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BRIEF COMMUNICATION

Pharmacological Effects on Two Inbred Substrains of AB Mice

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BECKER, A , H -L RUETHRICH, R SCHNEIDER, G GRECKSCH AND H MATTHIES. *Pharmacological effects on two inbred substrains of AB mice*. PHARMACOL BIOCHEM BEHAV **38**(2) 471–473, 1991 —Mice of the two substrains AB/Gat and AB/Hal from the Jena AB inbred strain differ in behavior from each other by their aggressiveness occurring especially in the latter group after maturity. In order to ascertain the neurobiological background of aggressiveness, we injected mice of both substrains with either haloperidol, diazepam, or hexobarbital and measured their response on motor activity In a second experiment, the reaction to a seizure evoking agent (pentylenetetrazol) was determined Mice of both substrains were found to differ significantly in their reaction to haloperidol or diazepam injection In contrast to that no changes in motor activity could be detected following hexobarbital administration Animals of the aggressive AB/Hal substrain reacted more pronounced to pentylenetetrazol than those of the AB/Gat group. In conclusion, the varying aggressiveness of both AB mice substrains may be due to differences in dopaminergic and GABAergic neurotransmission.

AB mice Aggressiveness Haloperidol Diazepam Hexobarbital Pentylenetetrazol Motor activity

EXTENSIVE investigations on mice of the two substrains from the Jena AB inbred strain (3), viz. AB/Gat and AB/Hal, revealed considerable behavioral differences in the open field, in the exploration of the hole board, and in learning performance. However, the most pronounced difference was observed with regard to their aggressive behavior. After maturity, male AB/Hal mice developed an abnormally high aggressiveness during group-housing, whereas the closely related AB/Gat substrain never exhibited aggressive behavior under such conditions. In order to elucidate the pharmacological background of these differences in aggressiveness we treated male mice of both lines with drugs affecting different neurotransmitter systems and measured the effect by means of motor response. In a second experiment the sensitivity to a seizure-evoking agent was determined.

METHOD

Subjects

The mice have been bred in our own colony since 1984 and were kept under controlled laboratory conditions under a lighting regime of LD 12 12 (light on at 6.00 a.m.), temperature 20 ± 2°C, and relative air humidity 60–70%. They had free access to commercial pellet food (R 13). The animals, being 7 weeks old at the beginning of the experiments, were caged in groups of 4–6.

Apparatus

The locomotor activity of the animals was registered using an optoelectronic activity meter. The apparatus consisted of 4 single plates (30 × 50 cm) surrounded by a frame 25 cm high. Each bottom plate was equipped with 18 equidistantly spaced photocells. Two 40-W white fluorescent tubes mounted 2 m above the apparatus served as luminous source. Whenever an animal interrupted the light beam the impulses were recorded, added, and printed every minute.

Drugs

In order to find out the neurobiological reasons for the differ-

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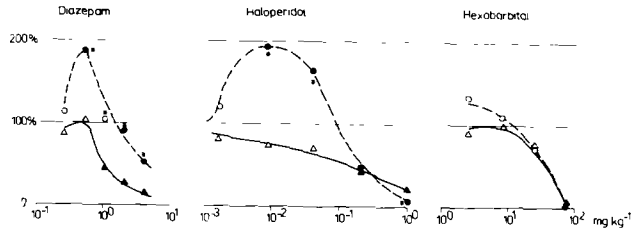

FIG 1 Locomotor activity of mice from the two substrains of AB/Hal (●) and AB/Gat (○) after treatment with different substances (standardized to controls = 100%) Solid symbol $p<0$ 05 in comparison to controls of the same substrain, *$p<0$ 05 comparison between the substrains (U-test)

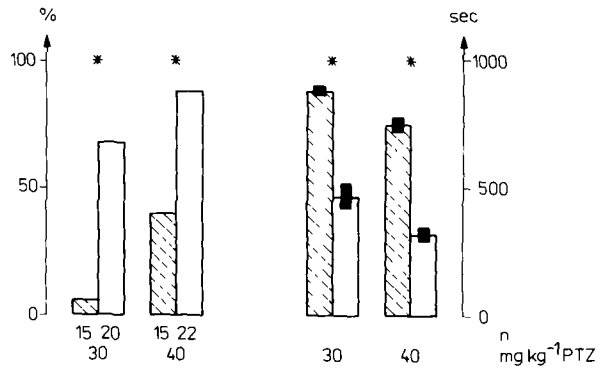

FIG 2 Percentage of animals of the two substrains AB/Gat (hatched) and AB/Hal (white) in developing seizures and latency time until seizure occurrence (mean ± SEM) after a single injection of pentylenetetrazol (PTZ) *$p<0$ 001

ences in behavior between both substrains of AB mice the following drugs were tested. diazepam· 0 25, 0.5, 1.0, 2.0, 4 0 mg/kg, haloperidol· 0.0016, 0 008, 0.04, 0.2, 1.0 mg/kg; hexobarbital 2.5, 8.0, 25.0, 75.0 mg/kg. The substances were dissolved in physiological saline and injected intraperitoneally at a volume of 1 ml/0 1 kg body weight For control, the solvent alone was administered. Thirty min after injection the animal was placed on one of the plates of the apparatus for 10 min. Each experimental group consisted of 10–15 animals During the experiments the mice were observed for stereotype reactions or grooming which never occurred.

In a second experiment, we tested the response of the animals of both substrains to two doses (30 and 40 mg/kg) of pentylenetetrazol. This substance was dissolved in saline (0.9%) and injected intraperitoneally at a volume of 1 ml/0.1 kg body weight. After injection the animals were placed singly and were observed for 15 min. The number of mice developing clonic-tonic seizures as well as the latency until the onset of seizures was recorded. The experiments were performed between 8.00 a.m. and 11.00 a.m. Generally, each animal was tested once only.

Statistics

Statistical analysis was performed using the Mann-Whitney U-test and the Chi^2-test (two-tailed)

RESULTS

Saline-treated controls of both substrains of AB mice did not significantly differ in their motor activity (AB/Gat 101 ± 13.2, AB/Hal 79 ± 14.7, mean ± SEM, $p>0$ 05, U-test) Hexobarbital, producing a dose-dependent decline in motor activity, did not cause any differences in the dose-response curves of the two substrains either. However, the action of diazepam was found to differ widely in both substrains. In AB/Gat mice, diazepam resulted in a dose-dependent depression of motor activity only. In AB/Hal mice, low doses of diazepam produced an increase in motor activity, thus revealing a biphasic dose-response curve A similar result was obtained after haloperidol· AB/Gat mice showed only a dose-dependent depression of motor activity, whereas AB/Hal mice were considerably more active at a low dosage level (Fig. 1).

In the second experiment, the reaction from mice of both lines to different doses of pentylenetetrazol was recorded. As shown in Fig. 2, Hal mice responded much more sensitive to pentylenetetrazol as Gat did. The number of animals developing seizures was considerably higher and the latency until seizure onset was significantly shorter compared to Gat (Fig. 2).

DISCUSSION

The results showed that saline-injected mice of both substrains reached similar activity scores This provides a reliable basis for comparing drug effects.

In animals who received different hexobarbital doses the response was nearly identical (Fig. 1). Similar results were obtained after diazepam injection. Assuming that both barbiturates and benzodiazepines act on the GABA/benzodiazepine receptor complex, an involvement of different structures in the central nervous system cannot be ruled out. Barbiturates display their action mainly by inhibiting the impulse transfer from the rostrally ascending part of the formatio reticularis to cortical circuits playing a dominant role in arousal reactions. It seems, therefore, likely that arousal differences are not the very reason for the described behavioral differences.

Obvious changes in the animals motor activity occurred after diazepam treatment (Fig. 1). Comparing diazepam-injected groups the Hal mice are significantly more active than the Gat animals after administration of more than 0.5 mg/kg. This finding does not contrast with the results obtained with hexobarbital. Although hypnotics and tranquilizers have some effects in common, their domain in the central nervous system is not identical. Hexobarbital develops its effect over the formatio reticularis-cortical circuits, whereas diazepam interferes mainly with limbic structures. In comparison to saline-treated controls we could not detect an increase in motor activity in Gat generally referred as "anxiolysis" at lower dosage levels. This strengthens the view that the differences in behavior may be due to the effectiveness in the GABA/benzodiazepine neurotransmission system.

This assumption was supported by the experimental data of the second experiment (Fig. 2) Male Hal animals reacted more sensitively to the GABA antagonist pentylenetetrazol than Gat did. The percentage of animals with seizures and the shorter latency time until seizure onset differed significantly suggesting a less effective GABAergic system in AB/Hal

The influence of sex hormones on the results of our experiments on animal activity can, of course, be minimized since only immature animals were used.

In haloperidol-injected groups (Fig. 1) mice of the Hal substrain were found to be highly activated after administration of 0 008 mg/kg, whereas the reaction of Gat animals was insignificant After receiving higher doses of this substance, animals of both lines showed a similar decrease in motor activity. The motor activation induced by low doses of the dopamine antagonist haloperidol can be considered to be the result of presynaptic dopamine receptor blockade. It is evident, therefore, that apart from differences in the GABAergic system the mice of both substrains

react specifically to stimulations of the dopaminergic system. It has to be clarified, however, whether dopamine or GABA plays a major role in behavioral differences between mice of both lines. According to (4) GABA mechanisms may be able to influence dopamine-mediated behavior Further studies will be required to clear up the background

Nevertheless, mice of both lines of the AB strain appear to be suitable objects for psychopharmacological research. Two sets for experimental strategies for investigating aggressive behavior were proposed (2):

1. behavioral aggression is elicited and the neurophysiological and neurochemical changes are correlated with changes in the behavior;
2. the supposed neuroanatomical or neurochemical substrates are manipulated and changes in behavioral aggression are monitored.

Faced with the fact that AB/Hal mice develop a pronounced aggressive behavior spontaneously after maturation, these animals might make up the third set for investigating aggressiveness.

REFERENCES

1 Haugh, M , Simler, S , Chiesolski, L , Mandel, P , Moutier, R Influence of castration and brain GABA levels in three strains of mice on aggression towards lactating intruders Physiol Behav 32 767–770, 1984

2 Sheard, M H Animal models of aggressive behavior In Hanin, I , Usdin, E , eds Animal models in psychiatry and neurology Oxford Pergamon Press, 1977 247–258

3 Staats, J Standardized nomenclature for inbred strains of mice sixth listing Cancer Res 36 4333–4377, 1976

4 Westerling, P , Lindgren, S , Hoglund, U Dopamine mediated behavior and GABA influence Pharmacol Biochem Behav 31 593–596, 1989