SYNERGISM OF GUANIDINE AND THE MUSCLE-RELAXANT PARAMYON ON NEUROMUSCULAR SYNAPSES

A. I. Podlesnaya

UDC 615.777.156-015.21:615.785.3

In experiments on rats and mice guanidine acted synergically on the blocking of neuromuscular transmission caused by paramyon. Guanidine acts as an antagonist to D-tubocurarine and decamethonium, and has no significant effect on the action of succinylcholine.

* * *

Guanidine selectively stimulates neuromuscular transmission. It acts on motor nerve endings [2, 7, 10, 11]. Antagonism between guanidine and curare was discovered by Rothberger [12] on the gastrocnemius muscle of anesthetized cats during stimulation of the sciatic nerve.

The object of the present investigation was to study antagonism between guanidine and the Soviet muscle-relaxant paramyon, similar to D-tubocurarine in its mechanism of action [1, 3, 9].

EXPERIMENTAL METHOD

Experiments were performed on albino rats weighing 200-300 g anesthetized with sodium amytal (100 mg/kg). Electrical stimulation of the peripheral end of the divided sciatic nerve was carried out using square pulses (0.5 msec, 1-50/sec) from a type IG-6 generator. The voltage varied from 0.2 to 3 V depending on the threshold for each animal. Action potentials in the gastrocnemius muscle were recorded on photographic paper by a "DISA" electromyograph, using coaxial needle electrodes implanted into the muscle.

EXPERIMENTAL RESULTS

In doses of 100-200 mg/kg, themselves capable of producing spontaneous bioelectrical activity of the muscle [8], guanidine inhibited neuromuscular transmission in response to electrical stimulation of the nerve (Fig. 1). Inhibition of muscle electrical activity was particularly intensive when stimulation was

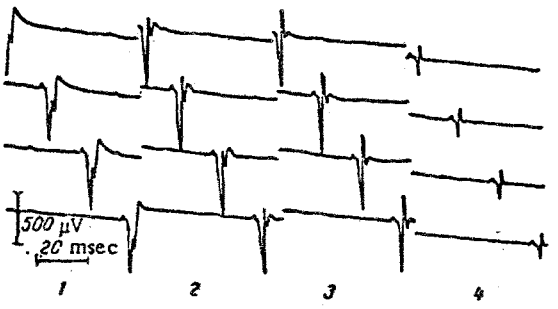

Fig. 1. Effect of guanidine on action potential of gastrocnemius muscle in response to electrical stimulation of sciatic nerve. Parameters of stimulation 10/sec, 0.35 V, 0.5 msec. 1) Normal conditions; 2) 1 min; 3) 3 min; and 4) 20 min after injection of guanidine (100 mg/kg). Amplification 1000 μV/mm; speed 2 mm/msec.

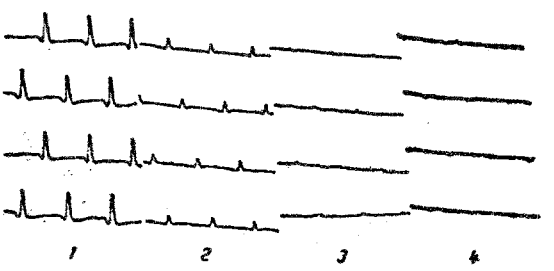

Fig. 2. Combined action of guanidine and paramyon on action potentials of gastrocnemius muscle in response to electrical stimulation of nerve. Parameters of stimulation 0.45 V, 0.5 msec, 50/sec. 1) Normal conditions; 2) 5 min after injection of guanidine (100 mg/kg); 3) 1 min; 4) 45 min after injection of paramyon (0.3 mg/kg). Amplification 100 μV/mm; speed 2 msec/mm.

Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad (Presented by Active Member of the Academy of Medical Sciences of the USSR S. V. Anichkov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 5, pp. 82-84, May, 1968. Original article submitted January 14, 1967.

TABLE 1. Effect of Guanidine on Toxic Action of Muscle-Relaxants

Muscle-relaxant	Dose (in mg/kg)	Control		After guanidine	
		No. of animals dying		No. of animals dying	
		absolute	%	absolute	%
D-tubocurarine	0,5 0,7	56/30	53	34/9	26
Paramyon	0,2	15/4	26,6	20/14	70
Decamethonium	1—2—3	30/13	43	30/2	6,6
Succinylcholine	5	10/8	80	15/11	73

Note. Numerator gives total number of animals; denominator gives number of animals dying.

applied at a frequency of 50 pulses/sec. Paramyon inhibited neuromuscular transmission in doses of 0.3-0.5-1 mg/kg. In some experiments, paramyon in doses of 0.3-0.5 mg/kg did not inhibit neuromuscular transmission, although against the background of guanidine these doses produce a complete block (Fig. 2). Paramyon (1 mg/kg), like guanidine, inhibited neuromuscular transmission initially and for a longer period (up to 2 h) if the nerve was stimulated at the rate of 50 pulses/sec. This was followed by inhibition of the muscle reponse (for 10-15 min) to stimulation of the nerve at the rate of 20, 10, and 1 pulses/sec.

The synergism discovered in the action of guanidine and paramyon on neuromuscular transmission was tested and verified in experiments on albino mice. D-tubocurarine and muscle-relaxants succinylcholine and decamethonium, with depolarizing action, were used for comparison. The experiments showed that guanidine, if injected 30-40 min before the muscle-relaxant, reduced the toxic effect and mortality from poisoning by D-tubocurarine and decamethonium, had no influence on the effects of succinylcholine, and potentiated the toxic action of paramyon (Table 1).

The difference between the toxic action of the muscle-relaxants (except succinylcholine) after guanidine and in the control group is statistically significant ($P < 0.05$). The increase in toxicity of paramyon against the background of guanidine is particularly noteworthy.

In the mechanism of its curare-like action, paramyon is similar to D-tubocurarine [1, 3, 9], but in some effects it differs from the latter. For instance, paramyon inhibits cholinesterase activity [6]. Neostigmine does not prevent paramyon poisoning in mice [4]. The isolated dorsal muscle of the leech, when treated with neostigmine, reacts by contracture to subsequent administration of paramyon [5]. Paramyon stimulates bioelectrical activity of the chronically denervated muscle without subsequent inhibition [8]. These earlier experimental observations demonstrate similarity between paramyon, on the one hand, and decamethonium and succinylcholine on the other. The synergism between guanidine and paramyon distinguishes the latter from muscle-relaxants possessing depolarizing action.

LITERATURE CITED

1. B. M. Butaev, in: Pharmacology of New Therapeutic Agents [in Russian], Leningrad (1953), p. 82.
2. V. M. Karasik, in: Pharmacology of New Therapeutic Agents [in Russian], Leningrad (1953), p. 151.
3. D. S. Paskov, in: Gangliolytics and Blockers of Neuromuscular Synapses [in Russian], Leningrad (1958), p. 158.
4. A. I. Podlesnaya, in: Annual Report of the Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, for 1960 [in Russian], Leningrad (1961), p. 262.
5. A. I. Podlesnaya, Byull. Éksperim. Biol. i Med., No. 5, 78 (1963).
6. A. I. Podlesnaya, Farmakol. i Toksikol., No. 2, 213 (1965).
7. A. I. Podlesnaya, Byull. Éksperim. Biol. i Med., No. 3, 73 (1966).
8. A. I. Podlesnaya, Farmakol. i Toksikol., No. 3, 409 (1966).
9. Hsiao K'un-tsieh, Farmakol. i Toksikol., No. 4, 352 (1959).
10. H. H. Meyer and R. Gottlieb, Experimental Pharmacology as the Basis of Therapeutics [in Russian], Vol. 1, Leningrad (1940).
11. M. Otsuca and M. Endo , J. Pharmacol. Exp. Ther., 128 , 273 (1960).
12. J. C. Rothberger, Pflüg. Arch. Ges. Physiol., 92, 398 (1902).