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Desipramine Enhances Isolation-Induced Aggressive Behavior in Mice

KINZO MATSUMOTO, BING CAI, TAKASHI SATOH, HIROYUKI OHTA AND HIROSHI WATANABE[1]

Section of Pharmacology, Research Institute for Wakan-Yaku (Oriental Medicines)
Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama-shi, Toyama 930-01, Japan

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MATSUMOTO, K., B. CAI, T. SATOH, H. OHTA AND H. WATANABE. *Desipramine enhances isolation-induced aggressive behavior in mice.* PHARMACOL BIOCHEM BEHAV **39**(1) 167–170, 1991.—Effects of desipramine on aggressive behavior induced by long-term (6–7 weeks) isolation of mice were examined. Aggressive behavior was measured as duration of biting attack and/or wrestling during a 20-min observation period. Desipramine (5, 10 and 20 mg/kg, IP) and imipramine (10 and 20 mg/kg, IP) dose-dependently increased the duration of aggressive behavior in isolated mice, without inducing aggressive behavior in group-housed animals. Desipramine-induced increase in aggressive behavior was blocked by phentolamine (3 mg/kg, IP) and yohimbine (0.3 mg/kg, IP), but not prazosin (0.5 mg/kg, IP). Clonidine (0.001 mg/kg, IP), an α_2 agonist, significantly blocked desipramine-induced enhancement of aggressive behavior in isolated mice without affecting the basal aggression. These data suggest that long-term isolation may induce functional changes in the sensitivity of α_2 receptor in the noradrenergic system and that desipramine enhancement of aggressive behavior in isolated mice is modulated by drugs acting onto α_2 noradrenergic receptors.

Aggressive behavior Isolation Desipramine Imipramine Clonidine α_1-Adrenoceptors α_2-Adrenoceptors Mice

A variety of methods including lesioning of specific areas of the brain, stressful manipulations such as foot shock, pharmacological manipulations using clonidine, and individual housing of animals have been shown to induce aggressive behavior in non-aggressive laboratory animals (1). Changes in behavioral responses induced by isolation of mice have been extensively studied and used as an animal model for elucidating drug actions on aggression and/or social behavioral deficits (3, 16, 19). Several neuronal pathways which use noradrenaline (NA), dopamine (DA) or 5-hydroxytryptamine (5-HT) have been suggested to be involved in the behavioral changes induced by isolation of animals (4, 9, 15). For example, isolated mice show an increase in brain DA turnover (22). Furthermore, the rate of brain NA synthesis in isolated mice is reported to be lower than that in group-housed animals, although these findings are controversial (19,24). However, little is known about the neuronal basis of aggression induced by isolation.

The present study examined the effects of desipramine, a NA reuptake blocker, on isolation-induced aggressive behavior, to further clarify the functional changes in the noradrenergic system during the period of long-term isolation.

METHOD

Isolated Housing

Male ddY mice, weighing approximately 18–20 g, were obtained from SLC Co., Shizuoka, at the age of 28 days old. Mice were either housed in groups of five in cages of 24 × 17 × 12 cm or isolated in the same size cage for 6–7 weeks. Housing conditions were thermostatically maintained at 22 ± 1°C, with a 12-h light/dark cycle. Food and water were given ad lib.

Measurement of Aggressive Responses

When testing aggressive behavior 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 the same size as their home cage. Duration of biting attacks and/or wrestling observed during a 20-min observation period was measured. Effects of drugs on aggressive behavior were evaluated using 5 to 9 pairs of mice per group.

Measurement of Spontaneous Motor Activity

Spontaneous motor activity in mice was measured using a system described in detail in our previous reports (7,8) or Animate (MATYS, Toyama, Japan), which is mechanically the same as ours. Briefly, 60 min after administration of desipramine, mice were placed into the doughnut-shaped cages and changes in parameters (total activity, locomotor activity and No.

[1]Requests for reprints should be addressed to H. Watanabe, Ph.D., Section of Pharmacology, Research Institute for Wakan-yaku, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama-shi, Toyama 930-01, Japan.

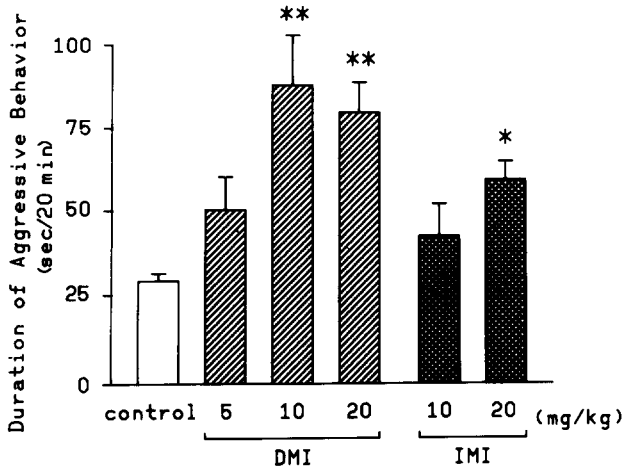

FIG. 1. Desipramine- and imipramine-induced enhancement of aggressive behavior in isolated mice. Mice were injected with either saline, desipramine (DMI) or imipramine (IMI) 60 min before tests. Fighting duration was measured as described in the text. Each datum represents the mean ± S.E.M. from 6–7 pairs of animals. *$p<0.05$, **$p<0.01$, compared to the respective saline control values.

of rearings) of spontaneous motor activity were measured and accumulated for 20 min. Animal movements were detected by scanning 36 photosensor units which were radially arranged from the center of the cage.

Drugs

Drugs were intraperitoneally injected to each mouse 60 min before experiments except for specifically stated cases. Drugs used were as follows: desipramine HCl (5, 10 and 20 mg/kg; Fujisawa Pharm. Co. Ltd.), imipramine HCl (10 and 20 mg/kg) and phentolamine mesylate [3 and 10 mg/kg; CIBA GEIGY (Japan) Ltd.], yohimbine HCl (0.03, 0.1 and 0.3 mg/kg; Nakarai Chem. Ltd.), prazosin HCl (0.3 and 0.5 mg/kg) and clonidine HCl (0.001, 0.003, 0.1 and 30 mg/kg) (Sigma).

Statistics

The results were analyzed using the Kruskal-Wallis test for nonparametric data, followed by the Mann-Whitney U-test for subsequent multiple comparisons between groups and one-way analysis of variance with Duncan's multiple range test.

RESULTS

Enhancement of Isolation-Induced Aggressive Behavior

As shown in Fig. 1, the aggressive behavior observed in isolated mice during a 20-min period was about 30–40 s in duration. Desipramine (5–20 mg/kg) administration markedly increased the duration of aggressive behavior by 80–90%. Imipramine, at a dose of 20 mg/kg, slightly but significantly increased the duration of aggressive behavior in isolated animals. In contrast to the effects on isolated animals, desipramine (20 mg/kg) neither induced aggressive behavior in group-housed mice nor changed any parameters (total activity, locomotor activity and No. of rearings) of spontaneous motor activity stimulated by long-term isolation of mice (Table 1). Pretreatment of isolated animals with phentolamine (3 mg/kg, IP), a nonspecific α-adrenoceptor blocker, significantly blocked desipramine

TABLE 1

EFFECTS OF DESIPRAMINE ON SPONTANEOUS MOTOR ACTIVITY IN ISOLATED MICE

Mice	Desipramine (mg/kg)	Parameters: Total Activity (counts/20 min)	Locomotor Activity (cm/20 min)	No. of Rearings (counts/20 min)
Group-housed	0	2239 ± 265	2536 ± 360	109 ± 23
Isolated	0	4623 ± 200*	5505 ± 323*	284 ± 20*
	20	4976 ± 254*	5839 ± 526*	270 ± 29*

Desipramine (20 mg/kg) was intraperitoneally injected to mice which were isolated for 6–7 weeks. Sixty min after injection, a mouse was put into the doughnut-shaped cage and changes in parameters such as total activity, number of rearings and locomotor activity were measured for 20 min. Each datum represents the mean value obtained from 10 mice, with the S.E.M. indicated. *$p<0.01$ compared to the group-housed mice (Duncan's multiple range test).

(10 mg/kg)-induced enhancement of the duration of aggressive behavior without affecting the basal aggression (Fig. 2). Prazosin, a specific α_1 antagonist, significantly decreased the basal duration of aggressive behavior at 0.5 mg/kg, but this antagonist did not affect the effect of desipramine (10 mg/kg) on the aggressive behavior in isolated mice (Fig. 3). In contrast to prazosin, yohimbine (0.1 and 0.3 mg/kg), an α_2 antagonist, significantly reduced the duration of aggressive behavior enhanced by 10 mg/kg desipramine to the control level, whereas this agent did not affect the basal aggression at the same range of dosages (Fig. 4).

Effect of Clonidine on Desipramine-Induced Increase in Aggressive Behavior in Isolated Mice

In contrast to desipramine, clonidine, a specific α_2-adrenoceptor agonist, decreased the duration of aggressive behavior in

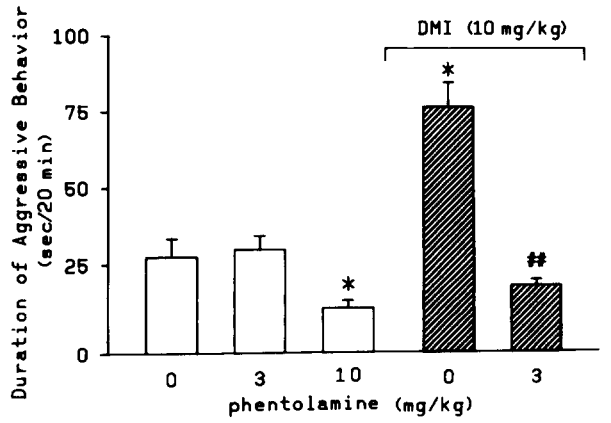

FIG. 2. Effects of phentolamine on desipramine enhancement of aggressive behavior in isolated mice. Animals were pretreated with either saline or desipramine (DMI) (10 mg/kg, IP) 60 min before the experiments. Either saline or phentolamine mesylate was intraperitoneally injected 50 min after desipramine administration. Each datum represents the mean ± S.E.M. of 5–8 pairs of mice. *$p<0.05$, compared to the drug-untreated control. ##$p<0.01$, compared to desipramine alone.

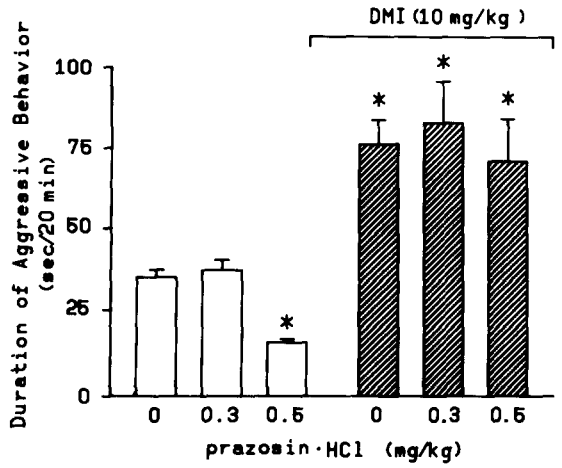

FIG. 3. Effects of prazosin on desipramine enhancement of aggressive behavior in isolated mice. Animals were pretreated with either saline or desipramine (DMI) (10 mg/kg, IP) 60 min before the experiments. Either saline or prazosin·HCl was intraperitoneally injected immediately after desipramine administration. Each datum represents the mean ± S.E.M. of 6–9 pairs of mice. *$p<0.05$, compared to the drug-untreated control.

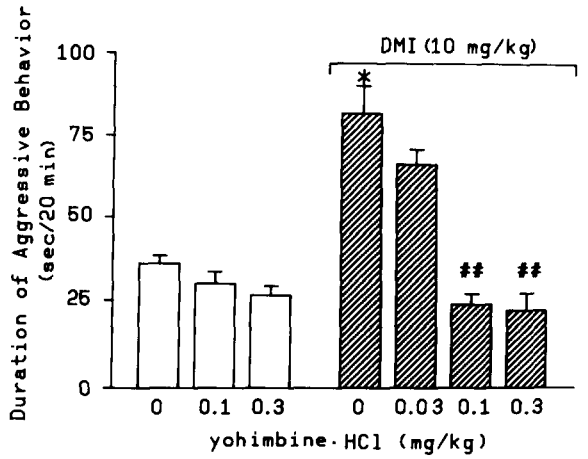

FIG. 4. Effects of yohimbine on desipramine enhancement of aggressive behavior in isolated mice. Animals were pretreated with either saline or desipramine (DMI) (10 mg/kg, IP) 60 min before the experiments. Either saline or yohimbine·HCl was intraperitoneally injected 40 min after desipramine administration. Each datum represents the mean ± S.E.M. of 6–9 pairs of mice. *$p<0.05$, compared to the drug-untreated control. ##$p<0.01$ compared to desipramine alone.

isolated mice in a dose-dependent manner (Fig. 5A), whereas it induced aggressive behavior in group-housed mice at higher doses (≥30 mg/kg) (data not shown). However, a lower dosage of clonidine (0.001 mg/kg), which did not affect the behavior in either isolated or group-housed mice, significantly blocked desipramine (10 mg/kg)-induced enhancement of aggressive behavior in isolated mice (Fig. 5B).

DISCUSSION

The present study clearly demonstrates that stimulation of α_2-adrenoceptors participates in desipramine-induced enhancement of aggressive behavior in isolated mice. In spite of the proposed role of catecholamines in this aggressive behavior, the effects of catecholamine-related drugs on the aggressive behavior induced by isolation are controversial. Sofia (16) reported that both desipramine and imipramine decreased isolation-induced aggression in mice with ED_{50} values of 17.2 and 21.7 mg/kg (IP), respectively. In contrast to his observations, we found that at dosages of 10–20 mg/kg, desipramine markedly increased rather than decreased the duration of aggressive behavior in long-term isolated mice. The discrepancy between his and our findings remains unclear, but it may be due to the differences between the analyzing methods of aggressive behavior and/or animal strains used. Nevertheless, stimulatory effects of desipramine on isolation-induced aggressive behavior seem to relate to its pharmacological but not nonspecific neurotoxic effects, since this drug did not induce aggressive behavior in group-housed mice nor affect the spontaneous motor activity, which was increased by long-term isolation of mice, at a dose of 20 mg/kg.

Desipramine and imipramine both increased the duration of aggressive behavior in isolated animals in a dose-dependent manner. However, the stimulatory effect of the former was more potent than that of the latter. These results suggest that desipramine enhancement of isolation-induced aggressive behavior may be mediated by NA accumulated in the catecholaminergic synaptic cleft, since desipramine has been shown to be a more preferential blocker of NA reuptake mechanisms in central noradrenergic transmission than imipramine (14). This possibility is further supported by the finding that phentolamine (3 mg/kg,IP), a nonselective α-receptor blocker, decreased the effect of desipramine without affecting the duration of aggressive behavior by itself. The hypothesis that NA accumulation may be involved in the enhancement of aggressive behavior in isolated mice might explain the results reported by Poshivalov (12) that low doses of DOPA appeared to increase the aggression. Furthermore, desipramine enhancement of the duration of aggressive behavior appears to be due to stimulation of α_2-receptors by excessive NA, because yohimbine, an α_2-receptor blocker, but not prazosin, a selective α_1-receptor blocker, antagonized the effect of desipramine in a dose-dependent manner. It has been postulated that most drugs which potentiate or decrease noradrenergic transmission in the brain, more or less affect the aggressive behavior in isolated mice at higher doses which influence either rotarod performance or spontaneous motor activity (1, 5, 13, 16). However, this does not seem to be the case in the present study, since none of the α-receptor antagonists tested affected the duration of aggressive behavior in isolated animals at dosages which significantly decreased the effect of desipramine.

In agreement with other reports (13,16), clonidine decreased the duration of aggressive behavior in isolated mice in a dose-dependent manner (ED_{50} >0.003 mg/kg), but at higher doses over 10 mg/kg, it induced aggressive behavior in nonaggressive group-housed animals. These effects of clonidine have been suggested to be dependent on the range of dosages used and to be mediated by different neuronal mechanisms (2, 6, 11, 21). The present findings indicate that clonidine blocks desipramine (10 mg/kg)-induced enhancement of aggressive behavior in isolated mice at a much lower dosage (0.001 mg/kg) than those required to affect the basal aggression and/or behavior in isolated or group-housed mice. The fact that clonidine, a selective α_2 agonist, blocked desipramine-induced enhancement of aggressive behavior in isolated mice in a similar way with yohimbine, a selective α_2 antagonist, seems difficult to understand. While the discrepancy remains unclear, a speculative explanation is that in isolated mice, NA accumulated by desipramine pretreatment may stimulate different types of α_2 receptors which have different localization (20) and/or affinities to clonidine and/or yohim-

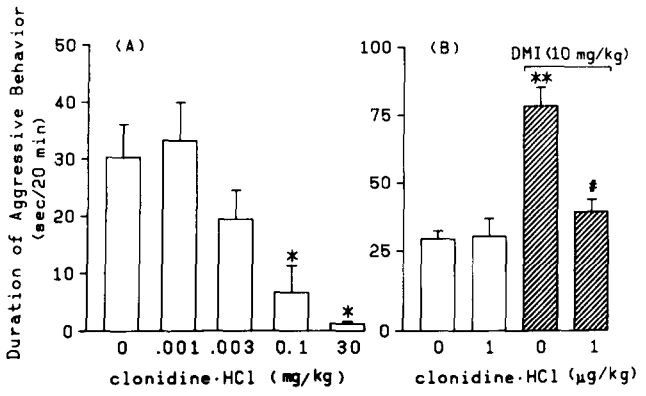

FIG. 5. Effects of clonidine on basal aggressive behavior (A) and desipramine-induced enhancement of aggressive behavior (B) in isolated mice. (A) Either clonidine·HCl or saline was intraperitoneally injected 10 min before the experiments. (B) Animals were pretreated with either saline or desipramine (DMI) (10 mg/kg, IP) 60 min before the experiments. Either saline or clonidine·HCl (1 μg/kg, IP) was injected 10 min before the experiments. Each datum represents the mean ± S.E.M. of 6–7 pairs of mice. $*p<0.05$ and $**p<0.01$, compared to the respective drug-untreated control. $\#p<0.05$, compared to desipramine alone.

bine; e.g., one is postsynaptic and more sensitive to yohimbine and the other presynaptic and less sensitive to yohimbine. It is well known that lower doses of clonidine selectively interact with α_2-autoreceptors, decreasing firing of NA neurons (18) and NA release from nerve terminals (17). Therefore, there is a possibility that these effects of clonidine may decrease the efficacy of desipramine in isolated mice and that yohimbine may block the stimulation of postsynaptic α_2 receptors by NA accumulated. These potential mechanisms remain to be clarified, however.

It is generally accepted that decrease in transmitter utilization by blocking of receptor sites and/or depletion of transmitters for a long-term period can induce receptor supersensitivity. On the other hand, long-term isolation of mice has been reported to decrease NA synthesis in the brain (10,23). Such plasticity of central adrenergic systems may explain the differences of drug action between group-housed and isolated mice. Blockade of α_2-receptors by yohimbine selectively antagonized the effect of desipramine on aggressive behavior in isolated mice, suggesting the possibility that α_2-adrenoceptor may be the primary target of plastic changes in noradrenergic transmission and that a decrease in NA synthesis may induce a supersensitive state of α_2-receptors during the isolation period. Nevertheless, the mechanisms underlying aggressive behavior induced by long-term isolation of mice and its enhancement by desipramine remain to be elucidated.

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