

EFFECT OF COCAINE ON THE CENTRAL ACTION
OF NORADRENALIN

V. V. Zakusov*

UDC 612.821.41:615.216.2.015.2:615.357.452

The impulse-summation method was used to study the effect of cocaine on the central action of noradrenalin in experiments on rabbits. Cocaine was found to increase this action. Cocaine thus potentiates not only the peripheral effects of noradrenalin, as was already known, but also its central action.

KEY WORDS: cocaine; noradrenalin; impulse summation.

Cocaine is known to potentiate many peripheral effects of catecholamines and, in particular, the stimulant action of adrenalin on the smooth musculature of the eye and blood vessels and its inhibitory action on the smooth musculature of the gastrointestinal tract and urinary bladder [5, 6]. This property of cocaine is nowadays regarded as explaining its effect on catecholamine metabolism and, in particular, on obstruction to the transport of adrenergic mediators back from the synaptic space [7, 8].

The effect of cocaine on the central action of catecholamines, so far as the writer knows, has not been studied and the investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

The effect of cocaine on the central action of noradrenalin was studied by the impulse-summation method [3] in rabbits. The number of stimuli required to produce a flexor reflex of the hind limb was determined. In the first place the doses of cocaine at which facilitation or impairment of impulse summation took place in the central nervous system were found. The doses of noradrenalin, determined in the writer's previous experiments [1, 2], at which it facilitates or impairs impulse summation in the CNS were then verified. For comparison with cocaine amphetamine was used in doses at which facilitation or impairment of impulse summation arises in the CNS.

Experiments were then carried out in accordance with the scheme: cocaine + noradrenalin; noradrenalin + cocaine; amphetamine + noradrenalin; noradrenalin + amphetamine.

All drugs were injected into the auricular vein at intervals of 5, 10, or 15 min.

Three experiments were carried out with each dose of the drug and with each combination of drugs. The active dose of the preparation was regarded as that at which the effect (facilitation or impairment of impulse summation) was observed in not less than 2 of 3 experiments. Altogether 136 experiments were performed. The penetration of noradrenalin into the brain after intravenous injection was demonstrated by the writer previously [4].

EXPERIMENTAL RESULTS

The experimental results are summarized in Table 1.

*Academician of the Academy of Medical Sciences of the USSR.

Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 80, No. 11, pp. 43-45, November, 1975. Original article submitted March 14, 1975.

TABLE 1. Effective Doses of Preparation

Conditions	Dose	
	causing facilitation of summation	causing impairment of summation
Cocaine	0.5 mg/kg	2.5-5 mg/kg
Noradrenalin	0.1 μ g/kg	1 μ g/kg
Amphetamine	0.5 mg/kg	1.5-3 mg/kg
Cocaine + noradrenalin	0.5 mg/kg + 0.01 μ g/kg	2.5 mg/kg + 0.1 μ g/kg
Noradrenalin + cocaine	0.1 μ g/kg + 0.1 mg/kg	1 μ g/kg + 1 mg/kg
Amphetamine + noradrenalin	0.5 mg/kg + 0.01 μ g/kg	1.5 mg/kg + 0.1 μ g/kg
Noradrenalin + amphetamine	0.1 μ g/kg + 0.1 mg/kg	1 μ g/kg + 0.6 mg/kg

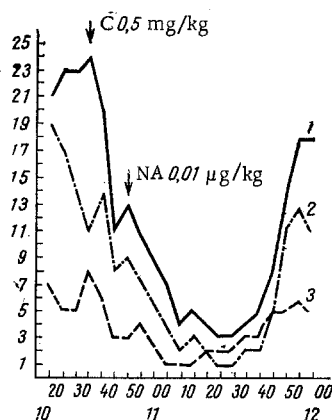


Fig. 1

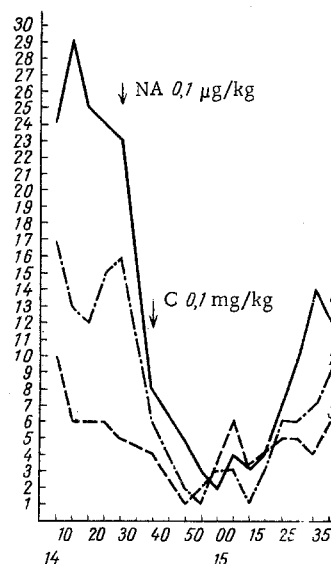


Fig. 2

Fig. 1. Potentiation of action of noradrenalin on impulse summation by cocaine: 1) amplitude of stimuli 5 V; 2) amplitude of stimuli 6 V; 3) amplitude of stimuli 7 V. Arrows indicate times of injection of cocaine (C) and noradrenalin (NA). Abscissa, time (in min); ordinate, number of stimuli.

Fig. 2. Potentiation of action of cocaine on impulse summation by noradrenalin. Legend as in Fig. 1.

As Table 1 shows, both cocaine and amphetamine potentiate the effect of noradrenalin on impulse summation in the CNS, for after injection of these drugs in effective doses noradrenalin had the analogous action in doses equivalent to one-tenth of the threshold (Fig. 1). In precisely the same way, after injection of noradrenalin in an effective dose, cocaine and amphetamine had a stimulant effect on impulse summation in the CNS in doses 3-5 times smaller than the threshold (Fig. 2). Facilitation or impairment of impulse summation could also be obtained by simultaneous injection of cocaine or amphetamine with noradrenalin in doses equivalent to 50% of those giving rise to the corresponding effect separately.

Like amphetamine, cocaine thus potentiates the central action of noradrenalin and noradrenalin potentiates the action of cocaine. Consequently, cocaine potentiates not only the peripheral, but also the central effects of catecholamines.

Considering modern views on the mechanism of action of cocaine, the effects described above must be regarded as the result of impairment of the reassimilation of noradrenalin from the synaptic space of central adrenergic synapses, as a result of which the action of the mediator is potentiated. The mechanism of action of amphetamine is similar. When cocaine is given together with noradrenalin potentiation of the effect occurs because these substances, in combination, exhibit activity in doses equivalent to 25%-10% of the threshold doses.

LITERATURE CITED

1. V. V. Zakusov, Farmakol. Toksikol., No. 1, 8 (1946).
2. V. V. Zakusov, Farmakol. Toksikol., No. 2, 131 (1969).
3. V. V. Zakusov, Farmakol. Toksikol., No. 1, 7 (1971).
4. V. V. Zakusov, N. B. Vysotskaya, and N. S. Tolmacheva, Byull Éksp. Biol. Med., No. 5, 64 (1972).
5. A. Fröhlich and O. Loewi, Arch. Exp. Path. Pharmac., 62, 159 (1910).
6. V. V. Zakusov (W. W. Sakussow), Arch. Exp. Path. Pharmac., 160, 393 (1931).
7. U. Trendelenburg, J. Pharmacol. Exp. Ther., 125, 55 (1959).
8. U. Trendelenburg, in: Handbuch der Experimentellen Pharmacologie (ed. by A. Heffter et al.), Vol. 33, Berlin (1972), p. 726.