0.42	+0.50*	+0.48*	+0.40	+0.49*	+0.35
3		+1.0	+0.77*	+0.25	+0.33	+0.43	+0.37
4			+1.0	+0.37	+0.47*	+0.55*	+0.32

Note. *$p<0.01$ compared to zero.

TABLE 2. TBA of Control and Resuscitated Rats in the Open Field (*M*±*m*)

Group	Before resuscitation, sessions				After resuscitation, sessions			
	1	2	3	4	5 (day 3)	6 (day 4)	7 (day 9)	8 (day 10)
Control (*n*=32)	243.0±6.7°	196.2±12.4*°	139.9±14.0*	127.1±12.3	113.8±12.0	104.4±11.0	106.3±11.2	87.9±9.8*
Resuscitation (*n*=34)	245.7±5.5°	190.1±12.0*°	141.7±13.7*	117.0±12.8	157.3±10.4*+°	114.5±9.8*	109.9±9.8	114.0±8.5*

Note. *p<0.01 compared to the previous session. p<0.05: +compared to control rats in the same session; °compared to the same group in session 4.

n=52). A strong negative partial correlation *r* (after elimination of horizontal locomotor activity) between the number of VRP and EH was found in rats with high (*r*=-0.50, $p_t \leq 0.01$), but not low TBA (*r*=-0.17). The integral response of CNS to novelty involved reciprocal relations between functional systems for VRP and hole exploration. Therefore, these behavioral reactions are directed to satisfy different biological needs. The systems providing orientation and exploratory activity operate independently of each other after extinction of this behavior.

Partial coefficients of correlation *r* (elimination of horizontal locomotor activity) between the number of VRP and EH in session 7 approached zero for control and resuscitated rats (0.03 and 0.16, respectively). Resuscitated animals exhibited a positive correlation between the number of VRP and EH in session 8 (*r*=0.40, p_t<0.05). However, the partial correlation coefficient for control rats remained low (*r*=-0.12) and significantly differed from that for resuscitated animals (p<0.05). A strong negative partial correlation *r* (elimination of horizontal locomotor activity) between the number of VRP and EH was characteristic of rats exposed to 10-min circulatory arrest (*n*=19) and subjected to the first open-field session 9-10 days after resuscitation (*r*=-0.73). Hence, a positive correlation between the number of VRP and EH resulted from repeated open-field trials after resuscitation. The appearance of this correlation was probably associated with the formation of a strong structural relationship in the general behavioral subsystem for horizontal locomotor activity. It can be hypothesized that the formation of structural relationships is associated with the compensatory response to ischemic damage, which includes reorganization of synapses and dendrites [4]. These changes result in the appearance of a self-maintaining system: VRP initiate hole exploration, and vice versa. This self-maintaining system is pathological because these behavioral reactions are directed to satisfy different biological needs. The increased formation of intracerebral intersystem relationships in the post-resuscitation period is confirmed by published data on

TABLE 3. Overall Coefficients of Correlation between Behavioral Parameters of Control Rats (*n*=104) in the Open Field during Extinction of Orientation and Exploratory Activity

Parameter	Session 1		Session 4	
	VRP	HA	VRP	HA
HA	+0.31*		+0.76*	
EH	-0.17	+0.26**	+0.55*	+0.74*

Note. *p<0.01 and **p<0.05 compared to zero. HA, horizontal locomotor activity.

accelerated acquisition of a conditioned response to positive and negative reinforcement in resuscitated rats [1].

Our results indicate that postresuscitation changes in the brain produce various effects on behavioral activity. They promote the formation of pathological systems and contribute to the adaptation to environmental conditions, which is realized via the same mechanisms.

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