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Brief Report

5-Methoxy-*N,N*-Dimethyltryptamine: Behavioral and Toxicological Effects in Animals

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INTRODUCTION

In preparing for human studies with 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), we report here the effects of 5-MeO-DMT in sheep, rats, mice, and monkeys.

5-MeO-DMT, an important constituent of several plants with hallucinogenic properties (Holmstedt and Windgren, 1967), has been implicated as a possible endogenous psychotogen in psychotic illnesses. Urinary excretion of 5-MeO-DMT has been reportedly correlated with clinical exacerbations in schizophrenic patients (Narasimhachari *et al.*, 1971a; 1971b). Banerjee and Snyder (1973) suggested that it could by synthesized by *O*-methylation of bufotenin. Mandel and Walker (1974), were, however, unable to confirm this finding; nevertheless, they demonstrated that indoleamine-*N*-methyltransferase from human lung could catalize the *in vitro* synthesis of 5-MeO-DMT from 5-methoxy-tryptamine (5-MeO-T). 5-MeO-T is found in rat brain (Green *et al.*, 1973) and human CSF (Koslow *et al.*, unpublished results).

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5-MeO-DMT is apparently a potent, rapidly acting hallucinogen of short duration in man (Shulgin, 1970) and has been used unsupervised since it is not a legally controlled drug (Anon, 1973).

Three young male rhesus monkeys (2.7-2.8 kg) were given intravenous injections of 5-MeO-DMT (10 μg to 16 mg/kg). No behavioral effects were noted at or below 100 μg/kg. At 250 μg/kg or more, dose-related effects were observed: marked ataxia, decreased spontaneous movement and climbing, and unresponsiveness to loud noises, threatening gestures, or even touching the face with the experimenter's hand. Normal direct and consensual pupillary light reflexes and corneal reflexes were preserved. Slow nystagmoid movements and mydriasis, stringy salivation, apparent tetany of the massector muscles precluding forceable opening of the jaws, loss of plantar and placing reflexes, and diminished muscle tone in limbs were also observed. At the higher doses, the animals were comatose and could not be aroused. The onset occurred within 30-60 sec of injection and lasted from 5 min to 2 hr depending on the dose. Although animals received numerous injections over short periods of time, they continued to exhibit full responsiveness to the next injection (one animal, for example, received nine injections ranging in ascending order from 50 μg/kg to 8 mg/kg over 3 hr, but still responded fully to 250 μg/kg after a 3-hr delay).

The EKG was monitored in one rhesus anaesthetized with sodium thiomylal. No significant EKG changes were observed in doses from 50 μg/kg to 8 mg/kg, although a slight bradycardia and reduction in respiratory rate was noted at doses of 500 μg/kg or more. No fatalities occurred.

In contrast, we found 5-MeO-DMT to be fatal in sheep, consistent with the earlier finding of Gallagher *et al.* (1964) who suggested that it might be responsible for a syndrome of sudden collapse and death observed in sheep who graze on *Phalaris tuberosa,* a plant known to contain 5-MeO-DMT. Our subjects were two adult male Hampshire sheep. A dose of 10 μg/kg had no effect on behavior or EKG, but dose-related effects were observed at doses of 20 μg/kg and above. Within 15 to 45 sec of iv injection, the sheep exhibited increasing restlessness, head nodding, ear twitching, dry mouth and stringy salivation, defecation, urination, incoordination, and mydriasis. A syndrome of hindlimb flaccidity, noted also in rats (see below) rendered the sheep incapable of supporting their hindquarters while making flailing movements with their rear legs. At a dose of 50 μg/kg, heart rate increased from 100 to 174 beats/min within 1 min after injection; at 100 μg/kg, it increased to 250 beats/min. A dose of 1 mg/kg was fatal, apparently because of respiratory failure. Respiration ceased 7 min post-injection. A maximal sinus tachycardia of 340 beats/min occurred, but unlike Gallagher *et al.* (1964) we did not observe cardiac arrhythmias until after the cessation of respiration. Death occurred 12 min following injection.

We also confirmed previous observations that 5-MeO-DMT produces tremors, biting of paws, and convulsions in rats (Gessner *et al.,* 1961; Gessner and Page, 1962; Ahlborg *et al.,* 1968; Grahame-Smith, 1971). In the course of

studying the behavioral effects of 5-MeO-DMT on shock avoidance (shuttlebox) behavior in male hooded rats, we observed forelimb tremors (approximately 1 cycle/2 sec) and shivering in 30% of animals receiving 8 or 16 mg/kg. No tremors or shivering were observed at doses of 2 mg/kg or less. Convulsions occurred in 10% of rats at 8 mg/kg and 16 mg/kg, characterized by 3 sec or more of bilateral clonus, first of forepaws and later of hindpaws. During electrical stimulation in the shuttlebox, the incidence of convulsions increased to 30% at 4 mg/kg, 60% at 8 mg/kg, and 80% at 16 mg/kg. Preceding convulsions, rats also exhibited; (i) brief coarse spasms or twitches of muscles of lower back; (ii) prostrate posture on back, rocking from side to side; (iii) blanching of blood vessels of ears and paws; (iv) abnormal gait and posture, such as lowering of pelvis, arching of back, dragging abdomen, flaccid hindlimbs, and counterextension of hindlimbs with plantor surface of foot facing upwards. and (v) unusual behaviors, such as compulsively biting grid floor, facing in reverse direction for escape from shock and walking backwards, failure to orient to warning stimulus, and "taking shock" without observable effect. Nevertheless, no deaths were observed in the doses tested.

In addition, unusual aggressive behavior was observed following the shuttlebox test. Rats made extremely vigorous running-escape responses to handling attempts by the experimenters and tried to bite or scratch in 10% to 75% of the groups, depending upon dose.

Toxicology studies in mice revealed the following results: LD_{50} iv was 48 mg/kg; subcutaneous, 113 mg/kg; and oral, 278 mg/kg. Benington *et al.* (1965) previously reported an LD_{50} of 75 mg/kg ip in mice. They also reported that in cats doses of 1 or 5 mg/kg produced rage reactions, while doses above 15 mg/kg iv were usually fatal.

Since sheep appear to be more susceptible to 5-MeO-DMT than monkeys, rats, or mice, or apparently cats, species differences may be important, although at this time the mechanism for these differences is unknown.

The consistent responsiveness of the monkeys to repeated 5-MeO-DMT provides tentative evidence that tolerance may not develop to this compound. In contrast, tolerance develops to LSD with repeated administration during one day (Freedman *et al.*, 1964). We have found no tolerance to DMT administered either twice daily for 15 days or every 2 hr for 24 hr in cats (Gillin *et al.*, 1973) and humans (Kaplan *et al.*, unpublished data). Further studies need to be conducted, however, before concluding that 5-MeO-DMT fails to produce tolerance.

In summary, these studies indicate that 5-MeO-DMT has potent, rapidly appearing effects in the central nervous system. It has fatal effects in sheep at low doses, but not in monkeys, rats, or mice.

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