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EFFECT OF PSYCHOTROPIC DRUGS ON BEHAVIOR OF INBRED MICE UNDER EMOTIONAL STRESS

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The behavior of C57BL/6, CBA, and BALB/c mice in an "open field" test was studied after administration of phenazepam in doses of 0.05, 0.075, and 0.1 mg/kg and of sydnocarb in doses of 6, 12, and 24 mg/kg. The initial response to emotional stress was characterized by greatest motor activity (MA) in C57BL/6 mice and minimal in BALB/c mice. Phenazepam lowered MA in C57BL/6 mice proportionally to the dose. A biphasic effect of the tranquilizer was found in BALB/c mice. Depending on the dose, sydnocarb stimulated MA of C57BL/6 mice, did not effect the behavior of CBA mice, and in a dose of 24 mg/kg, it increased MA of BALB/c mice.

KEY WORDS: emotional stress; psychotropic agents.

Clinical and experimental investigations have shown that responses to psychotropic drugs reflect individual differences [1, 6].

The object of this investigation was to study genetically determined differences in the action of new Soviet preparations phenazepam and sydnocarb on the behavior of mice under emotional stress.

EXPERIMENTAL METHOD

Experiments were carried out on C57BL/6 (B6), CBA, and BALB/c (C) mice weighing 18-20 g (from the Stolbovaya nursery, Academy of Medical Sciences of the USSR), which were kept on a standard diet and with 12-hour periods of daylight for 21 days before the experiments, in cages accommodating three mice.

A stressor situation was simulated in an "open field" test by switching on four 60-W lamps creating an intensity of illumination of 1500 lx on the cage floor.

The preparations were injected intraperitonally in a suspension of Tween-80 with water 30 min before the beginning of the experiments: phenazepam was given in doses of 0.05, 0.075, and 0.1 mg/kg and sydnocarb in doses of 6, 12, and 24 mg/kg. The corresponding volume of a suspension of Tween-80 in water were injected into the control animals.

The behavior of the mice in an open field was observed for 3 min. Total motor activity (MA) was recorded (as the number of crossings of sectors over the whole area, the number of times the animals stood on their hind limbs), the horizontal MA (the total number of sector crossings), the peripheral MA (the number of peripheral sectors crossed), and the central MA (the number of sectors crossed in the center) were recorded. Each animal was used once only in the experiments. Student's method for dependent samples was used for the statistical analysis.

EXPERIMENTAL RESULTS AND DISCUSSION

The study of the open field behavior of inbred mice showed that their response to emotional stress is genetically dependent. B6 mice showed the highest activity for all indices

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TABLE 1. Effect of Phenazepam on Behavior of C57BL/6, CBA, and BALB/c in an Open Field Test (M±m)

Line of mice	MA	Control	Dose of drug, mg/kg		
			0.05	0.75	0.1
C57BL/6	Total	126,4±7,8 (25)	111,5±7,9*(25)	92,4±6,7 † (15)	58,5±9,8 ‡ (15)
	Horizontal	112,7±7,3	101,1±7,2*	84,1±8,6 *	55,6±8,4 ‡
	Peripheral	83,8±3,6	87,2±6,9	72,5±7,9*	49,6±7,7‡
	Central	28,9±3,8	16,1±2,4 †	10,6±2,3 †	8,5±1,7†
CBA	Total	46,6±6,9 (19)	43,0±7,1 (14)	44,7±5,9 (19)	20,7±3,8† (14)
	Horizontal	42,6±6,5	42,5±6,6	44,0±6,0	20,7±3,1†
	Peripheral	40,0±4,8	35,7±4,1	36,5±4,7	17,7±3,0†
	Central	8,9±2,5	4,7±2,8	6,9±1,9	3,0±1,3†
BALB/c	Total	24,5±3,6 (27)	39,5±6,9*(27)	32,7±11,7 (15)	14,8±1,8† (15)
	Horizontal	24,5±3,0	39,5±6,9*	32,7±11,7	14,8±1,8†
	Peripheral	23,5±4,0	38,9±7,1*	32,4±11,6	14,4±1,9*
	Central	0,9±0,5	0,5±0,4	0,2±0,1	0,4±0,2

Legend. Here and in Table 2: number of animals given in parenthesis; *) P<0.05, †) P<0.01, ‡) P<0.001.

TABLE 2. Effect of Sydnocarb on Behavior of C57BL/6, CBA, and BALB/c Mice in an Open Field Test

Line of mice	MA	Control	Dose of drug, mg/kg		
			6	12	24
C57BL/6	Total	112,1±6,4 (21)	138,0±6,1*(21)	154,2±8,5† (21)	176,2±6,1‡ (21)
	Horizontal	102,1±7,3	130,2±8,6*	143,3±5,9†	163,2±5,2‡
	Peripheral	86,3±5,2	116,5±5,6 †	132,2±6,7†	150,8±6,8‡
	Central	15,5±2,7	14,1±2,7	11,2±2,3	12,4±3,0
CBA	Total	50,9±8,6 (11)	37,4±3,9 (11)	59,7±6,3 (11)	67,0±2,5 (11)
	Horizontal	49,7±8,9	37,1±4,1	58,9±6,8	67,0±2,5
	Peripheral	47,2±8,3	36,5±3,7	57,8±6,5	65,4±2,1
	Central	4,4±2,6	0,5±0,4	1,0±0,7	1,7±0,8
BALB/c	Total	21,2±6,2 (21)	19,9±3,2 (21)	19,1±3,7 (21)	40,9±6,6*(21)
	Horizontal	21,0±6,1	19,8±3,2	19,0±3,7	40,9±6,6*
	Peripheral	20,9±5,2	19,4±3,2	19,0±3,7	40,8±6,5*
	Central	1,0±0,8	0,6±0,5	0	0

tested, C mice showed minimal activity, and CBA were in an intermediate position (Tables 1 and 2). These observations completely confirmed those of Borodin et al. [2], on the basis of which they concluded that B6 animals are resistant to the type of stress, and C mice are most reactive.

Phenazepam caused a decrease in all types of MA in proportion to the dose in B6 mice. In CBA mice a similar effect was observed only if phenazepam was given in a dose of 0.1 mg/kg. Meanwhile in C mice, total, horizontal, and peripheral MA were all increased after administration of the tranquilizer in a dose of 0.05 mg/kg, whereas after injection of 0.075 mg/kg phenazepam these parameters still showed a tendency to increase, and only with a dose of 0.1 mg/kg was a decrease observed (Table 1).

Judging from data in the literature, the behavior of animals in an open field is due to competition between feelings of "fear" and "curiosity" [5]. Phenazepam may perhaps depress the orienting reaction in B6 mice, as reflected in a decrease in the indices of MA. In initially "passive" animals of the C line, because of its tranquilizing action phenazepam evidently leads to activation of behavior. In this case a dose-dependent biphasic effect was observed (Table 1).

As Table 2 shows, sydnocarb increased total, horizontal, and peripheral MA in B6 mice but did not effect the number of squares they crossed in the center. With an increase in the dose of the psychostimulant, its effect became more marked. In CBA animals sydnocarb did not cause a statistically significant deviation of these parameters from the control levels. The behavior of C mice likewise was unchanged after injection of sydnocarb in doses of 6 and 12 mg/kg, and only after administration of a dose of 24 mg/kg was their peripheral MA increased (Table 2).

Differences detected in the behavior of intact mice of lines B6, CBA, and C in the open field test were very similar to those of emotional behavior discovered previously in three

groups of Wistar rats. The effect of sydnocarb on B6 mice coincided in this respect with its effect on rats categorized by Katkova et al. as "behaviorally active" animals, and the action of this drug on C animals with its effect on "behaviorally passive" animals [3]. Poshivalov [4] demonstrated that as a result of artificial isolation B6 mice can be divided into spontaneously aggressive and spontaneously nonaggressive groups. We also observed intralinear differences in MA, which evidently depended partly on the conditions under which the animals were kept, although the interlinear differences always remained greater. These observations point to the complexity of the problem of determining the relative roles of hereditary and environmental factors in responses to stress situations and to psychotropic drugs.

It can nevertheless be concluded from the results of the present experiments, conducted on large groups of animals with different genotypes, that the initial response to stress and its correction by phenazepam and sydnocarb are genetically dependent. In mice of different lines the effect of the tranquilizer may be different or even opposite. Sometimes it gives rise to the same behavioral changes as a psychostimulant.

Probably individual responses to psychotropic compounds of similar structure and action that are observed in clinical practice are also largely due to genotypic differences. Further intensive investigation of the central mechanisms of action of the drugs, their pharmacokinetics and metabolism, on the one hand, and a thorough neurochemical and hybridologic analysis of experimental animals differing in their sensitivity to these drugs, on the other hand, are required before the causes of these effects can be established.

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