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Social Model of Depression in Mice of C57BL/6J Strain

N. N. KUDRYAVTSEVA, I. V. BAKSHTANOVSKAYA AND L. A. KORYAKINA

Institute of Cytology and Genetics, Siberian Department of USSR Academy of Sciences, Novosibirsk, USSR

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KUDRYAVTSEVA, N. N., I V BAKSHTANOVSKAYA AND L A KORYAKINA *Social model of depression in mice of C57BL/6J strain* PHARMACOL BIOCHEM BEHAV **38**(2) 315–320, 1991 —Long experience of defeat in daily social intermale confrontations and permanent living with aggressive males under sensory contact conditions [Kudryavtseva (8)] has been shown to produce changes in the patterns of submissive behavior of male mice of C57BL/6J strain. The submissive males after 20 defeats demonstrated passive defense postures instead of active defense and withdrawal which they had displayed in first encounters Moreover, new immobile postures appeared, which were very rare in the first confrontations. Submissive animals displayed a decrease of ambulation in the open-field test and increase the immobility time in the Porsolt's test Chronic treatment with imipramine prevented the increase of "depressiveness" estimated by means of the Porsolt's test There was a loss of weight and some disturbances in gastrointestinal functions The data are discussed in terms of the development of depression in submissive male C57BL/6J mice as a result of chronic unavoidable social stress

Submissive male Experience of defeat Depression Sensory contact model

THE contribution of stress to the induction or exacerbation of depression has been emphasized in recent years. Uncontrollable electric shocks have been reported to induce remarkable behavioral deficits, such as deficits in motor activity, in appetite and grooming behavior, sleep disturbance, decreases in food and water consumption, weight loss and loss of normal aggressiveness or competitiveness in rats [reviewed by Weiss et al. (23)] These disturbances bear similarities to clinical depression with respect to etiology, susceptibility to treatment, and symptomatology (22,23).

Katz (4) has employed multiple stressors to produce a model of endogenous depression in rats. Chronic stress in this experiment consisted of a regimen of unpredictable aversive stimulations, involving a 21-day exposure to electric shock, food and water deprivation, a cold swim at 4°C, exposure to heat stress, reversal of the day/night cycle. Rats exposed to such treatment were reported to exhibit a decrease of sucrose and saccharin consumption (5) as well as a blockade of behavioral activation caused by a particular noise stress (7).

Antidepressant treatment was capable of reversing chronic stress-induced behavioral deficits and physiological changes brought about by the chronic stress (6). These evidences suggest that the unpredictable chronic stress as suggested by Katz (4) is behaviorally, physiologically and also pharmacologically similar to the clinical disorder and is a potentially useful animal model of human depression.

An animal model of human depression should satisfy at least four criteria, as suggested by McKinney and Bunney (15). similarity of etiology, biochemistry, symptomatology and treatment. In the described animal model of depression, the supposed etiologic factors of physical treatment (such as electric shock, cold swim, heat and shaker stress and so on) are scarcely similar to causes inducing the human depressive disease. It is well known that the development of depression in humans depends mainly on emotional negative stress factors. Some authors (18) have tried to distinguish the effects of chronic emotional stress and chronic physical stress on the development of depression in male rats. As chronic emotional stressful factors they used exposure to white noise, individual housing, cage blows, novel environment, exposure to darkness and bright light, group housing on highly stressed rat scented bedding, placing on a little platform surrounding by water. The results show that the emotional chronic stress caused minor behavioral effects and did not alter hormonal responses, unlike to the chronic physical stress [analogous to that in Katz et al. (4,5)] that induced a number of alterations· decrease of food consumption, clear-cut behavioral deficit, and a slight increase in basal level of corticosterone and prolactin (18). This experiment shows that chronic physical stress but not chronic emotional stress induces depressive symptoms in rats. Results in this study may be explained by the too small "power" of so-called emotional stressors

The most adequate and strongest effects on behavior and physiology of animals living in groups may be obtained through manipulations of socially significant factors, such as individual housing, overpopulation, change of hierarchy relations (21). When we studied the neurochemical and physiological mechanisms of aggressive and submissive behavior in male mice of CBA/Lac and C57BL/6J strains using the sensory contact model (8–12), we noticed that submissive mice of C57BL/6J strain with long experience of defeats in daily consecutive encounters and permanent living in one cage with aggressive animal being separated by a transparent partition with holes permitting to see, hear and smell it, induced dramatic changes in behavior which were similar to symptoms of human depression. We hypothesized that social (emotionally negative) stress is a pathogenic factor leading to development of those behavioral changes. The aim of this paper is

to summarize evidence to support this assumption.

METHOD

Experimental Animals

Mice of C57BL/6J strain maintained at the Institute of Cytology and Genetics of USSR Academy of Sciences (Novosibirsk) were used The animals were housed under standard vivarium conditions and natural regimen. Food and water were available ad lib. Weaned at the age of one month, the males were housed before the experiment by one-litter groups of 8–10 individuals in steel $36 \times 23 \times 12$ cm cage. The age of mice used in the experiments was 10–12 weeks

The Technique of Formation of Submissive Behavior in Male Mice

In order to induce submissive behavior in male mice the model of sensory contact (8,10) was used. Males were weighed and caged individually for 5 days to abolish group effects. Then every pair of animals of nearly the same weight was placed into steel $28 \times 14 \times 10$ cm cage separated into halves by a transparent partition with holes permitting animals to see and smell each other but preventing them from physical contact After two days adaptation to the housing conditions and sensory contact the testing was started. every afternoon (1400–1700 h local time) the steel cover of the cage was replaced by transparent one and 5 min later (period of individuals activation) the partition was removed for 10 min, which led to agonistic interaction between males. When the undoubted superiority of one of the partners was evident (within 2–3 tests in daily social confrontation with the same partner) each defeated male was placed every day after the test into an unfamiliar cage across the partition from another partner with experience of victories A depression-like state in submissive mice was achieved after 20 days of consecutive defeats agonistic confrontations. Simultaneously, the model produced the same number of aggressive animals with successive experience of victories permanently demonstrating an expressed aggression during tests (8).

Behavioral Tests

The open-field test. Open-field observations were carried out in a 9×9 square blue painted 100×100 cm Plexiglas open field. It was illuminated by a 150 W electric bulb, 150 cm above the open-field floor. The mice were placed individually in the center of the box, and the following behavioral variables were recorded for 5 minutes ambulation rate on squares (number), the latency of starting the exploration (latency to leave the center, s); rearing activity (number)

Exploratory activity test. Exploratory activity in mice was estimated in clean neutral $28 \times 14 \times 12$ cm steel cage by the number of nose pushing into holes in the cage cover for 5 min. Latency of the first pushing was also recorded (s).

Porsolt's test (17). Each male was placed in a glass (20 cm height, 9 cm inner diameter) containing 9 cm of water at $t = 25 \pm 1°C$ for a 5-min period. The total duration of immobility was recorded (s).

Hot-plate pain test. The tested mice were placed on metallic plate with $t = 55 \pm 1°$. The time elapsed before the first paw-lick (paw-lick latency) was registered to estimate the pain sensitivity (s)

Partition test (9). Partition test (9,10) was used for estimation of behavioral reaction to social stimuli (other male), i.e., the level of sociability The number of approaches to the partition, and the total time (s) of staying near it during approaches as the reaction to another male in the neighboring compartment during 5-min period were recorded. The relation of the total time of activity near the partition to the number of approaches to the partition was used as an estimate of average duration of activity near the partition during each approach.

Behavioral variables in different tests were recorded by a semiautomatic device "Etograph" (14) permitting the simultaneous recording of the frequency and the length of behavioral acts

Statistical Analysis

The statistical treatment of data was carried out according to Wilcoxon-Mann-Whitney's criterion (U-criterion). Results are expressed as medians with ranges.

EXPERIMENT 1 CHANGES OF SUBMISSIVE BEHAVIOR PATTERNS AS A RESULT OF DEFEATS IN SOCIAL CONFRONTATIONS

Experiment 1 deals with behavior of submissive males in the second, tenth and twentieth confrontations with an aggressive partner. It was supposed that in the first and second encounters the defeated male would show behavior similar to one in a natural situation at the meeting with unfamiliar male on a neutral territory. In tenth and twentieth tests submissive mice demonstrate behavior that was changed by unavoidable social stress conditions.

METHOD

The duration of the following components of submissive behavior during the second (T2), tenth (T10) and twentieth (T20) test (agonistic confrontations) with aggressive animals (aggressors) were registered in seconds during a 10-min test. 1) active defense (sideways and upright postures), 2) withdrawal; 3) position "on the back" after persecution by the aggressor; 4) "freezing" evoked by aggressor's grooming.

To eliminate the differences in partner's aggressiveness, the percentage of each posture's duration of the total time of defensive behavior for each animal was calculated.

Several categories and new elements of submissive behavior were recorded in T2 and T20 during intervals between the aggressor's attacks (s): 1) waiting, when the submissive animal sits at the corner or at the cage's wall and watches the aggressors movements, 2) freezing after cessation of aggressive grooming—preservation of freezing position after aggressor's leaving; 3) "nose in the corner"—posture of "depression": the submissive male is sitting with its nose in the cage's corner or in the sawdust and does not pay any attention to movements of the aggressor or to experimentator's manipulations in the cage.

RESULTS

The submissive behavior of mice with increasing defeat experience changed essentially. The active defense including withdrawal and sideways or upright defense postures predominated in T2 (near 90% of total time of submissive behavior), and decreased in T10 (Table 1) Some animals fell on their backs after vain attempts to avoid the aggressor's attacks, and remained in this position for more than 2–3 min. Passive defense ("freezing" or "on the back") became prevalent in T20 (60% of total time of submissive behavior). In intervals between aggressor's attacks, a submissive mouse remained in the position of "waiting," watching the movements of the aggressor. These mice demonstrated new immobile postures more often than in T2 The major part of submissive animals (40–50% of mice—very intensively) demon-

TABLE 1

COMPONENTS OF SUBMISSIVE BEHAVIOR UNDER AGGRESSOR'S ATTACKS

Postures, s	T2	T10	T20
Active defense	131 (36–249)	69 (22–149)*	23 (0–59)†§
Withdrawal	62 (11–159)	48 (23–77)	16 (0–41)†§
"On the back"	9 (0–27)	54 (1–128)*	27 (0–96)
"Freezing"	3 (0–16)	8 (0–65)	31 (0–113)*‡
Total time of submissive behavior	194 (80–340)	143 (24–337)	120 (32–259)*

*$p<0.05$, †$p<0.01$, differ from T2, ‡$p<0.05$, §$p<0.01$, differ from T10, U-criterion, n = 9

strated so-called "depression," i.e., "nose in the corner" posture when they did not react to the aggressor's approach and smelling at all. In many cases, the submissive male kept freezing after the aggressor finished grooming and went away. The total time of all these postures was two times more in mice with long experience of defeat (in T20) than in the primary period of forming submission (in T2) (Table 2). The submissive mice never demonstrate any aggression to an unfamiliar partner.

Thus the aggressor's attacks and fights, its presence behind the partition, and the odors, demonstrations of threats, daily defeats in agonistic encounters seem to create strong unavoidable social stress conditions influencing the submissive males and changing their behavior. Immobile postures demonstrated by "victims" of aggression even without any attacks, in free behavior during the test indicate the development of behavioral deficit The decrease of submissive activity in the cage, absence of reaction to socially meaningful stimuli (behavior of aggressive male) show a disturbance of communicative behavior, which probably means (2,20) an increase of anxiety The maintenance of immobile postures after the disappearance of inducing stimuli can be considered as a change of adaptive behavior and sign of developing pathology

EXPERIMENT 2 THE BEHAVIOR OF SUBMISSIVE MICE IN BEHAVIORAL TESTS

It can be hypothesized that the development of pathological behavior in submissive mice as a result of consecutive defeats in social confrontations may lead to disturbances of other aspects of the animals life, to changes of other forms of individual behavior and some physiological parameters To check this hypothesis, different behavioral tests were used for submissive mice after 20 defeats in daily consecutive confrontations.

TABLE 2

COMPONENTS OF PASSIVE BEHAVIOR OF SUBMISSIVE MICE IN INTERVALS BETWEEN AGGRESSOR'S ATTACKS

Postures, s	T2 (n = 8)	T20 (n = 10)
Waiting	88 (27–281)	134 (23–283)
Freezing after grooming	3 (0–16)	15 (0–52)*
'Nose in the corner"	"	33 (0–107)†
Total time of passive behaviors	91 (27–284)	184 (27–331)*

*$p<0.05$, †$p<0.01$, differ from T2, U-criterion

TABLE 3

BEHAVIOR OF SUBMISSIVE MICE AFTER 20 DEFEATS IN STANDARD BEHAVIORAL TESTS

Values	Control Animals	Submissive Animals
Open-field test		
latency, s	9 (2–20)	12 (1–45)
number of crossed squares	129 (40–209)	88 (47–127)*
number of rearing	15 (0– 33)	11 (2–26)
Exploratory activity test		
latency, s	61 (15–110)	46 (15–88)
number of nose pushing	10 (1–17)	7 (1–12)*
Porsolt's test		
total time of immobility, s	132 (41–224)	170 (140–217)†
Hot-plate pain test		
latency of paw-licking, s	13 (10–17)	13 (6–21)
Partition test		
number of approaches	6 (3–12)	5 (2–10)
total time of staying, s	42 (12–89)	26 (7–55)*
average time of staying, s	3 (2–6)	2 (1–3)

*$p<0.05$, †$p<0.01$, differ from control group, U-criterion, 8–13 animals in each group

METHOD

The behavior of submissive males after T20 was investigated in open-field test, exploratory activity test, Porsolt's test, hot-plate pain test, and partition test As a control group, males housed individually for 5 days without any experience of defeats or victories were used (8).

RESULTS

Results of this experiment are presented in Table 3. The data obtained demonstrate significant decrease in ambulation and exploratory activity of submissive mice: the number of nose pushing in cage cover holes in exploratory activity test, and the number of crossed squares in the open-field test were less in the submissive than in the control group These results may be interpreted as a motor inhibition which is one of the symptoms of human depression. More obvious results were obtained in Porsolt's test· the time of immobility was longer in submissive mice than in the control ones. This may be considered as the most important evidence of the depressive character of pathological changes in submissive males, because the behavior of mice and rats in this test is sensitive to antidepressants (16,17).

There were no significant differences in pain sensitivity between submissive and control males their paw-lick latencies did not differ.

It was shown earlier (9) and was confirmed in this experiment that submissive males reacted more slowly to the other partner in the neighboring compartment than the control animals. they rarely approached the partition and stayed significantly less time near it It indicates the decrease of aspiration for social contact and can be considered as an index of increased anxiety after repeated defeats. Therefore, the data obtained seem to provide evidence for the similarity between some symptoms of human depression and of the state of submissive mice, because submissive animals, as well as patients, demonstrate a motor inhibition and symptoms of anxiety in different situations.

TABLE 4

EFFECTS OF CHRONIC IMIPRAMINE TREATMENT ON BEHAVIOR OF SUBMISSIVE MICE AFTER 20 DEFEATS IN BEHAVIORAL TEST

Values	Submissive Mice After Chronic Treatment With Vehicle	Imipramine
Open-field test		
latency, s	13 (4–25)	7 (2–20)*
number of crossed squares	75 (13–140)	79 (26–110)
number of rearing	10 (3–23)	10 (0–32)
Exploratory activity test		
latency, s	74 (9–195)	91 (15–160)
number of nose pushing	6 (2–10)	5 (4–7)
Porsolt's test		
total time of immobility, s	173 (146–206)	145 (92–189)*
Hot-plate pain test		
latency of paw-licking, s	17 (11–24)	13 (9–17)*
Partition test		
number of approaches	8 (0–16)	5 (0–17)
total time of staying, s	34 (0–77)	21 (0–75)
average time of staying, s	4 (0–8)	2 (0–6)*

*$p<0$ 05, differ from vehicle group, U-criterion, 8–10 animals in each group

EXPERIMENT 3· EFFECTS OF IMIPRAMINE TREATMENT

The positive effect of chronic treatment with imipramine on submissive mice with depressive symptoms could be another proof of development of depression in animals as a result of prolonged social stress The submissive mice after imipramine treatment were investigated in behavioral test to distinguish possible influences on some behavioral variables

METHOD

After 5 consecutive days of social confrontations with aggressive partners, submissive males were treated with intraperitoneal injections of vehicle (0.9% sodium chloride) or 10 mg/kg imipramine HCl (Sigma) twice a day (at 0900 and 1800 h local time) for two weeks with daily agonistic encounters (ten-minute tests). After drug treatment, control and experimental groups of submissive mice were examined in behavioral tests.

RESULTS

Effects of chronic treatment with imipramine on submissive mice behavior in behavioral tests are presented in Table 4. There were three kinds of behavioral variable changes. The exploratory activity estimated by the number of nose pushing into the holes and ambulation rate in the open-field test after imipramine treatment did not change in comparison with vehicle-injected submissive mice. The second group of changes was observed in the partition test. In Experiment 2 and earlier (9), it was noticed that the submissive males' behavioral activity near the partition as a reaction to another male in the neighboring compartment was dramatically diminished in comparison with the control animals' behavior. Imipramine treatment against the background of defeats intensified this process the average time spent near partition decreased compared with that of submissive control animals. It may be supposed that imipramine increased the anxiety in submissive mice. These data may be considered as a negative side effect of the drug. Finally, the third kind of behavioral change deals with the positive effect of imipramine treatment on the state of submissive animals. The decrease of the latency of locomotion in the open-field test may reflect some changes in the emotional reactivity of submissive mice. Treatment with the antidepressant also decreased the threshold of pain sensitivity (in the hot-plate pain test). The decrease of immobility time in Porsolt's test seems to be the most apparent result of the specific antidepressive action of imipramine. Chronic ethanol treatment in analogous experiment did not influence on behavior of submissive mice in Porsolt's test (unpublished data). Data obtained suggest that Porsolt's test may be effective not only for screening of antidepressants but also for testing the level of depression in experimental animals. It can be concluded that the effects of imipramine treatment on the behavior of submissive mice, first of all in Porsolt's test, are similar to its effects on human depression. It should be noted that imipramine effects were present even against the background of continuing daily agonistic encounters

EXPERIMENT 4 SOME SOMATIC SYMPTOMS IN SUBMISSIVE MICE

It is well known that depression in humans is accompanied by weight loss and disturbances in gastrointestinal functions (3) In earlier experiments (8), the absence of significant changes in the basal corticosteroid level in submissive mice after long experience of defeat in comparison with control animals has been shown. In this experiment the neurogenic damage of gastric mucosa, erosions and haemorrhages, in both groups of mice was investigated.

METHOD

All animals were weighed at the beginning of the experiment (before the first defeat) and at the end of it (after the twentieth defeat). After T2, T10, and T20, groups of submissive animals were decapitated, the stomach was unfolded and washed by cold saline. The number of erosions and haemorrhages in the gastric mucosa were counted visually by stereomicroscope. As the control, males after 5 days of isolation without agonistic experiences were used.

RESULTS

The weight of submissive mice after 20 social confrontations (after T20) significantly decreased as compared with control animals 26.1 and 22.7 g in control and submissive groups respectively (medians, $p<0.05$, U-criterion) As Experiments 1 and 2 showed, the behavioral parameters at this time were essentially changed in submissive mice. There were many open wounds and scars on their body

The study of gastric mucosa resulted in a suggestion that defeats induce a neurogenic damage (Fig. 1): there was a significant increase in number both of erosions and of haemorrhages in submissive mice after the second and tenth agonistic confrontations in comparison with the control animals. This may provide evidence for severity of stress induced by defeats in submissive males. There were no differences in gastric mucosa damage between submissive mice after T20 and control animals The latter data may be interpreted as absence of stress reactions to the negative stimuli in this period as it has been described for depressive patients in expressed stages of this disease.

GENERAL DISCUSSION

The results presented here show that the experience of defeats in daily consecutive social confrontations and permanent living with an aggressor in a common cage under sensory contact conditions lead to the development of pathological forms of behavior in submissive mice, which is similar to the depressive state. Mice demonstrated a disturbance of social behavior active de-

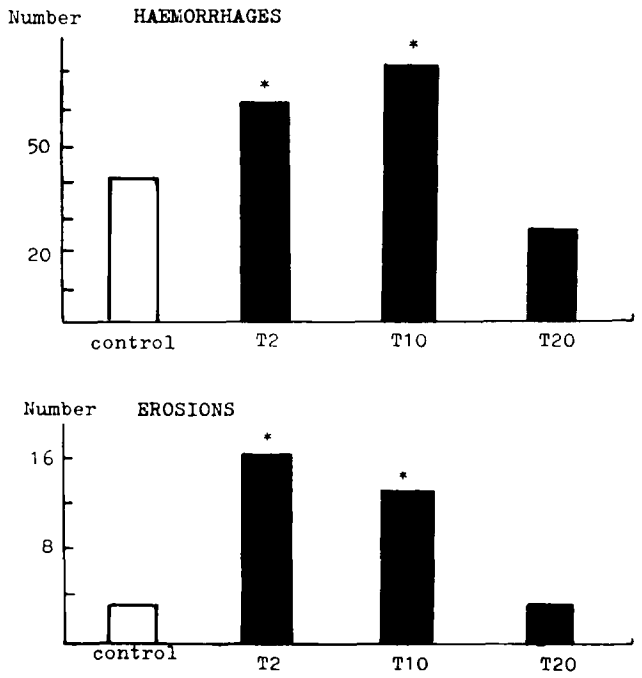

FIG 1 Erosions and haemorrhages in gastric mucosa of control (white columns) and submissive (black columns) males after second (T2), tenth (T10), twentieth (T20) confrontations with aggressive males *$p<0.05$, differ from controls

fense behaviors (such as withdrawal from aggressor's attacks or sideways and upright postures) which had been displayed in the first fights were replaced by passive behaviors ("freezing" or "on the back"). Moreover, new immobile postures appeared in T20: submissive males spent much time in position of "nose in the corner"), not reacting to the social stimuli (aggressor's movements) which may mean complete indifference The maintenance of "freezing" or "on the back" positions after the disappearance of the inducing stimuli may be considered as a pathological behavior. It may be interpreted as an inadequate response to social situations Together with the decrease ambulation in the open-field test and the increased immobility time in Porsolt's test, these data show the total behavioral deficit developing in submissive mice under unavoidable social stress conditions.

It had been shown earlier (9,10) that the submissive mouse behavioral reaction to the species-specific stimuli, the pheromones of unfamiliar males, was less than reactions of control and aggressive mice. These results had been interpreted as a loss of olfactory perception. Now we believe that these data and data on the partition test presented here can be considered as an increase of anxiety in submissive mice, because some authors consider the decrease of social communication as an index of anxiety (2,20) Our unpublished data about anxiolytic treatment with cyproheptadine confirm this supposition: the submissive males after cyproheptadine injection increased their behavioral activity near partition The loss of weight in the submissive mice compared with the control animals also coincide with the somatic symptoms of human depression (3).

The absence of behavioral reactions of submissive mice to aggressor's movements and experimentor's manipulations in the cage (during "depression" postures), and likewise the disappearance of significant differences in gastric mucosa damage between experimental groups after T20 in spite of continuing stressful conditions, indicate a decrease of stress reactivity in submissive mice. The chronic imipramine treatment improved some characteristics of submissive mice even against the background of continuing stressful influences. The main positive result of antidepressant treatment to our mind is the decrease of immobility time in Porsolt's test. In a preliminary investigation (10), changes in serotonergic activity in some brain areas were described in submissive mice. Many data suggest serotonin abnormalities in depression (1)

Summarizing, it may be concluded that symptomatology, effects of an antidepressant in submissive mice with long experience of defeats in social confrontations are similar to depression in humans.

We would like to draw attention to factors leading to the development of depression-like states in mice. First of all, the only emotional negative social stress appear to be the cause of that because submissive males received physical painful influences only during 2–3 min aggressor's attacks in a 10-min test. They lived for days with the aggressor under sensory contact conditions, saw its threats and attempts to overcome the partition, perceived it odors, heard its voice and noise. It can be proposed that these conditions induce permanent fear, intensified in agonistic intermale encounters. Fear and social lack of success are more adequate for human pathogenic factors which in most cases include emotional but not physical stress.

In conclusion, this model of sensory contact appears to allow to develop aggressive and submissive behaviors as a result of social confrontations in mice of different strains (8). Submissive mice of C57BL/6J strain have been shown to develop of depression-like state The mice of CBA/Lac strain, likewise used in such experiments, are dissimilar to C57BL/6J by emotionality, pain sensitivity, motor activity and submissive behavior patterns (8,12) These mice are characterized by a high susceptibility to development of catatonic (10,11) or cataleptic (13) states in different tests We noticed that some submissive mice of CBA/Lac strain with long experience of defeat demonstrated cataleptic postures in free behavior, freezing near the wall or at the partition for more than 3–5 min (11). It may be proposed that social emotional stress in other strains of mice with other individual physiological and psychological parameters determined by their heredity can induce other psychopathologies and that the model of sensory contact will be useful for the development of different pathological behaviors on a different genetic basis This supposition is confirmed by the data on inescapable shock treatment-induced strain dependent alterations of some forms of behavior (19).

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