Sensory Contact Model: Protocol, Control, Applications

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Among the models that become more and more popular in behavioral neuroscience are biosocial models, which allow studying the consequences of chronic social conflicts and social stress in animals. The sensory contact model appears to represent one of such models. Repeated experience of aggression or social defeats in daily agonistic interactions in male mice of different strains leads to the formation of opposing kinds of social behavior: one attributable to winners (aggressors) and another attributable to losers (defeated males, victims of aggression). A large variety of behavioral pathologies (anxious depression, catalepsy, social withdrawal, pronounced aggression, anxiety, hyperactivity, cognitive disturbances, anhedonia etc.), which are accompanied by somatic changes (reduced gonad function, psychogenic immune deficiency etc) in animals, suggest that this approach could be used for different aims of biomedical studies. Putative mechanisms of release and maintenance of aggressive and submissive behaviors in male mice under the sensory contact model, criteria of correct application, basic experimental setups and problem of the control, methodical capabilities and potentials of the sensory contact model applications are discussed in this paper.

Key words: sensory contact model, social defeats, aggression, depression, anxiety, psychopathology of aggression, chronic social conflicts

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Content

Introduction. Background

Small cage divided into two compartments by a perforated transparent partition (wire mesh barrier) allowing mice see, hear and smell each other, but preventing physical contact was used by investigators intensively starting with 1960ies to study the effects of pheromones on physiology and behavior of mice. Distant influence of males of different social status on each other's hormonal background [16, 17], as well as behavioral reactions in male-female interactions depending on the stage of female estrous cycle [61] were studied. A similar cage was used to study sensor communication in terms of its effect on isolation-induced social aggressiveness in mice [24].

In the 1980ies, the cage found applications in the studies of Professor E.V. Naumenko and his colleagues (Institute of Cytology and Genetics, Novosibirsk) [56, 57]. As before [16], cage was used to investigate the effect of social stress on the hormonal response of male mice subjected to attacks of trained fighters which were obtained by the Scott method [60]. During the experiment the trained fighter held behind the partition except the time of social interactions. In other studies receptive female were shown to induce distantly the elevation of testosterone levels in the blood plasma of male mice [3, 54, 55, 57].

Later, a similar cage was used to study aggressive and submissive behaviors in male mice. Fist observations have shown that sensory contact *per se* enhances aggressiveness in male mice [33] and repeated experience of victories or defeats in daily agonistic interactions leads to the formation of persistent opposing kinds of social behavior: one attributable to winners (aggressors) and another attributable to losers (defeated males, victims of aggression). Search for optimal experimental design, which would steadily reproduce this phenomenon led to the development of so-called "sensory contact model" [33, 34].

In the first period, technique of sensory contact model has underwent some changes as a result of acquiring a better understanding of its stages. But most important was growing experience in how to work with aggressive and submissive behavior in male mice, the skill to select the pairs and predict the behavior of mice during formation of agonistic behavior patterns, the understanding of a particular stage of the methodology ensuring the desired outcome in each particular experiment. Experimental setups were developed depending on the goals and tasks of experiments. Then the use of the unified methodology allowed comparison of the results of the studies carried out over two decades. Notably, the reproducibility of observed behavioral phenomena revealed in the early period of studies has been high throughout many years.

1. Sensory Contact Model

1.1. Description

All stages of the methodology are significant, theoretically justified and based on experimental data [34, 37]. Animals of approximately the same weight were then placed by pairs in steel cages (28x14x10 cm) divided into halves by a perforated transparent partition (sensory contact), thereby permitting visual and olfactory contact but preventing any physical contact. Testing commenced after 2-3 days of adaptation to the housing conditions and sensory contact. Every afternoon (14:00-17:00 p.m. local time), the steel cover of the cage was replaced by a transparent one, and 5 min later (the period necessary for individuals' activation), the partition was removed for 10 min to allow agonistic interactions begin. Undoubted superiority of one of the partners was evident within 2 or 3 tests in daily social encounters with the same opponent. During the tests, one animal was seen to attack, bite, and chase the other who only displayed defensive behavior (sideways, upright postures, withdrawal, lying on the back or 'freezing'). As a rule, in our experiments, aggressive confrontations between males are discontinued by lowering the partition if the aggression has lasted more then 3 min or less. Then, every day after the test, each defeated member of one pair was paired with the winning member of another pair behind the partition in an unfamiliar cage. The winners remained resident in their compartments. The sensory contact technique permits the investigator to simultaneously obtain as many animals with positive fighting experience (winners) as those with repeated experience of social defeats (losers).

It has been shown, that these experimental conditions ensure formation of aggressive and submissive behaviors in male mice of three strains (CBA/Lac, C57BL/6J, Swiss). Latest data have demonstrated this phenomenon in mice of DBA strain (Avgustinovich, Vishnivetskaya, 2009, unpublished). In our experiments, we used mainly animals of low-aggression mice of the CBA/Lac strain and high-aggression mice of the C57BL/6J strain, which also differ in other behavioral and physiological parameters [14, 32, 35]. The winners and losers were investigated following different periods of repeated victories or defeats experiences - during or after 2-3 (T3 Winners and T3 Losers), ten (T10 Winners and T10 Losers) and twenty (T20 Winners and T20 Losers) tests - days of agonistic interactions.

1.2. Release and maintenance of aggressive and submissive behaviors in male mice under the sensory contact model: step-by-step

The key condition of result reproducibility in experiments is maintaining day-to-day demonstration of aggression by the males which had won in the first agonistic encounters. Preliminary procedures preceding dyadic interactions and testing procedures as such, are of equal significance in the sensory contact model.

1.2.1. Preliminary procedures

Strange as it may seem at first sight, the peer-rearing since infancy in friendly groups is an essential condition for aggression enhancement in male mice. In the peer groups social pressure of hierarchic relations is not pronounced, the level of aggression is low, thereby the pups do not acquire the experience of defeats, which is critical for their behavior later in life and reduces the manifestation of aggression as compared with the mice which were housed in social groups with unstable dominant-subordinate relations. Since aggression in group-housed mice is low, two males placed in different compartments of experimental cage should be taken from different home cages. They should be aligned as much as possible by weight. Difference in weight might predetermine the outcome of the encounter and might be factor precluding agonistic interactions between the males as a result of distant mutual evaluation of partner. Alignment by weight is a factor preventing the development of inversion of aggressive or submissive behavior in male mice in the next agonistic interactions with partner of opposite type of behavior.

Of great importance is short-term sensory contact before agonistic interactions - cohabitation of males in the one cage divided by a transparent perforated partition. During this time the animals are exploring and marking a new territory, nesting and establishing a soiling site (latrine), i.e. they are adapting to territory of habitation. Animals see, hear and perceive the smells of the partner in the neighboring compartment. It was hypothesized that continuous sensory contact results in accumulation of impact of species-specific pheromone signals [33, 34] which is a factor promoting aggression in male mice [59].

Of much importance is the size of the cage. Its enlargement may reduce olfactory stimulation, which might influence the degree of aggressiveness. Reduction of cage sizes would create stressful conditions and might also strongly affect subsequent behavior of male mice.

Two to three days of sensory contact prior to agonistic encounters have been chosen empirically as an optimum period to ensure demonstration of aggressive behavior in 90-100% of all males after partition removal. A longer period of sensory contact, as has been shown in experiments, may enhance aggressiveness in mice of some strains and reduce it in others. First observations and studies were demonstrated that the sensory contact *per se* could have considerable influence on many neurophysiologic components of behavior [33, 34]. Subsequently these observations were confirmed in the special studies [19, 65, 66]. It was shown that prolonged sensory contact without the physical interactions between males is quite stressful, as evidenced by the significant physiological and neurochemical consequences up to changes in gene expression in the brain structures.

1.2.2. Testing procedures

The steel cover of the cage is replaced by transparent lid for five minutes for activation of animals and adaptation to new light conditions (stimuli for activation may vary). The period of activation before partition removal is necessary to bring all the males, which may at this time be asleep or busy building a nest or eating, into the same alert state. The males begin to pay attention to each other. They approach the partition, try to dig hereunder, follow the movements of the neighbor, climb the partition, poke the nose into its holes etc. Special studies have demonstrated [35] that without the period of activation the attack latency extends considerably, which may influence the duration of agonistic interactions if the test time is limited. Moreover, eventually with the formation of aggressive type of behavior the period of activation becomes conditioned signal of upcoming confrontations and associated victory anticipation, which might be a mechanism supporting the outburst of aggression.

After period of activation the partition is removed for 10 min. Agonistic interactions between males are observed in the overwhelming majority of cages (90-100%). For some pairs the winning and defeated males reveal themselves at once: the winner attacks and the loser demonstrates active defense or runs away. In encounters of other pairs attacks and flights alternate with the roles being mainly due to location of a male on own or the other male's territory. If the males do not fight during two tests, the partners are changed after the test. The undoubted superiority of one of the partners becomes evident within 2-3 tests in daily encounters with the same partner and joint living in one cage with him under distant sensory contact conditions. It is noteworthy that each male occupies its own compartment after the test when the partition is lowered. Three days of agonistic interactions with the same neighbor, during which one male becomes the winner and the other a loser, are an essential element for the remaining part of the method. Then aggressive and submissive behaviors are only maintained in subsequent social encounters with an opponent with opposite social behaviors.

To prevent aggression attenuation, after the third test defeated male is transferred to another male's compartment with strange litter while the aggressor is left in his own compartment. Daily transfer of males after the fighting precludes habituation of males to each other and consolidates the submissiveness of the defeated animal put on an alien territory. For defeated males the latter creates the conditions of social instability and serves as an additional stressor. At the same time, the new opponent in the neighboring compartment and the necessity to establish superiority at the encounter with a new opponent elicit the exhibition of aggression by the winner. Consecutive daily victories stimulate aggression in the male that became the winner in the first agonistic interactions. If stages of methods being implemented correctly, inversion of behavioral pattern to the opposite at the replacement of the opponent is usually seldom. Since some winners may exhibit aggression rather severely, to stop the confrontation and avoid acute damage to defeated mice the partition is pulled down after 3 minutes or less. Besides a male defeated in the fighting with a strong aggressor after the test is put into a cage with a less aggressive winner to give it an opportunity to recover after the distress.

In conclusion it is to be noted that the sensory contact model allows for rapid formation of alternative kinds of social behaviors in males of the same strain. The key mechanisms of maintenance of the aggressive and submissive behaviors in male mice are continuous sensory contact and repeated experience of victories or defeats, which is in fact social learning.

1.2.3. Frequently asking questions

Have the mice you are dealing with been predisposed to either aggressive or submissive behavior or are these induced by sensory contact technique?

Answer: It is a case of induction due to repeated agonistic experience. The following facts favor the conclusion.

a. Would-be winners and would-be losers within any strain did not differ significantly. Furthermore, it has been experimentally shown that there is little difference between future winners and future losers in emotionality or exploratory activity in the open-field and exploratory activity tests or in pain sensitivity in the hot-plate pain test [Kudryavtseva, 1987]. The males had been so tested before agonistic interactions. Then the winners and losers were fixed in following intermale interactions.

b. Many behavioral, physiological, neurochemical characteristics change in the winners and losers from test to test. Expression of these changes depends on the duration and the result of agonistic confrontations. Thus, rather than selection, formation of opposite social behaviors is under way.

c. It has been demonstrated that varying experimental conditions may cause inversion in behavior [30, 33, 36]. By the way, the winners are very easy to convert, but not so the losers.

And these facts defy the conclusion. A preliminary sensory contact only for 24 hours is enough to differentiate future winners and future losers before the agonistic interactions in the partition test [33]. Thus, early ontogenetic effects cannot be neglected as a factor of predisposition to the aggressive or submissive type of behavior. However, one may assert that random pairing may neutralize this effect. In combination with another male, every individual stands a chance of acquiring opposite agonistic experience.

What is the cause and what is the consequence in the formation of either aggressive or submissive behavior in male mice under this model?

Answer: The cause of victory or defeat in first confrontation(s) may be unknown ontogenetic influences, partner or chance. The first social experience is maintained in the next agonistic interactions with a partner of opposite behavioral experience.

1.3. Criteria of correct application of the sensory contact model

To run sensory contact model successfully, make sure that the following criteria are satisfied [38]:

a. In the first test, aggressive interactions between male mice occur in at least 90% of experimental cages;
b. Every day most part of winners demonstrate direct (attacking, chasing, aggressive grooming and threats) or indirect (diggings on the loser's territory) aggression during the test period;
c. No inversion from aggressive to submissive type of behavior or vice versa takes place during the test.

It is to be noted that in addition to step-by-step requirements there are other elements essential for correct use of the methodology. These elements are based on the knowledge of animal behavior in general and murine agonistic behavior in particular. The knowledge can be acquired from the literature or in the process of work. Furthermore, the methodology should be adapted to particular conditions, which may differ in different laboratories. For instance, preliminary housing conditions might not be the same in different laboratories, which may strongly affect the expression of aggressiveness in male mice. Probably the sensory contact model will satisfy all the correctness criteria only when supplemented with some additional stages or slightly modified for some mouse strains. Time intervals as referred to the duration of preliminary sensory contact or period of activation may vary from strain to strain. There are some tricks to avoid the inversion and maintain aggression in winners at a high level during the experiment. Behavior of the researcher during daily animal testing is critical, which becomes self-obvious after some practice in sensory contact technique application.

In the most modifications of the sensory contact model (sensory contact paradigm) used for studying the effect of chronic social defeat stress the role of aggressor is played by a male of a different strain larger than C57BL/6J males chosen by the experimenters to play the role of losers [11, 29, 49, 63]. These authors fondly hope that if the neighbor behind a wire mesh barrier was a larger mouse of a different strain, the smaller mouse would certainly be fearful of it. However, for me it was quite obvious that this modification of model originally has a defect, which the authors do not take into consideration. In nature (and in laboratory), males normally do not attack a smaller by weight or a juvenile male or males which demonstrate the posture of full submission. A fascinating fact pointed out by K. Lorentz many years ago is that in the majority of cases aggression fails to progress or has ritual character [48]. On the other hand, a male of a smaller weight after assessing its odds for winning a larger rival as low (is it a rival?), immediately exhibits the postures of full submission, thereby reducing the outburst of severe aggression in the larger male and protecting itself from its attack. It may be assumed that it is the prearranged experimental superiority of one individual over another that is the cause of appearance of males "not susceptible (resilient)" to social stress vs "susceptible (vulnerable)" mice [29]. It is unlikely that highly inbred and uniformly housed mice react in a different way to a similar intimidating impact. Rather it may be assumed that during the first tests the mice intended for being the losers are taught the forms of behavior that do not elicit strong aggression in a larger male and, thus, adapt to psychoemotional impact, i.e. they realize that nothing bad is to be anticipated in this situation. That is why subordinate status formed in a male with a smaller weight does not evolve to strong submissiveness. The mice that, according to the authors, demonstrated susceptibility to social stress might have been susceptible to such stress before a large male came to settle next to them. In general, all reasoning about susceptible and not susceptible to stress defeated mice of the same highly inbred strain could hardly be correct as it allows a different interpretation of the results obtained.

However, it should be admitted that this discussion is but an attempt to explain why the groups of losers vulnerable and resilient to stress are formed [29]. It may be taken also into consideration that development of a disease (in this case depression-like state) under social stress is a process in time [review, 4, 27]. Exposure to social defeat stress during 10 days does not lead to the development of genuine depression [review, 4]. Obvious signs of depression-like state do appear after 20 days or more of such exposure. Besides, the explanation of the experiments gives no clear description of comparison groups, i.e. the question on the control used remains open in their studies. At the same time, a focal point for revealing the consequences of social stress is to understand which psychoemotional state of the animals may be considered as ***native, intact, norm***. It is obvious for me that neither the mice after prolonged social isolation, neither the mice after prolonged sensory contact without agonistic interactions can not be used as the control for the winners and losers with repeated social experience in agonistic interactions.

1.4. The Control

In our first experiments, animals that shared a partitioned cage but had not fought yet were used as control for the winners and losers. Although the control like this seemed the most appropriate at that time, eventually it was found that the sensory contact *per se* can affect some behavioral and physiological characteristics [40]. Moreover, the consequences of distant sensory contact for mice depended on the duration of sensory contact and were strain-specific [7, 33]. It was concluded, therefore, that animals with sensory contact experience cannot be considered as a valid control (intact state of mice).

The problem of appropriate control in this model has been discussed in detail earlier [33, 34, 38]. Controls were selected as follows. Briefly, aggressive behavior has been considered as an ***innate*** behavior exhibited by animals occupying different steps of the evolutionary ladder, from insects to primates. Thus, the ability to demonstrate aggressive behavior in provoking conditions may be found in all animals and thus may be considered as a starting point. If this is the case, then animals demonstrating aggressive behavior would provide controls for all non-aggressive animals with aggression manifestation inhibited by some influences (those with experience of defeat, those kept in groups, castrated animals, etc.). However, it has been shown that repeated experience of aggression alters many aspects of individual and social behaviors. It was therefore concluded that the permanent winners need a special control.

Since 1987 [33], the controls both for winners and losers received under the sensory contact model were the mice that had been housed individually for 5-7 days. They were thought to be the better controls with native social and emotional responses. Moreover, in my view, it was this control that provides many advantages. The 5-day period of individual housing was established empirically for mice of C57BL/6J and CBA/Lac strains. It is a minimum period for group males to restore ability to demonstrate aggressive behavior in provoking conditions. Shorter-term individual housing would not have eliminated the submissiveness of group-housed males while longer individual housing would act as social isolation stressor. In special studies it was shown that after 5 days of individual housing 90-100% of males display aggression in the first confrontation following the 2-3 days of sensory contact. This means that group-housed animals reach the state of "social intactness" when social pressure (hierarchical relations inhibiting aggression in subordinates in groups) is removed. This control was used both for the winners and losers and for all periods (duration) of agonistic interactions.

The problem of valid control in the sensory contact model has been the subject of some disagreement. It was the opinion of many reviewers of our works that this control is not correct and therefore experimental design is not correct also. Some colleagues have suggested using group-housed animals as control because these animals are not stressed. However, mice in group have a despotic hierarchy: one male is dominant, the others are subordinates [53]. Dominant males demonstrate aggression, the others are non-aggressive and show subordinate behavior. Thus, group-housed males are not identical with respect to social status, they are not intact and therefore they are not appropriate as a control in the sensory contact model. It would be erroneous to compare subordinate (group-housed) males with losers having repeated experience of defeats.

Others have suggested direct comparisons between winners and losers. However, although such comparisons may yield significant differences, the nature of such differences cannot be determined: it would be impossible to distinguish between the winners' and losers' contribution to such changes. Moreover, winners and losers may not differ from each other in some characteristics, but both could differ from a control group. This means that a single reference point is required — a common control for winners and losers independent of the duration of confrontational interactions, i.e. animals in an intact state with native reactions.

Males that have been housed individually during experiment were used by other authors as the control in modified versions of sensory contact model. However, it is common knowledge that social isolation has a drastic effect on animal conditions, changing many neurophysiologic characteristics and behavior: 10-40% of males do display a high level of aggression while the remainders become timid [58, 64]. The percentage of aggressive and timid animals was different in different strains. In some studies, to avoid the effect of social isolation males housed with females for a long time were used as the control. But in this case comparison of sexually naïve and sexually experienced males is unavoidable, which is not quite correct.

In conclusion it is to be noted that the mice that had been housed individually for five days may be considered as adequate and correct control both for the winners and losers obtained under the sensory contact model at least for mice of C57BL/6J and CBA/Lac strains. They were thought to be a better control having native social and emotional responses. Special investigations have demonstrated that these animals are less anxious, demonstrate a higher level of exploratory and motor activity as well as higher level of communicativeness [5] in comparison with other possible controls which could be used for chronically stressed animals – animals after long social isolation, group-housed animals etc.

Nonetheless, it should be noted that a choice of an optimum control for each particular experiment is to be made by the researcher based on the experiment goals and setup. For instance, in our study demonstrating that social defeat stress significantly increases the number of metastases in the lungs of defeated males [26, 46], males housed in groups with stable hierarchical relations were used as control. This control was an optimum one for the experiments, the duration of which depended on metastases development in the lung. In this experiment we took into consideration the results of special investigations, indicating that animals living in groups for a long time are not stressed [8, 9] and therefore our control is not exposed to the key factor stimulating metastasis growth - stress.

2. Basic experimental setups

It has been shown that prolonged social agonistic experience leads to development of psychoemotional and psychosomatic pathologies in male mice [review, 50]. In our studies, behavioral pathology was acknowledged if several of the following eight criteria were met [39]:

- Change (increase or decrease) in the ***duration*** and/or ***expression*** of demonstration of behavioral forms;
- Emergence of ***novel behavioral forms***, that is, the forms that were not demonstrated by the animals before;
- ***Inadequacy*** of behavioral response to some social or environmental stimuli; uncontrollable behavior in some circumstances;
- ***Generalization*** of dominating motivation;
- ***Nonadaptive*** behavior under given environmental conditions or in given experimental situations;
- ***Persistency*** of a changed behaviors and a psychoemotional state after cessation of the action of a psychopathogenic factor;
- Expressed multiple ***neurochemical alterations*** in the brain;
- ***Similarity*** between behavioral pathology in mice and the clinical picture of human disease: a similarity in etiology, symptomatology, sensitivity to the drugs used for treatment and a similarity in neurochemical alterations in mice and humans as the disease progresses. This criterion originally proposed for models of depression [50] can be extended for all experimental psychopathologies.

Observations of the behavior of animals participating in agonistic interactions helped to identify three critical time periods during which differences between the compared groups of animals manifest themselves most clearly (control – losers; control – winners; winners - losers): 2-3 days of agonistic interactions or acute stress stage; 10 days of agonistic interactions or the stage of incipient behavior pathology and 20-21 days - the stage of severe pathology [4, 39, 43]. However, for the whole variety of goals and tasks one principle is strictly adhered to in our experiments, namely all compared groups of animals should be studied during the same period of time (Figure).

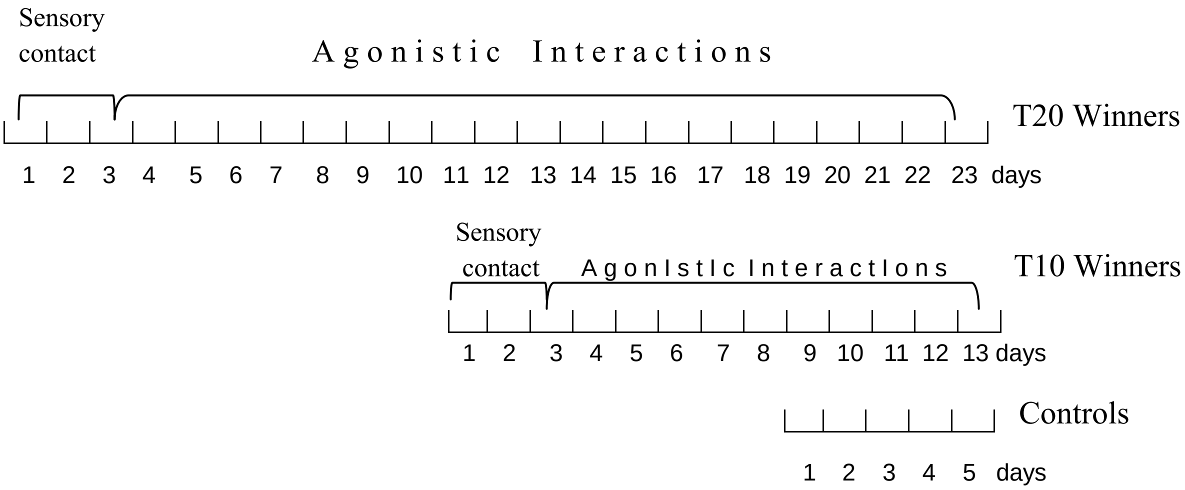

Figure. Standard scheme of experiments for the studying effects of repeated agonistic interactions in the male mice after ten (T10 Winners or T10 Losers) and twenty (T20 Winners or T20 Losers) tests (days) of social confrontations.

Therefore, the groups of males with 10-day and 20-day agonistic experience should not be the same since, for example, the behavior of animals may not be tested several times in behavioral tests. The only test that allows repeated use is the "partition" test [36], measuring the behavioral response to a neighbor placed in the adjacent cage compartment. In this case testing is carried out in the home cage without any additional impact.

3. Potentials and application of sensory contact model

Long-term use of the sensory contact model for studies of the mechanisms of agonistic behavior in male mice has led to an understanding of its methodical possibilities and potential applications.

3.1. Methodical capability

Formation of alternative types of social behaviors in males of the ***same strain*** provides a number of benefits compared to the studies using the sensory contact paradigm with a conspecific of another strain serving as a stressor. First of all, the latter is inappropriate for studying the consequences of repeated aggression, which finally leads to formation of behavioral pathology, a phenomenon of interest by itself. In addition [37]:

a. Comparison of animals with alternative social behaviors with each other and the control allows differentiation of ***specific*** changes, which are characteristic for the formation of aggressive or submissive behaviors, from ***common*** changes occurring in both social groups, for instance, under social stress;

b. The model makes it possible to form alternative types of social behavior in male mice of the ***same strain***, which have no significant differences in terms of physiological and behavioral characteristics which could have non-specific effects on the magnitude and features of displayed aggression and submission. Comparison of winners and losers of ***different strains*** provides an opportunity for recognizing specific effects of chronic agonistic interactions on individuals with different hereditary defined features of the nervous system. Besides, it has been shown that exposure of mice of different strains to the same stressor (for example, social defeat stress) may promote the formation of varied psychopathological states;

c. The sensory contact model is useful for studying the mechanisms of inversion (switch over) from aggressive to submissive behaviors and vice versa in individuals with respective social behaviors. Such studies with a focus on behavioral [7, 33], neurochemical [30] and immunological [2] parameters were conducted and demonstrated that some of such parameters do change following changes in the social status;

d. One of the most important methodological advantages of the sensory contact model is the opportunity to study step by step dynamic rearrangement of neurochemical regulation, changes in behavior and physiological reactions depending on the duration of agonistic interactions – from norm to severe psychopathology developed in animals [reviews, 4, 39, 43]. This model gives possibility to study neurochemical mechanisms of psychoemotional disorders relapse.

3.2. Prospects of Application

It was shown that repeated experience of victory or defeat in daily agonistic interactions leads to the formation of persistent opposing kinds of social behavior: the winners (aggressors) and the losers (victims of aggression). Depending on the emotional state (positive or negative), multiple neurochemical alterations in the synthesis, catabolism and reception of key brain neurotransmitters are followed by behavioral and physiological changes in male mice. As a consequence, the winners and losers exhibited significant differences in emotionality, motor and exploratory activities, levels of sociability, alcohol intake as well as in the state of the immune system and gonad function [review, 38]. It has also been shown that long exposure to social confrontations leads to psychoemotional disturbances, somatic disturbances and behavioral pathologies [4, 39, 40]. The kind of pathology depends on both social behavior and the duration of agonistic interactions. Additionally, mice from different strains develop different pathologies, even though they share the same experience [35, 42]. For example, in males of the C57BL/6J strain, a long experience of social defeat leads to the development of a mixed anxiety-depression state [4, 40, 45]. At the same time, the same stress caused by social confrontations in the defeated males of the CBA/Lac strain leads to the development of catalepsy [44, 47].

Therefore, the sensory contact model, on the one hand, is useful in inducing and investigating various psychoemotional and psychosomatic disturbances in animals [review, 43]. On the other hand, it gives the opportunity of using animals with behavioral pathology as means to investigate the action of novel and commonly used psychotropic drugs and to conduct their screening under simulated clinical conditions. The most extensive studies have been conducted and the most satisfactory validating results have been obtained on mice for ***anxious depression, generalized anxiety, psychopathology of aggression*** and ***psychogenic immune deficiency.***

Mixed anxiety/depression state. Anxiety, phobias and depression are the most wide-spread psychoemotional pathologies in humans produced by stress. Repeated defeat experiences in daily agonistic interactions induce dramatic changes in social and individual behaviors as well as in somatic state of submissive mice (losers) of C57BL/6J strain, which were similar to human depression with respect to etiology, susceptibility to treatment, symptoms and brain neurochemical changes [reviews, 4, 40, 45]. A remarkable behavioral deficit, indifference, depressiveness, generalized anxiety, anhedonia, alcohol addiction as well as a loss of weight, decreased stress reactivity and sexual dysfunction were found in the losers. Antidepressants or anxiolytics treatment had therapeutic effects. Chronic unavoidable social stress is considered as a relevant (social defeat, negative emotions, permanent anxiety) pathogenic factor, which provokes the development of mixed anxiety/depression state in animals. The study of brain monoaminergic activity in the losers allowed hypothesizing dynamic changes of brain serotonergic and dopaminergic activities depending on the duration and depth of depressive disorder. Pathological state was kept after stopping stress action on mice and next placing males in the comfortable conditions with females on 1-2 weeks [6].

Pharmacological studies. The sensory contact model allows experimentally to form different pathological states produced by chronic social conflicts and to study the therapeutic and protective properties of any drug as well as its efficiency under simulated clinical conditions [41, review, 43]. This approach can be useful in the search of novel antidepressants and anxiolytics, other psychotropic drugs, and in a better understanding of the drugs' action. It has been shown also that many drugs have different effects in the winners, losers and controls that suppose different efficacy of drugs in persons with different emotional states. Thus, this model can be used for the search of methods of individual therapy. The study of the state of the brain's mediator systems at each time point of the pathological process, too, could give valuable results for pharmacological study. An experimental study of dynamic changes in brain neurotransmitter systems could help identify adequate methods of pharmacological correction and propose a complex therapeutic strategy for any particular stage of disease. Our animal experiments with psychotropic drugs, which are commonly used in medical practice for treatment of depression and anxiety, show a strong similarity between the effects these drugs have on animals and humans [43].

Psychogenic immune deficiency. Cell and humoral immune suppression developing in the mice due to repeated social defeats was confirmed by many authors using the sensory contact model [18, 25, 62] or its modifications [review, 67]. That means that chronic social defeat stress leads to quick development of psychogenic immune deficiency under chronic social conflicts. It has been shown also that transplanted tumor growth depends on social status of animals [26, 46].

Learned and abnormal aggression. The sensory contact model allows the aggressive type of behavior to be formed as a result of repeated experience of victories in daily agonistic interactions in male mice. Some behavioral domains confirm the development of learned aggression in males similar to those in humans [review, 37]. The features are: repeated experience of aggression reinforced by victories; elements of learned behavior after period of confrontations; intent, measured by increase of the aggressive motivation; decreased emotionality. Relevant stimuli (boundary aggression) provoke demonstration of aggression. Positive fighting experience in daily social confrontations changes many characteristics of individual and social behaviors, these having been estimated in varied situations. Some physiological parameters are also changed in the winners. Neurochemical data confirm the activation of brain dopaminergic systems and functional inhibition of serotonergic system in the winners under influence of repeated aggression, that create the low threshold for aggressive reaction in even weakly provoking environment. Changes in opioidergic systems form aggression abuse in male mice. Long experience of aggression is accompanied by development of psychopathology of aggressive behavior accompanying by abnormal and violent aggression, hyperkinetic and stereotypic reaction, hostile behavior, pronounced anxiety, addictive state etc [review, 39].

Molecular studies: From behavior to gene. It has been shown, that changes of brain monoaminergic systems activity under daily agonistic interactions in mice are accompanied by changes in expression of monoaminergic genes [review, 31]. Repeated aggression is accompanied by increase of mRNA levels of dopamine transporter, tyrosine hydroxylase and alpha-sinuclein genes in ventral tegmental area of aggressive male mice [15, 20]. Repeated experience of social defeats produced increase of mRNA levels of serotonin transporter and monoamine oxidase A genes in the midbrain raphe nuclei [21]. There are more experimental studies that provide support to the hypothesis that many genes in some brain regions can change their functional state due to social confrontations [1, 10, 12, 13, 22, 23, 28, 51, 52]. Supposed ethological approach discovers methodological perspectives for the study of molecular mechanisms of psychoemotional disorders in the context of fundamental problem of seeking the ways of regulation from behavior to gene.

Conclusion

The sensory contact model can be used for the study of neurophysiological consequences of chronic social conflicts. Expression and direction of neurophysiological changes depends on genetic predisposition (mouse strains), social status and on duration of social agonistic experience. A large variety of behavioral pathologies (anxious depression, catalepsy, social withdrawal, abnormal aggression, anxiety, hyperactivity, cognitive disturbances, anhedonia etc.), which are accompanied by somatic changes (reduced gonad function, immune deficiency, gastric mucosa damage and others) in animals, suggest that this approach could be extensively used in basic and applied studies in the social biology, biological psychiatry and pharmacology.

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