ACTION OF FRAGMENTS OF THE COCAINE MOLECULE ON THE CNS

V. V. Zakusov,* L. M. Kostochka, and A. P. Skoldinov

UDC 612.822.014.46:615.216.2:547.944.5

The effect of ecgonine, tropine, tropinone and some of their derivatives, tropane, N-methylpyrrolidine, and N-methylpiperidine on impulse summation in the CNS, the conditioned avoidance reflex, antagonism with hexobarbital, synergism with cocaine, and also their toxicity (LD_{50}) were investigated experimentally. Benzoylecgonine, the methyl ester of ecgonine, ecgonine itself, tropine, pseudotropine, carbomethoxytropinone, tropinone, tropane, N-methylpyrrolidine, and N-methylpiperidine were shown to have a definite stimulating effect on the activity of the CNS and, in this respect, are similar to cocaine. It is concluded that compounds whose molecules contain the structure of tropane or one of its fragments have a central stimulant effect and that the stimulant action of cocaine on the CNS may be associated with the tropane moiety of its molecule.

KEY WORDS: cocaine and its analogs; CNS.

The activity of pharmacological agents depends on their chemical structure and certain types of action of drugs may be associated with particular fragments of their molecule. It was from this standpoint that the writers undertook the analysis of the cocaine molecule, with local-anesthetic and central stimulant effects. It has been known for a long time as a result of many investigations that the local anesthetic effect of cocaine is due to the presence of an ester group attached to the C_2 atom and a benzoyl radical attached to the C_3 atom. Thus benzoylecgonine and the methyl ester of ecgonine have no local-anesthetic properties [1]. No information could be found in the accessible literature on the fragments of the cocaine molecule with which its stimulating action on the CNS is connected.

A pharmacological investigation was accordingly conducted on compounds which could logically be regarded as fragments of the cocaine molecule. The compounds tested were synthesized in the Department of Organic Synthesis, Institute of Pharmacology, Academy of Medical Sciences of the USSR.

EXPERIMENTAL METHOD

The physiological activity of the compounds listed in Table 1 was judged by reference to the following indices: impulse summation in the CNS, the conditioned avoidance reflex, antagonism with hexobarbital, and synergism with cocaine. The local anesthetic action of these compounds also was tested and their toxicity (LD_{50}) determined.

Impulse summation in the CNS was investigated in experiments on rabbits by the method described previously, with determination of the effect of the number and amplitude of the stimuli on the unconditioned reflex response (flexion of the hind limb) [2].

The conditioned avoidance reflex was investigated in rats by the method suggested by Knoll, with recording of the latent period of the motor reflex [jumping on a vertical rod in response to electrical stimulation of the limbs on an "electrode" floor (unconditioned stimulus) combined with acoustic and photic stimuli (conditioned stimuli)].

Antagonism with hexobarbital was determined in albino mice on the basis of shortening the duration of sleep induced by hexobarbital in a standard dose (67 mg/kg), produced by the action of the compound. Synergism with cocaine was determined in rabbits in experiments to

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

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 86, No. 10, pp. 435-438, October, 1978. Original article submitted November 19, 1977.

0007-4888/78/8610-1325$07.50

TABLE 1. Action of Cocaine and Its Analogs on the CNS

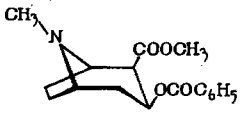
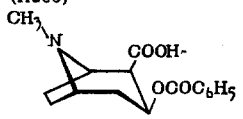
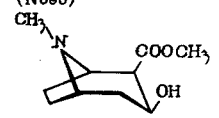
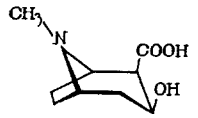
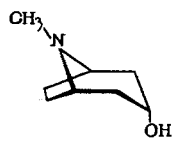
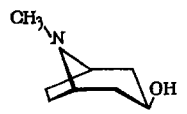
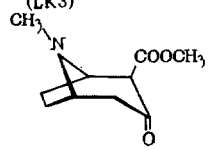
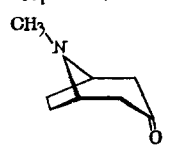
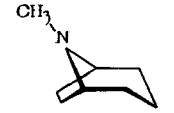
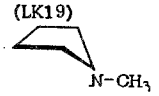
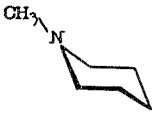
Structure of compounds	Local anesthetic action	Impulse summation		Avoidance reflex (latent preiod)		Effect on activity of			Toxicity (LD_{50}, mg/kg)
		facilitation	impairment	shortening	lengthening	hexabarbital 67 mg/kg (as shortening of sleep)	cocaine (as impulse summation) facilitation	cocaine (as impulse summation) impairment	
Cocaine (methyl ester of benzoylecgonine) 	Strong	0.5-1 mg/kg	2.5-5 mg/kg	1 mg/kg	—	6 mg/kg by 16%	—	—	80
Benzoylecgonine (A285) 	Absent	—	1 mg/kg	1 mg/kg	20 mg/kg	6 mg/kg by 9%	—	A285 0.5 mg/kg C 0.5 mg/kg	152
Methyl ester of ecgonine (N588) 	Absent	0.5 mg/kg	3 mg/kg	1 mg/kg	20 mg/kg	6 mg/kg by 8%	N588 0.25 mg/kg C 0.25 mg/kg	N588 2.5 mg/kg C 1 mg/kg	1000
Ecgonine (N590) 	Absent	0.5 mg/kg	1 mg/kg	1 mg/kg	10 mg/kg	6 mg/kg by 21%	N590 0.25 mg/kg C 0.25 mg/kg	N590 0.5 mg/kg C 0.5 mg/kg	1100
Tropine (LK2) 	Absent	1 mg/kg	10 mg/kg	1 mg/kg	10 mg/kg	6 mg/kg by 5%	—	LK2 1.0 mg/kg C 1.0 mg/kg	800
Pseudotropine (LK6) 	Absent	1 mg/kg	10 mg/kg	1 mg/kg	5 mg/kg	6 mg/kg by 38%	LK6 0.5 mg/kg C 0.5 mg/kg	LK6 2.5 mg/kg C 2.5 mg/kg	690
Carbomethoxytropinone (LK3) 	Absent	1 mg/kg	10 mg/kg	1 mg/kg	20 mg/kg	6 mg/kg by 16%	—	LK3 0.8 0.5 mg/kg C 0.5 mg/kg	140
Tropinone (LK1) 	Absent	1 mg/kg	10 mg/kg	1 mg/kg	10 mg/kg	6 mg/kg by 27%	LK1 0.5 0.5 mg/kg C 0.5 mg/kg	LK1 1 1 mg/kg C 1 mg/kg	430
Tropane (LK17) 	Absent	0.5 mg/kg	10 mg/kg	0.5 mg/kg	10 mg/kg	6 mg/kg by 59%	LK17 0.25 mg/kg C 0.5 mg/kg	LK17 1 mg/kg C 1 mg/kg	160

TABLE 1 (Cont'd)

Structure of compounds	Local anesthetic action	Impulse summation		Avoidance reflex (latent period)		Effect on activity of			Toxicity (LD_{50}, mg/kg)
		facilitation	impairment	shortening	lengthening	hexobarbital 67 mg/kg (as shortening of sleep)	cocaine (as impulse summation) facilitation	cocaine (as impulse summation) impairment	
N-Methylpyrrolidine (LK19) 	Absent	1 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg	6 mg/kg by 18%	LK19 0.1 mg/kg C 0.1 mg/kg	LK19 0.5 mg/kg C 0.5 mg/kg	280
N-Methylpiperidine (LK20) 	Absent	0.5 mg/kg	20 mg/kg	1 mg/kg	10 mg/kg	6 mg/kg by 16	LK20 0.1 mg/kg C 0.1 mg/kg	LK20 0.5 mg/kg C 0.5 mg/kg	400

*All compounds were tested as the hydrochlorides.

study impulse summation in the CNS in response to a combination of cocaine and the test compound.

The toxicity of the compounds was evaluated as the LD_{50} values for albino mice for intraperitoneal injection.

EXPERIMENTAL RESULTS

Examination of Table 1 clearly shows that of all the compounds included in it only the methyl ester of benzoylecgonine (cocaine) has a local anesthetic action. The other compounds, which are fragments of the cocaine molecule, do not possess this property but do have a marked central stimulant effect. According to the data given in Table 1 this effect is a feature of ecgonine and its derivatives (benzoylecgonine, methyl ester of ecgonine), tropine, pseudotropine, tropinone and its derivative carbomethoxytropinone, tropane, N-methylpyrrolidine, and N-methylpiperidine. On the basis of these facts two important conclusions can be drawn: first, a central stimulant action is a feature not only of cocaine, but also of ecgonine, tropine, tropinone, tropane, N-methylpyrrolidine, and N-methylpiperidine, and second, the central stimulant effect of cocaine is due to the tropane moiety of its molecule. If it is recalled that ecgonine, pseudotropine, tropine, tropinone, tropane, N-methylpyrrolidine, and N-methylpiperidine possess an additive effect with cocaine, it can be postulated that their mechanism of action must be similar to that of cocaine.

LITERATURE CITED

1. E. Poulsson, in: Handbuch der Experimentallen Pharmakologie (edited by A. Heffter), Vol. 2, Berlin (1920), p. 103.
2. V. V. Zakusov, Farmakol. Toksikol., 37, 389 (1974).