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Abstract

The effect of 6-hydroxydopamine on repeated nicotine-induced tail-tremor was investigated in rats. Tail-tremor induced by nicotine (0.5 mg/kg/day, subcutaneously) became more pronounced in intensity with daily administration for 9 days. Rats pretreated with 6-hydroxydopamine (250 micrograms, intracerebroventricularly) showed almost the maximum degree of tail-tremor during the whole experimental period. However, in rats pretreated with 6-hydroxydopamine plus desipramine, enhancement of tail-tremor was slight in the beginning but increased with the daily nicotine administration. Fourteen-day administration of nicotine did not result in significant changes in noradrenaline and dopamine levels in the cortex, hypothalamus, striatum and nucleus accumbens. These results suggest that nicotine-induced tail-tremor is associated with the supersensitivity of postsynaptic catecholaminergic receptors in the central nervous system, and that the noradrenergic system may be more important than the dopaminergic system in this phenomenon.

KEYWORDS: nicotine, tail-tremor, 6-hydroxydopamine, noradrenaline, dopamine

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Involvement of the Central Catecholaminergic System in Nicotine-Induced Tail-Tremor in Rats

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The effect of 6-hydroxydopamine on repeated nicotine-induced tail-tremor was investigated in rats. Tail-tremor induced by nicotine (0.5 mg/kg/day, subcutaneously) became more pronounced in intensity with daily administration for 9 days. Rats pretreated with 6-hydroxydopamine (250 μ g, intracerebroventricularly) showed almost the maximum degree of tail-tremor during the whole experimental period. However, in rats pretreated with 6-hydroxydopamine plus desipramine, enhancement of tail-tremor was slight in the beginning but increased with the daily nicotine administration. Fourteen-day administration of nicotine did not result in significant changes in noradrenaline and dopamine levels in the cortex, hypothalamus, striatum and nucleus accumbens. These results suggest that nicotine-induced tail-tremor is associated with the supersensitivity of postsynaptic catecholaminergic receptors in the central nervous system, and that the noradrenergic system may be more important than the dopaminergic system in this phenomenon.

Key words: nicotine, tail-tremor, 6-hydroxydopamine, noradrenaline, dopamine

Nicotine produces various behavioral and physiological responses via its action on the central nervous system (1, 2), and these responses to nicotine are related to catecholaminergic neurons. For example, the locomotor stimulating action of nicotine has been reported to be due largely to dopaminergic activation in the mesolimbic system (3, 4), and the action of nicotine is attenuated by 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens in rats (5).

Drug-induced tremors, such as oxotremorine-induced

whole body tremor, are accompanied by rigidity and immobility of the whole body. However, we have found that repeated administration of nicotine causes a tremor only in the tail (tail-tremor) of rats (6). This tremor is accompanied by locomotor hyperactivity without rigidity or immobility of the whole body (7). Furthermore, nicotine-induced tail-tremor is observed not only at rest but also during movement. It is especially marked at the start of movement. Clinically, tremors are generally classified as those appearing at rest and those associated with body movement (8). The tremor at rest is observed only in Parkinson's disease. The essential tremor is the most frequently occurring movement disorder and these tremors are usually associated with movement. Therefore, we have proposed that the tail-tremor is a useful animal model for studying the essential tremor (7).

We have previously shown that nicotine-induced tail-tremor is associated with central nicotinic (6) and β -adrenergic receptors (9). However, the role of central noradrenaline (NA) and dopamine (DA) in nicotine-induced tail-tremor remains unknown. In the present study, we investigated the effect of 6-OHDA-induced depletion of brain catecholamines (CA) with or without desipramine on nicotine-induced tail-tremor, and also examined the effect of repeated nicotine administration on CA levels in the rat brain.

Materials and Methods

Animals. Male Wistar rats (Charles River Lab., Atsugi, Japan) weighing 220-250 g were housed in the experimental animal center of Okayama University School of Medicine at an ambient room temperature ($22 \pm 2^\circ\text{C}$) with a 12-h light/dark cycle (lights on at 7:00 a.m.).

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Food and water were given *ad libitum*.

Tail-tremor observation. It is known that subcutaneous (s.c.) administration of nicotine at doses of 0.25–0.75 mg/kg causes a dose-dependent increase in tail-tremor (7). Nicotine-induced tail-tremor was observed in individual cages (20 × 15 × 15 cm) for 15 min immediately after the administration of nicotine s.c. at a dose of 0.5 mg/kg as described previously (6). The degree of tail-tremor was scored every minute as follows: no tremor, 0; occasional slight tremor, 1; moderate intermittent tremor, 2; gross tremor with occasional quiescent periods, 3; gross intense continuous tremor, 4. Tremor intensity was expressed as the total of the scores per min for 15 min.

Drugs and drugs administration. (–)-Nicotine tartrate (Sigma Chemical Co., St. Louis, MO, USA) and desipramine hydrochloride (CIBA-GEIGY pharmaceutical Co., Basel, Switzerland) were dissolved in 0.9 % saline. These drugs were administered in a volume of 0.1 ml per 100 g body weight. 6-OHDA hydrobromide (Sigma) was dissolved in 0.9 % saline containing 0.1 % ascorbic acid and injected intracerebroventricularly (i.c.v.) in a volume of 10 μl under pentobarbital anesthesia.

Experiment 1

Effect of 6-OHDA on nicotine-induced tail-tremor. Three groups of animals were established for the experiment of 6-OHDA treatment. Rats were injected with 6-OHDA (250 μg / 10 μl) or saline (10 μl) i.c.v. Some 6-OHDA treated-rats were administered desipramine (25 mg/kg, intraperitoneally (i.p.)) 30 min before 6-OHDA treatment to protect the uptake of 6-OHDA into noradrenergic neurons. Seven days after 6-OHDA treatment, all rats were administered nicotine (0.5 mg/kg, s.c.) once daily, and tail-tremor was measured.

Experiment 2

Effect of repeated nicotine administration on brain CA. Four groups of animals were established. Two of the groups were administered saline and the other two groups were administered nicotine (0.5 mg/kg, s.c.) once daily for 13 days. Twenty-hours after the 13th administration, one of the groups that had received repeated saline or nicotine was administered saline, and the remainder were administered nicotine (0.5 mg/kg, s.c.). Four groups were thus formed: group 1, repeated saline-saline-exposure; group 2, repeated saline-nicotine-exposure; group 3, repeated nicotine-saline-exposure; group 4, repeated nicotine-nicotine-exposure. It is known

that tail-tremor begins 3 min after nicotine administration and reaches a peak at approximately 8–10 min after administration (6). In the present study, animals were decapitated 10 min after the last administration of saline or nicotine and CA were measured.

Assay of brain CA. To determine the levels of CA, four brain regions (cerebral cortex, nucleus accumbens, striatum and hypothalamus) were rapidly dissected after decapitation. The tissue was homogenized with 0.4 M perchloric acid containing 0.1 % L-cysteine and an appropriate amount of dihydroxybenzylamine as an internal standard. Noradrenaline (NA), dopamine (DA) and 3, 4-dihydroxyphenylacetic acid (DOPAC) levels were determined by direct injection of the membrane-filtered supernatant into a high-performance liquid chromatograph with an electrochemical detector.

Statistical analysis. Behavioral data was evaluated by Friedman's test followed by the Mann-Whitney U-test, and biochemical data was evaluated by analysis of variance followed by Tukey's test.

Results

Experiment 1

Effect of 6-OHDA on nicotine-induced tail-tremor. Figure 1 shows the effect of 6-OHDA treatment on the development of tail-tremor induced by

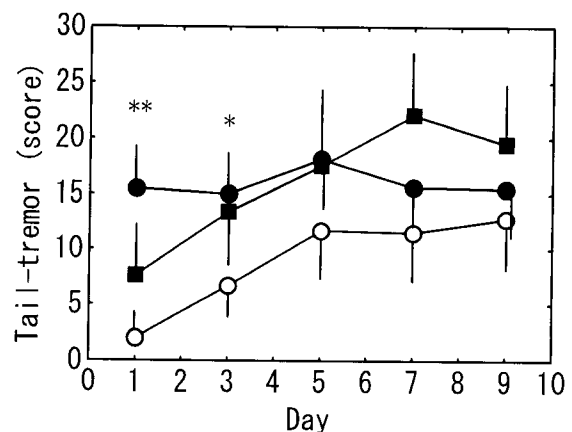


Fig. 1 Development of tail-tremor induced by daily administration of nicotine (0.5 mg/kg/day, subcutaneously). Rats were treated with 6-hydroxydopamine (6-OHDA) (250 μg/10 μl, intracerebroventricularly) with or without desipramine (25 mg/kg, intraperitoneally). ○: Control group; ●: 6-OHDA group; ■: 6-OHDA plus desipramine group, (n = 5 for each). Each point represents the mean score of tail-tremor for 15 min with SEM. * $P < 0.05$, ** $P < 0.01$ compared with the control group.

daily administration of nicotine (0.5 mg/kg/day, s.c.). In the control (i.c.v. saline-injected) group, the tail-tremor score increased gradually with daily administration of nicotine for 9 days. The tail-tremor scores in the 6-OHDA-treated group on the first and second day were

significantly higher ($P < 0.01$ and $P < 0.05$) than those of the control group, but further increases were not observed for the rest of the experimental period. In the rats treated with 6-OHDA plus desipramine, the tail-tremor score was slightly but not significantly higher than

Table 1 Effect of 6-hydroxydopamine (6-OHDA) treatment on noradrenaline (NA) and dopamine (DA) levels in rats brain

Brain region	Treatment	NA	DA
Cortex	Saline	143 ± 14	101 ± 25
	6-OHDA	34 ± 10**	55 ± 16**
	6-OHDA + Desipramine	163 ± 23	63 ± 27**
Hypothalamus	Saline	3009 ± 204	626 ± 60
	6-OHDA	712 ± 107**	367 ± 66*
	6-OHDA + Desipramine	2195 ± 239*	377 ± 38*
Nucleus accumbens	Saline	ND	8698 ± 728
	6-OHDA	ND	3528 ± 940**
	6-OHDA + Desipramine	ND	2595 ± 202**
Striatum	Saline	ND	11938 ± 1428
	6-OHDA	ND	4942 ± 1511**
	6-OHDA + Desipramine	ND	5105 ± 1273**

Rats were injected intracerebroventricularly with 6-OHDA (250 µg/10 µl) with or without desipramine (25 mg/kg, intraperitoneally). Each value represents mean ± SEM (ng/g) for 5 animals. * $P < 0.05$, ** $P < 0.01$ compared with the saline control. ND: Not determined.

Table 2 Effect of repeated administration of nicotine on noradrenaline (NA), dopamine (DA) and 4-dihydroxyphenylacetic acid (DOPAC) levels in the rat brain

Brain region	Group	NA	DA	DOPAC	DOPAC/DA
Cortex	1	114 ± 18	133 ± 11	37 ± 4	0.324 ± 0.020
	2	123 ± 28	115 ± 7	44 ± 4	0.383 ± 0.035
	3	115 ± 29	96 ± 8	36 ± 4	0.375 ± 0.039
	4	116 ± 16	125 ± 7	49 ± 2	0.392 ± 0.025
Hypothalamus	1	3356 ± 395	606 ± 54	64 ± 6	0.106 ± 0.010
	2	2543 ± 137	582 ± 65	63 ± 6	0.108 ± 0.011
	3	3410 ± 216	650 ± 68	87 ± 12	0.134 ± 0.016
	4	3059 ± 145	733 ± 38	89 ± 6	0.121 ± 0.013
Nucleus accumbens	1	ND	8684 ± 861	1959 ± 187	0.226 ± 0.024
	2	ND	9161 ± 455	2397 ± 247	0.262 ± 0.015
	3	ND	9533 ± 760	1837 ± 135	0.193 ± 0.011
	4	ND	9419 ± 823	2404 ± 174	0.255 ± 0.018*
Striatum	1	ND	12260 ± 1132	2115 ± 231	0.173 ± 0.014
	2	ND	11383 ± 1069	2298 ± 370	0.202 ± 0.016
	3	ND	11670 ± 917	1935 ± 228	0.166 ± 0.012
	4	ND	13042 ± 742	2508 ± 157	0.192 ± 0.015

Rats were administered saline (1 ml/kg/day) or nicotine (0.5 mg/kg/day, subcutaneously) for 13 days, and each group was administered saline or nicotine 10 min before decapitation on the 14th day. Each value represents the mean ± SEM (ng/g) for 6 rats. * $P < 0.05$. Group 1: Rats treated with repeated saline-saline-exposure; Group 2: Repeated saline-nicotine-exposure; Group 3: Repeated nicotine-saline-exposure; Group 4: Repeated nicotine-nicotine-exposure; ND: Not determined.

that of the control on the first day, and thereafter increased gradually with subsequent administration of nicotine. There were significant differences in the effect of daily nicotine treatment on the control ($S = 82.5$, $P < 0.05$) and the 6-OHDA plus desipramine groups ($S = 69.0$, $P < 0.05$).

Intracerebroventricular 6-OHDA markedly decreased both NA and DA levels in the rat brain. However, combined treatment with desipramine decreased DA levels only (Table 1).

Experiment 2

Effect of repeated nicotine administration on brain CA. Table 2 shows CA levels in four groups of animals administered saline or nicotine (0.5 mg/kg, s.c.) 24h after repeated treatment with saline or nicotine for 13 days. No significant differences were found among the four groups (repeated saline-saline-exposure, repeated saline-nicotine-exposure, repeated nicotine-saline-exposure and repeated nicotine-nicotine-exposure) in NA, DA and DOPAC levels in the cortex, nucleus accumbens, striatum and hypothalamus. The DOPAC/DA ratios were higher in the repeated saline-nicotine-exposed group and the repeated nicotine-nicotine-exposed group, and there was a significant difference ($P < 0.05$) in the nucleus accumbens between the repeated nicotine-saline-exposed group and the repeated nicotine-nicotine-exposed group.

Discussion

Nicotine receptors are present in catecholaminergic nerve terminals and cell bodies, and nicotine accelerates the release of NA (10) and DA (11). Nicotine at a dose of 1 mg/kg s.c. has been reported to decrease NA and DA levels and to increase the levels of their metabolites, 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) and DOPAC, in the rat brain (12), suggesting enhancement of CA turnover by nicotine. In the present study, acute (repeated saline-nicotine-exposure) and repeated administration of nicotine at a dose of 0.5 mg/kg s.c. caused increases in DOPAC levels and DOPAC/DA ratios, and there was significant difference ($P < 0.05$) in the ratio of DOPAC/DA in the nucleus accumbens between the repeated nicotine-saline-exposed group and the repeated nicotine-nicotine-exposed group. However, no significant differences were found in CA levels and the DOPAC/DA ratios between the repeated saline-nicotine-exposed group and the repeated nicotine-nicotine-exposed group. Thus,

the enhanced effect of DA turnover by nicotine may not be affected by repeated administration of nicotine.

The locomotor stimulating action of nicotine has been reported to be eliminated by 6-OHDA lesions of the nucleus accumbens in rats (5), suggesting involvement of presynaptic dopaminergic neurons in the nicotine action on this behavior. However, nicotine-induced tail-tremor was enhanced by 6-OHDA treatment in the present experiment. β -adrenoceptor antagonists such as propranolol (9) and DA receptor antagonists such as haloperidol (7) suppress nicotine-induced tail-tremor. Therefore, the facilitation of tail-tremor by 6-OHDA may be due to pharmacological postsynaptic supersensitivity of CA receptors.

It is well known that intracerebroventricular 6-OHDA treatment degenerates catecholaminergic neurons and produces a postsynaptic supersensitivity to NA and DA in the rat brain (13, 14). In addition to this, prolonged administration of nicotine has been reported to increase the number of nicotinic (15) and dopaminergic receptors (16) in the rat brain. Although NA and DA levels did not change in response to repeated administration of nicotine, we previously observed that 14-day treatment of nicotine enhances apomorphine- and methamphetamine-induced stereotypical behavior in rats (17). In the present study, rats pretreated with 6-OHDA showed almost the maximum degree of nicotine-induced tail-tremor during the whole experimental period; significantly higher scores than those of the control group were recorded on the first and second day of nicotine administration. Furthermore, in the rats pretreated with 6-OHDA plus desipramine, tail-tremor was slightly higher than in the control group throughout the experimental period, and significant increases with daily administration of nicotine were observed. These results suggest that the central CA system is associated with nicotine-induced tail-tremor, and, in particular, that noradrenergic postsynaptic supersensitivity is more important in the development of tail-tremor.

Behavioral changes manifested in the tails of rodents have been reported in Straub tail response by morphine and tail rattle which shown in fighting behavior between resident and intruder mice. Straub tail response induced by morphine is associated with central opioid (18), dopaminergic (19) and serotonergic receptors (20), and tail rattle is inhibited by β -adrenoceptor antagonists (21) and benzodiazepines (22). Nicotine-induced tail-tremor has been observed in rats but not in mice, and this nicotine-induced tail-tremor becomes more marked in intensity

with repeated administration of nicotine. We have shown that central nicotinic (6) and β -adrenergic receptors (9) are involved in the mechanisms underlying tail-tremor. Furthermore, the present study suggests that repeated nicotine-induced tail-tremor is associated with central catecholaminergic neurons and that the postsynaptic supersensitivity of the noradrenergic system is more important than that of the dopaminergic system in this phenomenon.

References

1. Clarke PBS: Nicotine and smoking, a perspective from animal studies. *Psychopharmacology* (1987) **92**, 135-143.
2. Silvette H, Hoff EC, Larson P and Haag HB: The action of nicotine on central nervous system functions. *Pharmacol Rev* (1962) **14**, 137-173.
3. Imperato A, Mulas A and Chiara GD: Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. *Eur J Pharmacol* (1986) **132**, 337-338.
4. Kita T, Okamoto M and Nakasima T: Nicotine-induced sensitization to ambulatory stimulant effect produced by daily administration into the ventral tegmental area and the nucleus accumbens in rats. *Life Sci* (1992) **50**, 583-590.
5. Clarke PBS, Fu DS, Jakubovic A and Fibiger HC: Evidence that mesolimbic dopaminergic activation underlies the locomotor stimulant action of nicotine in rats. *J Pharmacol Exp Ther* (1988) **246**, 701-708.
6. Gomita Y, Suemaru K, Furuno K and Araki Y: Nicotine-induced tail-tremor and drug effects. *Pharmacol Biochem Behav* (1988) **34**, 817-821.
7. Suemaru K, Oishi Y and Gomita Y: Characteristics of tail-tremor induced by nicotine in rats. *Naunyn-Schmiedeberg's Arch Pharmacol* (1994) **350**, 153-157.
8. Hallett M: Classification and treatment of tremor. *JAMA* (1991) **226**, 1115-1117.
9. Suemaru K, Gomita Y, Furuno K and Araki Y: Effects of β -adrenergic receptor antagonists on nicotine-induced tail-tremor in rats. *Pharmacol Biochem Behav* (1993) **46**, 131-133.
10. Yoshida K, Kato Y and Imura H: Nicotine-induced release of noradrenaline from hypothalamic synaptosomes. *Brain Res* (1980) **182**, 361-368.
11. Sakurai Y, Takano Y, Kohjimoto Y, Honda K and Kamiya H: Enhancement of [3 H] dopamine release and its [3 H] metabolites in rat striatum by nicotine drugs. *Brain Res* (1982) **242**, 99-106.
12. Kubo T, Amano H, Kurahashi K and Misu Y: Nicotine-induced regional changes in brain noradrenaline and dopamine turnover in rats. *J Pharmacobio-Dyn* (1989) **12**, 107-112.
13. Skolnick P, Stalvey LP, Daly JW, Hoyle E and Davis J: Binding of α - and β -adrenergic ligands cerebral cortical membranes: Effect of 6-hydroxydopamine treatment and relationship to the responsiveness of cyclic AMP-generating in two rat strains. *Eur J Pharmacol* (1978) **47**, 201-210.
14. Sporon JR, Harden TK, Wolfe BB and Molinoff PB: β -adrenergic receptor involvement in 6-hydroxydopamine-induced supersensitivity in rats cerebral cortex. *Science* (1976) **194**, 624-626.
15. Fung YK and Lau YS: Receptor mechanisms of nicotine-induced locomotor hyperactivity in chronic nicotine-treated rats. *Eur J Pharmacol* (1988) **152**, 263-271.
16. Fung YK and Lau YS: Effect of nicotine pretreatment on striatal dopaminergic system in rat. *Pharmacol Biochem Behav* (1989) **32**, 221-226.
17. Suemaru K, Gomita Y, Furuno K and Araki Y: Chronic nicotine potentiates behavioral responses to dopaminergic drugs in rats. *Pharmacol Biochem Behav* (1993) **46**, 135-139.
18. Narita M, Suzuki T, Misawa M and Nagase H: Antagonism of the morphine-induced Straub tail reaction by α -opioid receptor activation in mice. *Psychopharmacology* (1993) **110**, 254-256.
19. Hasegawa Y, Kurachi M, Okuyama S, Araki H and Otomo S: Dopamine D2 receptors and spinal cord excitation in mice. *Eur J Pharmacol* (1990) **184**, 207-212.
20. Hasegawa Y, Kurachi M and Otomo S: 5-HT3 receptor antagonists inhibit the response of α -opioid receptors in the morphine-induced Straub tail. *Eur J Pharmacol* (1990) **190**, 399-401.
21. Yoshimura H, Kihara Y and Ogawa N: Psychotropic effects of adrenergic β -blockers on agonistic behavior between resident and intruder mice. *Psychopharmacology* (1987) **91**, 445-450.
22. Yoshimura H and Ogawa N: Pharmacological analysis of agonistic behavior between resident and intruder mice: Effects of psychotropic drugs. *Folia Pharmacol Jpn* (1984) **84**, 221-228 (in Japanese).

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