THE PHARMACOLOGICAL CHARACTERISTICS OF NEURONS PARTICIPATING IN TREMOR FORMATION

V. B. Prozorovskii

Laboratory of Pathophysiology (Head, S. S. Krylov) of the Institute
of Toxicology (Director - S. N. Golikov) Academy of Medical Sciences, AMS USSR Leningrad
(Presented by Active Member, AMS, USSR, V. M. Karasikov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 52, No. 10,
pp. 64-66, October, 1961.
Original article submitted November 9, 1960.

Shivering, or tremor, is a very frequently encountered reaction of the normal (chilling, fear) and of the diseased organism (hyperthyroidism, Parkinson's disease). Pathological shivering, analogous to that which is observed in Parkinsonism, may also be aroused by some pharmaceutical agents – harmine, adrenaline, and also by substances which excite the cholinoreactive systems. On the basis of the fact that antagonists to substances of the latter group are able to weaken the tremor in Parkinsonism patients, it was proposed that the tremor caused by several representatives of the cholinomimetics – M-cholinomimetic arecoline [1] and N-cholinomimetic nicotine [4] be used as a model of Parkinson's disease. The tremor aroused by tremorin also approaches Parkinsonism [7].

The research of Ward and his coworkers [11], Birsis and Hemingway [3], Himwich and Rinaldi [9], and others, showed that the manifestation of a tremor upon the administration of cholinomimetics and anticholinesterases, (AChE) depends on the stimulation of cholinoreactive neurons of the thalamus and mid-brain. The excitation arising here spreads via the nerves, while still not precisely defined morphologically, across the lateral part of the reticular formation of the pons varolii and the medulla oblongata and beyond – to the anterior spinal crescent. The spread of the impulses, evoked in the M- and N-cholinoreactive neurons take place, apparently, in some part, along separate pathways. Testifying in favor of this are the findings of N. A. Kharauzov [2] which indicated that blockade of a tremor evoked by arecoline, with the aid of a M-cholinolytic, does not prevent the stimulation of a nicotine tremor; on the other hand, blockade of a tremor evoked by nicotine, with N-cholinolytics, does not prevent the arousal of an arecoline tremor. These different paths to some level or other of the brain, must probably be switched to a common end path. The common link for them cannot be cholinergic, since it is not blocked by a cholinolytic. Proceeding from the fact that the tremor, observed during the administration of nicotine, is blocked by the adrenoblocking agent dibenamine [6], and aminazine [10], and, furthermore, taking into account findings on the alternation of cholinergic and adrenergic neurons in the central nervous system [8, 12], it can be supposed that, in the conduction of an excitation, evoked in the cholinoreactive neurons and apparently causing a tremor, an adrenoreactive link is participating. Support for this is the known fact that a tremor can be observed during the administration of adrenaline.

The aim of the present work was to determine whether it was possible to prevent the tremor, stimulated not only by nicotine but also by arecoline and some AChE-agents, with the help of simpatolitin (a bromide analog of dibenamine). We compared the tremor-resistant activity of simpatolitin with the activity of the M-cholinolytic atropine and the N-cholinolytic nicotine (having in view the second nicotinolytic phase of its action).

EXPERIMENTAL METHOD

The experiments were carried out on 400 male rats weighing 150-180 g. We determined the magnitude of the tremor visually and estimated it as + when the tremor was quite pronounced, and as ± if the tremor was very weak. Lessening of the force of the tremor was considered reliable if the probability of the error of differentiation (according to the criterion of Pearson) does not exceed 0.01. We registered the tremor oscillographically for individual animals.[1] For the sensor, we used a plastic tubule filled with carbon powder; one end of the tube was fixed to the animal (usually at the root of the tail or on the skin in the parietal region). We supplied a steady current to the oscillograph across the sensor and wheatstone bridge. All substances were administered subcutaneously.

[1] The method was worked out with Engineer D. M. Belov.

We applied the simpatolitin in alcohol-water solution, and the other substances in water solutions. We injected the nicotine and simpatolitin at 30 minutes, and the atropine, at 20 minutes, before the administration of the tremor-evoking substances.

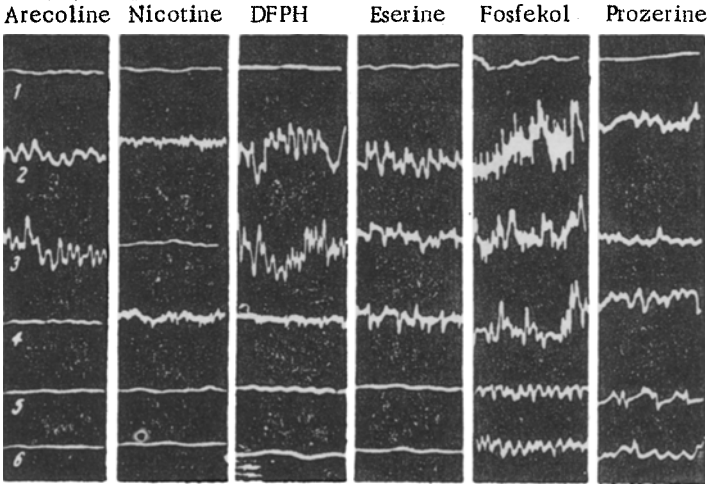
EXPERIMENTAL RESULTS

The results obtained, which are presented in the table and in the figure, testify to the clearly expressed anti-tremor activity of simpatolitin. (The administration of alcohol to the control animals, in the quantity contained in the alcohol-water solution of simpatolitin, did not prevent the evocation of a tremor.)

Changes in the Tremor Aroused in Rats by Cholinomimetic and AChE Substances After Preliminary Administration of Cholinolytics and Simpatolitin

Pharmacological Agent	Dose (in mg/kg)	Dose of Cholinopositive Substances					
		10 mg/kg arecoline	2 mg/kg nicotine	0.7 mg/kg diisopropyl-fluorophosphate	0.4 mg/kg ezerine	0.2 mg/kg fosfakol	0.3 mg/kg prozerine
	Experiment						
Nicotine	2	+	-	+	+	+	+
Atropine	30	-	+	+	+	+	+
Nicotine + Atropine	30	-	-	-	-	±	+
Simpatolitin	120	-	-	-	-	±	+
	Control						
	None Administered	+	+	+	+	+	+

Designations: + Expressed tremor, ± weak tremor, - absence of tremor



Effect of Preliminary Administration of Simpatolitin, Atropine, and Nicotine on the Tremor Evoked by Cholinomimetic and AChE Agents. Doses of the Substances Are the Same as Those in the Table.

Oscillographic Registration of a Tremor Evoked by the Administration of Only One Cholinomimetic or AChE Substance (Control, 2); the Same After Preliminary Administration of Nicotine (3), Atropine (4), a Mixture of Nicotine and Atropine (5), Simpatolitin (6). The Top Graph (1), Is the Recording on an Intact Animal (No Substance Administered).

Simpatolitin completely prevents the tremor evoked by nicotine, arecoline, ezerine (physostigmine) and diisopropylfluorophosphate, and weakens the tremor, evoked as the result of the administration of phosphacol. A prozerine tremor is not weakened by simpatolitin.

Simpatolitin is effective in the same cases where a mixture of atropine and nicotine is effective. The ability of simpatolitin to block a tremor evoked by stimulation of M- and N-cholinoreactive neurons of the brain testifies in favor of the assumption of the presence of an adrenergic link in the chain of processes responsible for the manifestation of a tremor. It is still not clear whether an adrenoreactive link is common for "tremor" paths, at the start of which are M- and N-cholinoreactive neurons, or whether this link is included in each of them. Since Bradley and Mollica [5] showed the presence of a dual (cholino- and adreno-) reactivity of some neurons of the reticular formation, it is also probable that simpatolitin suppresses a tremor, exerting an effect on the metabolism of the same neurons which are excited by cholinomimetic and AChE substances.

SUMMARY

Experiments on rats demonstrated simpatolitin (bromide analog of dibenamine) to be capable of preventing the appearance of tremor following introduction of nicotine, arecoline, eserine, diisopropylfluorophosphate, tends to deminish tremor after injections of phosphacol and does not produce any effect when the tremor is provoked by proserine. A suggestion is made that "tremor" paths, commencing from both M- and H-cholinoreactive neurones of the central nervous system, include an adrenoreactive link.

LITERATURE CITED

1. N. V. Golyakhovskii, Farmakol. i Toksikol., 11, No. 1 (1948), p. 8.
2. N. A. Kharauzov., Pharmacotherapy of Experimental Hyperkineses of Central Origin [in Russian] Doctorate Dissertation (1954).
3. L. Birsis, and A. J. Hemingway, Neurophysiol., 20, No. 1 (1957), p. 91.
4. D. Bovet, and V. J. Longo, Pharmacol. Exp. Ther., 102, No. 1 (1951), p. 22.
5. P. B. Bradley, and A. J. Mollica, Physiol., 140 No. 1 (1958), p. 11.
6. R. L. Cahen, J. M. Thomas, and K. M. Tvede, J. Pharmacol. Exp. Ther., 107, No. 4 (1953), p. 424.
7. G. H. Evert, Nature, 177 (1956), p. 1238.
8. W. S. Feldberg, Pharmacol. Revs., 6, No. 1 (1954), p. 85.
9. H. E. Himwich, and F. Rinaldi, Brain Mech.-M. A. Drug Action - Symposium (Springfield, 1956), p. 15.
10. V. G. Longo, G. P. Berger, and D. Bovet, J. Pharmacol. Exp. Ther., 111, No. 3 (1954), p. 349.
11. A. A. Ward, W. S. McCulloch, and H. W. Magoun, J. Neurophysiol. 11 No. 4 (1948), p. 317.
12. R. P. White, and E. A. Daigneault, J. Pharmacol. Exp. Ther., 125, No. 4 (1959), p. 339.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
