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Biphasic Effects of Typical Antidepressants and Mianserin, an Atypical Antidepressant, on Aggressive Behavior in Socially Isolated Mice

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CAI, B., K. MATSUMOTO, H. OHTA AND H. WATANABE. *Biphasic effects of typical antidepressants and mianserin, an atypical antidepressant, on aggressive behavior in socially isolated mice.* PHARMACOL BIOCHEM BEHAV **44**(3) 519–525, 1993. – Effects of several typical antidepressants and of an atypical antidepressant, mianserin, on the aggressive behavior (AGB) in long-term isolated mice were examined. IP administration of maprotiline (2.5 and 5 mg/kg), amitriptyline (5 and 10 mg/kg), clomipramine (2.5 and 5 mg/kg), and mianserin (5 mg/kg) significantly increased the duration of AGB. However, at higher doses (maprotiline, 10 mg/kg; amitriptyline, 20 mg/kg; clomipramine, 10 and 20 mg/kg; mianserin, 10 and 20 mg/kg) these antidepressants either did not affect AGB or inhibited it. Amitriptyline (20 mg/kg) and mianserin (10 mg/kg) but not maprotiline (10 mg/kg) or clomipramine (20 mg/kg) decreased spontaneous motor activity in isolated mice. Yohimbine (0.5 mg/kg, IP), an α_2-antagonist, changed the antidepressant-induced enhancement of AGB into inhibition without affecting the basal aggressive responses. Prazosin (0.3 mg/kg, IP), an α_1-antagonist, did not affect either maprotiline- or clomipramine-induced enhancement of AGB, but it changed the mianserin-induced enhancement of AGB into inhibition. These results indicate that antidepressants that inhibit noradrenaline uptake and/or stimulate noradrenaline output from nerve terminals have biphasic effects on AGB in isolated mice and that the antidepressant-induced enhancement of AGB is mediated by noradrenergic stimulation of α_2-adrenoceptors, whereas the antidepressant-induced inhibition of AGB may be mediated by non-α_2-adrenoceptors or by nonadrenergic system(s).

Aggressive behavior Isolation Antidepressants Noradrenaline α_1-Adrenoceptors α_2-Adrenoceptors Mice

AGGRESSIVE behavior (AGB) in laboratory animals can be induced by a variety of methods that include lesion of the brain, isolated housing, aversive stimuli such as foot-shock, etc. (2). Isolation-induced behavioral changes in mice have been extensively studied and used to test the effects of drugs on aggression or social behavioral deficits or both (6,21, 26,27). Several neuronal pathways, including the catecholaminergic, serotonergic, and GABAergic systems, appear to be involved in aggression (9,17,21,23). In particular, central catecholaminergic systems relate to various forms of animal aggression (2,4). For example, Eichelman and Barchas (5) reported that antidepressant medication facilitates foot-shock-induced aggression through a noradrenergic rather than a serotonergic system. Moreover, we previously reported that desipramine, a selective noradrenaline (NA) reuptake blocker, increases AGB in isolated mice and that this effect can be modulated by drugs acting on α_2- but not α_1-adrenoceptors (16). These observations suggest that functional changes in the central noradrenergic system, especially changes in the sensitivity of α_2-adrenoceptors, may be induced in mice by long-term social isolation and seem to be closely related to the data that the rate of NA synthesis in the brain tissue of isolated animals is reported to be lower than that in group-housed animals (18,27–29).

In the present study, to determine whether the increase in NA in the brain modulates the AGB in isolated mice by interacting with α_2-adrenoceptors we examined the effects of several NA reuptake blockers with different abilities to block 5-hydroxytryptamine (5-HT) reuptake on isolation-induced AGB. We also studied the effect of an atypical antidepressant,

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mianserin, which can interact with α_2-autoreceptors and 5-HT_2 receptors (7,20,22) and weakly inhibits NA uptake (1).

METHOD

Isolated Housing

Animals were housed in isolation as described in our previous report (16). Briefly, male ddY mice, weighing approximately 18–20 g (SLC Co., Shizuoka, Japan), were obtained at the age of 28 days. Mice were either housed in groups of five in 24 × 17 × 12-cm cages or isolated in the same size cage for 6–7 weeks. Housing conditions were thermostatically maintained at 22 ± 1°C, with a 12 L : 12 D cycle. Food and water were given ad lib.

Measurement of Aggressive Responses

To test AGB between isolated mice, one isolated mouse was placed in the home cage (24 × 17 × 12 cm) of another. In the case of group-housed mice, each pair of animals was placed in a clear plastic cage of the same size as their home cage. The duration of biting attacks, wrestling, or both observed during a 20-min period was measured. In some experiments, the latency to the first attack was also recorded using an event recorder connected with a computer (PC 9801NS, NEC). Effects of drugs on AGB were evaluated using six to nine pairs of mice per group.

Measurement of Spontaneous Motor Activity

Spontaneous motor activity was measured with a system described in detail in our previous reports (13,15) or with ANIMATE (MATYS, Toyama, Japan), mechanically the same as ours (14,16). Briefly, 60 min after administration of test drugs mice were placed into doughnut-shaped cages and changes in locomotor activity were measured and recorded over 20 min. Movements were detected by scanning 36 photosensor units that were radially arranged from the center of the cage.

Drugs

Drugs were IP injected 60 min before each experiment except as otherwise stated. The drugs used were: clomipramine HCl, mianserin HCl, amitriptyline HCl, maprotiline HCl, prazosin HCl (Sigma Chemical Co., St. Louis, MO) and yohimbine HCl (Nacalai Tesque, Inc., Kyoto, Japan).

Statistics

Nonparametric data were analyzed with the Kruskal-Wallis analysis of variance (ANOVA) followed by the Mann-Whitney *U*-test for multiple comparisons between groups. Parametric data were analyzed with one-way ANOVA followed by Duncan's multiple-range test. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Effects of Antidepressants on Aggressive Behavior

Maprotiline at 2.5 and 5 mg/kg significantly and dose-dependently increased the duration of AGB in isolated mice (Fig. 1A) without affecting the latency to the first attack (Fig. 1B). However, 10 mg/kg maprotiline did not increase the duration of AGB but significantly prolonged the latency to the first attack.

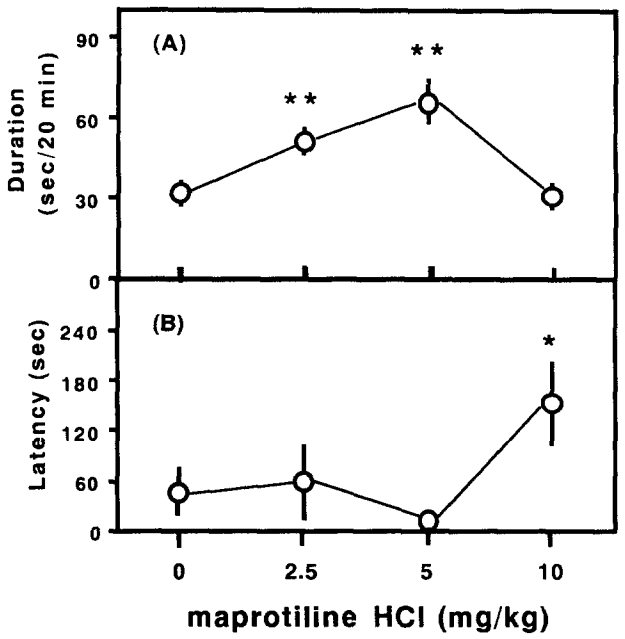

FIG. 1. Maprotiline modulation of aggressive behavior in socially isolated mice. Maprotiline HCl (2.5–10 mg/kg) or saline was IP injected 60 min before the experiments. Duration (A) and the latency to the first attack (B) were measured as described in the text. Each datum represents the mean ± SEM from nine pairs of animals. $*p < 0.05$ and $**p < 0.01$ compared to the respective saline control values (Mann-Whitney *U*-test).

Amitriptyline, a mixed NA and 5-HT uptake blocker, had a biphasic effect on AGB, that is, at 5 and 10 mg/kg it dose-dependently increased the duration of AGB but at 20 mg/kg it almost completely eliminated AGB (Fig. 2). As shown in Fig. 3, clomipramine, a selective 5-HT uptake blocker, had a similar effect. It dose-dependently increased the duration of AGB at 2.5 and 5 mg/kg without significantly affecting the latency to the first attack. In contrast, at doses over 10 mg/kg it significantly decreased the duration of AGB and prolonged the latency to the first attack (Figs. 3A and 3B).

Mianserin, an atypical antidepressant that can interact with NA α_2-autoreceptors and with 5-HT_2 receptors, significantly increased the duration of AGB at 5 mg/kg (Fig. 4). However, at higher doses (10 and 20 mg/kg) mianserin decreased AGB in a dose-dependent manner.

Effects of Yohimbine and Prazosin on Antidepressant-induced Increase in Aggressive Behavior

Yohimbine (0.5 mg/kg, IP), an α_2-adrenoceptor antagonist, did not affect the duration of AGB when administered alone (Fig. 5) but significantly decreased the duration of AGB after 5 mg/kg maprotiline (Fig. 5), 5 mg/kg clomipramine (Fig. 6A), and 5 mg/kg mianserin (Fig. 6B) to below the saline-treated control level. In contrast, prazosin, an α_1-adrenoceptor antagonist, slightly but not significantly decreased maprotiline (5 mg/kg)- and clomipramine (5 mg/kg)-induced increase in AGB. Prazosin significantly decreased the duration of AGB after 5 mg/kg mianserin to below the control level (Fig. 6B).

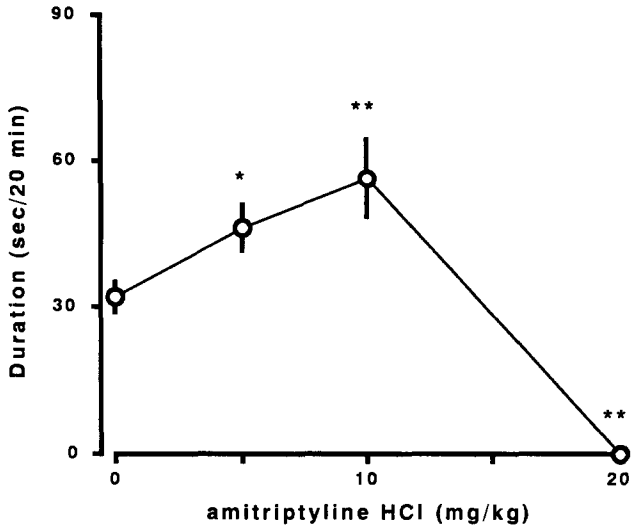

FIG. 2. Amitriptyline modulation of aggressive behavior in socially isolated mice. Amitriptyline HCl (5–20 mg/kg) or saline was IP injected 60 min before the experiments. Duration of aggressive behavior during a 20-min observation period was measured. Each point and bar represents a mean ± SEM from seven to nine pairs of animals. $*p < 0.05$ and $**p < 0.01$ compared to the saline control value (Mann-Whitney *U*-test).

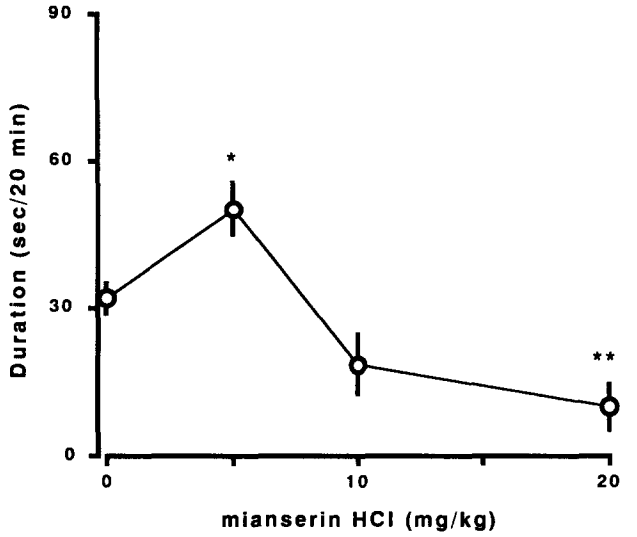

FIG. 4. Mianserin modulation of aggressive behavior in socially isolated mice. Mianserin HCl (5–20 mg/kg) or saline was IP injected 60 min before the experiments. The total duration of aggressive behavior during a 20-min observation period was measured. Each point and bar represents a mean ± SEM from seven to nine pairs of animals. $*p < 0.05$ and $**p < 0.01$ compared to the saline control value (Mann-Whitney *U*-test).

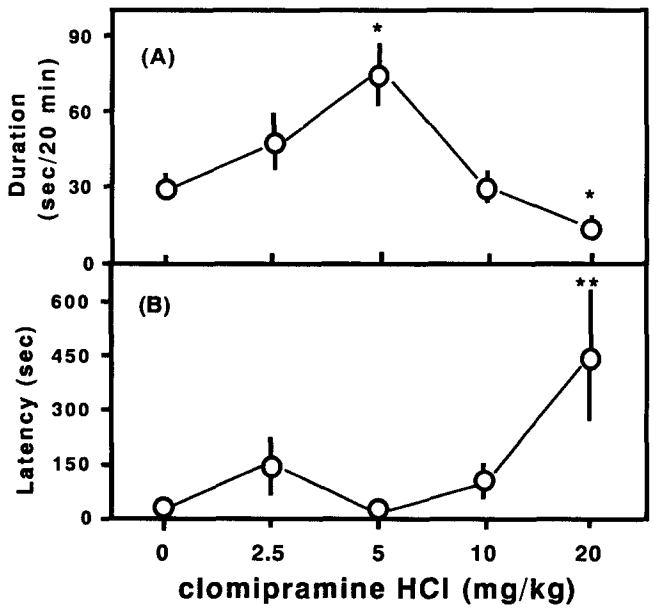

FIG. 3. Clomipramine modulation of aggressive behavior in socially isolated mice. Clomipramine HCl (2.5–20 mg/kg) or saline was IP injected 60 min before the experiments. Duration (A) and the latency to the first attack (B) were measured as described in the text. Each datum represents a mean ± SEM from seven pairs of animals. $*p < 0.05$ and $**p < 0.01$ compared to the respective saline control values (Mann-Whitney *U*-test).

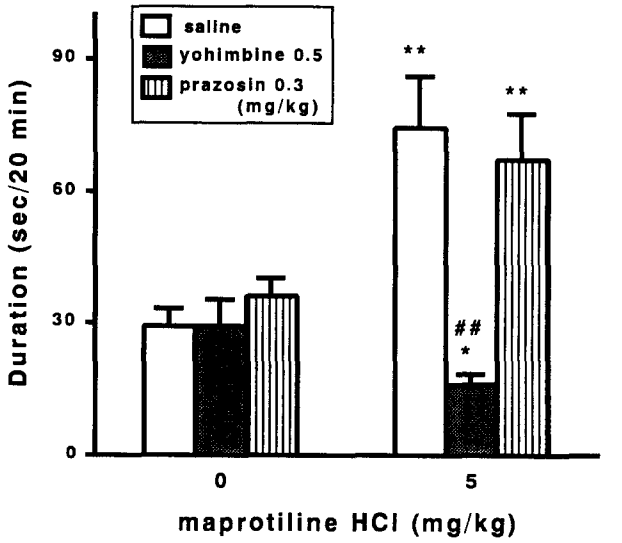

FIG. 5. Effect of yohimbine and prazosin on maprotiline-induced increase in aggressive behavior in isolated mice. Maprotiline HCl (5 mg/kg, IP) or saline was injected 60 min before the experiments. Yohimbine HCl (0.5 mg/kg, IP) or saline was injected 40 min after maprotiline. Prazosin HCl (0.3 mg/kg, IP) but not saline was injected immediately after maprotiline. The total duration of aggressive behavior during a 20-min observation period was measured. Each bar height represents a mean ± SEM of six to seven pairs of mice. $*p < 0.05$, $**p < 0.01$ compared to control animals given saline alone. $\#\#p < 0.01$ compared to animals given maprotiline alone (Mann-Whitney *U*-test).

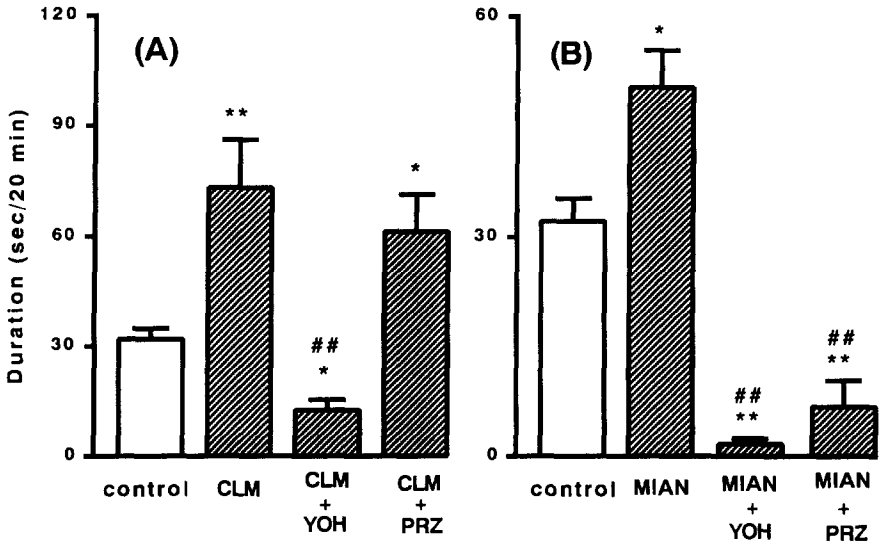

FIG. 6. Effect of yohimbine and prazosin on clomipramine (5 mg/kg)- and mianserin (5 mg/kg)-induced increases in aggressive behavior in socially isolated mice. Clomipramine HCl (CLM, 5 mg/kg, IP) (A), mianserin HCl (MIAN, 5 mg/kg) (B), or saline was injected 60 min before the experiments. Yohimbine HCl (YOH, 0.5 mg/kg) or saline was IP injected 40 min after the antidepressant. Prazosin HCl (PRZ, 0.3 mg/kg, IP) but not saline was injected immediately after the antidepressant. The total duration of aggressive behavior during a 20-min observation period was measured. Each bar height represents a mean ± SEM of seven pairs of mice. $*p < 0.05$, $**p < 0.01$ compared to control animals. $\#\#p < 0.01$ compared to animals given either clomipramine or mianserin alone (Mann–Whitney *U*).

Effects of Antidepressants on Spontaneous Motor Activity

Consistent with our previous report, the level of spontaneous motor activity in isolated mice was higher than that in group-housed animals (Fig. 7). Amitriptyline significantly decreased spontaneous motor activity in isolated animals at 20 mg/kg, a dose that almost completely eliminated AGB. In addition, as summarized in Table 1, when mianserin (20 mg/kg), maprotiline (10 mg/kg), and clomipramine (20 mg/kg) were given at doses that either decreased or had no effect on AGB only mianserin significantly decreased spontaneous motor activity in isolated mice. Neither mianserin (5 mg/kg), yohimbine (0.5 mg/kg), nor prazosin (0.3 mg/kg) affected spontaneous motor activity in isolated animals. However, the spontaneous motor activity in animals treated with prazosin plus mianserin, but not yohimbine plus mianserin, was significantly lower than in those given 5 mg/kg mianserin alone (Fig. 8).

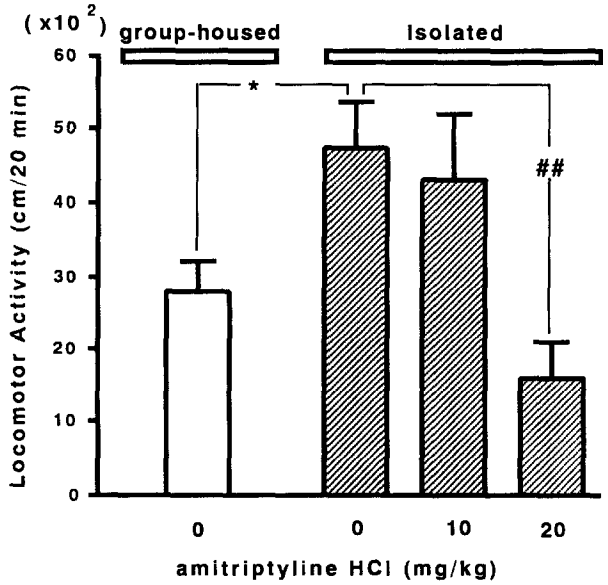

FIG. 7. Effect of amitriptyline on spontaneous motor activity in socially isolated mice. Amitriptyline HCl (10–20 mg/kg) or saline was IP injected into mice that were isolated for 6–7 weeks. Sixty minutes after injection, the mouse was placed in a doughnut-shaped cage and changes in locomotor activity were measured for 20 min. Each bar height represents a mean value ± SEM of 10 mice. $*p < 0.05$ compared to group-housed animals. $\#\#p < 0.01$ compared to isolated animals given saline (Duncan's multiple-range test).

DISCUSSION

The present data clearly show that three typical antidepressants, maprotiline, amitriptyline, and clomipramine, and an atypical antidepressant, mianserin, have biphasic effects on AGB in isolated mice, that is, they can increase and decrease AGB. They also show that increase in aggression caused by these drugs is mediated by NA stimulation of α_2-adrenoceptors, whereas the inhibition may be mediated by non-α_2-adrenoceptors or by nonadrenergic system(s).

We measured two parameters, the duration of AGB and the latency to the first attack. The latency to the first attack was variable and seemed to be prolonged only in parallel with decreases in the duration of AGB. These observations indicate that the duration of AGB is more sensitive than the latency to

TABLE 1

EFFECTS OF HIGH DOSES OF MAPROTILINE, CLOMIPRAMINE AND MIANSERIN, ON LOCOMOTOR ACTIVITY IN ISOLATED MICE

Drug	Dose (mg/kg)	Locomotor Activity (% control)
Saline (control)		100.0 ± 15.5
Maprotiline	10	81.6 ± 15.1
Clomipramine	20	81.4 ± 20.8
Mianserin	20	24.7 ± 4.1*

Maprotiline HCl (10 mg/kg), clomipramine HCl (20 mg/kg), or mianserin HCl (20 mg/kg) was IP injected into isolated mice. After 60 min, each mouse was placed in a doughnut-shaped cage and changes in locomotor activity were measured for 20 min. Each datum is a mean value obtained from 10 mice. The SEM is also indicated.
*$p < 0.01$ compared to the saline-treated control.

the first attack to the effects of drugs on AGB in isolated mice.

Maprotiline, amitriptyline, and clomipramine are known to selectively antagonize NA uptake in the following order: maprotiline > amitriptyline > clomipramine (1,12,24,25, 31). However, despite this difference all these antidepressants had biphasic effects on AGB in isolated mice. These data

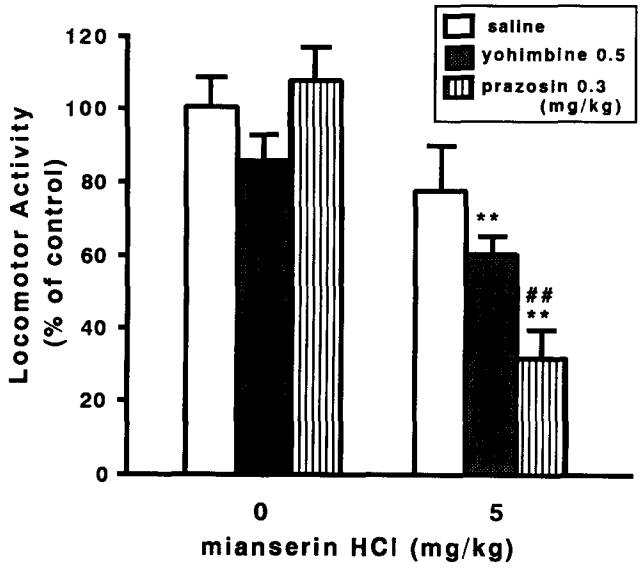

FIG. 8. Effects of coadministration of mianserin with prazosin and yohimbine on spontaneous motor activity in socially isolated mice. Mianserin HCl (5 mg/kg) or saline was IP injected into isolated mice 60 min before the experiments. Yohimbine HCl (0.5 mg/kg, IP) or saline was injected 40 min after mianserin. Prazosin HCl (0.3 mg/kg, IP) but not saline was injected immediately after mianserin. Each mouse was placed in a doughnut-shaped cage and changes in locomotor activity were measured for 20 min. The mean of locomotor activity in the group given saline was expressed as 100%. Each bar height represents a mean ± SEM of 10 mice. **$p < 0.01$ compared to the group given saline. ##$p < 0.01$ compared to the group given mianserin alone (Duncan's multiple-range test).

suggest that these antidepressants share a common mechanism responsible for their effects on AGB in isolated animals.

Yohimbine, a specific α_2-adrenoceptor antagonist, but not prazosin, a specific α_1-adrenoceptor antagonist, blocked the maprotiline-induced increase in AGB, which indicates that α_2-adrenoceptor stimulation by NA is involved in the increase in AGB caused by maprotiline (5 mg/kg) in isolated mice. These observations are consistent with our previous report that the increase in AGB caused by desipramine, an NA uptake blocker, is mediated by α_2- not α_1-adrenoceptors. Long-term isolation has been reported to decrease NA synthesis in the brain (18,28). Our previous report (16) suggested the possibilities that decrease in NA synthesis during the isolation period may induce a supersensitive state of α_2-adrenoceptor and that these plastic changes in noradrenergic transmission may relate to desipramine enhancement of AGB. The present findings also support such possibilities. Further, it is noteworthy that despite the more selective blocking effect on 5-HT rather than on NA uptake in vitro (24,25) the clomipramine (5 mg/kg)-induced increase in AGB was clearly blocked by yohimbine but not by prazosin. This effect of yohimbine in isolated animals indicates that the increase in aggression caused by clomipramine is mediated by NA rather than by 5-HT, also true of maprotiline. The present results do not completely exclude the possibility that 5-HT may be involved in the clomipramine enhancement of aggressive behavior because yohimbine is also thought to be an antagonist of 5-HT (10). However, the involvement of NA in the effect of clomipramine is also indicated by previous data that shows administration of clomipramine in vivo can inhibit both NA and 5-HT uptake into brain synaptosomes in vitro (12).

Our previous data (16) show that both desipramine and imipramine increase AGB in isolated mice at 5–20 and 10–20 mg/kg, respectively. However, all the antidepressants tested in the present study decreased the duration of AGB in isolated mice at high doses, although there were some differences in potency of these effects. Several factors may explain the inhibitory effects of these antidepressant drugs on AGB in isolated mice. First, a nonspecific sedative action could decrease the duration of AGB. Amitriptyline and mianserin significantly decreased spontaneous motor activity in isolated animals at the same doses that decreased AGB. Second, other neuronal mechanisms could be involved in this effect. This is supported by the findings that 10 mg/kg maprotiline and 20 mg/kg clomipramine not only decreased the duration of AGB but also significantly increased the first attack latency without affecting spontaneous motor activity in isolated mice. These typical antidepressant drugs have been shown to partially block 5-HT uptake mechanisms and cholinergic activity in addition to inhibiting NA uptake (3,12,19,24,25). Therefore, serotonergic or cholinergic systems, or both, may be involved in the decrease in AGB. Indeed, recent data reported by White et al. (30) show that both the 5-HT_2 antagonist ritanserin and serotonergic drugs that are active at the 5-HT_{1A} receptor selectively antagonize isolation-induced AGB in mice at doses below those that produce debilitation in the rotarod motor coordination test. Further, anticholinergic drugs have been shown to inhibit isolation-induced AGB in mice (8).

Yohimbine (0.5 mg/kg, IP) completely blocked the increase in aggression caused by maprotiline (5 mg/kg) and clomipramine (5 mg/kg) and decreased the duration of AGB to below the control level without affecting the basal level of AGB. This indicates that α_2-adrenoceptors mediate increases in AGB but other receptors mediate inhibition of AGB and that α_2-adrenoceptor-mediated increase in AGB may mask the

inhibitory effects of antidepressant drugs on aggression. These different neuronal mechanisms may underlie the biphasic effects of the three typical antidepressants tested.

The atypical antidepressant mianserin had biphasic effects on AGB that were similar to those of amitriptyline, a typical antidepressant. The increase in AGB caused by a low dose of mianserin is in contrast to the inhibitory effect of clonidine, an α_2-autoreceptor agonist, in isolated mice (16) and seems to be closely related to its antagonistic action at α_2-autoreceptors (11). In the present study, the increase in aggression caused by mianserin (5 mg/kg) was blocked by yohimbine, an α_2-receptor antagonist. The exact mechanisms of interaction between these two α_2-antagonists on the isolation-induced aggressive behavior remain unclear. However, recent study using brain microdialysis technique (11) has shown that yohimbine increases NA release at doses higher than that used in the present study. Further, yohimbine stimulation of NA release accompanies the increase in 3,4-dihydroxyphenylethyleneglycol (DOPEG), one of the major metabolites of NA, whereas mianserin stimulation of NA release either does not affect DOPEG level or accompanies the decrease of DOPEG. Together, the present data suggest that the sites sensitive to yohimbine in vivo are not always the same as those sensitive to mianserin and clonidine (16).

In contrast to its effects on maprotiline- and clomipramine-induced increases in AGB, prazosin significantly decreased the mianserin-induced increase in the duration of AGB to below the control level, also an effect of yohimbine. However, this apparent antagonism between mianserin and prazosin does not seem to reflect α_1-adrenoceptor involvement in the mianserin-induced increase in AGB but rather is due to prazosin enhancement of the sedative action of mianserin because prazosin but not yohimbine further reduced the locomotor activity decreased by mianserin. Nevertheless, the exact mechanisms underlying the apparent antagonism between prazosin and mianserin in isolation-induced AGB require further study.

ACKNOWLEDGMENTS

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REFERENCES

1. Baumann, P. A.; Maitre, L. Neurobiochemical aspects of maprotiline (Ludiomil) action. J. Int. Med. Res. 7:391–400; 1979.
2. Bell, R.; Hepper, P. G. Catecholamine and aggression in animals. Behav. Brain Res. 23:1–21; 1987.
3. Bohman, B. D.; Karbowski, M. J.; Halaris, A. E. Central cholinergic effects of tricyclic antidepressants in mouse. Arch. Int. Pharmacodyn. Ther. 255:68–80; 1982.
4. Eichelman, B. The catecholamines and aggressive behavior. Neurosci. Res. 5:109–129; 1973.
5. Eichelman, B.; Barchas, J. Facilitated shock-induced aggression following antidepressive medication in the rat. Pharmacol. Biochem. Behav. 3:601–604; 1975.
6. Frances, H.; Lienard, C. Isolation-induced social behavioral deficit test: Effect of tranquilizing drugs. Pharmacol. Biochem. Behav. 34:293–296; 1989.
7. Gandolfli, O.; Barbaccia M. L.; Costa, E. Different effects of serotonin antagonists on ^{3}H-mianserin and ^{3}H-ketanserin recognition sites. Life Sci. 36:713–721, 1985.
8. Herbut, M.; Rolinski, Z. The cholinergic influences on aggression in isolated mice. Pol. J. Pharmacol. Pharm. 37:1–10; 1985.
9. Hodge, G. K.; Butcher, L. L. Catecholamine correlates of isolation-induced aggression in mice. Eur. J. Pharmacol. 31:81–93; 1975.
10. Hoffman, B. B.; Lefkowiz, R. J. Adrenergic receptor antagonists. In: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. The pharmacological basis of therapeutics. New York: Pergamon Press; 1990:221–243.
11. Itoh, Y.; Oishi, R.; Nishibori, M.; Saeki, K. In vivo measurement of noradrenaline and 3,4-dihydroxyphenylethyleneglycol in the rat hypothalamus by microdialysis: Effects of various drugs affecting noradrenaline metabolism. J. Pharmacol. Exp. Ther. 255: 1090–1097; 1990.
12. Manias, B.; Taylor, D. A. Inhibition of in vitro amine uptake into rat brain synaptosomes after in vivo administration of antidepressants. Eur. J. Pharmacol. 95:305–309; 1983.
13. Matsumoto, K.; Cai, B.; Nakamura, S.; Watanabe, H. A new system for the measurement and analysis of motor activity: Effect of several central stimulants. Folia Pharmacol. Japon. 96:31–39; 1990.
14. Matsumoto, K.; Cai, B.; Ohta, H.; Imamura L.; Watanabe, H. Apparent enhancement by SCH 23390 of apomorphine-induced locomotor activity in mice. Pharmacol. Biochem. Behav. 39:699–703; 1991.
15. Matsumoto, K.; Cai, B.; Sasaki, K.; Watanabe, H. Methamphetamine- and apomorphine-induced changes in spontaneous motor activity using a new system to detect and analyze motor activity in mice. J. Pharmacol. Meth. 24:312–320; 1990.
16. Matsumoto, K.; Cai, B.; Satoh, T.; Ohta, H.; Watanabe, H. Desipramine enhances isolation-induced aggressive behavior in mice. Pharmacol. Biochem. Behav. 39:167–170; 1991.
17. Modigh, K. Effects of isolation and fighting in mice on the rate of synthesis of noradrenaline, dopamine and 5-hydroxytryptamine in the brain. Psychopharmacologia 33:1–17; 1973.
18. Mogilnicka, E. REM sleep deprivation changes behavioural responses to catecholaminergic and serotonergic receptor activation in rats. Pharmacol. Biochem. Behav. 15:149–151; 1981.
19. Muck-Seler, D.; Deanovic, Z.; Jamnicky, B.; Jakupcevic, M.; Mihovilovic, M. Maprotiline in the treatment of endogenous depression: Comparison of therapeutic effect with serotonin level in blood platelets. Psychopharmacology (Berl.) 79:262–265; 1983.
20. North, R. A.; Uchimura, N. 5-Hydroxytryptamine acts at 5-HT$_2$ receptors to decrease potassium conductance in rat nucleus accumbens neurons. J. Physiol. 417:1–12; 1989.
21. Rolinski, Z. Pharmacological studies on isolation-induced aggressiveness in mice in relation to biogenic amines. Pol. J. Pharmacol. 27:37–44; 1975.
22. Rose, A.; McCulloch, M. W.; Sarantos-Laska, C.; Rand., M. J. Effects of mianserin on noradrenergic mechanisms. J. Psychiat. Res. 18:79–88; 1984.
23. Ross, S. B.; Ogren, S.-O. Anti-aggressive action of dopamine-β-hydroxylase inhibitors in mice. J. Pharm. Pharmacol. 28:590–592; 1976.
24. Ross, S. B.; Renyi, A. L. Tricyclic antidepressant agents. I. Comparison of the inhibition of the uptake of ^{3}H-noradrenaline and ^{14}C-5-hydroxytryptamine in slices and crude synaptosome preparations of the midbrain–hypothalamus region of the rat brain. Acta Pharmacol. Toxicol. 36:382–394; 1975.
25. Ross, S. B.; Renyi, A. L. Tricyclic antidepressant agents. II. Effect of oral administration on the uptake of ^{3}H-noradrenaline and ^{14}C-5-hydroxytryptamine in slices of the midbrain–hypothalamus region of the rat. Acta Pharmacol. Toxicol. 36:395–408; 1975.
26. Sofia, R. D. Effects of centrally active drugs on four models of experimentally-induced aggression in rodents. Life Sci. 8:705–716; 1969.
27. Tizabi, Y.; Massari, V. J.; Jacobowitz, D. M. Isolation induced aggression and catecholamine variations in discrete brain areas of the mouse. Brain Res. Bull. 5:81–86; 1980.

28. Valzelli, L. The isolation syndrome in mice. Psychopharmacologia 31:305–320; 1973.
29. Welch, A. S.; Welch, B. L. Isolation, reactivity and aggression: Evidence for an involvement of brain catecholamines and serotonin. In: Eleftheriou, B. E.; Scott, J. P., eds. The physiology of aggression and defeat. New York: Plenum Press; 1971:99–142.
30. White, S. M.; Kucharik, R. F.; Moyer, J. A. Effects of serotonergic agents on isolation-induced aggression. Pharmacol. Biochem. Behav. 39:729–736; 1991.
31. Wyllie, M. G.; Wood, M. D.; Moser, P. C. Assessment of noradrenaline and 5-hydroxytryptamine uptake in intact rat brain. J. Neurochem. 45:456–460; 1985.