GENETICS

Genetic Models of Impaired Prestimulus Inhibition of the Shudder Reaction

N. K. Popova and M. V. Mal'tseva

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 126, No. 7, pp. 86-89, July, 1998
Original article submitted July 4, 1997

Prestimulus inhibition of the fear reaction (weakening of reflex shudder when the standard sound stimulus is preceded by a weak sound) was studied in eleven inbred mouse strains. Inhibition is regarded as a selective suppression of sensorimotor reactions typical of schizophrenia. Considerable genotype-related differences were revealed in this inhibition. The reaction was not observed in DBA/2 mice and was weak (31%) in PT mice. Inhibition of the shudder reflex was practically the same (54.8%) in mice with abnormal behavior: C57Bl (high inclination to alcohol) and CBA (predisposition to catalepsy). There was no correlation between reflex shudder and prestimulus inhibition.

Key Words: *fear reaction; prestimulus inhibition; role of genotype; genetic model of prestimulus inhibition*

Psychotic disorders such as fleeting attention, disorganization and fragmentation of thought, and fixed ideas or emotions have been associated with disturbances in the inhibition of insignificant or anxious information. A model of prestimulus inhibition of reflex shudder (PIRS) caused by sound stimulus (SS) seems to be a convenient tool for the investigation of selective inhibition. In the PIRS model a weak SS, which causes to fear reaction, precedes the standard SS. The weakening of reflex shudder by a weaker SS is regarded as a selective inhibition of sensorimotor reactions which are an important mechanism providing normal functioning of the brain. Pronounced disorders of PIRS were observed in schizophrenia and some psychopatho-logic conditions [8], which excited interest in this phenomenon and stimulated the search for the means of its modeling. Several pharmacological models of PIRS employing amphetamines, apomorphine, and agonist of dopamine D_2-receptors have been developed [9]. Considerable investigative effort has been focused no genetic modeling of PIRS [3,8].

In the present study we examined genetically determined peculiarities of PIRS in an attempt to find out a suitable genetic model of PIRS.

MATERIALS AND METHODS

The following mouse strains were tested: BALB/c, C57Bl/6J, CC57BR, PT (high determinacy of social hierarchy [1]), DD, A/Sn, C3HA, C3H/Sn, SWR, CBA (genetically determined predisposition to catalepsy [6]), DBA/2 (high predisposition to audiogenic seizures at the age of 25-30 days [4]), C57Bl (high inclination to alcohol [5]).

The mice (age of 2-3 months, body weight 12-26 g) were maintained in cages (8-10 animals) under normal illumination conditions and free access to food and water. Two days before experiment, the mice were placed into individual cages to eliminate sociobiological influences. Experiments were performed in autumn. They were started at 14:00 and included 8-16 mice of each strain.

Laboratory of Behavioral Phylogenetics, Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences, Novosibirsk

0007-4888/98/0007-0718$20.00

The mice were tested in an SR-Pilot apparatus (San-Diego Instruments). The apparatus is a 15×19×25 cm Plexiglass box with a highly sensitive piezosensor mounted on a platform on the floor and a microphone attached to the ceiling. "White sound" (65 dB) was applied after switching on the sensor. A 115-dB sound was employed as a stimulus provoking the fear reaction and shudder. It was applied for 40 msec simultaneously with recording the movements of the mouse on the platform. The movements of the platform were digitized via a computer. The prestimulus (a 85-dB sound, 40 msec) was discharged before the standard SS. After a 3-min adaptation period four successive standard SS were discharged at a 15-sec intervals, after which the prestimulus-standard stimulus combination was applied. PIRS was calculated from the following formula:

$$\frac{\text{reaction to the prestimulus-standard stimulus}}{\text{reaction to the standard stimulus}} \times 100.$$

Results were statistically analyzed by ANOVA using Microsoft Origin 3.0 and Statgraphics 3.5 software.

RESULTS

Considerable interstrain differences were revealed in the reaction to the standard SS and to the prestimulus-standard SS combination. The intensify of the fear reaction was the highest in PT, C3HA, SWR, and CBA mice and the lowest in BALB/c and DBA/2 mice. The intensity of the fear reaction in PT and DBA/2 mice differed about 7-fold (Fig. 1, *a*). The interstrain differences were confirmed by the exact Fischer test ($F_{(10,113)}$=25.49, p<0.001), which points to a considerable influence of genotype.

Prestimulus markedly decreased the intensity of the fear reaction to the standard SS in 10 out of 11 mouse strains (Fig.1, *b*). Similar phenomenon was observed in rats and humans [7]. In the majority of the studied strains, prestimulus decreased the intensity of fear reaction to the standard stimulus 1.5-2-fold. In DBA/2 mice, the reaction to the prestimulus-SS combination did not differ considerably from the reaction to SS (p<0.05). In 22 out of 64 DBA/2 mice, the reaction to the prestimulus-SS combination was more pronounced than the reaction to SS.

Considerable genetically determined differences ($F_{(10,113)}$=7.04, p<0.001, Fig. 2) were revealed in PIRS intensity. The percentage of PIRS was the highest in CBA mice (70.6±3.9) and the lowest in the PT mice (31.1±8.2). PIRS was not observed in DBA/2 mice (p>0.05 compared with zero value).

In 10 mouse strains, the mean intensity of the reaction to the standard SS was 93.7±51.7, the mean PIRS being 54.8±2.2%. Since DBA/2 mice did not develop PIRS, its parameters were not taken into account in the calculation of the mean values characteristic of the "normal" reaction. There was no correlation between the fear reaction and PIRS

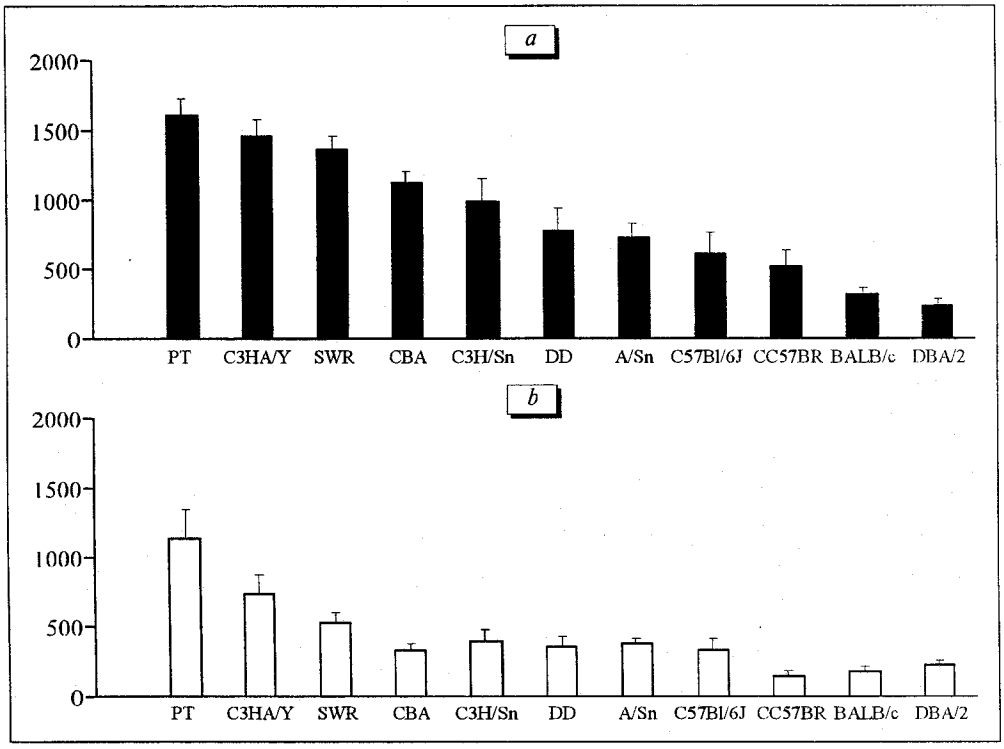

Fig. 1. Interstrain differences in the intensity of the fear reaction (*a*) and reaction to the prestimulus+standard SS (*b*) in mice. Ordinate: intensity of the shudder reaction, arb. units.

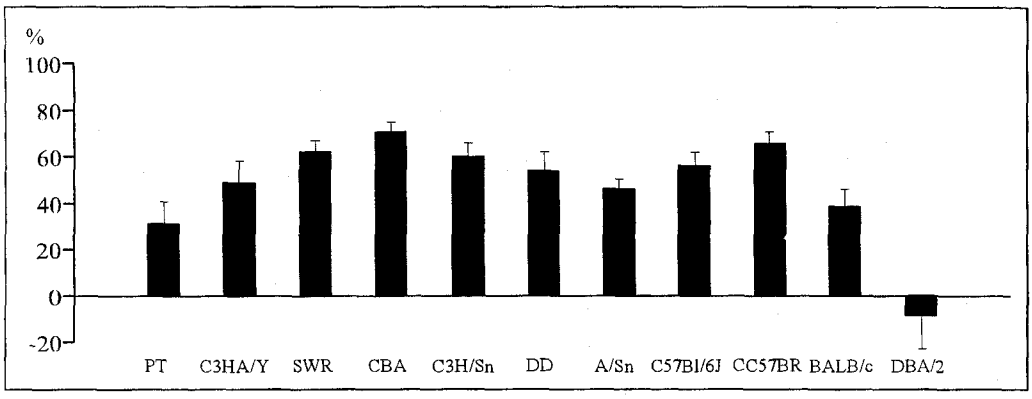

Fig. 2. Interstrain differences in PIRS in mice.

expression in the studied mouse strains. It can be suggested that PIRS does not depend on the intensity of genetically determined fear reaction. This suggestion is consistent with the finding that the fear reaction and PIRS are controlled by different nervous system structures. Reflex shudder in response to an unexpected sound is realized via the involvement of the spine, telencephalon, and mesencephalon, while PIRS involves the prosencephalon [7].

In comparison with other mice strains, in DBA/2 mice PIRS is markedly impaired. DBA/2 mice have high sensitivity to sound stimuli at the age of 3-5 weeks, which is displayed in audiogenic seizures [4]. We used 2-3-month-old DBA/2 mice that should not develop audiogenic seizures. However, PIRS in these mice was markedly impaired, implying a psychopathological condition.

In other strains with behavioral abnormalities (C57Bl and CBA) the fear reaction and PIRS did not differ considerably from the mean level. It should be noted that the shudder reaction was slightly lower in C57Bl mice and did not differ in the PIRS from other strains. In CBA mice, the fear reaction and PIRS were slightly higher. In PT mice, which are characterized by domination in social hierarchy [1], the fear reaction was high and PIRS was low. It can be suggested that the high-level fear reaction is an element of guarding behavior which allows the dominating animal to react quickly to potential danger. The weak PIRS may account for the extremely long latency after the first attack in PT males [2].

Since the impossibility of modeling schizophrenia, a complex psychopathological condition, in animals has been generally accepted, investigative effort was focused on modeling some symptoms of schizophrenia. Impaired mechanism of selective inhibition is one of these symptoms. We propose a genetic model of a very low PIRS (PT mice) and the absence of PIRS (DBA/2 mice).

The study was supported by the Russian Foundation for Basic Research (grant N0. 96-04-49960).

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