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O EKSPERIMENTALNOM TREMORU

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THE INFLUENCE OF CNS-DRUGS ON THE ACUTE TOLERANCE TO THE DIFFERENT ACTIVITIES OF OXOTREMORINE

Tolerance is known to develop to certain effects of chronically administered oxotremorine (OT) (1, 2). Acute tolerance to the tremorigenic action of OT has been described in cats decorticated (3), or given the drug into specific cerebral areas (4). In work done last year (5), we found that in mice premedicated on one occasion with tremorine or on two occasions with OT, some effects of OT — such as tremor, motor disturbances, etc. — weakened precipitately, within from a few to 24 hours. The activity of three consecutive intraperitoneal OT injections grew gradually less, as observed on the rotarod (6) (Table I).

Table I

ROTAROD ACTIVITY OF 3 SUBSEQUENT **OT** INJECTIONS (GIVEN AT 0, AT 60 OR 90 MIN, AND AT 120 OR 150 MIN)

Dose and route	% mice dropped off the rotarod after the			
	n	1st	2nd	3rd injection
0.5 mg/kg all i. p.	56	89	29	5
1.0 mg/kg all i. p.	40	100	50	25
0.5 mg/kg i. p., i. p., i. v.,	16	100	19	13
1.0 mg/kg i. p., i. p., i. v.	16	100	40	13

This decline cannot be ascribed to impaired absorption, because when administered intravenously the effect of the third injection was also very weak. We, further, demonstrated that repeated OT injections reduced nicotine and physostigmine lethality in the mouse.

In more recent work, we wished to find out whether acute tolerance might not develop to other effects of OT, and if so, by what mechanism.

We studied OT for its analgesic activity in randomized mice by the hot-plate method. 0.1 mg/kg of OT prolonged the reaction time in the control animals, but exerted no effect whatsoever on mice pretreated 24 hours earlier with 20 mg/kg of tremorine (Table II).

Table II

ANALGESIC ACTIVITY OF OT ASSESSED ON THE HOT PLATE

Pretreatment — 24 hours	n	Dose of OT, i. p. O hour	Increments in reaction time (seconds) (median and range)
NaCl	12	0.05 mg/kg	5.5 (—7 and 41)
Tremorine 20 mg/kg	12	0.05 mg/kg	— 1.5 (—13 and 9)
NaCl	12	0.10 mg/kg	32.5 (20 and 47) x
Tremorine 20 mg/kg	12	0.10 mg/kg	0 (—24 and 22) xx

x — xx : $p < 0.01$

Tremorine administered twice daily for three consecutive days did not diminish the ability of OT to potentiate pentobarbital narcosis.

Spontaneous motility in mice was measured with the motimeter devised by Knoll and Vajnovszky (7) in 10 times 50 cm channels, in which the animals close the circuit each time they step over from one square into another. 0.05 mg/kg of OT substantially weakened spontaneous motility, even when administered repeatedly. In animals treated at five 90-min intervals with physiological saline, motility — as measured after each injection for 30 min — was found to decline substantially from one measurement to the other, presumably due to gradual extinction

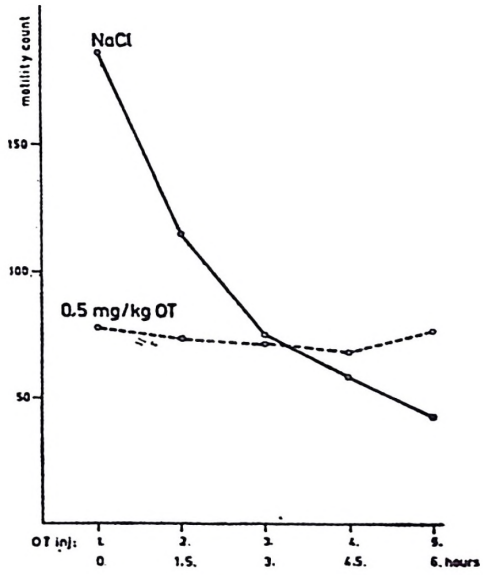

Fig. 1

of the orientatory searching reflex. (Fig. 1). In mice treated with 0.5 mg/kg of OT in the same manner, the first injection decreased motility to 41% of control value, but the subsequent three injections did not cause it to decline parallel with that value; on the contrary, the fifth increased it as compared with the saline-group.

In other experiments we found that premedication with OT did not inhibit the lethality of carbachol and neostigmine not passing through the blood-brain barrier; in contrast to nicotine and physostigmine lethality which repeated OT injections did reduce. On this basis we assumed that acute tolerance is of central nervous system origin and studied the question whether it is influenced by certain pharmaca that act on the CNS. Pretreatment with 40 mg/kg of phenobarbital prolonged the effect of OT and inhibits the development of acute tolerance. (Fig. 2).

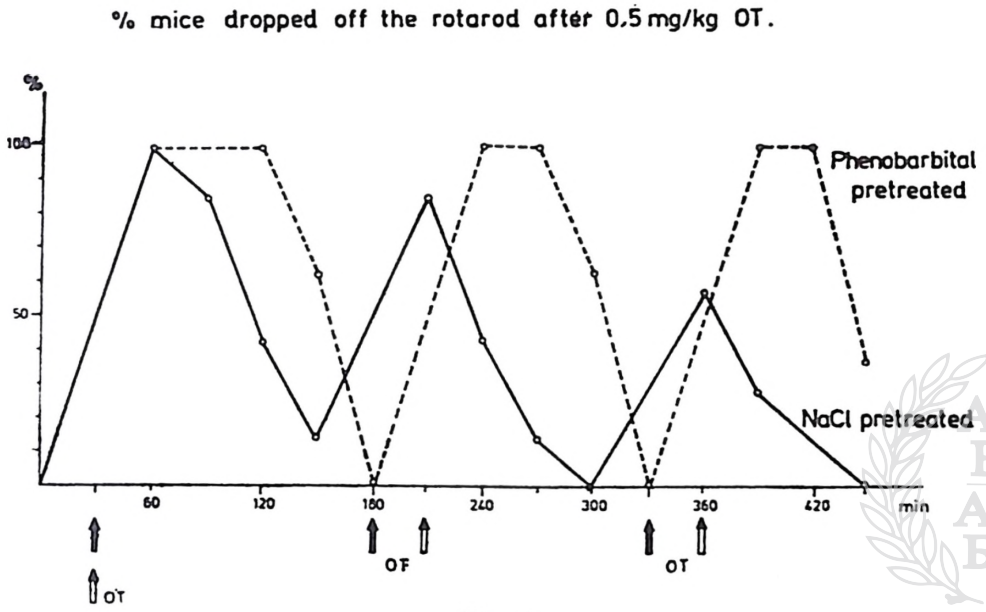

Fig. 2

When acute OT tolerance had already developed, the fourth injection of the drug was ineffective, but 0.05 to 0.1 mg/kg of haloperidol, which possesses anticatecholamine activity, given before the fourth injection, re-established its effect (Table III). For that matter, these haloperidol doses failed to potentiate the activity of small doses of OT.

Table III

INFLUENCE OF HALOPERIDOL ON THE ACUTE OT-TOLERANCE ASSESSED ON THE ROTAROD

Treatment after the 3rd 0.5 mg/kg OT-dose i. p.	n	Number of mice dropped off the rotarod after the 4th dose of OT	
NaCL	46	6	(13%)
0.05 mg/kg haloperidol	46	26	(57%)
0.10 mg/kg haloperidol	37	30	(81%)

Acute tolerance to OT was inhibited by 1 mg/kg of reserpine administered 18 hours before the drug; 10 mg/kg of tranylcypromine, 2 mg/kg of desmethylimipramine or 2 mg/kg of DL-amphetamine accelerated it. Such small doses of the three last mentioned compounds possess no anti-OT activities.

The behavioral effects of, and vegetative reactions to, OT were studied on cats. When preceded by 0.5 mg/kg of atropine methylbromide, the same dose of OT elicited a typical rage reaction Three or four daily OT injections repeated on three to four consecutive days — with atropine methylbromide given once daily — failed to slacken the intensity of the reaction, and no tolerance to it developed. Rage reaction was invariably accompanied by a sympathetic excitatory process. This was evident from our finding that in cats superficially anaesthetized with urethane, immobilized with gallamine, and premedicated with atropine methylbromide, the drugs, OT, arecoline, and pilocarpine caused contraction of the innervated, but not of the decentralized, nictitating membrane. This action is definitely central in origin, for ganglionic blocking agents and small doses of haloperidol or reserpine inhibit it. Its cholinergic origin is borne out by the fact that physostigmine increases it. This sympathetic response presents itself in animals pretreated with OT, and repeated injections of the drug heighten rather than lessen it.

To sum up, in the mouse tolerance develops to various effects of OT and is probably of central origin, possibly mediated by catecholamines. No acute tolerance to the stimulating effects of oxotremorine has been observed in cat-experiments.

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UTJECAJ CNS-LIJEKOVA NA AKUTNU TOLERANCIJU RAZLIČITIH AKTIVNOSTI OKSOTREMORINA

KRATAK SADRŽAJ

Dvije ili tri konsekutivno 0,5 do 1,0 mg/kg davane doze oksotremorina u mišu postepeno oslabe aktivnosti grupa za izazivanje koordinativnog motornog poremećaja (rotarod) koji izaziva tremor i pri reduciranju spontanog motiliteta. Jedna doza tremorina sprečava ova djelovanja oksotremorina, kao i njegovu analgetsku aktivnost, ali ne utiče na njegovu sposobnost jačanja pentobarbitalne narkoze. Dvije slijedeće doze 1,0 mg/kg oksotremorina reduciraju smrtonosnu toksičnost fizostigmina i nikotina, ali ne utiču na karbahol i neostigmin. Premedikacija fenobarbitonom sprečava razvoj koordinativne motorne smetnje izazvane oksotremorinom, a naredno liječenje vrlo niskom dozom haloperidola dovodi do intolerancije.

Nagoviješteno je da u razvoju akutne tolerancije na oksotremorin glavnu ulogu igra centralno proturegulatorno stimulativno djejstvo pokreta izazvanog aktivnošću grupa. Moguće je da je stimulativno djej-

stvo oksotremorina skriveno iza nekog drugog jačeg djejstva. U eksperimentima sa mačkama nije ispitivana akutna tolerancija na karakteristični stimulativni efekt.

REFERENCES

1. Decsi, L., Varszegi, M. and Méhes, Gy.: Tolerance to tremorine. J. Pharm. Pharmacol., **13:** 127, 1961.
2. Keranen, G. M., Zaratzian, V. L., and Coleman, R.: Studies on 1,4-Dipyrrolidino-2-butyne (Tremorine) in Mice. Toxicol. Appl. Pharmacol., **3:** 481 — 492, 1961.
3. Decima, E. E. and Rand, R. W.: Oxotremorine induced tremor in the decorticated cat. Int. J. Neuropharmacol., **4:** 139—148, 1965.
4. George, R., Haslett, W. L., Jenden, D. J.: The production of tremor by cholinergic drugs: central sites of action. Int. J. Neuropharmacol., **5:** 27 — 34, 1966.
5. György, L., Gellén, B., Pfeifer, A. K., Dóda, M. and Bite, Á.: Oxotremorine: acute tolerance to it and its central »cholinolytic« effect in mice. J. Pharm. Pharmacol., **22:** 385 — 386, 1970.
6. Oelszner, W.: Der Tremor und seine pharmakologische Beeinflussung, insbesondere durch Antiparkinsonmittel. Acta Biol. Med. Germ. suppl. 1., 46 — 64, 1961.
7. Knoll, J. and Vajnovszky, B.: Motimeter, a new sensitive apparatus for the quantitative measurement of hypermotility caused by psychostimulants. Arch. Int. Pharmacodyn. Ther., **130:** 141 — 154, 1961.

DISCUSSION

Stern: I think that the tolerance to oxotremorine can be explained by acting of increased quantities of ACh upon cholinacetylase. It is well known that oxotremorine activates cholinacetylase, because of that more ACh is produces and that inhibits this ferment.

György: We have not examined the effect of oxotremorine on the cholinacetylase; we have some negative results about the role of acetylcholinesterase inhibiting activity of OT. We do not suppose that these activities of OT play a role in the tolerance phenomenon.