Application of the Sensory Contact Model for Pharmacological Studies under Simulated Clinical Conditions

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Abstract
The sensory contact model allows forming different psychopathological states (anxious depression, catalepsy, social withdrawal, pathological aggression, cognition disturbances, anhedonia, addictive states etc.) produced by repeated agonistic interactions in male mice and investigating the therapeutic and preventive properties of any drug as well as its efficiency under simulated clinical conditions. This approach can be useful for a better understanding of the drugs’ action in different stages of disease development in individuals. It is suggested that this behavioral approach and pharmacological designs may be applied for the screening of novel psychotropic drugs*.

Key words: antidepressants, anxiolytics, behavioral psychopathologies, psychotropic drugs, sensory contact model, screening

Introduction
Pharmacological approach is based on the model of chronic social conflicts or the so-called “sensory contact model” [1-4], which was originally used for study the mechanisms of aggressive and submissive behaviors of male mice (beginning at 1987-1991 years). Pairs of male mice are placed in cages divided in two compartments by a perforated transparent partition allowing the animals to see, hear and smell their neighbor, but not to contact them physically. Every day the partition was removed for 10 min to allow agonistic interactions. Superiority of one of the partners was evident within 3 daily test sessions with the same partner. One partner attacked, bitted, and chased the other, who displayed defensive behavior only (sideways, upright postures, withdrawal, lying on the back or freezing). Agonistic interactions were discontinued by lowering the partition if intensive attacks lasted more than 3 min. Every day after the test session, each defeated mouse was placed in another two compartments cage with a partition, in which another winner was present in the other compartment. The winners remained in their own compartments. The sensory contact model yielded equal numbers of males with experience of aggression, evidenced by victories (aggressors, winners) and with social defeats (defeated mice, losers) in agonistic interactions. Winners and losers after 2-3, 10 and 20 tests of daily agonistic interactions were used in the experiments. Control males were housed individually for 5 days. They were regarded as the most appropriate controls for the sensory contact model, because the submissiveness of grouped males was removed, and the effects of social isolation were not yet acquired [1, 2].

It was shown that repeated experience of social victories or defeats in daily agonistic interactions leads to the formation of persistent opposing kinds of social behavior in male mice – the winners (aggressors) and losers (defeated animals, victims of aggression). Depending on emotional state (positive or negative) of an individual, multiple neurochemical alterations in the synthesis, catabolism and receptors of key brain neurotransmitters are followed by behavioral and physiological changes in mice. In general, it was shown that repeated experience of aggression is accompanied by the activation of brain dopaminergic and opioidergic systems and hypofunction of serotonergic system [reviews, 2, 3] while repeated experience of social defeats leads to the attenuation of the dopaminergic and serotonergic brain activity [review, 2, 4]. As a consequence, the winners and losers were found to exhibit significant differences in emotionality, motor and exploratory activities, level of sociability, alcohol intake as well as in the state of immune system and gonadal function [2]. It was also shown that long exposure to social confrontations leads to the formation of psychoemotional and somatic disturbances with...
Table. Different psychoemotional and somatic pathologies developing in aggressive and submissive male mice of C57BL/6J (C57) and CBA/Lac (CBA) strains after long experience of agonistic interactions under the sensory contact model

<table>
<thead>
<tr>
<th><strong>SUBMISSIVE MICE</strong></th>
<th><strong>AGGRESSIVE MICE</strong></th>
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<tr>
<td><strong>Behavioral Pathologies and Psychosomatic Disorders</strong></td>
<td><strong>Strain</strong></td>
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<td>Anxious depression</td>
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<td>Depression</td>
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<td>Low communication</td>
<td>C57</td>
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<td>Social withdrawal (autism?)</td>
<td>CBA</td>
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<td>Increased ethanol intake</td>
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<td>Anhedonia</td>
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<td>Decreased fertility</td>
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<td>Immune deficiency</td>
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<td>Increased metastasis</td>
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the forming behavioral pathology depending on kind of social behaviors, duration of agonistic interactions and strain of mice (Table). In our studies, eight criteria used were thought to point to the formation of behavioral pathology (Box) [3]. The most extensive studies have been conducted and the most satisfactory validating results obtained on mice for anxious depression, generalized anxiety, pathological aggression and psychogenic immune deficiency [3-7]. Generating different psychoemotional and psychosomatic disturbances in animals under the sensory contact model gives the opportunity to investigate the action of novel (along with widely used) psychotropic drugs and conduct their screening in the simulated clinical conditions. In this respect, it would be useful to outline possible applications of the proposed experimental method and new pharmacological designs for detecting therapeutic and protective effects and efficacy of prospective psychotropic drugs.

The study of therapeutic (medicative) effect of drugs with prospective psychotropic properties

The general design of the experiments is as follows (Fig. 1a): during 20-30 days a psychoemotional disorder is induced in male mice.
mice by repeated social agonistic interactions, which are inevitably followed by psychosomatic changes. Then the “sick” animals are put into comfortable housing conditions without confrontations and are treated during 2 weeks with drug or placebo (vehicle). Upon treatment the three groups of animals - placebo-treated and drug-treated depressive mice as well as the control are compared (using relevant behavioral tests) to detect therapeutic effect of the drug. Behavior of depressive mice in the plus-maze test, open-field test and Porsolt’s tests after medicative chronic treatment by lithium-based enterosorbent noolit (665 mg/kg) (b,c) [5] and fluoxetine (25 mg/kg) (d) were shown. Depressive animals (vehicle-treated) have high level of anxiety (increased % entries to enclosed arms) in elevated plus-maze test (b), reduced exploratory activity (decreased number of rearing) in the open field test (c) and high level of depressiveness (total time of passive swimming) in Porsolt’s test (d) as compared with the control (intact state). Noolit reduced level of anxiety and increased exploratory activity as compared with placebo-treated mice. Number of rearings (c) under noolit treatment restored to the level in the control. Enclosed arm time (b) and time of passive swimming (d) were decreased in drug-treated animals as compared with vehicle-treated animals but differ from intact animals. * p < 0.05, ** p < 0.01 vs controls; # p < 0.05; ## p < 0.01, vs vehicle-treated depressive mice.

Fig. 1. Regimen of medicative treatment. A psychoemotional disorder (for example, depression state) is induced in male mice by repeated social agonistic interactions during 20 days (a). Then the depressive animals are put into comfortable housing conditions without confrontations and are treated during 2 weeks with drug or placebo (vehicle). Upon treatment the three groups of animals - placebo-treated and drug-treated depressive mice as well as the control are compared (using relevant behavioral tests) to detect therapeutic effect of the drug. Behavior of depressive mice in the plus-maze test, open-field test and Porsolt’s tests after medicative chronic treatment by lithium-based enterosorbent noolit (665 mg/kg) (b,c) [5] and fluoxetine (25 mg/kg) (d) were shown. Depressive animals (vehicle-treated) have high level of anxiety (increased % entries to enclosed arms) in elevated plus-maze test (b), reduced exploratory activity (decreased number of rearing) in the open field test (c) and high level of depressiveness (total time of passive swimming) in Porsolt’s test (d) as compared with the control (intact state). Noolit reduced level of anxiety and increased exploratory activity as compared with placebo-treated mice. Number of rearings (c) under noolit treatment restored to the level in the control. Enclosed arm time (b) and time of passive swimming (d) were decreased in drug-treated animals as compared with vehicle-treated animals but differ from intact animals. * p < 0.05, ** p < 0.01 vs controls; # p < 0.05; ## p < 0.01, vs vehicle-treated depressive mice.
similarly to the clinical treatment of depression in humans. Besides, additional studies of animals after treatment are needed to predict the probability and incidence of relapses, which are quite common in patients with psychoemotional disorders.

Detection of protective properties of drugs

As a rule, an individual is incapable of avoiding or at least minimizing negative influence of social environment and surroundings, in which he or she lives or has to stay in particular living circumstances. In such cases the questions arise on how to prevent the development of a disease under long exposure to psychopathogenic factors? Our approach allows detecting protective effects of drugs administered for preventive purposes under exposure to chronic agonistic interactions. For that, after five days of social interactions, animals are treated chronically by drugs on the background of continuing daily agonistic interactions (Fig. 2a). At the same time, in analogous way a group of animals receives a placebo (vehicle). After a period of time, which is to be not shorter than two weeks for drugs with assumed psychotropic properties, all animals are investigated in relevant behavioral or physiological tests. This regimen was used to administer the drugs that are used in the clinical practice for reduction of depression and anxiety and that influence the serotonergic system, which undergoes alterations in the process of depression formation in male mice [4, 9]. It has been shown (as example, see Fig. 2b,c,d) that buspirone, ipsapirone and tianeptine (but not fluoxetine and citalopram) produced anxiolytic effect, i.e. the level of developing anxiety on the background of chronic preventive drug administration was lower at least in one of the behavioral test as compared with placebo-treated animals, which points to protective effect of these drugs. Imipramine and tianeptine were shown to prevent the development of high level of depressiveness estimated by Porsolt’ test (decrease of immobility time) [4]. * p < 0.05 as compared with defeated male mice receiving vehicle (placebo).

Fig. 2. Regimen of preventive treatment. After five days of social interactions forming opposite social behaviors, animals are treated chronically by drugs with assumed or known therapeutic properties. At the same time, in analogous way a group of animals receives a placebo. Agonistic interactions are continuing all period of treatment (a). After two weeks all animals are investigated in relevant behavioral tests. This regimen was used to administer the drugs that are used in the clinical practice for reduction of depression and/or anxiety. 5-HT1A receptors agonists buspirone (1 mg/kg) (b) and ipsapirone (3 mg/kg) (c) decreased high level of anxiety developing in defeated mice during agonistic interactions and increased % open arm time in elevated plus-maze test. Antidepressant tianeptine (10 mg/kg) (d) prevented development of high level of depressiveness estimated by Porsolt’ test (decrease of immobility time) [4]. * p < 0.05 as compared with defeated male mice receiving vehicle (placebo).
Study of the drug effects depending on the stage of psychoemotional disorder

Neurochemical studies have produced a bulk of evidence that under repeated experience of aggression or social defeats the brain neurotransmitter systems undergo specific dynamic changes in synthesis, catabolism and receptors [3, 4]. The consequences of chronic confrontations seem to be accumulated and the occurring neurochemical changes may differ depending on the duration of psychoemotional stress and the depth of developing behavioral pathology. An obvious implication of all the experiments is that psychoemotional disorders like many other ailments do not emerge out of the blue (all at once), this is rather a process in time, when the accumulating changes aggravate the state. Direct evidence was obtained in the study of the mouse brain serotonergic system during the formation of anxious depression, revealing dynamic alterations of serotonin synthesis, catabolism and receptors [4, 9]. On the base of these studies it was concluded that during the first days of confrontations social stress evokes the activation of the brain serotonergic system in animals. Subsequently, under systematic psychoemotional negative impact a hypofunction of the serotonergic system is formed at least in limbic brain areas of depressive mice.

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In our studies we develop pharmacological approach, which allows estimating possible changes in brain neurochemical activity during the formation of psychoemotional disorders (Fig. 3a). For this purpose, preliminarily chosen dose of a drug is administered into intact animals and animals in different stages of “disease” – after
Fig. 4. Effect of selective k-opioid receptor agonist U-50,488H (0.6, 1.25 and 2.5 mg/kg) on communicative behavior of the control, the winners and losers after 10 days of agonistic interactions. Level of communicative behavior was estimated in the partition test, measuring behavioral reaction to the partner in the neighboring compartment of common cage. It was shown that U-50,488H produced decrease of total time spent near the partition (social withdrawal) in the control animals, had no effect on the winners and increased this behavior in the losers (anxiolytic effect) [40]. * p < 0.05; ** p < 0.01 – as compared with vehicle (0); # p < 0.05 – as compared with previous dose of the drug.

2-3 days of confrontations – initial stage (acute social stress), 10 days – developing pathology and 20 days of confrontations – deep pathology. Comparison of the drug effect is conducted in the every experimental group by comparing the tested behavior of drug-treated animals with that of the vehicle-treated. Diverse effects of the drug as regards the intensity or direction in intact and “sick” mice point to a changed state of a mediator system involved in the pathogenic process. With the help of this method it was shown that different stages of disease are often characterized by dissimilar reaction to many drugs. We have obtained experimental evidence supporting these views for many drugs used in clinics: haloperidol, naltrexone, buspirone, diazepam etc (as example, see Fig. 3) [3, 4]. Therefore, it is obvious that different stages of a disease require different drug correction depending on the status of brain neurotransmitter activity. In this respect the sensory contact model, which allows monitoring the changes in neurochemical activity of the brain as a disease progresses from norm to deep pathology, could be used for screening psychotropic drugs to determine their efficacy in different stages of the pathological process.

The study of the individual sensitivity to drug depending on psychoemotional states

It is well known that the many of modern drugs are effective in less than half of all psychiatric patients. This is thought to be due to individual peculiarities of diseased organisms having varying hereditary sensitivity to drugs. The role of hereditary factor can be elucidated in the experiments with animals of inbred strains reacting differently to the drugs administered. However, our experiments demonstrated that one and the same behavioral or physiological parameter under the influence of a drug could change in different ways in animals of one inbred strain but with the opposite kinds of social behavior – in the winners and losers (as example, see Fig. 4). It was natural to presume that psychoemotional disorders induced by repeated experience of aggression and accompanied by victories (positive emotional background) or by repeated experience of social defeats (negative emotional background) would evoke different changes in the brain, triggering different reactions to the drugs. Since the many of drugs used act on the receptors, it is natural to assume that receptors might become more sensitive to neurotransmitters (sensitization) and, thus, more susceptible to drugs, or less sensitive (desensitization). It is clear that such changes in the receptors arise in response to changes in mediator metabolism evoked by social confrontations. Therefore, on the one hand, psychoemotional states modify the effect of drugs. On the other hand, psychoemotional states themselves can exert significant influence on the development of a disease. It is also evident that different drugs may be needed to arrest the same modified behaviors or physiological changes in different individuals since such individuals may have varying susceptibility to those drugs. The proposed model allows investigating the responses of individuals with opposite psychoemotional states to the administration of the same drug. In modern pharmacology priority has been attached to personal therapy, which is thought to be a key to effective treatment.

Conclusion: perspectives of the use of social models for pharmacological screening of psychotropic drugs

Over many years the studies have focused on search of adequate models of psychoemotional disorders, which would allow screening of psychotropic drugs [10-24]. The models that are gaining in popularity include biosocial models to study the consequences of acute or chronic social conflicts and social stress in animals [16, 18, 19, 25-29]. In this connection our experimental behavioral approach is up to date and in the
mainstream of contemporary studies. It allows screening of novel psychotropic drugs in simulated clinical conditions and detecting their preventive and therapeutic properties and efficacy. In our view, this method could help if not to entirely avoid but to minimize the phase of clinical trials of novel drugs on patients. Study of dynamic changes in brain neurotransmitter systems (metabolism, receptors, genes expression) – from norm to severe pathology may also give valuable results and could help to identify adequate methods of pharmacological correction depending on the stage of a disease. The action of drugs should be investigated with respect to the neurochemical background specifically altered under the influence of emotional pathogenic factors. Studies on animals treated with psycho-

tropic drugs that are commonly used in medical practice for treatment of depression, anxiety and aggression have shown a close correspondence of their effect to that in humans. A large variety of behavioral pathologies (anxious depression, reduced sociability, pronounced aggression, anxiety, anhedonia etc.), which are accompanied by somatic changes (gastric mucosa damage, reduced gonadal function, psychogenic immune deficiency and others) in animals gives grounds to suppose that this approach could be extensively used in many medical-biological investigations for the study of a broad spectrum of problems in social biology and biological psychiatry.

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