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Effects of β-Adrenergic Blockers on Drug-Induced Tremors

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IWATA, S.-I., M. NOMOTO AND T. FUKUDA. *Effects of β-adrenergic blockers on drug-induced tremors.* PHARMACOL BIOCHEM BEHAV 44(3) 611–613, 1993.—We studied the effect of various kinds of β-adrenergic blockers on oxotremorine-, harmaline- and thyrotropin-releasing hormone (TRH)-induced tremors in mice. To investigate what property of β-blockers plays the main role in suppressing tremor, we employed five β-blockers (propranolol, atenolol, butoxamine, pindolol, and arotinolol). All drugs suppressed oxotremorine-induced tremors but none reduced harmaline-induced tremors. Even though TRH-induced tremors were decreased significantly only by propranolol and high doses of arotinolol, all drugs had a tendency to reduce the tremor. We concluded that neuropharmacological mechanisms underlying to harmaline-induced tremors were different from those of TRH- and oxotremorine-induced tremors and that features of β-blockers (β_1- or β_2-selectivity, intrinsic sympathomimetic activity, and membrane stabilizing activity) did not primarily contribute to the suppression of tremors.

Tremors β-Blockers Thyrotropin-releasing hormone Oxotremorine

ESSENTIAL tremor is a monosymptomatic disorder with tremor being the sole manifestation. β-Adrenergic blocking agents such as propranolol have been shown to be effective in alleviating the tremor (17). Oxotremorine produces tremor in rodents, which can be reduced by β-blockers (22). Harmaline has been known to produce tremor in various mammals (11), which is mediated by the olivocerebellar system via the climbing fiber projection to the Purkinje cell (15) and inhibited by β-blockers (18). Thyrotropin-releasing hormone (TRH) produces tremor (5), which can be suppressed by propranolol (12). But, we do not know what properties of β-blockers contribute to the alleviation of tremors because β-blockers have actions in addition to β-adrenergic blocking activity. We investigated the effect of various kinds of β-blockers on drug-induced tremors to elucidate the primary feature of β-blockers in controlling tremors.

METHOD

Animals

Male ddY mice (Kuroda Junkei Dohbutu Ltd., Japan), weighing 36–59 g were used. Animals were housed with free access to standard foods (Clea Japan Inc.) in an air-conditioned room under a constant 12 L : 12 D cycle (light on 8:00 a.m.) at 20–26°C and 40–70% humidity.

Apparatus

Tremor was quantitatively recorded by a capacitance transducer, and its intensity and frequency were evaluated using power arrays (12). The capacitance transducer consists of two pairs of parallel aluminum plates (3 × 10 cm) that were vertically and horizontally attached to acrylic box (8 × 15 × 8 cm). A mouse was placed near the plate and the tail was fixed to the box. A radio frequency capacitance field was generated between the plates. Change of capacitance was converted to the change in voltage, then amplified with polygraph (RM-6000, Nihonkoden). The signal was subsequently processed every minute through fast Fourier transform on a signal processor 7T08 (San-Ei Instrument Co. Ltd.) to provide a spectral estimation of the tremor frequency and power.

Procedure

β-Blockers were injected IP 20 min before administration of tremorogenic drugs. Oxotremorine- and harmaline-induced tremors were measured for 30 min as a horizontal movement. TRH-induced tremor was recorded for 40 min as a vertical movement. Statistical analysis was done by analysis of variance (ANOVA).

Drugs

Oxotremorine (Sigma Chemical Co., St. Louis, MO) 0.25 mg/kg, harmaline HCl (Sigma) 20 mg/kg, and TRH analog, protireline tartrate (given by Takeda Chemical Industry Co. Ltd., Osaka, Japan) 40 mg/kg, were employed as tremorogenic agents. Propranolol HCl (Inderal, ICI) 5 mg/kg, atenolol (Sigma) 5 mg/kg, pindolol (Carvisken, Sandoz Inc., East Hanover, NJ) 0.77 mg/kg, and arotinolol Hcl (Almarl, Sumi-

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tomo Pharmaceutical Co. Ltd., Osaka, Japan) 1 and 2.5 mg/kg were used as representatives of β-blockers. All drugs were diluted with 0.9% saline and injected IP.

RESULTS

Oxotremorine induced intense horizontal tremor that started 2–3 min and ended about 15–20 min after injection (Fig. 1). The power of the tremors pretreated with saline, propranolol, atenolol, butoxamine, pindolol, arotinolol 1 mg/kg, and arotinolol 2.5 mg/kg was 2,120 ± 408, 338 ± 133, 214 ± 75, 688 ± 221, 848 ± 382, 1,512 ± 350, and 566 ± 220 points, respectively (mean ± SEM). All β-blockers significantly suppressed the tremors.

Harmaline produced characteristic horizontal tremors that were vigorous for a moment but suddenly disappeared and sporadically reappeared (Fig. 1). The power of the tremors pretreated with saline, propranolol, atenolol, butoxamine, pindolol, arotinolol 1 mg/kg, and arotinolol 2.5 mg/kg was 53.5 ± 11.3, 24.8 ± 11.9, 33.8 ± 7.1, 36.8 ± 14.2, 44.8 ± 13.0, and 53.1 ± 18.1 points, respectively (mean ± SEM). No β-blockers reduced the tremors (Fig. 2).

TRH induced vertical tremor that started 15–20 min and stopped 30–40 min after injection (Fig. 1). There was a large variability of intensity of the TRH-induced tremors in the individual animal. The power of the tremors pretreated with saline, propranolol, atenolol, butoxamine, pindolol, arotinolol 1 mg/kg, and arotinolol 2.5 mg/kg was 260 ± 94.7, 24.8 ± 11.9, 116 ± 32.6, 77.1 ± 27.5, 70.3 ± 34.7, 69.4 ± 37.2, and 64.3 ± 27.7 points, respectively (mean ± SEM). Only propranolol and dose of 2.5 mg/kg arotinolol significantly suppressed the tremors but all drugs had tendency to reduce the tremors.

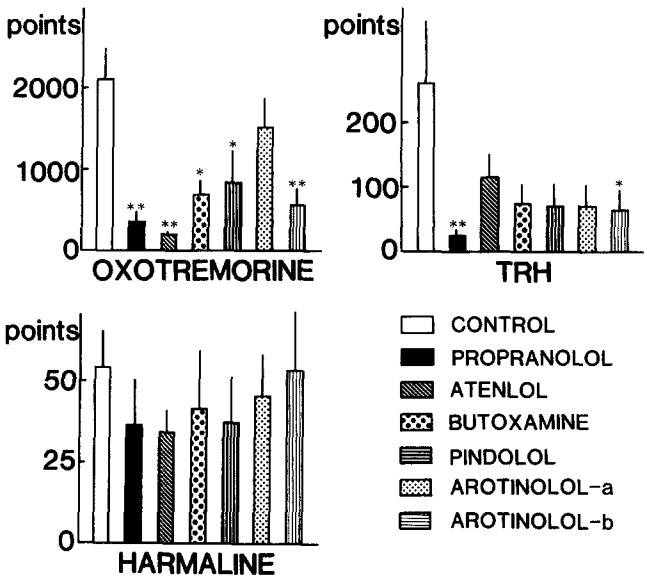

FIG. 2. Effect of β-blockers on oxotremorine-, harmaline-, or thyrotropin-releasing hormone (TRH)-induced tremors. The ordinate is the power of the tremor, expressed as "points." The doses of propranolol, atenolol, butoxamine, pindolol, arotinolol-a, and arotinolol-b was 5, 5, 5, 0.77, 1, and 2.5 mg/kg, respectively. Each column is the mean ± SEM of six experiments in oxotremorine and harmaline and eight experiments in TRH. $*p < 0.05$, $**p < 0.01$ as compared to control, one-way ANOVA. F-ratio of oxotremorine, harmaline, and TRH is $F(6, 35) = 5.93, p < 0.01$, $F(6, 35) = 0.43, p < 0.05$, and $F(6, 49) = 2.88, p < 0.05$, respectively.

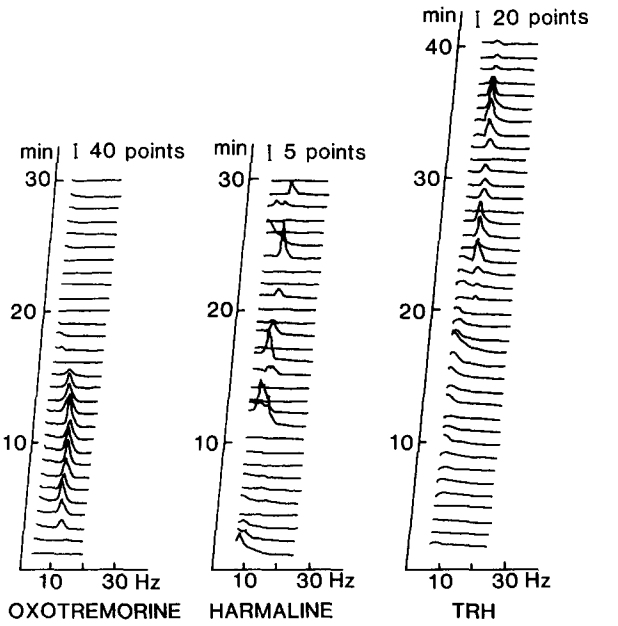

FIG. 1. Fourier-transformed records of drug-induced tremors. The abscissa is the frequency and the ordinate is the minutes after injection of oxotremorine, harmaline, or thyrotropin-releasing hormone (TRH). The height of the curve represents the power of tremor, expressed as "points."

DISCUSSION

We examined the effect of β-blockers on oxotremorine-, harmaline- and TRH-induced tremor, each of which show characteristic features. Propranolol, atenolol, butoxamine, pindolol, and arotinolol were representatives of a prototype of β-blockers, a selective β_1-blocker, selective β_2-blocker, a drug whose intrinsic sympathomimetic activity is strong, and mixed α-β blocker, respectively. We used a dosage of each β-blocker that had the same β_1-blocking activity. Because the comparative potency of atenolol, pindolol, and arotinolol against propranolol is 1, 6.5, and 5, respectively (24), we adopted the dosage of drugs as mentioned in the Method section. Butoxamine, however, has little β_1-blocking activity; this agent was administered in the same dosage as propranolol.

Oxotremorine produced the most intense tremors of the three tremorogenic agents. The tremorogenic mechanism of the drug has not been elucidated but Weinstock indicated it was involved predominantly in the CNS because the tremor was completely abolished by atropine but not by atropine methyl nitrate, which cannot penetrate the blood-brain barrier (23). It was reported that it was involved predominantly in the parasympathomimetic stimulation of cholinergic pathways in the midbrain (9). On the other hand, chemosympathectomy with 6-hydroxydopamine of adrenalectomy inhibited the tremor intensity by about 40% (22) and the apparent reduction of tremorine tremor in the intact limb of a chronic spinal rat where the opposite leg has undergone a section of its dorsal roots (4). These results showed peripheral systems were necessary to induce the tremor. Hence, oxotremorine-induced tremor is generated from the CNS and peripheral

system are demanded for full expression of the tremor. The tremorogenic activity of oxotremorine depends upon the muscarinic agonist property of the drug because a good correlation exists between peripheral muscarinic activity in vitro and central tremorogenic activity in a series of oxotremorine analogs (19). In our experiment, oxotremorine-induced tremor was blocked by all β-blockers. A dose-dependent antagonism of oxotremorine-induced tremor in mice was observed after pretreatment with propranolol (1,2,8,10). There were reports that selective β_1- and β_2-blockers exhibited no antitremor activity (1) and that a hydrophilic nonselective β-blocker and a selective β_1-blocker were ineffective to suppress the oxotremorine-induced tremor (10). We tried to elucidate what properties of β-blockers contribute to the suppression of oxotremorine-induced tremor but found there was no correlation between antitremor activity and their ability to produce β_1- or β_2-blockade, membrane stabilizing action. or intrinsic sympathomimetic activity. Our results that atenolol, butoxamine, and arotinolol showed antitremor action even though they cannot cross the blood-brain barrier indicated that β-blockers reduce the tremor mainly by affecting the peripheral system. These results are consistent with the those of Doggett that propranolol produced no significant effect on oxotremorine-induced tremor (8).

The characteristics of harmaline-induced tremor were different from others. The tremor appeared sporadically (Fig. 1). The origin of the tremor is believed to be in the olivocerebellar system because Lamarre et al. found that harmaline induced sustained rhythmic activity at the same frequency as the tremor in neurons of the cerebellar cortex, inferior olive, fastigial nucleus, and medullary reticular formation (6,14,15). Paul et al. reported that acebutolol (β_1-blocker) and butoxamine suppressed harmaline-induced tremor in rats (18), but we found no β-blockers influenced the tremors. The reason might exist in the characteristic feature of harmaline-induce tremor.

TRH-induced tremor is probably produced by central nervous effects because Costall et al. reported that injection of TRH into the brain caused body shakes, limb tremor, and repetitive head and limb movement (5). The tremor was significantly suppressed by propranolol (12). In our experiment, only propranolol and arotinolol (2.5 mg/kg) significantly reduced the tremor. But, the rest of the β-blockers had a tendency to suppress the tremor.

There are several methods to evaluate tremor quantitatively, for example, a pressure transducer (13), a force transducer (20), a phonocartridge assembly (3,16), an accelerometer (25), and an analysis of random current induced by a magnet (21). A device attached to the body of an animal might alter the frequency and intensity of the tremor. From this point, the apparatus employed in this study has an advantage to measure the natural properties of the tremor (12).

In conclusion, β-blockers reduced oxotremorine- and TRH-induced tremors but antitremor activity was not solely due to β_1- or β_2-blocking activity, membrane stabilizing activity, or intrinsic sympathomimetic action.

REFERENCES

1. Alkondon, M.; Ray, A.; Sen, P. Effect of beta-adrenergic blocking agents, with differing ancillary properties on oxotremorine induced tremor in mice. Ind. J. Exp. Biol. 22:382-383; 1984.
2. Alkondon, M.; Ray, A.; Sen, P. Cholinergic involvement in the modulation of oxotremorine-tremor in mice by propranolol. Arch. Int. Pharmacodyn. 277:161-167; 1985.
3. Baker, W. W.; Zivanovic, D.; Malseed, R. T. Tremorogenic effects of intracaudate *d*-amphetamine and their suppression by dopamine. Arch. Int. Pharmacodyn. 223:271-281; 1976.
4. Chalmers, R. K.; Yim, G. K. W. Tremorine tremor in chronic spinal rats. Proc. Soc. Exp. Biol. Med. 109:202-205; 1962.
5. Costall, B.; Hui, S.-C. G.; Metcalf, G.; Naylor, R. J. A study of the changes in motor behaviour caused by TRH on intracerebral injection. Eur. J. Pharmacol. 53:143-150; 1979.
6. De Montigny, C.; Lamarre, Y. Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat. Brain Res. 53:81-95; 1973.
7. Doggett, N. S.; O'Frrell, S. A. Modification of oxotremorine tremor and hypothermia by injections of drugs into the cerebral ventricles of the mouse. Naunyn Schmiedeberg's Arch. Pharmacol. 294:149-155; 1976.
8. Ganguly, D. K. Antioxotremorine action of propranolol. Br. J. Pharmacol. 56:21-24; 1976.
9. George, R.; Haslett, W. L.; Jenden, D. J. The central action of a metabolite of tremorine. Life Sci. 8:361-363; 1962.
10. Hallberg, H.; Almgren, O. Modulation of oxotremorine-induced tremor by central β-adrenoceptors. Acta Physiol. Scand. 129: 407-413; 1987.
11. Hara, S. Pharmacological studies in the functions of the extrapyramidal system. Jpn. J. Pharmacol. 2:127-138; 1953.
12. Koja, T.; Nomoto, M.; Shimizu, T.; Izumi, K.; Fukuda, T. Power spectral analysis of tremor induced by TRH and oxotremorine in mice. Folia Pharmacol. Japon. 88:159-165; 1986.
13. Kruse, H. Thyrotropin releasing hormone (TRH): Restoration of oxotremorine tremor in mice. Naunyn Schmiedeberg's Arch. Pharmacol. 294:39-45; 1976.
14. Lamarre, Y.; de Montigny, C.; Dumont, M.; Weiss, M. Harmaline-induced rhythmic activity of cerebellar and lower brain stem neurons. Brain Res. 32:246-250; 1971.
15. Llinas, R.; Volkind, R. A. The olivo-cerebellar system: Functional properties as revealed by harmaline-induced tremor. Exp. Brain Res. 18:69-87; 1973.
16. Mattews, R. T.; Chiou, C. Y. Cholinergic stimulation of the caudate nucleus in rats: A model of Parkinson's disease. Neuropharmacology 17:879-882; 1978.
17. Neophytides, A. N. Tremor, hereditary essential. In: Vinken, P. J.; Bruyn, G. W., eds. Handbook of clinical neurology. vol. 42. Amsterdam: North Holland; 1981:267-269.
18. Paul, V. Involvement of β2-adrenoceptor blockade and 5-hydroxytryptamine mechanism in inhibition of harmaline-induced tremors in rats. Eur. J. Pharmacol. 122:111-115; 1986.
19. Ringdahl, B.; Jenden, D. J. Pharmacological properties of oxotremorine and its analogs. Life Sci. 32:2401-2413; 1983.
20. Schenkel-Hulliger, L.; Koella, W. P.; Hartmann, A.; Maitre, L. Tremorogenic effect of thyrotropin releasing hormone in rats. Experientia 30:1168-1170; 1974.
21. Shinozaki, H.; Hirate, K.; Ishida, M. A quantitative analyzing method for drug-induced tremor. Folia Pharmacol. Japon. 83: 479-483; 1984.
22. Weinstock, M.; Zavadil, A. P.; Kopin, I. J. Peripheral catecholamines mediate certain responses to central cholinergic receptor stimulation by oxotremorine. Monogr. Neural Sci. 7:138-145; 1980.
23. 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.
24. Westfall, D. P. Adrenoceptor antagonists. In: Craig, C. R.; Stitzel, R. E., eds. Modern pharmacology. 3rd ed. Boston: Little, Brown and Company; 1990:165.
25. Yamanaga, H. Quantitative analysis of tremor in Minamata disease. Tohoku J. Exp. Med. 141:13-22; 1983.