Pharmacology Biochemistry and Behavior, Vol. 46, pp. 131–133, 1993
Printed in the U.S.A

0091-3057/93 $6.00 + .00

BRIEF COMMUNICATION

Effects of β-Adrenergic Receptor Antagonists on Nicotine-Induced Tail-Tremor in Rats

KATSUYA SUEMARU, YUTAKA GOMITA,[1] KATSUSHI FURUNO AND YASUNORI ARAKI

Department of Hospital Pharmacy,
Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700, Japan

Received 24 August 1992

SUEMARU, K., Y. GOMITA, K. FURUNO AND Y. ARAKI. *Effects of β-adrenergic receptor antagonists on nicotine-induced tail-tremor in rats.* PHARMACOL BIOCHEM BEHAV **46**(1) 131–133, 1993.—The effects of various β-adrenergic receptor antagonists on nicotine-induced tail-tremor were investigated in rats. Atenolol (5 and 10 mg/kg, IP), arotinolol (5 and 10 mg/kg, IP), and carteolol (5 and 10 mg/kg, IP), hydrophilic β-adrenergic receptor antagonists, did not affect the tail-tremor induced by nicotine given at a dose of 0.5 mg/kg SC. However, propranolol (5–20 mg/kg, IP) and pindolol (5–20 mg/kg, IP), nonselective and lipophilic β-adrenergic receptor antagonists, did suppress the tail-tremor dose dependently. In contrast, metoprolol (5–20 mg/kg, IP), lipophilic and β_1-selective adrenergic receptor antagonists, did not show such an effect. These results suggest that nicotine-induced tail-tremors may be mediated through central β_2-adrenergic receptors as an appearance and developmental mechanism.

Nicotine Tail-tremor β-Adrenergic antagonists Rats

β-ADRENERGIC receptor antagonists are clinically used for not only therapy of cardiovascular diseases but also for essential tremors (6,7,10). In behavioral studies on animals, it is known that β-adrenergic receptor antagonists reduce tremors evoked by stimulation of the brain cholinergic and serotonergic systems in rodents (3,5,11). On the other hand, we already observed that long-term exposures to cigarette smoke, as well as repeated administrations of nicotine, cause a tremor appearing only in the tail (tail-tremor) of rats (1,2), and these tremors are mediated through central nicotinic receptors (1). However, it is not clear whether the β-adrenergic receptor system is involved in nicotine-induced tail-tremors. In the present study, we investigated the effects of lipophilic and hydrophilic β-adrenergic receptor antagonists on these tremors to clarify whether the effects are due to a central or to a peripheral blockade of the β-adrenergic receptors.

METHOD

Animals

Male Wistar rats (supplied by Charles River Lab., Japan) weighing 180–200 g were used as subjects. They were housed five animals per plastic cages (26 × 36 × 25 cm) in a room with a 12 L : 12 D cycle (light on 0700–1900) at 22 ± 1°C and with 60% relative humidity. Rats were allowed free access to food and water throughout the experiment.

Drugs and Administration

Drugs used were pure nicotine solution (donated by the Smoking Research Foundation of Japan), propranolol HCl (Sigma Chemical Co., St. Louis, MO), pindolol (Sigma), atenolol (Sigma), arotinolol HCl (Sumitomo Pharmaceutical Co., Osaka, Japan), carteolol HCl (Otsuka Pharmaceutical Co., Tokyo, Japan), and metoplolol tartrate (CIBA-GEIGY Pharmaceutical Co., Basel, Switzerland). Pindolol and atenolol were dissolved in an excess of equimolar tartaric acid solution, with subsequent dilutions in saline. Arotinolol was suspended in 0.5% methylcellulose 400. The other drugs were dissolved in saline solution. All drugs were injected in a volume of 0.1 ml per 100 g body weight.

Tail-Tremor Observation

The observations on nicotine-induced tail-tremor were performed as previously described (1). Briefly, nicotine-induced tail-tremors were observed for 15 min in rats housed in individual cages (20 × 15 × 15 cm) immediately after SC administration of nicotine at a dose of 0.5 mg/kg. In the present

[1] To whom requests for reprints should be addressed.

study, β-adrenergic antagonists were IP administered 30 min before nicotine administration.

The degree of tail-tremor was measured as follows: tail-tremors that continued for less than 1 s, scored 0.5; for 1–2 s, scored 1; for 2–3 s, scored 2; and for over 3 s, scored 3. All observations were made by the same observer, who was unaware of the treatment schedule.

Statistical Analysis

Tail-tremor data were analyzed by Kruskal-Wallis analysis of variance of the drug's effect. When a significant difference was noted, the Mann-Whitney *U*-test for group comparisons was conducted.

RESULTS

Daily administration of nicotine at a dose of 0.5 mg/kg caused tail-tremors from the fourth day after initial administration. Thereafter, the degree of tail-tremors gradually increased with daily administration of nicotine until the 14th day. When nicotine at doses of 0.25, 0.5, and 0.75 mg/kg was administered to rats pretreated with nicotine for 14 days, the tail-tremors increased in a dose-dependent manner. These scores were 0.25, 20.7, and 36.1, respectively. There were significant differences in doses of 0.5 and 1.0 mg/kg compared with the saline control group (score 0) ($U = 0$, $p < 0.01$, respectively). Therefore, in the present study of the effects of drugs on tail-tremors nicotine was administered at a dose of 0.5 mg/kg to rats that had been treated daily with nicotine for more than 14 days.

As shown in Fig. 1, administrations of atenolol (5 and 10 mg/kg), arotinolol (5 and 10 mg/kg), and carteolol (5 and 10 mg/kg) did not affect tail-tremors induced by nicotine at a dose of 0.5 mg/kg. However, arotinolol and carteolol administered at a dose of 20 mg/kg significantly ($U = 5.5$, $p < 0.05$; $U = 2$, $p < 0.01$, respectively) reduced the tail-tremors. Administrations of propranolol at doses of 5–20 mg/kg markedly reduced the tail-tremors in a dose-dependent manner. Further, there were significant differences when compared with the saline control group ($U = 5.5$, $p < 0.05$; $U = 0$, $p < 0.01$; $U = 0.5$, $p < 0.01$, respectively). Administrations of pindolol at doses of 5–20 mg/kg also significantly reduced the tail-tremors ($U = 5$, $p < 0.05$; $U = 0$, $p < 0.01$; $U = 0$, $p < 0.01$, respectively). In contrast, administration of metoprolol at doses of 5–20 mg/kg did not show such an effect.

DISCUSSION

High doses of nicotine cause tremors through out the whole body of animals. However, we previously observed that repeated administration of nicotine at a dose of 0.5 mg/kg SC does not produce such whole-body tremors but causes tremors appearing only in the tail (tail-tremor) of the rat. The nicotine-induced tail-tremor is suppressed by mecamylamine but not by hexamethonium, atropine, or scopolamine (1). These suggest that tail-tremors induced by nicotine are due to activation of the central nicotinic system.

On the other hand, it is well known that oxotremorine, a muscarinic cholinergic agonist, causes whole-body tremors in rats. Leslie et al. (9) reported that oxotremorine-induced tremors were reduced by IP propranolol (ED_{50} = 62 mg/kg). In the present study, nicotine-induced tail-tremors were also reduced by IP propranolol (5–20 mg/kg), but the effective dosage was markedly lower than those of the oxotremorine-induced tremors.

Hallberg et al. (5) reported that oxotremorine-induced tremors in rats were reduced by lipophilic β-adrenergic antagonists such as propranolol, but not by hydrophilic β-adrenergic antagonists such as nadolol, and enhanced by lipophilic β_2-agonists such as clenbuterol. Further, they reported that SC administrations of hydrophilic β_2-agonists did not cause the tremor in rats (4). These suggest that oxotremorine-induced tremor is mediated through the central β_2-adrenergic receptor.

In the present study, neither the nonselective β-antagonists such as arotinolol (5 and 10 mg/kg) and carteolol (5 and 10 mg/kg) nor β_1-selective antagonists such as atenolol (5 and 10 mg/kg) had any effect on the tail-tremor induced by nicotine. However, the nonselective β-adrenergic antagonists such as propranolol (5–20 mg/kg) and pindolol (5–20 mg/kg) markedly reduced the tail-tremors in a dose-dependent manner. Further, metoprolol, a lipophilic β_1-selective antagonist, did not affect tail-tremors. These results suggest that nicotine-induced tail-tremors were markedly reduced by β_2-adrenergic receptor antagonists, which include the central β_2-blocking effect.

Propranolol and pindolol, nonselective and lipophilic β-

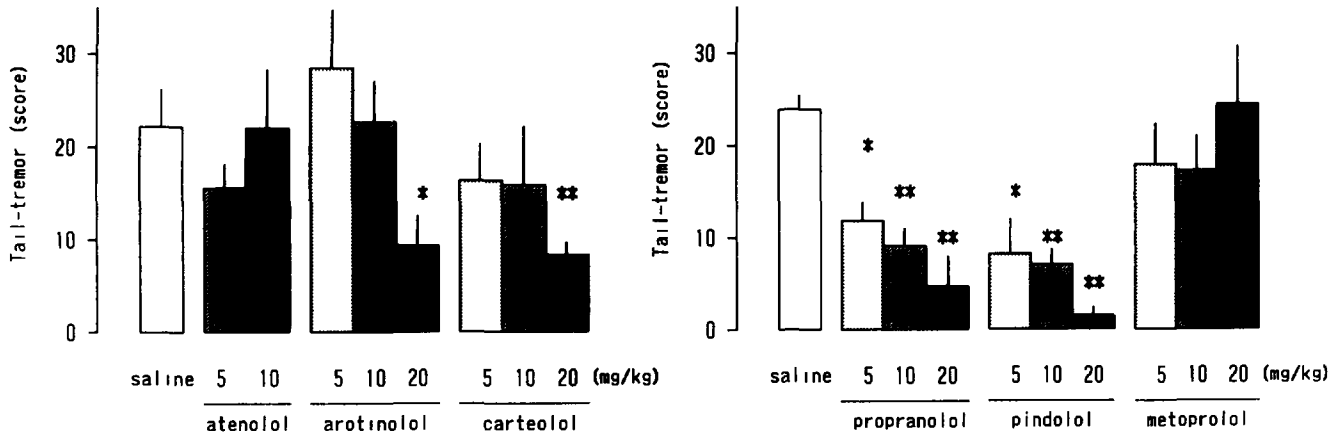

FIG. 1. Effects of β-adrenergic antagonists on nicotine-induced tail-tremors. Nicotine was SC administered at a dose of 0.5 mg/kg 30 min after each β-adrenergic antagonist was IP injected. Each value represents the mean score with SEM for 15 min (n = 5–6). *$p < 0.05$, **$p < 0.01$.

adrenergic antagonists, are mainly used for essential tremor diseases in man (6). However, it has been reported that nonselective and hydrophilic β-antagonists such as arotinolol reduced the essential tremor (8). In behavioral studies on animals, it has been reported that peripheral catecholamines mediate with the oxotremorine-induced tremors in rats (12). In addition, in the present study high doses of arotinolol and carteolol reduced tail-tremors. Therefore, nicotine-induced tail-tremors might be partly related to peripheral β-adrenergic receptors.

In conclusion, the present study indicates that lipophilic β-receptor antagonists such as propranolol and pindolol suppress nicotine-induced tail-tremors. However, hydrophilic antagonists such as atenolol, arotinolol, and carteolol do not. Further, lipophilic and β_1-selective antagonists such as metoprolol did not affect tail-tremors. These results suggest that nicotine-induced tail-tremors may be mediated through central β_2-adrenergic receptors.

ACKNOWLEDGEMENTS

This study was supported in part by grants from the Smoking Research Foundation of Japan. The authors thank Sumitomo Pharmaceutical Co., CIBA-GEIGY Pharmaceutical Co., and Otsuka Pharmaceutical Co. for their generous gifts of arotinolol, metoprolol, and carteolol, respectively.

REFERENCES

1. Gomita, Y.; Suemaru, K.; Furuno, K.; Araki, Y. Nicotine-induced tail-tremor and drug effects. Pharmacol. Biochem. Behav. 34:817–821; 1989.
2. Gomita, Y.; Suemaru, K.; Furuno, K.; Araki, Y. Tail-tremor induced by exposure to cigarette smoke in rats. Pharmacol. Biochem. Behav. 40:453–455; 1991.
3. Hallberg, H. Blockade of central β-adrenoceptors attenuates tremor induced by 5-hydroxytryptamine (5-HT)-receptor activation in rats. Acta Physiol. Scand. 129:421–428; 1987.
4. Hallberg, H.; Almgren, O. β-Adrenoceptor agonists do not cause tremor in the conscious rat. Acta Physiol. Scand. 124:149–152; 1985.
5. Hallberg, H.; Almgren, O. Modulation of oxotremorine-induced by central β-adrenoceptors. Acta Physiol. Scand. 129:407–413; 1987.
6. Hallett, M. Classification and treatment of tremor. JAMA 226; 1115–1117; 1991.
7. Jefferson, D.; Jenner, P.; Marsden, C. D. Beta-adrenoceptor antagonists in essential tremor. J. Neurol. Neurosurg. Psychiatry 42:904–949; 1979.
8. Kuroda, Y.; Kakigi, R.; Sibasaki, H. Treatment of essential tremor with arotinolol. Neurology 38:650–952; 1988.
9. Leslie, G. B.; Hayman, D. G.; Ireson, J. D.; Smith, S. The effects of some beta adrenergic blocking agents on the central and peripheral actions of tremorine and oxotremorine. Arch. Int. Pharmacodyn. 197:108–111; 1972.
10. Ogawa, O.; Takayama, H.; Yamamoto, M. Comparative studies on the effects of β-adrenergic blockers in essential tremor. J. Neurol. 235:31–33; 1987.
11. Tugimoto, A.; Dohi, T. Characteristics of sustained tremor induced by nicotine in pilocarpine-treated animals. Neuropharmacology 15:421–426; 1976.
12. Weinstock, M.; Zavadil, A. P.; Rosin, A. J.; Chiueh, C. C.; Kopin, I. J. The role of peripheral catecholamines in oxotremorine tremor in the rat and its antagonism by beta adrenoceptor blocking agents. J. Pharmacol. Exp. Ther. 206:91–96; 1978.