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# Role of Brain Norepinephrine in Neuroleptic-Induced Catalepsy in Rats

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HONMA, T. AND H. FUKUSHIMA. *Role of brain norepinephrine in neuroleptic-induced catalepsy in rats.* PHARMAC. BIOCHEM. BEHAV. 7(6) 501–506, 1977. – Bis (4-methyl-1-homopiperazinylthiocarbonyl) disulfide (FLA 63) and diethyldithiocarbamate enhanced the catalepsy induced by haloperidol in rats. The norepinephrine (NE) content of the diencephalon in rats treated with haloperidol and FLA 63 was less than that in rats treated with haloperidol alone. The dopamine (DA) decrease in the striatum of haloperidol-treated rats was not altered by FLA 63. Intraperitoneally or intraventricularly administered phentolamine enhanced the catalepsy induced by haloperidol, and clonidine counteracted this effect. Propranolol failed to change haloperidol-induced catalepsy. FLA 63 enhanced the catalepsy induced by ID-4708 (a new butyrophenone compound) by an extent greater than that caused by haloperidol. ID-4708 was more potent in increasing the NE turnover than haloperidol. The combined administration of ID-4708 and FLA 63 produced a greater decrease in the NE content than the combination of haloperidol and FLA 63. These results suggest that the neuroleptic-induced catalepsy would be facilitated when the activity of the NE neurons is lowered or when α-receptors are blocked. A decrease in the activity of DA neurons or the blockade of the DA receptors is essential to elicite catalepsy in rats, and the function of NE neurons would play a role in regulating the degree of catalepsy.

Catalepsy Dopamine Norepiniphrine Haloperidol ID-4708 Clonidine Phentolamine FLA 63 Diethyldithiocarbamate

NEUROLEPTICS induce catalepsy in laboratory animals, and this activity of neuroleptics may be an index for the extrapyramidal side effects elicited by neuroleptics in men [19,29]. High doses of neuroleptics decrease striatal dopamine (DA) content in rats [14,23], and this decrease appears to be related to the intensity and time-course of catalepsy [17]. It is known that Parkinson's disease is associated with a marked decrease of striatal DA content [4,12], thus extrapyramidal symptoms in men and the catalepsy in experimental animals may be due to a deficiency of striatal dopaminergic function. The catalepsy induced by neuroleptics is enhanced by α-methylparatyrosine [9, 10, 26]. Since α-methylparatyrosine reduces the content of both DA and NE [8,27], it is not clear whether the decrease of DA or that of NE enhances the neuroleptic-induced catalepsy.

In this paper, we have shown that drugs which relatively modify the function of NE neurons modify the neuroleptic-induced catalepsy in rats.

## METHOD

### *Animals and Experimental Conditions*

Male albino rats (Wistar strain), weighing 190–200 g, were used. They were allowed free access to food and water except during the testing procedures. All experiments were carried out in a room at 26 ± 1°C and 55 ± 5% humidity.

### *Assessment of Catalepsy*

Groups of 4–8 rats were used for assessment of catalepsy [17,30]. Both paws of the rat were put on a horizontal metal bar, 8.8 cm in height, and the rat was forced to rest on hind legs only. The duration of this abnormal position was measured, and the duration was regarded as an intensity of catalepsy. When catalepsy lasted for more than 300 sec, the duration was recorded as 300 sec. The mean and SEM of the duration of catalepsy were calculated. Doses and time schedules are specified in the RESULTS.

### *Measurement of Catecholamine Content*

Rats were decapitated with a guillotine. The brain was rapidly removed and on an ice-cold beaker dissected into 5 parts: striatum, diencephalon containing thalamus and hypothalamus, cerebellum, cortex and remaining brain. DA and NE contents in these brain regions except the remaining brain were measured after homogenization. The remaining brain was discarded. Catecholamines were extracted and estimated quantitatively with spectrophotofluorometric assay [6]. Recoveries of these catecholamines added to tissue homogenate ranged between 60 and 80% throughout the experiments. The catecholamine contents of the drug-treated rats were represented as percentages of the mean catecholamine content of the control group. Doses and time schedules are specified in the RESULTS.

### *Microinjection Experiments*

The rat was placed in a standard stereotaxic instrument

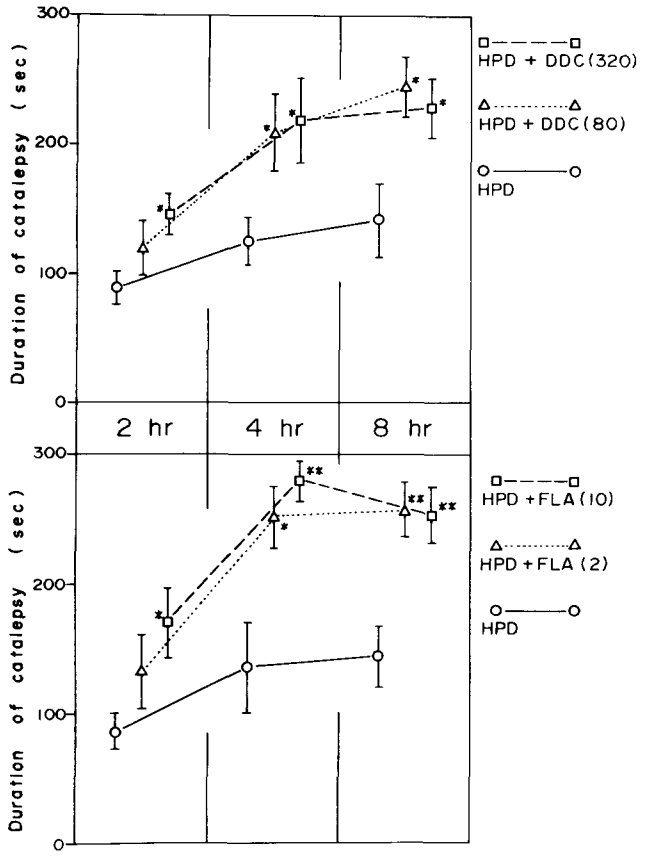


FIG. 1. Effects of diethyldithiocarbamate (upper graph) and FLA 63 (lower graph) on the duration of catalepsy induced by haloperidol in rats. FLA 63 (FLA, 2 or 10 mg/kg) or diethyldithiocarbamate (DDC, 80 or 320 mg/kg) was given IP to rats at 15 min after the SC administration of haloperidol (HPD, 5 mg/kg). Instead of FLA and DDC, a 5% gum arabic solution was given to control rats pretreated with HPD alone. The duration of catalepsy was measured at 2, 4 and 8 hr after the administration of haloperidol. The mean and SEM of the duration of catalepsy were calculated. The vertical bars represent ± SEM. The statistical significances of the differences between the groups of rats treated with HPD + gum arabic and HPD + FLA or DDC were calculated using Student's *t*-test. *: $0.05>p$. **: $0.01>p$.

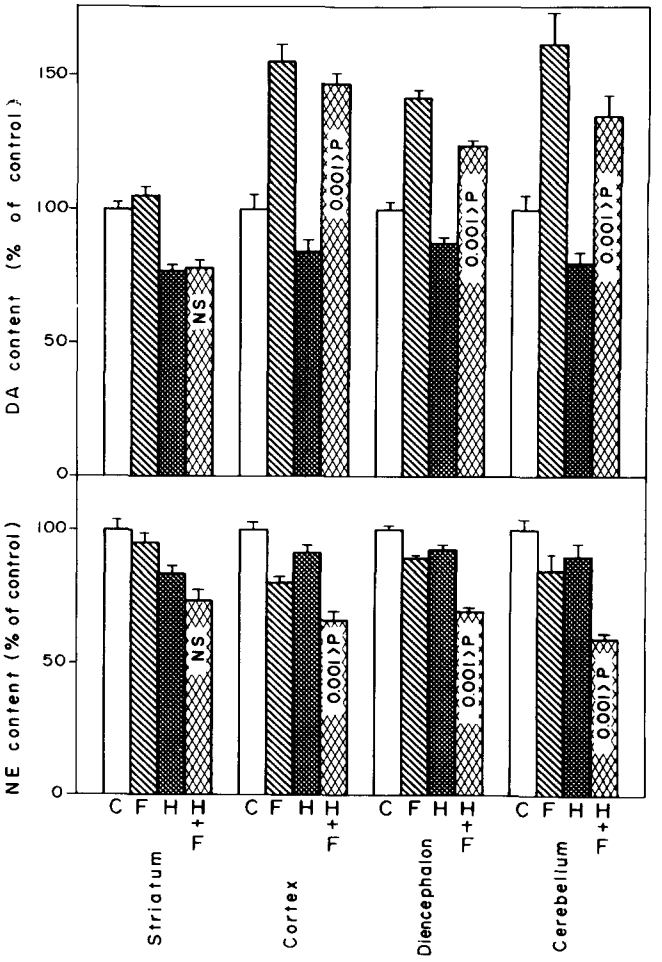


FIG. 2. Effects of FLA 63 and haloperidol (HPD) on the CA contents in 4 regions of rat brain. FLA 63 (2 mg/kg IP) was given to rats at 15 min after the administration of HPD (5 mg/kg SC). Rats were decapitated at 4 hr after the administration of HPD. CA contents are expressed as percentages of control groups. C: control. F: FLA 63. H: HPD. H+F: HPD + FLA 63. The vertical bars represent SEM. Statistical comparison was performed between H group and H+F group with *t*-test. NS: not significant. Mean DA contents of the striatum, cortex, diencephalon and cerebellum of control group were 7.10, 0.134, 0.353 and 0.075 μg/g tissue, respectively. Mean NE contents of these 4 regions of control group were 0.213, 0.379, 0.720 and 0.274 μg/g tissue, respectively.

under sodium pentobarbital (40 mg/kg IP) anesthesia. The skull was exposed, and a guide cannula made of 20 gauge stainless steel was chronically implanted on the right lateral ventricle: anterior 7.8 mm, lateral 1.2 mm, according to the coordinates of De Groot [11], and 4.0 mm ventral to the brain surface. The guide cannula was fixed to the skull bone with dental cement. At least 24 hr were allowed for recuperation before tests were made. A 10 μg phentolamine was dissolved in 5 μl physiological saline and injected to the right lateral ventricle through an injection cannula consisted of 27 gauge stainless steel pipe, which protruded a distance of 0.6 mm below the top of the guide cannula. The injection cannula was attached to a microsyringe with polyethylene tubing. The same volume of saline was intraventricularly given to control rats. The rate of infusion was 1 μl/min. After injection, the injection cannula remained in the place for 1 min.

*Drugs*

The following drugs were micronized prior to use and suspended in 5% gum arabic solution: Haloperidol, ID-4708 (a new butyrophenone compound, 4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]-2′-amino-4′-fluorobutyrophenone·HCl) [18] which were synthesized in our laboratory, and FLA 63 (K and K laboratories). The following drugs were dissolved in physiological saline: Diethyldithiocarbamate (Nakarai Kagaku), phentolamine (Ciba-Geigy), clonidine (Tanabe Seiyaku) and propranolol (ICI). All drugs were given to rats in a volume of 1 ml/100 g body weight except for the intraventricular administration. Doses of the drug are expressed in terms of base.

*Statistics*

Statistical comparison was performed with Student's *t*-test.

## RESULTS

### *Effects of FLA 63 and Diethyldithiocarbamate on the Catalepsy Induced by Haloperidol*

Groups of 8 rats were given haloperidol (5 mg/kg SC), and 15 min later received FLA 63 or diethyldithiocarbamate (DDC) IP. The duration of catalepsy was measured at 2, 4 and 8 hr after the administration of haloperidol. The mean durations of catalepsy in rats are shown in Fig. 1. The catalepsy induced by haloperidol was significantly enhanced by FLA 63 or DDC. FLA 63 at 10 mg/kg was more effective than at 2 mg/kg in enhancing the catalepsy. The enhancement of catalepsy by 320 mg/kg DDC was greater than that by 80 mg/kg DDC.

### *Effects of Haloperidol and FLA 63 on the Catecholamine Contents in the Rat Brain*

Each group of rats received haloperidol (5 mg/kg SC), and 15 min later was injected with FLA 63 (2 mg/kg IP). Rats were decapitated at 4 hr after the administration of haloperidol, and the contents of DA and NE in four parts of the brain were estimated. The mean catecholamine (CA) content of vehicle-treated control group was arbitrarily set to 100%. The mean CA contents of the drug-treated groups are shown in Fig. 2 as percentages of CA contents of control group. The administration of FLA 63 alone increased DA contents in the cortex, diencephalon and cerebellum by 42–61% and reduced NE contents in these 3 areas to 80–89% of CA contents of control animals. FLA 63 produced a 5% increase in DA and a 5% decrease in NE in the striatum compared to the CA contents of control rats. The fall in contents of DA and NE caused by haloperidol alone was the greatest in the striatum among the 4 brain regions. Treatment with FLA 63 did not alter the DA content in the striatum compared to that of animals given haloperidol alone. However, FLA 63 elevated DA levels in the cortex, diencephalon and cerebellum by 41–74% compared to those of haloperidol-treated animals. The combined administration of haloperidol and FLA 63 caused a greater fall in the NE contents in the 4 brain regions than the administration of haloperidol alone.

### *Effects of Clonidine, Phentolamine and Propranolol on the Catalepsy Induced by Haloperidol*

Groups of 8 rats were given haloperidol (2 mg/kg SC), and 4, 5 and 6 hr later the duration of catalepsy was measured. Clonidine (0.002 mg/kg), phentolamine (10 mg/kg) or propranolol (10 mg/kg) was given IP to rats at 30 min before the first assessment of catalepsy. Other groups of 4 rats with a guide cannula implanted in the right ventricle were injected with haloperidol (2 mg/kg SC), and 4, 5 and 6 hr later the duration of catalepsy was measured. A dose of 10 μg phentolamine was intraventricularly (IC) given to rats at 15 min before the first assessment of catalepsy. The mean durations of catalepsy are shown in Fig. 3. Clonidine significantly counteracted the catalepsy induced by haloperidol. On the other hand, phentolamine enhanced the catalepsy. Phentolamine given IC also enhanced the catalepsy, but the duration of its effect was short. Propranolol did not affect the catalepsy.

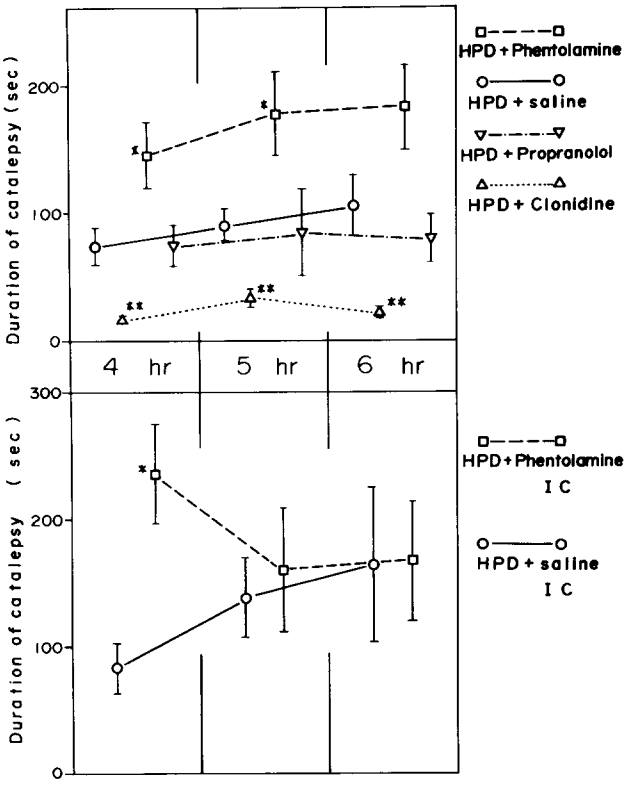


FIG. 3. Effects of clonidine, phentolamine and propranolol on the duration of catalepsy induced by haloperidol (HPD). Rats were given HPD (2 mg/kg SC) and 3.5 hr later injected with saline, clonidine (0.002 mg/kg IP), phentolamine (10 mg/kg IP) or propranolol (10 mg/kg IP). Other groups of rats were given HPD (2 mg/kg SC) and administered 10 μg phentolamine or its solvent (saline) intraventricularly (IC) at 15 min before the first assessment of catalepsy. The duration of catalepsy was measured at 4, 5 and 6 hr after the administration of HPD. Differences between the treatments with HPD + saline and HPD + clonidine, phentolamine or propranolol were tested with *t*-test. *: $0.05>p$. **: $0.01>p$.

### *Effect of FLA 63 on the Catalepsy Induced by ID-4708*

Groups of 8 rats were given ID-4708 or haloperidol (2 mg/kg SC), and 15 min later received FLA 63 (2 mg/kg IP). The mean durations of catalepsy are shown in Fig. 4. The duration of catalepsy in rats treated with ID-4708 was slightly longer than that in haloperidol-treated rats at 2 and 4 hr after the administration of neuroleptics. However, the order of the intensity of catalepsy induced by these two neuroleptics was reversed at 8 hr after the administration. FLA 63 enhanced the catalepsy induced by neuroleptics at each time of the assessment of catalepsy. Especially at 8 hr after the administration, FLA 63 caused a greater enhancement of catalepsy in rats pretreated with ID-4708 compared to haloperidol-treated rats.

### *Effects of Combined Administration of ID-4708 and FLA 63 on the Catecholamine Contents in the Rat Brain*

Groups of 6 rats were given ID-4708 or haloperidol (2 mg/kg SC), and 15 min later received FLA 63 (2 mg/kg IP). Rats were decapitated for the measurement of DA in the striatum and NE in the diencephalon at 8 hr after the administration of neuroleptics. The mean CA contents are shown in Fig. 5 as percentages of those of control rats. Haloperidol produced a slightly greater fall in DA level in

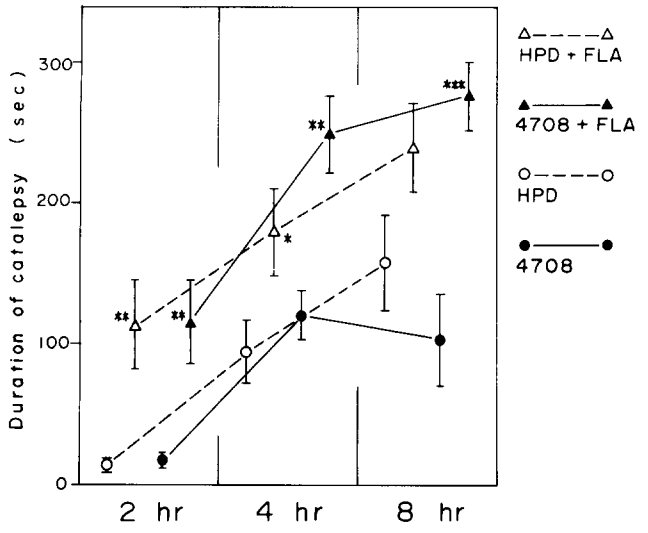


FIG. 4. Effects of FLA 63 (FLA) on the duration of catalepsy induced by haloperidol (HPD) and ID-4708 (4708). FLA (2 mg/kg IP) was given to rats at 15 min after the administration of HPD (2 mg/kg SC) or 4708 (2 mg/kg SC). Instead of FLA, its vehicle (5% gum arabic solution) was given to groups pretreated with HPD or 4708 alone. Differences between the groups (HPD vs. HPD + FLA, 4708 vs. 4708 + FLA) were tested with $t$-test. *: $0.05>p$. **: $0.01>p$. ***: $0.001>p$.

the striatum than ID-4708. Haloperidol and ID-4708 decreased the NE content in the diencephalon to the same extent. The DA level in the striatum of rats treated with each of these two neuroleptics was not affected by FLA 63. The combined administration of FLA 63 and ID-4708 caused a greater fall in the NE contents compared to the combination of FLA 63 and haloperidol.

## DISCUSSION

The present experiments show that the catalepsy induced by haloperidol was enhanced by FLA 63 and diethyldithiocarbamate (DDC). Both FLA 63 and DDC inhibit the activity of dopamine-β-hydroxylase (DBH). Injection of these compounds reduces the brain NE contents in mice and rats [5, 7, 28]. In our preliminary experiments, FLA 63 (2 mg/kg) and DDC (80 mg/kg) did not inhibit the exploratory behavior of rats in open-field test [unpublished observations]. However, these doses of the drugs enhanced the catalepsy induced by haloperidol. These findings show that the sedative action of DBH inhibitors is not a cause of the enhancement of catalepsy. The administration of FLA 63 caused an increase in DA and a reduction of NE content in the cortex, diencephalon and cerebellum. FLA 63 possessed neither NE uptake blocking activity nor any inhibitory effects on monoamine oxidase activity [7]. These results indicate NE synthesis is inhibitated by FLA 63 *in vivo*. FLA 63 produced little or no change of CA contents in the striatum. This ineffectiveness of FLA 63 would be due to the presence of endogeneous DBH inhibitors which strongly inhibit the DBH activity in the striatum [22]. Our data suggest that the fall in the activity of NE neurons enhances the catalepsy induced by haloperidol. The administration of FLA 63 or $p$-chlorophenylalanine did not produce catalepsy in rats [17], whereas reserpine produces monoamine depletion and catalepsy. These results suggest that the fall in the activity only in NE or serotonin neurons does not

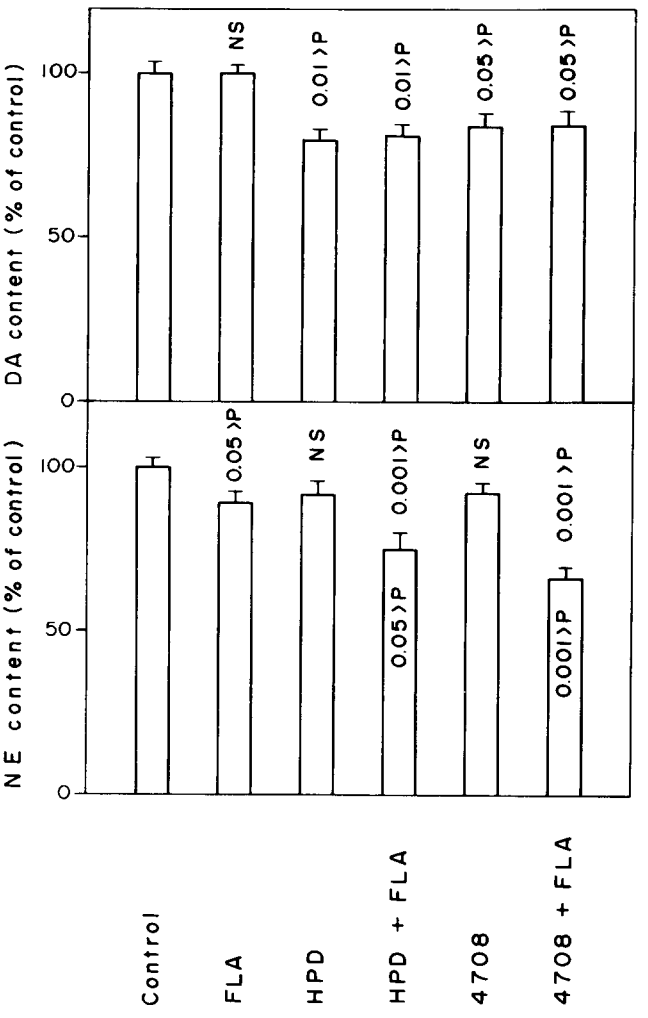


FIG. 5. Effects of combined administration of haloperidol (HPD) or ID-4708 (4708) and FLA 63 (FLA) on the contents of DA in the striatum and NE in the diencephalon in rats. FLA (2 mg/kg IP) was given to rats at 15 min after the administration of HPD (2 mg/kg SC) or 4708 (2 mg/kg SC). Rats were decapitated at 8 hr after the administration of neuroleptics. The mean contents of DA and NE of control rats were 9.15 and 0.725 μg/g tissue, respectively. Differences between control and drug-treated groups were tested with $t$-test and its results are shown above the column. Differences between the groups (HPD vs. HPD + FLA, 4708 vs. 4708 + FLA) were tested with $t$-test and its results are shown in the column. NS: not significant.

produce catalepsy. Neuroleptics are thought to block the DA receptors in the striatum [1]. After the administration of neuroleptics, the synthesis and release of DA are accelerated probably through a feedback activation [2]. If the synthesis of DA is not accelerated comparably to the acceleration of its release and destruction, the DA stored in the nerve terminals will be reduced gradually. This would be the reason for the reduction of DA by the administration of relatively high doses of haloperidol in rats. However, a further investigation is required for the explanation of this point.

The haloperidol-induced catelepsy was enhanced by phentolamine and antagonized by clonidine. Propranolol had no effect on it. As demonstrated previously, clonidine possesses a central α-sympathomimetic action, and phentol-

amine antagonizes the effect of clonidine on EEG and behavior in animals [15, 16, 25]. There are data indicating that propranolol may possess an action in the central nervous systems [13, 20, 21]. Therefore, our observations suggest that the catalepsy induced by haloperidol is enhanced by the blockade of the central α-adrenergic receptors, and antagonized by the stimulation of them. A specific depletion of cerebral NE by 6-hydroxydopamine significantly enhanced the catalepsy induced by haloperidol in rats [24]. This result supports the idea that the function of NE neurons regulates the degree of catalepsy. From the lack of effect of propranolol on the catalepsy, the β-adrenergic receptors may not be involved in the regulation of catalepsy.

FLA 63 enhanced the catalepsy induced by ID-4708 by an extent greater than that caused by haloperidol. At the same time, the decrease in NE content in rats treated with FLA 63 and ID-4708 was greater than that in rats treated with FLA 63 and haloperidol. The rapid disappearance of NE in rats treated with FLA 63 in combination with neuroleptics is due to the accelerated turnover of NE which is caused by neuroleptics [3]. ID-4708 would be more potent in accelerating the turnover of NE in the rat brain than haloperidol. This property of ID-4708 may be the cause of remarkable decrease in NE content and the pronounced potentiation of catalepsy when administered to rats with FLA 63. The different effect of FLA 63 on the catalepsy induced by haloperidol and ID-4708 supports the idea that the neuroleptic-induced catalepsy is potentiated by the decrease in the activity of the NE neurons.

From our experiments, it was concluded that a decrease in the activity of DA neurons or the blockade of DA receptors is essential to elicite catalepsy and that the function of NE neurons play a role in regulating the degree of catalepsy in rats.

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