Behavioral Peculiarities and Reactions of Brain Dopaminergic Systems in Rats with Different Resistance to Acute Hypobaric Hypoxia

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 130, No. 9, pp. 275-278, September, 2000
Original article submitted December 14, 1999

Locomotor activity in the open field test did not correlate with rat resistance to acute hypobaric hypoxia; there was a correlation between this resistance and rat behavior during acute stress. Immobility was characteristic of rats with low and particularly medium resistance to hypoxia; this reaction can be abolished by antidepressants. By contrast, highly resistant rats were mainly hyperactive. The resistance to hypoxia was associated with extreme parameters of dopaminergic neuron functioning. In low-resistant rats locomotor stereotypia was maximal, while perioral stereotypia was the minimal; highly resistant rats were characterized by an opposite pattern, and medium-resistant rats occupied an intermediate position.

Key Words: *open field behavior; extrapolation escape test; individual resistance; acute hypobaric hypoxia; dopamine receptors*

Dopaminergic activity of cerebral neurons depends on the functional status, which correlates with different behavioral patterns of animals. Tonic activity of dopaminergic neurons can be induced by injection of D-receptor agonists (apomorphine, amphetamine, L-DOPA). These drugs disturb purposeful behavior [2,3] and cause stereotypies. Functional increase of dopaminergic activity is observed in acute emotional stress affecting mainly the higher cognitive forms of behavior [1,4]. Open field (OF) test corresponds to a certain mean level of functioning of the brain dopaminergic systems.

Apart from involvement in the formation of behavioral reactions, cerebral D-receptors participate in the regulation of energy metabolism in the brain and play an important role in the formation of animal resistance to acute hypobaric hypoxia [5,10]. We investigated the behavioral reactions of rats with different resistance to hypoxia during different types of functioning of their dopaminergic systems.

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MATERIALS AND METHODS

The study was carried out on random-bred male albino rats (220-280 g). Rat behavior was tested in OF and extrapolation escape test (EET) modeling the effect of acute emotional stress on cognitive functions. Experiments were performed 1 week before hypoxic exposure in a pressure chamber. The rats were "elevated" to an altitude of 11,0000 m at a rate of 50 m/sec until apnea. Depending on the time of the second agonal inspiration (time of life) the rats were divided into low- (LR), medium- (MR), and highly resistant (HR) to hypoxia. The time of life of LR rats was 0.5-3 min, MR 5-7 min, and HR more than 10 min. The intensity of stereotypia induced by a high dose of apomorphine (0.75 mg/kg subcutaneously) was scored 4 weeks after hypoxic exposure using a 5-point scale [8]: 0 – no stereotypical behavior, 1 – short (5-10 sec) episodes of stereotypical behavior without disorders in exploration behavior; 2 – longer (up to 30 sec) episodes of stereotypical behavior; 3 – long-term stereotypical behavior with intact orientation; 4 – long persistent stereotypical behavior. The following stereotypies were

0007-4888/00/0009-849$25.00

evaluated using this scale: sniffing, licking, biting, and hyperactivity. Total score for all types of behavior was counted for each animal. The animals were observed for 2 min 30 and 60 min after apomorphine injection. The results were processed using the Mann—Whitney *U* test.

RESULTS

The resistance to hypoxia is a quantitative sign. We evaluated the correlation between time of life under conditions of hypoxia and locomotor activity of OF (peripheral and central ambulation, Table 1). No significant differences in OF behavior in rats of different groups were observed. Spearman's correlation coefficients were -0.38 and -0.41, respectively. The results indicate that locomotor activity in OF is not sufficient for predicting animal resistance to hypoxia, which is in line with the results of other scientists, who demonstrated that one more test, inevitable swimming, is needed for this purpose [6,7]. This model involves a stress situation, and we therefore expected that similar in modality EET will also be helpful in predicting rat resistance to hypoxia.

Three behavioral parameters in EET varied significantly in random-bred rats (Table 2): latency of first movement, number of ineffective avoidance attempts (jumps), and latency of escape (diving). It is noteworthy that differences in rat behavior in EET were qualitative (Table 2).

In group 1, jumps, *i. e.* avoidance behavior not attaining the purpose (jumping from the cylinder) predominated. Group 5 rats demonstrated behavioral immobility in EET (despair behavior), which also prevented their escape from acute stress. Similarly to group 1, group 2 rats first jumped, but then refused this inefficient strategy and tried diving. Group 3 rats demonstrated maximally effective escape behavior in EET. Immediately after the start of EET test they dived under the cylinder walls and almost never tried to jump before diving (Table 2). The behavior of group 4 rats was similar to that in group 3, but differed in the latency of first movement and latency of escape: a trend to immobility was observed in group 4, which they overcame at the moment of solving the problem (Table 2).

TABLE 1. OF Behavior and Intensity of Apomorphine-Induced Stereotypy in Rats with Different Resistance to Hypoxia

Parameter	LR	MR	HR
Number of crossed squares			
peripheral	33.3	31.3	30.4
central	3.6	4.6	3.6
Rearings			
with support	7.3	10.3	9.0
without support	7.3	5.1	4.0
Number of explored holes	5.3	4.3	3.0
Stereotypy, score			
sniffing	3.8	3.7	3.5
licking	0.42	0.58	0.33
bites	0.17	0.33*	0.41*
locomotion	0.58	0.25*	0.17*

Note. *$p<0.05$ *vs.* LR rats.

Hence, by their behavior in EET the animals of 5 groups can be placed on the hyperactivity-immobility coordinate axis in the following order: group 3 in the center, groups 1 and 5 at the periphery, and groups 2 and 4 intermediate.

In order to detect a correlation between hypoxic resistance and behavior in EET, the animals were pretested in EET (Table 3). LR rats exhibited primarily type 4 behavior and less frequently type 1 behavior. MR rats showed mainly type 5 behavior and almost never type 4 behavior. The number of HR rats among animals of different types corresponded to their incidence in the population.

Hence, there was a correlation between animal resistance to hypoxia and their behavior during acute stress. However this tendency was more pronounced in animals with the most rare behavioral types 1, 4, and 5 (Table 2), and therefore its prognostic value is low.

However these data provide new insight into central mechanisms of resistance to hypoxia. First, immo-

TABLE 2. Rat Behavior in EET (*n*=538)

Parameter	Groups of rats according to EET				
	1	2	3	4	5
Latency of first movement, sec	5.5	4.0	3.6	12.3*	21.2*
Number of escape failures	82.9*	18.7	1.4	1.0	4.8
Latency of diving, sec	N.d.	32.6	6.0	18.9	N.d.
Percentage in random-bred population	5	33	37	10	15

Note. N.d.: no diving. *$p<0.05$ *vs.* group 3.

TABLE 3. Distribution (in %) of Rats with Different Resistance to Hypoxia by Behavioral Patterns in EET

Group	LR	MR	HR
1	15.4	23.5	30.4+
2	15.4	23.6	17.4
3	15.4	11.8	17.4
4	46.2*	5.9+	26.1*+
5	7.7*	35.3+	8.7*

Note. $p<0.05$: *vs. LR rats, +vs. MR rats.

bility, the behavioral pattern used for evaluation of sensitivity to hypoxia is more typical of LR and MR rats [6,7]. Such behavior is altered by antidepressants and therefore can be related to exhaustion of cerebral monoamine systems [3]. Our results indicate that resistance to hypoxia is associated with extreme parameters of dopaminergic neuron functioning. It was therefore interesting to investigate the effects of the maximum (tonic) activation of D-receptors with a high dose of D-receptor agonist apomorphine in animals with different hypoxic resistance.

Rats of different groups did not differ by the intensity of low-rank elements of perioral stereotypical behavior (sniffing and licking, Table 1) but differed significantly by the severity of stereotypical bites, this severity decreasing in the following order: HR–MR–LR. The intensity of locomotor stereotypy also differed significantly in these groups, but, in contrast to bites, decreased in the HR–MR–LR series.

Therefore, locomotor stereotypies were most expressed and perioral stereotypies minimally expressed in LR rats. HR rats were characterized by an opposite pattern, while MR rats occupied an intermediate position. Since individual stereotypical acts possess different morphological substrata (mesolimbic for locomotion and nigrostriate dopaminergic system for perioral behavior) [9], parallel functioning of the two systems under extreme conditions can play an important role in the resistance to acute hypobaric hypoxia.

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