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N,N-DIISOPROPYLTRYPTAMINE (DIPT) AND 5-METHOXY-N,N-DIISOPROPYLTRYPTAMINE (5-MEO-DIPT). TWO ORALLY ACTIVE TRYPTAMINE ANALOGS WITH CNS ACTIVITY

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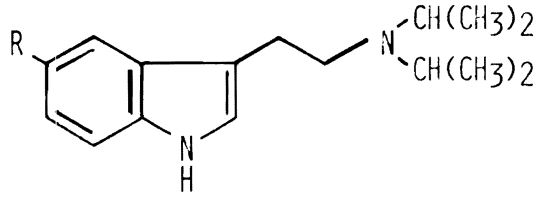
Abstract

Two of the major, naturally occurring, tryptamine hallucinogens are N,N-dimethyltryptamine (DMT and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). Although they are active in man only parenterally, it has been found that the N-isopropyl homologs of these two bases are both orally active, and have human potency similar to their methyl counterparts. N,N-Diisopropyltryptamine (DIPT, I) effects a passive and neutral psychotomimetic state, but one that embodies an unusual degree of auditory distortion, both in the pitch and the timbre of perceived sounds. N,N-Diisopropyl-5-methoxytryptamine (5-MeO-DIPT), on the other hand, produces a talkative and disinhibited state with easy emotional expression.

Introduction

N,N-Disubstituted tryptamines have been recognized as a major family of centrally active hallucinogens or psychotomimetic agents. A series of homologs, with straight-chain substituents on the basic nitrogen and unsubstituted in the aromatic ring, has been shown to contain moderately potent hallucinogens. N,N-Dimethyltryptamine (DMT), N,N-diethyltryptamine (DET), N,N-di(n)propyltryptamine (DPT) and its unsaturated counterpart N,N-diallyltryptamine are all parenterally active in man, with an effective dose range of 50 to 100 mg (1). Because of the short duration of action of these compounds (less than 3 hrs.) two of them (DET (2) and DPT (3)) have been studied as psychotherapeutic agents. With an oxygen atom in the 4-position one has the alkaloids psilocin (4-hydroxy-N,N-dimethyltryptamine) and

psilocybin (the phosphate ester of psilocin). These two bases, and the corresponding N,N-diethyl homologs CZ-74 and CEY-19, are orally active hallucinogens effective in man in the 5 - 10 mg range (4). The placement of the oxygen atom in the 5-position results in bufotenine, a natural alkaloid with the reputation of being hallucinogenic, but which is now considered to be a peripherally active pressor agent (5). The O-methyl ether is 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), which maintains the potency of the related positional isomers, but which



I DIPT R = H

II 5-MeO-DIPT R = OCH_3

requires parenteral administration for effectiveness (6).

The reasons for the lack of oral activity of the 5-H and the 5-OCH_3- substituted families of N,N-dialkyltryptamines have not yet been satisfactorily established. The metabolism of such compounds usually follows either of two routes; dealkylation or oxidative deamination to the corresponding indole-3-acetic acid. It has been assumed that the oral ineffectiveness of these compounds is due to a metabolic transformation which occurs before an active site in the brain can be reached.

We report here the synthesis and preliminary human psychopharmacology of two tryptamine analogs, N,N-diisopropyltryptamine (DIPT, I) and 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT, II), in which the basic amine function is sterically hindred. Our objective was to determine whether the potential resistance to metabolism presented by the steric bulk of the two isopropyl groups would allow these compounds to exhibit oral activity.

Materials and Methods

DIPT (I) and 5-MeO-DIPT (II) were synthesized by conventional routes from indole and from 5-methoxy indole, through the corresponding indole-3-glyoxylamide. Reduction with lithium aluminum hydride afforded the required amines

which were isolated as the hydrochloride salts. DIPT·HCl was recrystallized from benzene/methanol (m.p. 196-197, ref. 7a gives 198-199); 5-MeO-DIPT·HCl was recrystallized from ether/ethanol (m.p. 180-181, ref. 7b gives 180-181).

LD_{50}'s for both compounds have been previously determined (7). Nine human volunteers participated in the evaluation of DIPT and ten with 5-MeO-DIPT; eight of these were common to both assays. There were five men and four women within the age range of 26 - 55 years who, having understood the purpose and possible responses to be expected from these materials, gave their informed consent. The experimental setting was non-therapeutic and comfortable, with two observers present. DIPT trials were started at 0.5 mg, orally, and 5-MeO-DIPT trials at 0.1 mg; dosage increments were from 30 to 50% of the immediately prior level, and no trials were scheduled in the same subject closer than five days apart.

Results

Threshold effects were noted with DIPT at approximately 16 mg, and with 5-MeO-DIPT at 4 mg. This threshold level was defined as a subjective report of some deviation from the starting psychological baseline. This could take the form of some visual or emotional clue that reminded the person of the experiment, an inward awareness of social interactions that would change the pace of a conversation, or a shift of alertness or attention. False positive reactions are not uncommon in the estimation of a threshhold level, when there are not sufficiently developed central characteristics to accurately estimate either the nature or the duration of the drugs' effects. At these levels, neither material gave objective indicators of any change of state.

Effective levels of DIPT were found in the 20 - 50 mg range, and with 5-MeO-DIPT in the 6 - 10 mg range. Both drugs exhibited a roughly similar time course with onset of effects noted after 20 to 30 minutes following ingestion. Peak effects were reached after 1½ - 2 hours with DIPT, and 1 - 1½ hours with 5-MeO-DIPT. With DIPT in lower doses, effects had subsided after four hours, whilst with the 5-methoxy analog, even with the highest dose assayed (10 mg) the subject was clearly recovering at 3 hours, although not completely symptom-free until about the sixth hour.

Both drugs are relatively free of autonomic side-effects and indicators of toxicity. Within the initial hour, two subjects reported mild nausea, and three, some muscular hyperreflexia. In most subjects there was slight mydriasis, but there appeared to be little change in appetite or disruption of sleep patterns.

However, the subjective effects of these two tryptamines differ from each other in most respects, except for the absence of the intense sensory disturbances characteristic of dimethyltryptamine and psilocybin.

At a dose of 50 mg of DIPT, the full spectrum of effects appears to be present. At all doses above the threshold dose we observed a characteristic lethargy leading to a desire to lie down and remain passive. A feeling of withdrawal from the environment was often expressed. Some perceptual enhancement was always present, particularly during the peak period of effects. At no time was sensory distortion in the visual field observed. Eyes-closed imagery was not reported, although most subjects preferred to lie with their eyes shut for most of the time. This is in contrast with certain other hallucinogens (e.g., MMDA and harmaline) wherein eyes-closed imagery is a predominant symptom, and it is an interest or desire to become involved in these fantasies that encourages subjects to forego external visual stimuli.

One effect was persistently noted, however, even at the lower end of the active range of dosages; this was an unusual disturbance in the integrity of the auditory processes. Subjects noted that the sounds of observers' voices seemed much lower in pitch. Women observers' voices were heard in bass tones. Often subjects would be aware that something was unusual with their auditory perception but were not able to say what until prompted. Others noticed the disturbance without suggestion, though usually obliquely, e.g., "Do you have a bad cold?" or "How strange they would put such a poor recording on the radio." Individual musical notes appeared to waver and to be qualitatively wrong, due to harmonic distortion. Subjects varied in the degree to which this auditory phenomenon occurred, but there was consistently a complete return to normal perception coincident with the disappearance of the other symptoms described. Little or no euphoria was reported and the subjects were curiously neutral when asked whether the experience was unpleasant or pleasant. They felt that there was a distance between themselves and their surroundings and/or between themselves and their own feelings, which was neither disturbing nor stimulating. A single trial conducted at 80 mg revealed only a greater intensity of symptoms and a somewhat longer duration of activity (about 5 hours).

With 5-MeO-DIPT full effects were observed at 6 - 10 mg. In place of the lethargy and passivity found with DIPT we found a relaxation associated with an emotional enhancement rather than with a simple release of tension. Emotional enhancement is defined as an opening of affect, including easy communication with others without the usual guards and reservations. This "feeling enhancement" property is similar

to that produced by MDA and MDMA (6b, 8) except that the residual peripheral stimulation is not observed. In addition to somatic sensual development, there was an intellectual activation (a believed increase in ability to reason logically and to express onesself) which was outgoing rather than inwardly reflective. Subjects were frequently talkative and disinhibited. Only at the higher doses was some abstract eyes-closed imagery found.

Discussion

Clearly our discussion of these results must fall into two parts -- the novel oral activity of these two drugs, and the interesting psychological syndrome that our preliminary human trials have revealed.

It would appear that the steric hindrance associated with the basic amine function of these tryptamines may account for a considerable increase in resistance to metabolic degradation. Szara and Axelrod (9) have shown that there is an enzyme present in rabbit liver which could N-demethylate DMT, and it is possible that what we are observing with DIPT is some specific resistance to N-dealkylation. Alternatively, this effective isolation of the basic nitrogen atom with a cloud of aliphatic hydrocarbon may make difficult, or even impossible, an effective interaction between the drug and an oxidative deaminase. The conversion of DMT to indole-3-acetic acid is known to occur in man (1a) and of 5-methoxy-DMT to 5-methoxy-indole-3-acetic acid in animal studies (10). This possibility could be evaluated by kinetic and metabolic studies involving brain uptake and disposition of unchanged base, in a comparison of DIPT with the normal propyl isomer, DPT.

There is no *a priori* reason to assign the auditory phenomena associated with DIPT use specifically to central or to peripheral mechanisms. In human studies with DMT Arnold (11) shows a reduction of the acoustic evoked potential without apparent interference with either hearing or understanding. In a large clinical study by Gillin *et al* (12) only one subject out of 15 commented on distortions of perceived sound; similarly, DET produces auditory distortion only rarely (13). This may be a latent property inherent in the dialkyltryptamines which can be expressed only through oral administration, or in molecules with appropriately branched substituents on nitrogen.

Although DIPT and 5-MeO-DIPT did not exhibit the intense hallucinogenesis associated with these other active tryptamines, the demonstrated modifications of emotional and intellectual processes were nevertheless quite profound. In this respect we classify them with an increasing number of

"selective" hallucinogens which include DOET, 2C-D and 2C-B (4-ethyl-2,5-dimethoxyphenylisopropylamine, 4-methyl-2,5-dimethoxyphenylethylamine, and 4-bromo-2,5-dimethoxyphenylethylamine, respectively) (14). 5-MeO-DIPT is particularly interesting in this respect, as in general our observations suggest that sessions with this compound were more productive than with the somewhat neutral-negative response found with DIPT. Studies currently underway with homologs of 5-MeO-DIPT with varying degrees of steric hindrance in the area of the basic nitrogen hopefully will define more exactly the structural requirements for oral activity.

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