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# EFFECTS OF N,N-DIMETHYLTRYPTAMINE ON ELECTRICALLY EVOKED RESPONSES IN THE CAT VISUAL SYSTEM AND MODIFICATION BY NEUROLEPTIC AGENTS*†

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**Summary**—The effects of N,N-dimethyltryptamine on electrically evoked potentials in the visual system of the cat and the interaction of selected neuroleptic agents with dimethyltryptamine were studied. Dimethyltryptamine caused a dose-dependent decrease in the amplitude of the response evoked by stimulation of the optic chiasm as recorded in the lateral geniculate nucleus and the visual cortex. Dimethyltryptamine had no significant effect on antidromically evoked potentials in the lateral geniculate nucleus or potentials in the visual cortex produced by optic radiation stimulation. A dose-dependent biphasic effect was found in animals pretreated with various doses of chlorpromazine, haloperidol, thiothixene, molindone, methiothepin and octoclothepin. Methiothepin and octoclothepin were the most potent antagonists of dimethyltryptamine, while molindone was essentially ineffective. Low doses of the neuroleptics, with the exception of molindone, potentiated the inhibitory action of dimethyltryptamine on evoked responses.

N,N-Dimethyltryptamine is a known hallucinogen. When given parenterally to normal human volunteers, it produces a model psychosis with mental, autonomic and behavioural effects. One of the most prominent features is colourful, brightly-lit, rapidly-changing visual illusions and hallucinations (BÖSZÖRMENYI and SZARA, 1958; SAI-HALÁSZ, BRUNECKER and SZARA, 1958). EVARTS (1958) in a series of classical experiments demonstrated that intracarotid administration of dimethyltryptamine had a depressant effect on the cat lateral geniculate nucleus. The purpose of the present investigation was to establish the dose–effect relationships between intravenously administered dimethyltryptamine and electrically evoked potentials in the cat visual system. Additionally, the interaction of selected neuroleptic agents with dimethyltryptamine was studied in search of specific agents which may be of therapeutic value in the treatment of indole hallucinogen overdose, and as possible new treatments for some schizophrenic patients.

## METHODS

Adult cats (2–4 kg) were utilized. Anaesthesia was induced by ketamine (15 mg/kg, i.m.) and maintained by α-chloralose (60 mg/kg, i.p.). A tracheotomy was performed and a cannula inserted. The saphenous vein was cannulated for drug administration. The femoral artery was cannulated to record arterial blood pressure, which was monitored throughout the experimental period. The animal was fixed in a stereotaxic apparatus, gallamine (10 mg/kg, i.v.) was administered to produce skeletal muscle relaxation and the cat was artificially respired.

End tidal $CO_2$ was maintained between 3.5 and 4.0% and blood pH at 7.4. Body temperature was held between 37 and 40°C by means of a water-filled heating pad. Blood pressure was recorded from the femoral artery by means of a Statham P23AA pressure transducer and a Grass 7 polygraph.

The cranium was exposed by a midline scalp incision and a partial craniotomy performed in order to place electrodes in the optic chiasm, lateral geniculate nucleus, optic radiation and visual cortex. The exposed area was covered with a pool of mineral oil maintained at approx. 38°C. The optic chiasm was stimulated for orthodromic firing of the lateral geniculate nucleus and the visual cortex. A second pair of electrodes was inserted into the optic radiation, allowing antidromic stimulation of the lateral geniculate nucleus and monosynaptic stimulation of the visual cortex. The intensity of the stimuli was varied so as to produce a near maximal response.

A monopolar surface recording electrode was placed on the visual cortex (A17).

All drugs were given intravenously. Dosages were expressed as base content. Each dose of dimethyltryptamine was given following complete recovery from the previous dose. Recovery ranged from about

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15 min with the lowest dose of dimethyltryptamine (32 μg/kg) to approx. 1 hr with a dose of 1 mg/kg. For each drug tested a minimum of 4–6 cats were used to obtain the mean data.

Drugs used in this study included N,N-dimethyltryptamine (Sigma Chemical Company, St. Louis, MO), chlorpromazine hydrochloride (Smith, Kline & French Laboratories, Philadelphia, PA), haloperidol (McNeil Laboratories, Inc., Fort Washington, PA), methiothepin maleate and octoclothepin methane sulphonate (Hoffman–LaRoche, Inc., Nutley, NJ and SPOFA, Praha, Czechoslovakia), thiothixene (Pfizer, Inc., Brooklyn, NY) and molindone (Endo Laboratories, Inc., Garden City, NY).

## RESULTS

### *Effects of dimethyltryptamine on visual evoked potentials*

A dose-dependent relationship between dimethyltryptamine and depression of electrically evoked potentials in the visual system was established. The numerical values given refer to the percent change in the first wave of the potential as recorded in the visual cortex. This corresponds to the $P_1$ wave as described by BISHOP and O'LEARY (1938). The other waves measured were altered similarly to the initial negative wave in most instances.

Dimethyltryptamine caused a dose-dependent inhibition of the evoked potential induced by stimulation of the optic chiasm. A decrease in the size of the potential was recorded at the lateral geniculate nucleus and at the visual cortex as illustrated in Figure 1.

A dose of 32 μg/kg dimethyltryptamine decreased significantly ($P < 0.05$) the visual evoked response produced by optic chiasm stimulation as recorded at the visual cortex (Fig. 1). Increasing the dose of dimethyltryptamine to 320 μg/kg caused approximately a 50% reduction in the potential; a dose of 1 mg/kg completely suppressed the response.

In contrast to the depression of the potentials produced by stimulation of the optic chiasm, dimethyltryptamine had little effect on antidromic lateral geniculate nucleus or orthodromic cortical potentials evoked by stimulating the optic radiation as illustrated in Figure 1. No significant change in these potentials was seen until a dose of 3.2 mg/kg dimethyltryptamine was administered. Even at this dosage the mean depression ±S.E. was minimal (14 ± 3.2%).

### *Effects of chlorpromazine on dimethyltryptamine-induced suppression of visual evoked responses*

Pretreatment of the animals (15 min) with chlorpromazine (as well as the other neuroleptics studied) did not significantly alter the lateral geniculate nucleus or visual cortical potentials. In 4 animals pretreated with 1 mg/kg of chlorpromazine, the dose–response curve of dimethyltryptamine was shifted to the left (see Fig. 2). The dimethyltryptamine-induced suppression was potentiated so that 100 μg/kg caused over a 50% reduction and 320 μg/kg abolished the potential, as compared with 320 μg/kg and 1 mg/kg respectively in unpretreated animals. Increasing the dose of chlorpromazine to either 3.2 or 10 mg/kg partially antagonized the inhibitory effects of dimethyltryptamine. The dose–response curve was now shifted to the right so that a dose of 3.2 mg/kg dimethyltryptamine was required to completely inhibit the evoked response.

### *Effects of haloperidol on dimethyltryptamine-induced suppression of visual evoked responses*

Haloperidol pretreatment (1 mg/kg, i.v.) produced effects similar to those with the same dose of chlorpromazine. Again, the neuroleptic agent caused a potentiation of the inhibitory effect of dimethyltryptamine (see Fig. 3). Haloperidol (3.2 mg/kg) caused a slight antagonism of the depressant action of dimethyltryptamine (slightly to the right). Increasing the dose of haloperidol to 10 mg/kg shifted the dose–response curve of dimethyltryptamine even more to the right.

### *Effects of thiothixene on dimethyltryptamine-induced suppression of visual evoked responses*

With pretreatment doses of 1 or 3.2 mg/kg thiothixene, little or no antagonism of the inhibitory actions of dimethyltryptamine were seen (see Fig. 4). Indeed, with the lower pretreatment dose, there was some potentiation of dimethyltryptamine. By increasing the dose of thiothixene to 10 mg/kg, a shift of the dose–response curve to the right was obtained.

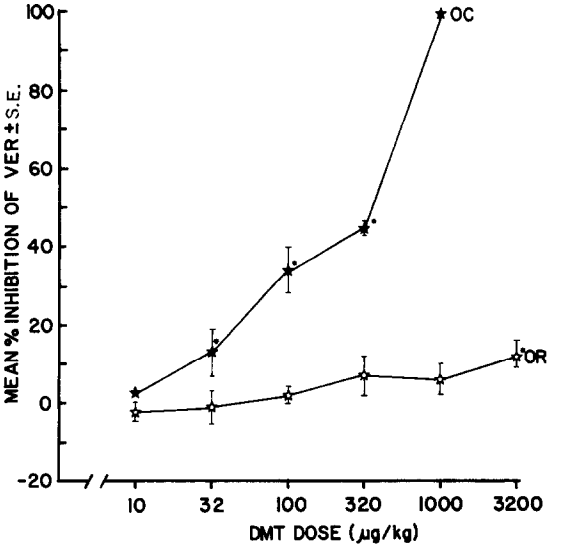


Fig. 1. Effects of increasing doses of dimethyltryptamine (DMT) on visual evoked responses (VER) induced by electrical stimulation of the optic chiasm (OC) or optic radiation (OR).

In this and all subsequent figures the asterisks (*) represent the $P$ values for a group comparison $t$-test to 0.9% NaCl control as follows: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. The VER graphed is the mean % amplitude of the $P_1$ potential in the visual cortex.

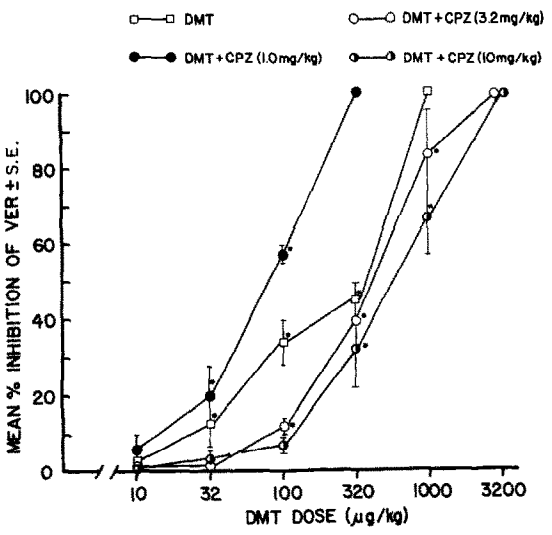


Fig. 2. Effects of chlorpromazine(CPZ) on dimethyltryptamine(DMT)-induced suppression of visual evoked responses(VER).

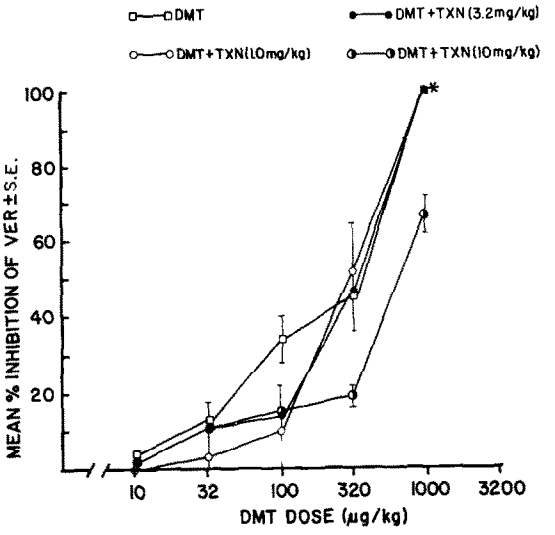


Fig. 4. Effects of thiothixene(TXN) on dimethyltryptamine(DMT)-induced suppression of visual evoked responses(VER).

*Effects of molindone on dimethyltryptamine-induced suppression of visual evoked responses*

Pretreatment of the animals with the indole molindone did not markedly alter the dimethyltryptamine dose–effect curve (Fig. 5). In doses of 1 and 3.2 mg/kg, molindone had little effect on dimethyltryptamine-induced inhibition, while 10 mg/kg of the drug produced a slight shift of the dose–effect curve to the right.

*Effects of methiothepin on dimethyltryptamine-induced suppression of visual evoked responses*

A dose-dependent biphasic effect on dimethyltryptamine-altered evoked potentials was obtained in animals pretreated with methiothepin. The inhibitory effects of dimethyltryptamine on potentials elicited by optic chiasm stimulation were antagonized in a dose-dependent manner by methiothepin in doses of 0.32 and 1 mg/kg (see Fig. 6). The results of experiments in which a pretreatment dose of 0.1 mg/kg methiothepin was given were superimposable on the dimethyltryptamine alone curve. Lowering the dose of methiothepin to 0.032 mg/kg potentiated the depressant action of dimethyltryptamine, with the larger doses (0.32 and 1 mg/kg) having the opposite effects.

*Effects of octoclothepin on dimethyltryptamine-induced suppression of visual evoked responses*

Octoclothepin, in a dose-related manner (1, 3.2 and 10 mg/kg) produced increasing antagonism of dimethyltryptamine depressed potentials (see Fig. 7). Octoclothepin (0.32 mg/kg) caused a slight shift of the dose–effect curve of dimethyltryptamine to the left.

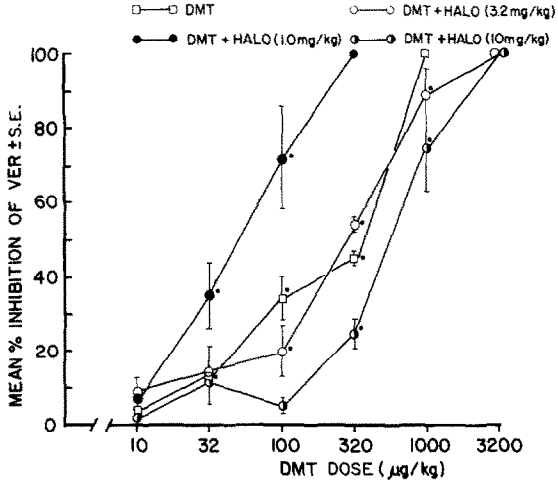


Fig. 3. Effects of haloperidol(HALO) on dimethyltryptamine(DMT)-induced suppression of visual evoked responses(VER).

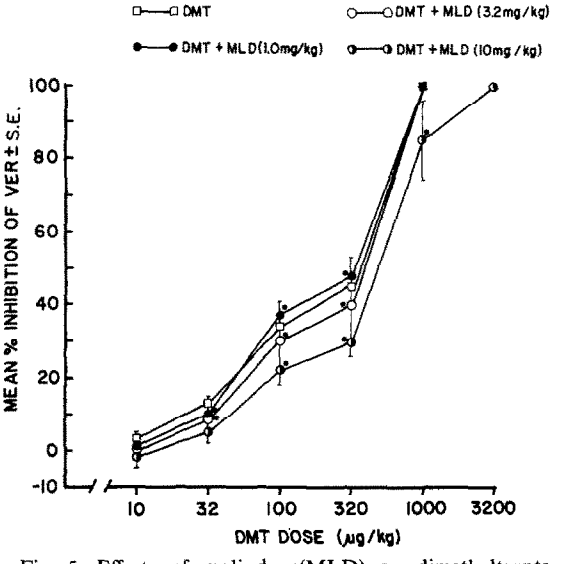


Fig. 5. Effects of molindone(MLD) on dimethyltryptamine(DMT)-induced suppression of visual evoked responses(VER).

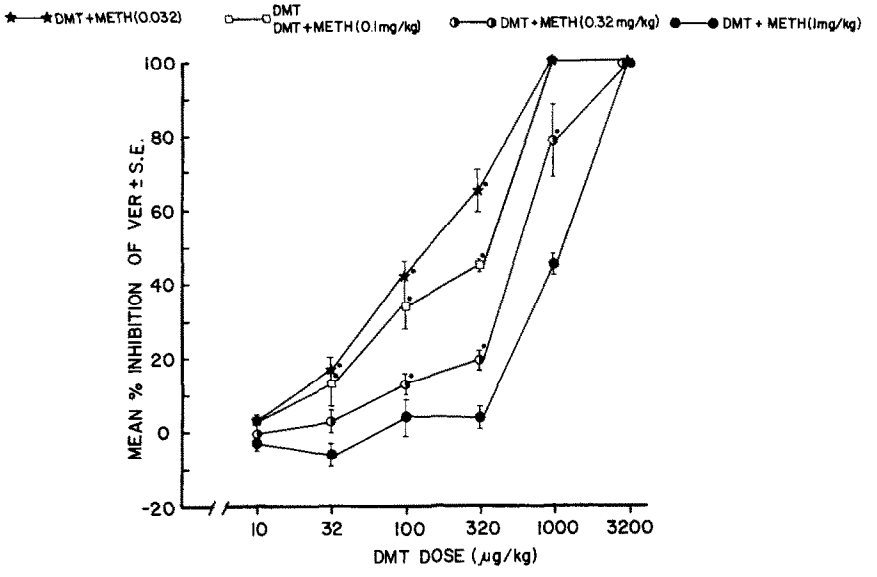


Fig. 6. Effects of methiothepin(METH) on dimethyltryptamine(DMT)-induced suppression of visual evoked responses(VER).

## DISCUSSION

This investigation stresses the dose–effect relationships between dimethyltryptamine and evoked potentials in the cat visual system. The results indicate that intravenous dimethyltryptamine in a dose-dependent manner had a depressant action on retino-geniculate transmission in doses that did not affect transmission between the lateral geniculate nucleus and the visual cortex. These results are in accordance with those previously reported by EVARTS (1958). In studying the effects of a series of indoles on lateral geniculate nucleus transmission in acute cat preparations, Evarts found that 400 μg/kg dimethyltryptamine administered intracarotid caused 80–100% inhibition of geniculate transmission, but had no effect on cortical responses to optic radiation stimulation. Similar results were obtained with lysergic acid diethylamide (LSD-25, 30 μg/kg, 30–100% inhibition), tryptamine (200 μg/kg, 50–100% inhibition), and bufotenin (200 μg/kg, 50–90% inhibition). Similarly, these latter agents decreased geniculate transmission without affecting geniculo-cortical transmission. KHAZAN and MCCASH (1965) found that LSD-25, dimethyltryptamine and N,N-diethyltryptamine administered intravenously exerted a depressant effect on photic evoked responses in unanaesthetized rabbits. Recently, HEISS, HOYER and POUSTKA (1973) also demonstrated that dimethyltryptamine had a depressant effect on photically evoked cortical potential in cats, results consistent with an action of dimethyltryptamine at the lateral geniculate nucleus.

Information on the interactions of dimethyltryptamine with neuroleptic drugs is scarce. KOVACIC and DOMINO (unpublished observations) have demonstrated that chlorpromazine pretreatment significantly prolonged the duration of disruption of food-rewarded barpressing ($FR_4$) produced by dimethyltryptamine in rats. DEFRANCE, MCCREA and YOSHIHARA (1975) reported dimethyltryptamine administered topically, 0.1–1.0% by weight; intravenously, 1.0–5.0 mg/kg; and microelectrophoretically caused excitation of cells in the hippocampus and this excitation was blocked by methiothepin, whereas chlorpromazine was ineffective in preventing dimethyltryptamine excitation.

Methiothepin (1 mg/kg) and chlorpromazine (1 mg/kg) were found to antagonize dimethyltrypta-

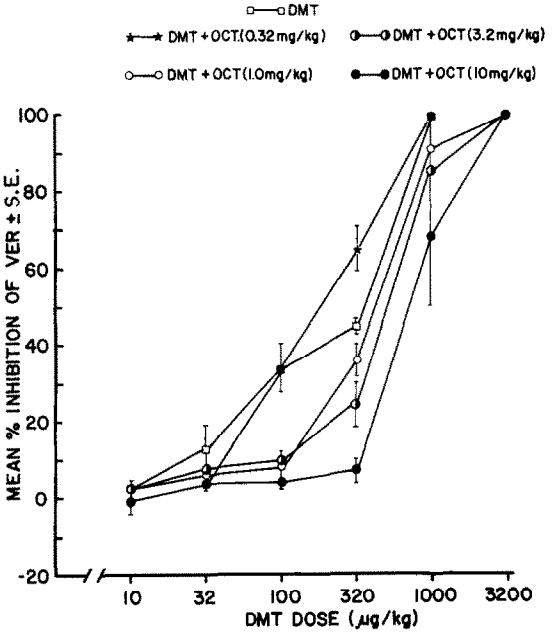


Fig. 7. Effects of octoclothepin (OCT) on dimethyltryptamine (DMT)-induced suppression of visual evoked responses (VER).

mine-induced hyperthermia, mydriasis and electroencephalographic activation in rabbits (MOORE, DEMETRIOU and DOMINO, 1975). Methiothepin has been reported to block serotonergic receptors in the brain as indicated by increased serotonin turnover (MONACHON, BURKARD, JALFRE and HAEFELY, 1972), to antagonize the depressant effects of iontophoretically administered serotonin on single cells in the lateral geniculate nucleus (TEBÉCIS, 1972), and to block dopamine and norepinephrine centrally as evidenced by elevated brain homovanillic acid and 3-methoxy-4-hydroxyphenylethylene glycol levels (KELLER, BARTHOLINI and PLETSCHER, 1973).

In the present study, methiothepin was found to be the most potent of the drugs employed in blocking the inhibitory effects of dimethyltryptamine on electrically evoked response. Doses of 0.32–1.0 mg/kg sequentially shifted the dose–response curve to the right. Octoclothepin ranked next in potency, while ten-fold increases in the dose over that of methiothepin were required for chlorpromazine, haloperidol and thiothixene to exhibit good antagonism. Even in doses as large as 10 mg/kg, molindone was a poor antagonist of dimethyltryptamine.

These results are somewhat consistent with the results of other workers in experiments comparing the potency of selected neuroleptics in blocking certain neurotransmitters. KELLER *et al.* (1973) showed that methiothepin was more potent than haloperidol, which in turn was more potent than chlorpromazine in increasing the content of 3-methoxy-4-hydroxyphenylethylene glycol in rat brain. The same order of potency has been reported in continuous shock avoidance studies in squirrel monkeys (Hoffman–LaRoche, Inc., personal communication). Methiothepin and haloperidol have been reported to be more potent than chlorpromazine in antagonizing apomorphine-induced stereotypy in rats (Hoffman–LaRoche, Inc., personal communication).

From the results obtained, it seems apparent that most neuroleptic agents, in sufficient dosages, are capable of blocking dimethyltryptamine-induced depression of responses at the lateral geniculate nucleus and visual cortex produced by electrical stimulation of the optic chiasm. The potency of the agents in blocking the actions of dimethyltryptamine may well be related to their relative antagonism of serotonin or tryptamine. As stated earlier, all three of these agents block apomorphine-induced stereotypy in mice, methiothepin and haloperidol being more potent than chlorpromazine (Hoffman–LaRoche, Inc.). Such stereotypy is thought to be due to stimulation of dopamine receptors. Concerning serotonin antagonism, methiothepin increased *p*-chlorophenylalanine or 2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo-α-quinolizine (Ro4-1284)-induced post-geniculo-occipital spikes, while chlorpromazine and haloperidol were without effect (MONACHON *et al.*, 1972).

A unique finding in the present study was that potentiation of the effects of dimethyltryptamine were seen with all of the neuoleptics used, except molindone. This may be related to dopamine blockade, enhanced dimethyltryptamine brain levels due to altered metabolism, or to altered transport mechanisms, possibilities now being investigated in our laboratory.

The degree of antagonism of dimethyltryptamine by neuroleptics used in this investigation are probably related to their relative serotonergic and/or tryptaminergic antagonistic effects. It is of importance to discover if methiothepin and octoclothepin are merely acting like chlorpromazine and haloperidol or if they are unique in blocking indole receptors in doses that also block dopamine receptors.

In summary, it was found that dimethyltryptamine administered intravenously in a dose-dependent manner depressed retino-geniculate transmission of electrically evoked responses in the visual system, while not affecting potentials in the lateral geniculate nucleus or visual cortex produced by optic radiation stimulation. Neuroleptics, in sufficient doses, were capable of antagonizing the depressant effects of dimethyltryptamine. Low doses of neuroleptics surprisingly potentiated the effects of dimethyltryptamine.

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