Role of the Interaction between Different Types of Serotonin and α_2-Adrenergic Receptors in the Regulation of Audiogenic Seizures in DBA/2 Mice

T. P. Semenova and M. K. Ticku*

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 119, № 4, pp. 381-383, April, 1995
Original article submitted May 13, 1994

It is shown that the serotonin receptors 5-HT_{1c}, 5-HT_3, and 5-HT_4 and α_2-adrenergic receptors are involved in the regulation of audiogenic seizures in DBA/2 mice, and that the effects of these serotonin receptors on the duration and magnitude of convulsive activity are the opposite of those produced by α_2-adrenergic receptors.

Key Words: *audiogenic seizures; cyproheptadine; ICS 205-930; ketanserin; mianserin; yohimbine; zakopride*

Knowledge of how the susceptibility to audiogenic seizures correlates with the activity of neurotransmitter systems is essential for understanding the mechanisms by which these seizures are regulated [1]. Experiments have shown that DBA/2 mice, which are genetically predisposed to seizures, and C57Bl mice, which are resistant, also differ in the activity of the serotoninergic, noradrenergic, gamma-aminobutyric acid, and several other brain systems [3,4,13,14]. The DBA/2 brain has been found to have much lower levels of serotonin (5-HT) and norepinephrine (NE), fewer binding sites for ^{3}H-prazosin (a ligand of α_1-adrenergic receptors) [2], and a lower affinity of these receptors [5] than the C57Bl brain. Moreover, the temporal cortex of DBA/2 mice is reported to have far fewer monoamine-containing synapses than that of mice not susceptible to audiogenic seizures [8].

Our previous studies demonstrated the importance of a balance between the activities of the brain serotoninergic and noradrenergic systems for the regulation of behavior; in particular, the two systems were shown to interact in a reciprocal manner in influencing emotional behavior and the resistance to audiogenic seizures in rats [10]. In the study described here we explored what role antagonists of these two brain systems might play in the regulation of convulsive activity in DBA/2 mice of two age groups differing in their susceptibility to audiogenic seizures [12].

MATERIALS AND METHODS

DBA/2 mice aged 20-27 days and 30-37 days from the Charles River Nursery (Boston, USA) were used. They were all kept at a constant room temperature (25°C) on a 12-hour light-dark schedule (light from 07:00 h) and had free access to food and water.

Convulsive activity was evaluated separately for each mouse in a plastic chamber in response to a high-frequency tone of 118 dB delivered from a Bell Audioalarm apparatus (Floyd Bell Association, Columbus, Ohio).

The response to acoustic stimulation by mice susceptible to audiogenic seizures included tremor and spontaneous running succeeded by tonic or clonic convulsions (some mice did not develop convulsions after the running). The mean latency of seizures was calculated for each group.

Each of the drugs used - yohimbine hydrochloride, mianserin hydrochloride, cyproheptadine

Laboratory for Biophysics of Receptors, Institute of Cell Biophysics, Russian Academy of Sciences, Pushchino; *University of Texas Health Science Center, San Antonio, USA. (Presented by G. N. Kryzhanovskii, Member of the Russian Academy of Medical Sciences)

0007-4888/95/0004-0368$12.50

TABLE 1. Effects of α_2-Adrenergic and 5-HT Receptor Blockers on Audiogenic Convulsions in DBA/2 Mice Aged 20-27 Days

Group	No. of mice per group	Drug dose, mg/kg	Latency of convulsions, sec
Control	12	–	9.5±1.1
Yohimbine	12	0.5	4.3±0.9***
Mianserin	6	2	29.6±9.1
Cyproheptadine	8	2	18.5±3.0**
Ketanserin	6	3	11.8±2.2
Zakopride	6	1	23.2±6.3*
ICS 205-930	6	1	31.4±10.1*

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with the control group.

hydrochloride, ketanserin (Serva), zakopride (Wyeth Ayerst), and ICS 205-930 (Sandoz) - was dissolved in twice-distilled water in a volume of 1 ml per 10 g body weight and injected intraperitoneally, the dose being calculated by the dry weight of the salt. Yohimbine and the 5-HT receptor blockers were administered 15 min and 25 min, respectively, before the recording of convulsive activity was started. All substances were used in doses in which their activity was highest [6,7].

In the statistical treatment of the results, the means and their standard deviations were computed. Each group consisted of at least 6 mice. The significance of differences in the latency of convulsions between the control and six test (drug-treated) groups was estimated by ANOVA. The differences were considered significant at the $p<0.05$ level.

RESULTS

The younger control mice (20-27 days old) were more susceptible to audiogenic seizures than the older ones (aged 30-37 days). As can be seen from Tables 1 and 2, the former mice exhibited a much shorter latency of convulsive activity than the latter (9.5 sec *vs.* 43.4 sec; $p<0.005$) as well as stronger convulsions. Tonic and/or clonic convulsions in response to acoustic stimulations were observed in 92% of the younger mice, but only 8% of them were seen to run. In contrast, only 17% of the older mice developed convulsions, although 83% of them exhibited tremor and forced running.

The α_2-adrenergic blocker yohimbine (0.5 mg/kg) enhanced convulsive activity. It reduced the latency of convulsions from 9.5 to 4.3 sec ($p<0.005$) in the younger mice and from 43.4 to 17.2 sec ($p<0.005$) in the older ones as compared to the respective control groups.

In contrast, four of the five 5-HT receptor blockers weakened rather than enhanced convulsive activity. The 5-HT_{1c} receptor blockers mianserin (2 mg/kg) and cyproheptadine (2 mg/kg), the 5-HT_3 receptor blocker zakopride (1 mg/kg), and the 5-HT_4 receptor blocker ICS 205-930 (1 mg/kg) all lowered convulsive activity in the younger mice, increasing the latency of convulsions significantly by a factor of 3.1, 2, 2.4, and 3.3, respectively; the 5-HT_2 receptor blocker ketanserin did not have a significant effect on the latency (Table 1).

In the older mice, the latency of convulsions was significantly prolonged only by cyproheptadine. Mianserin and ketanserin had no significant effect on the latency while zakopride and ICS 205-930 significantly shortened it (Table 2).

TABLE 2. Effects of α_2-Adrenergic and 5-HT Receptor Blockers on Audiogenic Convulsions in DBA/2 Mice Aged 30-37 Days

Group	No. of mice per group	Drug dose, mg/kg	Latency of convulsions, sec
Control	12	–	43.4±2.9
Yohimbine	9	0.5	17.2±2.7***
Mianserin	6	2	33.4±8.0
Cyproheptadine	6	2	56.8±3.0**
Ketanserin	6	3	34.2±3.1
Zakopride	12	1	21.1±2.7*
ICS 205-930	12	1	18.3±1.8*

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with the control group.

The present study has shown, first, that the 5-HT and NE receptors we examined are involved in regulating the convulsive activity of DBA/2 mice and, second, that the effects exerted on these receptors by the drugs used is clearly age-dependent. The effect from blocking 5-HT receptors is, on the whole, the opposite of that of blocking α_2-adrenergic receptors. Thus, blockade of the former receptors enhances convulsive activity while blockade of the latter weakens it. A similar influence of NE receptors on convulsive activity was reported previously. For example, the predominantly α_2-adrenergic receptor agonist clonidine was found to lower this activity, but its protective effect was abolished by yohimbine [4,5,9].

In our study, the effects from blocking 5-HT or NE receptors were more pronounced in the younger DBA/2 mice, which are particularly susceptible to audiogenic seizures and, as indicated by biochemical data, show a greatly lowered activity of the monoaminergic systems [3,4,11,12]. Our finding that antagonists of 5-HT_{1c}, 5-HT_3, 5-HT_4 and α_2-adrenergic receptors influence the susceptibility of DBA/2 mice to audiogenic seizures in differing or opposite ways confirms the reciprocal nature of interactions between the serotoninergic and noradrenergic systems of the brain [10], which determines how these systems regulate complex behaviors in normal and pathological states.

The author is grateful to Dr. J. Thomas for support, to Dr. A. Mehtu for useful discussions, and to S. Phillips and G. Bliskowka for technical assistance. This study was funded by a grant from the U. S. National Institute of Health (NS 15339).

REFERENCES

1. G. N. Kryzhanovskii, *Determinant Structures in Nervous System Pathology* [in Russian], Moscow (1980).
2. C. Graillot, N. Baumann, and Y. Maurin, *Europ. J. Pharmacol.*, **118**, 231-237 (1985).
3. R. W. Horton, G. Anlezark, and B. Meldrum, *J. Pharmacol. Exp. Ther.*, **214**, 437-442 (1980).
4. R. W. Horton, S. A. Restwich, and S. P. Jazrawi, *Neurotransmitters, Seizures, and Epilepsy*, Eds. R. G. Fariello *et al.*, New York (1984), pp. 191-200.
5. S. P. Jazrawi and R. W. Horton, *J. Neurochem.*, **47**, 173-176 (1986).
6. G. A. Kennett and G. Curson, Brit. *J. Pharmacol.*, **94**, 137-147 (1988).
7. G. A. Kennett, P. Whitton, K. Shak, and G. Curson, *Europ. J. Pharmacol.*, **164**, 445-454 (1989).
8. D. A. Kristt, M. S. Shirley, and E. Kasper, *Neuroscience*, **5**, 883-891 (1980).
9. J. Papanicolaou, R. J. Summers, F. J. E. Vajdo, and W. J. Louis, *Europ. J. Pharmacol.*, **77**, 163-166 (1982).
10. T. P. Semenova and N. I. Grishchenko, *Trends and Prospects in the Pharmacology of Transmitter Interactions*, Eds. T. S. Stoytchev *et al.*, Sofia (1987), pp. 253-257.
11. T. N. Seyfried, *The Mouse in Biomedical Research*, Eds. H. L. Foster *et al.*, Vol. 2, New York (1982), pp. 92-124.
12. T. N. Seyfried, *Brain Res.*, **271**, 325-328 (1983).
13. B. A. Shaywitz, R. D. Yajer, and J. W. Gordon, *Dev. Psychobiol.*, **11**, 243-250 (1987).
14. M. K. Ticku, *J. Neurochem.*, **33**, 1135-1138 (1979).