Phenitrone: ineffective blockade of (—)-trans-Δ^9-tetrahydrocannabinol in mice and dogs

Phenitrone (*m*-nitrophenyl-2-azocycloheptylethyl ketone), when administered either before or after hashish, has been reported by Kudrin & Davydova (1968) to abolish intoxication in the dog as a result of inhalation of vaporized cannabis extract (10–20 mg/kg). In direct contrast, we have found in three separate experiments employing mice and dogs that phenitrone is completely *ineffective* in blocking the effects of (—)-*trans*-Δ^9-tetrahydrocannabinol (THC), the major active component of marihuana and hashish (Mechoulam, 1970).

Kudrin and Davydova claimed that phenitrone, which was originally studied in experimental hypertension, promptly eliminated all of the hashish effects, namely dilatation of the pupils, salivation, catalepsy, weakened muscle tone, inability to remain upright, and increased defecation and urination. In an earlier communication (Krantz, Berger, & Welch, 1971), we reported that cannabinol, a structural analogue of THC, blocked potentiation by THC of pentobarbitone sleeping time in mice. We were also interested in phenitrone as a possible antagonist to THC.

In the first experiment, we evaluated the effects of phenitrone* pretreatment on prolongation by THC (20 mg/kg, i.p., dissolved in propylene glycol with 1% Tween 80) of pentobarbitone (40 mg/kg, i.p.) sleeping time in male CD-1 mice, 30–40 g. The interval between all injections was 10 min. Phenitrone was administered at 20 and 50 mg/kg, i.p. The time from the loss to the regaining of the righting reflex was recorded as the "sleeping time." Whenever one animal was checked for the return of the righting reflex, animals still asleep were also checked to standardize external stimulation.

The pentobarbitone sleeping time was 44 $\pm$ 10·6 min. Phenitrone pretreatment did not significantly alter this control level, producing times of 46 $\pm$ 8·2 min for the 20 mg/kg dose and 41 $\pm$ 6·4 min for the 50 mg/kg dose. As expected, THC prolonged the pentobarbitone sleeping time to 91 $\pm$ 9·5 min. Administration of phenitrone before THC did not block prolongation by THC, yielding times of 87 $\pm$ 6·9 and 89 $\pm$ 4·3 min for the low and high doses.

In another experiment, we attempted to block the common dyssynergic effects of THC, using a rotating rod apparatus in mice. Untreated animals were placed on a horizontal wooden rod 3 mm in diameter and rotating at 5 revolutions per min. Animals that remained on the rod for 180 s or more in two successive trials were selected for inclusion in experimental groups. Mice were placed on the rod 30 min after THC administration. Results are expressed as the fall off time and as the mean reduction of group performance in comparison to controls.

Animals administered either phenitrone or vehicle remained on the rod for longer than 180 s. THC caused an 82% reduction in fall off time (32 $\pm$ 4·2 s), while phenitrone pretreatment produced approximately the same reduction, namely 77% and 80% for the 20 and 50 mg/kg doses (41 $\pm$ 3·1 and 36 $\pm$ 5·1 s). This would indicate that phenitrone unable to antagonize the effects of THC.

In an experiment in dogs (male mongrels, 8–12 kg), gross behaviour, ecg, and respiratory and heart rates were observed. Phenitrone (20 mg/kg, i.p.) administered to animals anaesthetized lightly with pentobarbitone caused a 20–25% decrease in heart and respiratory rates, but no changes in ecg.

To duplicate as closely as possible the study of Kudrin & Davydova, we injected THC in conscious dogs at 0·5 to 3·0 mg/kg (i.v.) preceded or followed by phenitrone

* Synthesized for us by Aldrich Chemical Co.

at 10, 20, 40, or 50 mg/kg (i.p.). *In no experiment* did phenitrone alter the ataxic state produced by THC or abolish its characteristic effects (Grunfeld & Edery, 1969).

The results of these three experiments, contrary to those of Kudrin & Davydova demonstrate that phenitrone is ineffective in the blockade of THC in dogs and mice. It seems improbable that these differences could be due to our use of THC by injection and their use of hashish extract by inhalation.

We thank Dr. John A. Scigliano, Executive Secretary, Psychotominetic Agents Advisory Committee, NIMH, for generously supplying the THC (Batch SSC-61958 95·4% pure) and Drs. Raymond N Burgison and Frieda G. Rudo, Department of Pharmacology, School of Dentistry of the University of Maryland for their assistance in the experiments with dogs.

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March 13, 1972

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Potentiation of responses to and inhibition of extraneuronal metabolism of catecholamines by veratrine

Uptake into neuronal structures is generally regarded as the dominant mechanism limiting the magnitude and duration of catecholamine action at the receptors of sympathetically innervated effectors (Trendelenburg, 1966; Iversen, 1971; Axelrod, 1971). Recent work has demonstrated, however, that the action of noradrenaline and adrenaline in vascular tissue is terminated by their penetration of effector cell membranes and subsequent metabolism (Kalsner, 1966; Kalsner & Nickerson, 1969a, b; Kalsner, 1971). In addition, the sensitization of responses to sympathomimetic amines by several diverse groups of agents (e.g. steroids, haloalkylamines, methylxanthines) has been linked to inhibition of amine inactivation in effector cells (Kalsner & Nickerson, 1969b; Kalsner, 1969a, b; Kalsner, 1971). We wish to report the finding that veratrine (cevadine), a veratrum alkaloid, also enhances responses of arterial strips to adrenaline and noradrenaline and inhibits the extraneuronal metabolism of these amines.

Rabbit aortic strips were prepared for isotonic recording as described previously (Kalsner & Nickerson, 1968a). The strips were suspended under 2 g tension at 37° in drain-out muscle chambers containing Krebs-Henseleit (Krebs) solution and contractions and relaxations were recorded on a slowly-moving kymograph drum (1·8 mm/min). The procedure of oil-immersion has been described in detail (Kalsner & Nickerson, 1968a). Aortic strips were contracted in the aqueous medium and after responses had plateaued the muscle chambers were emptied and filled with warmed (37°) and oxygenated (95% O_2 - 5% CO_2) mineral oil and relaxations recorded. The purpose of oil-immersion is to eliminate diffusion of agonist from the tissue into the aqueous bathing medium. Relaxation in oil is a measure of the rate of inactivation (termination of action) by intrinsic mechanisms (Kalsner & Nickerson 1968a, b). Concentrations of (−)-noradrenaline and adrenaline bitartrates, (±)-