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Behavioral Effects and Metabolic Fate of N,N-Dimethyltryptamine in Mice Pretreated with β-Diethylaminoethyl-Diphenylpropylacetate (SKF 525-A), Iproniazid and Chlorpromazine[1]

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SHAH, N. S. AND M. P. HEDDEN. *Behavioral effects and metabolic fate of N,N,-dimethyltryptamine in mice pretreated with β-diethylaminoethyl-diphenylpropylacetate (SKF 525-A), iproniazid and chlorpromazine.* PHARMAC. BIOCHEM. BEHAV. 8(4) 351–356, 1978. – Behavioral aspects and metabolic fate of N,N-dimethyltryptamine (DMT) were studied in mice pretreated with β-diethylaminoethyl-diphenylpropylacetate (SKF 525-A), iproniazid or chlorpromazine (CPZ). DMT at doses of 2.5, 10.0, and 25.0 mg/kg produced several behavioral changes in a dose-related manner: inhibition of spontaneous locomotor movement, enhanced fright responses to sound stimuli, trembling, head twitching, inco-ordinated movements of hind-legs, flat or extended tail and abnormal posture with the extension of hind-legs. Pretreatment with ipromiazid (153 mg/kg; 4 hr) but not SKF 525-A (50 mg/kg; 1 hr) prolonged the behavioral effects produced by 2.5 mg/kg DMT while CPZ (15 mg/kg; 0.5 hr) completely abolished the responses induced by 25 mg/kg DMT. Earlier behavioral effects generally coincided with the brain concentrations of DMT. Dose-dependent increases with rapid uptake and disappearance in the brain, plasma and hepatic levels of DMT were measured with doses of 10 and 25 mg/kg DMT. Iproniazid but not SKF 525-A markedly enhanced tissue levels of DMT. It is concluded that DMT is metabolized chiefly by monoamine oxidase rather than by drug-metabolizing hepatic microsomal enzymes and that DMT-induced behavioral effects are due to the parent compound rather than its metabolite.

DMT Behavior Tissue levels SKF 525-A Iproniazid CPZ

N,N-DIMETHYLTRYPTAMINE (DMT) is a potent indole-amine hallucinogen in man [25,40]. Its psychotomimetic potency is approximately 4 times that of mescaline (described as mescaline unit), a catecholamine hallucinogen [37]. A few clinical studies have indicated the endogenous production of DMT in schizophrenic patients [18,23] and proposed this compound to be a causative factor in the etiology of schizophrenic disorder [9]. Metabolic fate of DMT and related hallucinogen diethyltryptamine (DET) was examined in humans and animals. Studies in man, monkey and rat revealed that DET is chiefly metabolized by liver microsomes resulting in a more active metabolite following 6-hydroxylation [41]. Iproniazid, a mono- and di-amine oxidase inhibitor [36] when administered repeatedly, suppressed the DMT-induced hallucination in human volunteers [24]. In rat, iproniazid pretreatment, on the other hand, prolonged the half-life of DMT in the brain [15].

β-diethylaminoethyl-diphenylpropylacetate (SKF 525-A) is frequently employed in assessing the role of hepatic microsomal enzymes in the metabolism of a variety of psychoactive drugs including barbiturates, diphenylhydantoin, tranquilizers, Δ^1-tetrahydrocannabinol, narcotics and methaqualone [5, 21, 28, 32, 39]; the inhibition of the drug metabolizing enzymes resulted in potentiation of pharmacologic actions of several of them. Besides its' action on the hepatic microsomal enzymes, SKF-525-A has been shown to alter the tissue distribution of sulfacetamide [16], mescaline [29] and methadone [28].

The major purpose of the present investigation is to examine the influence of iproniazid and SKF 525-A on the behavioral alterations induced by DMT and to see any relationship to tissue concentrations of DMT. The effect of chlorpromazine (CPZ) which antagonizes the actions of several hallucinogens [2, 7, 27] is also examined.

METHOD

Drugs

DMT was purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI). CPZ hydrochloride, SKF 525-A hydrochloride (Smith, Kline and French Laboratories, Philadel-

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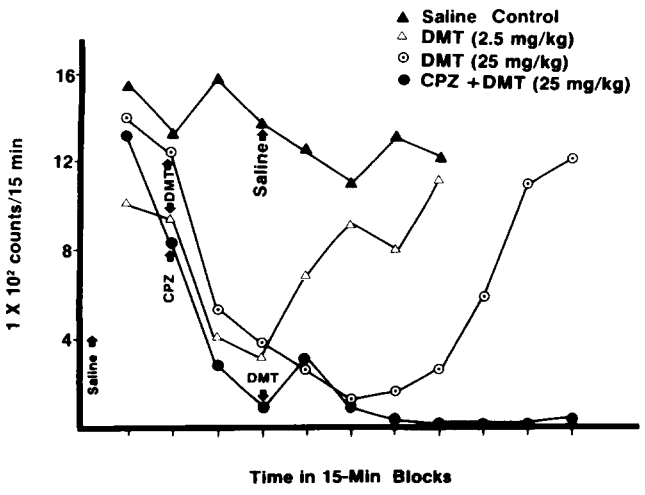

FIG. 1. Effect of saline (▲), 2.5 mg/kg DMT (△), 25 mg/kg DMT (○) or a combination of CPZ and 25 mg/kg DMT (●) on spontaneous locomotor activity. Saline or CPZ (15 mg/kg) was given 0.5 hr before DMT. Control animals received saline followed by saline containing 0.1 N HCl (vehicle). Ordinate: counts/15 min on the Animex. Abscissa: time in 15 min sessions. Arrows indicate the time of administration of saline, CPZ, or DMT.

phia, PA) and iproniazid phosphate (Hoffman LaRoche, Inc., Nutley, NJ) were received as gifts.

Animals

Several experimentally naive Swiss-Webster albino mice of either sex, born and raised in our animal quarters and weighing 28–32 g were used. They were housed in wire cages in groups of 6 with ad lib food and water. Temperature in animal quarters was maintained at 23°C with relative humidity at 55%.

Pharmacological Procedure

DMT was prepared in 0.1 N HCl and diluted with physiological saline to a desired volume; other drugs were made in saline. All drugs were freshly prepared and injected IP in a volume of 0.3 ml; doses are reported as their salts. Where indicated, the following drugs were given prior to DMT: iproniazid (153 mg/kg, 4 hr); SKF 525-A (50 mg/kg, 1 hr); saline or CPZ (15 mg/kg, 0.5 hr). The doses of DMT were 2.5, 10, or 25 mg/kg. In some animals, saline, iproniazid, CPZ or SKF 525-A in doses reported above was injected and after appropriate time intervals, a dose of saline instead of DMT was given; brain, liver and plasma from these animals were examined for any interference of these drugs with the fluorometric assay procedure for DMT. Mice were sacrificed by decapitation 0.25, 0.5, 1 and 2 hr after DMT injection. Blood was collected for the separation of plasma; whole brain and liver were promptly removed and frozen on dry ice. DMT was isolated from tissue homogenates prepared in 1 N HCl, by toluene extraction [4]; the native fluorescence of DMT was read in an Aminco-Bowman Spectrophotofluorometer at 280 nm (excitation) and 360 nm (emission).

Gross Behavior and Locomotor Activity

Two mice of identical body weights were placed in a Plexiglas cage (39 cm long, 25.5 cm wide and 15.5 cm high) and the locomotor activity was monitored using an Animex activity meter type O (Farad Electronics, Stockholm, Sweden). The instrument was kept in a quiet room at 23.5 ± 1.0°C. The settings of tuning 40 μA and of sensitivity 40 μA were used throughout. The activity of animals (body movement and locomotion) was recorded in 15 min periods for 2 hr and in some instances for additional 45 min (Fig. 1).

Statistics

Results are expressed as mean ± SD. The statistical significance of difference between mean values is determined with a Student's t test and p values of 0.05 or less are considered significant.

RESULTS

Gross Behavior and Locomotor Activity

The locomotor activity of mice injected twice with saline and saline containing 0.1 N HCl (vehicle) declined somewhat over a period of 2 hr (Fig. 1). In contrast, a rapid decline in spontaneous locomotor activity was displayed during the first 30 min following 2.5 mg/kg DMT with a gradual return approaching to normal activity in the next 30 min. During the first 30 min period, animals laid quietly in a corner of the cage assuming a flattened posture. The tail remained relaxed on the floor with occasional wiggling. There were no signs of Straub tail or fine tremors. Fright responses were evoked in the animals by ordinary sound or could be elicited by merely touching the cage or by snapping the fingers. A dose of 10 mg/kg DMT promptly declined the spontaneous motor activity (not shown in Fig. 1) which paralleled 2.5 mg/kg dose; the activity decreasing effects lasted for 60 min. Animals exhibited jerkiness of the movement, rigidity, head twitching, trembling and occasional extension of the tail. Head twitches were counted after the DMT injection and compared with saline treated controls; during first 15 min test period, no noticeable changes were measured between 2 groups; whereas the combined score for the next 30 min test period averaged 7 (n = 8) for control group and 20 (n = 6) for the DMT (10 mg/kg) group. Number of head twitches exhibited by mice receiving 2.5 mg/kg DMT was not different from controls for the 45 min observation period. A dose of 25 mg/kg of DMT produced marked behavioral changes; the spontaneous motor activity was markedly decreased (Fig. 1) within 5 to 10 min followed by incoordinated movements of hind-legs and an abnormal posture with the extension of hind-legs lasting for 90 to 105 min before they regained normal behavioral activity. During this period, alternate extension of the tail in an upward direction followed by flattening on the floor was frequently seen. Number of head twitches averaged 23 (n = 4) during 15 to 45 min time interval following the drug injection. Occasional trembling but no signs of aggressiveness or convulsions were observed. Scratching responses which are typical of mescaline effects in mice [33] were not displayed with any dose of DMT.

When injected alone, SKF 525-A or iproniazid did not disrupt the normal behavioral pattern or locomotor movements. Behavioral effects induced by 2.5 mg/kg DMT were neither intensified nor prevented by prior administration of SKF 525-A (not shown in Fig. 1).

Animals pretreated with iproniazid followed 4 hr later by DMT (2.5 mg/kg) displayed several similar behavioral

TABLE 1

THE LEVELS OF DMT IN THE PLASMA

Treatment	Dose mg/kg	μg/ml Time of Sacrifice (min) 15	30	60	120
Saline + DMT	10	2.3 ± 0.4 (3)	0.7 ± 0.1 (3)	ND (3)	–
Saline + DMT	25	4.7 ± 0.8 (5)	2.3 ± 0.3 (4)	0.6 ± 0.04 (3)	ND (3)
SKF 525-A + DMT	50 + 25	5.6 ± 1.1 (4)†	1.9 ± 0.5 (4)†	1.3 ± 0.01 (4)*	–
Iproniazid + DMT	153 + 25	–	–	2.6 ± 0.3 (6)*	–
CPZ + DMT	15 + 25	5.4 ± 0.9 (7)†	–	0.9 ± 0.2 (7)*	–

Mice were pretreated with saline (0.5 hr), SKF 525-A (1 hr), iproniazid (4 hr) or CPZ (0.5 hr) prior to DMT. Values are expressed as mean ± SD with number of separate experiments in parentheses.

ND = not detectable

*Significantly different from control (saline + DMT 25 mg/kg), $p<0.001$ to 0.01

†Not significantly different from control (saline + DMT 25 mg/kg), $p>0.2$ to 0.5

signs elicited by 25 mg/kg DMT alone. Under our experimental conditions, iproniazid extended the behavioral effects induced by 2.5 mg/kg DMT for a period of 90 min. Shortly after DMT, the animals lost locomotor activity (not shown in Fig. 1) and frequently exhibited trembling and head twitching. Sniffing was more prominent during the first 30 min. Number of head twitches between 15 and 45 min after DMT injection averaged 19 (n = 5). Animals regained normal activity about 90 min from the time of DMT injection. In one study, iproniazid (153 mg/kg) and DMT (2.5 mg/kg) were administered simultaneously instead of 4 hr apart to see whether the potentiating effect of iproniazid is related to monoamine oxidase (MAO) inhibition. Under this experimental situation the behavioral effects induced by 2.5 mg/kg DMT were not intensified by iproniazid. Since iproniazid is a slow acting irreversible MAO inhibitor [38], it is assumed that MAO was not inhibited, hence no potentiation of behavioral effects following simultaneous administration of both drugs.

As expected, administration of CPZ (15 mg/kg) produced inhibition of spontaneous locomotor activity (Fig. 1); animals became quiet and drowsy within 10 min after the injection. Administration of DMT (25 mg/kg) 30 min after CPZ showed no signs of DMT effects such as abnormal posture with the extension of hind legs, alternate extension and relaxation of the tail, fine tremors, fright responses to sound, rigidity or jerkiness of the movement. While lying flat in a corner of the cage, animals would raise one hind leg persistently touching the wall of the cage with that leg. Given alone, CPZ did not produce this latter effect. Number of head twitches during 15 and 45 min interval after DMT injection averaged 2 (n = 4) compared to 23 for saline + DMT (25 mg/kg) group.

DMT Tissue Levels

Spectrofluorometric analysis of tissue samples from animals receiving various pretreatments but without DMT revealed no evidence of interference with the DMT assays by iproniazid, SKF 525-A or CPZ. Tissue extracts from saline treated animals produced almost negligible readings.

Plasma, brain and hepatic levels of DMT after IP injections of 10 and 25 mg/kg doses are shown in Tables 1, 2, and 3. In saline-pretreated controls, the tissue levels of DMT increased in a dose-related manner. At both dose levels, the peak concentrations occured at 15 min; the tissue:plasma concentration ratios for the brain and the liver were 4.2 and 7.0 respectively after 10 mg/kg and 3.9 and 8.0 after 25 mg/kg. At both the doses, DMT concentrations declined rapidly. The 60 min levels in mice receiving 10 mg/kg were 0.06 ± 0.008 μg/g in the brain, 1.1 ± 0.3 μg/g in the liver and negligible in the plasma. At a dose of 25 mg/kg, small amounts of DMT in the brain and liver were detectable at 120 min.

The tissue levels of DMT in mice pretreated with various drugs followed by 25 mg/kg DMT were investigated (Tables 1, 2 and 3). The DMT contents in the plasma, brain and liver of mice pretreated with SKF 525-A were not significantly different ($p>0.02$ to 0.5) at various time intervals, the exception being the plasma content at 60 min ($p<0.001$). Iproniazid, on the other hand, markedly elevated brain ($p<0.001$), liver ($p<0.001$) and plasma ($p<0.001$) levels of DMT (only 1 hr levels reported). In CPZ pretreated mice, brain, plasma and hepatic concentrations of DMT 15 min after 25 mg/kg dose were not significantly different from those not given CPZ ($p>0.2$ to 0.4). CPZ pretreatment, however, produced small but significant increases in brain ($p<0.001$), plasma ($p<0.05$) and hepatic ($p<0.005$) levels at 1 hr after DMT.

DISCUSSION

A prompt onset of behavioral effects would suggest that DMT penetrates the blood-brain barrier with great ease. In contrast, studies with mescaline in mice, rats and rabbits have shown that this methylated catecholamine hallucinogen penetrates poorly in the CNS [30, 31, 35]. Furthermore, compared to mescaline, DMT appears to be taken up in the brain by an active transport mechanism as evidenced by the brain: plasma DMT concentration ratio of 4 as

TABLE 2

THE LEVELS OF DMT IN THE BRAIN

Treatment	Dose mg/kg	μg/g Time of Sacrifice (min) 15	30	60	120
Saline + DMT	10	9.6 ± 2.1 (3)	3.1 ± 0.7 (3)	0.06 ± 0.008 (3)	–
Saline + DMT	25	18.2 ± 2.9 (5)	7.4 ± 1.1 (4)	1.3 ± 0.3 (3)	0.1 ± 0.04 (3)
SKF 525-A + DMT	50 + 25	19.6 ± 3.7 (4)‡	6.5 ± 1.1 (4)‡	1.1 ± 0.07 (4)‡	–
Iproniazid + DMT	153 + 25	–	–	6.8 ± 0.8 (7)*	–
CPZ + DMT	15 + 25	20.0 ± 3.3 (7)‡	–	2.7 ± 0.3 (8)†	–

Mice were pretreated with saline (0.5 hr), SKF 525-A (1 hr), iproniazid (4 hr) or CPZ (0.5 hr) prior to DMT. Values are expressed as mean ± SD with number of separate experiments in parentheses.
*Significantly different from control (saline + 25 mg/kg DMT), $p<0.001$
†Significantly different from control (saline + 25 mg/kg DMT), $p<0.05$
‡Not significantly different from control (saline + 25 mg/kg DMT), $p>0.2$ to 0.5

TABLE 3

THE LEVELS OF DMT IN THE LIVER

Treatment	Dose mg/kg	μg/g Time of Sacrifice (min) 15	30	60	120
Saline + DMT	10	16.1 ± 3.4 (3)	10.5 ± 2.9 (3)	1.1 ± 0.3 (3)	–
Saline + DMT	25	37.9 ± 6.8 (5)	13.5 ± 3.9 (4)	3.1 ± 1.0 (3)	0.8 ± 0.09 (3)
SKF 525-A + DMT	50 + 25	32.6 ± 7.9 (3)†	12.3 ± 3.3 (4)†	4.0 ± 1.4 (4)†	–
Iproniazid + DMT	153 + 25	–	–	13.9 ± 3.6 (7)*	–
CPZ + DMT	15 + 25	41.1 ± 5.5 (7)†	–	5.4 ± 0.8 (8)*	–

Mice were pretreated with saline (0.5 hr), SKF 525-A (1 hr), iproniazid (4 hr) or CPZ (0.5 hr) prior to DMT. Values are expressed as mean ± SD with number of experiments in parentheses.
*Significantly different from control (saline + DMT 25 mg/kg), $p<0.001$ to 0.005
†Not significantly different from control (saline + DMT 25 mg/kg), $p>0.2$ to 0.5

opposed to mescaline ratio of 1 [31] under identical conditions. Short duration of action of DMT would indicate that the drug is rapidly metabolized in the brain.

DMT-induced behavioral effects generally coincided with its concentration in the brain more so during the earlier phases. This could be demonstrated by the dose-related prolongation of the abnormal behavior. For example, the behavioral effects elicited by 2.5 mg/kg DMT lasted for a short duration while these effects were markedly intensified and prolonged by elevating brain DMT concentration either by increasing the doses of DMT or by blockade of its metabolism. In the rat, the level of DMT in the brain necessary for abnormal behavior was approximately 1.3 μg/g of brain [4]. By enhancing brain levels of DMT following 25 mg/kg dose, we observed continued depression of locomotor movements (Fig. 1) as well as other behavioral changes for 60 min at which time the levels of DMT in the brain were 1.3 μg/g (Table 2), sufficient enough to maintain the abnormal behavior. These data therefore would establish a correlation between the brain DMT levels and the abnormal behavior. It was proposed that 6-hydroxylated metabolite of DMT or DET formed in the liver by microsomal enzymes could be responsible for abnormal behavioral effects of these indoleamine hallucinogens [41]. In view of these findings, we examined the effects of 2 agents on the DMT-induced changed behavior and its metabolism: SKF 525-A, a known inhibitor of a wide variety of hepatic microsomal drug-metabolizing enzymes

[3,19] and iproniazid, an inhibitor of mitochondrial and cytoplasmic MAO [36,44]. The findings of these studies provided evidence in support of involvement of MAO rather than hepatic microsomal drug metabolizing enzymes in the degradation of DMT. Furthermore, the findings that MAO-inhibitor prolongs the DMT-induced abnormal behavior suggests the involvement of the parent compound rather than 6-hydroxy metabolite as an active principle in DMT-induced behavioral effects. Support in favor of this argument is derived from the work of other investigators [4, 22, 42] who reported 6-hydroxy DMT to be significantly less potent than DMT in various behavioral responses. The prolongation of the DMT-induced hyperthermia and mydriasis in the rabbit [17] and increased half-life of injected DMT in the brain and liver of rat [15] pretreated with iproniazid uphold our proposition.

The finding that pretreatment with CPZ blocked the DMT effects is in accord with that of Moore *et al.* [17] who reported a partial antagonism of DMT-induced hyperthermia, mydriasis and EEG activation in rats by CPZ at a dose of 1 mg/kg. In a related study, hyperactivity induced in rats by a combination of tranylcypromine and 5-methoxy-N,N-dimethyltryptamine, a derivative of DMT, was shown to be prevented in a dose related manner by prior administration of 10 or 30 mg/kg CPZ [10]. It is interesting to note that CPZ and several phenothiazines are effective antagonists of mescaline previously shown by one of us [27,33].

Increased tissue levels of DMT at 1 hr in CPZ pretreated mice seem to be independent of the metabolic conversion of DMT by MAO. In fact CPZ has been shown to produce little or no effect on the MAO activity [8,12]. A few studies have shown a marked prolongation of the disappearance of injected melatonin [43] and amphetamine [1,13] in rats and mescaline [27, 29, 30, 33, 34] in mice pretreated with CPZ (15–20 mg/kg). Increased accumulation of mescaline in the brain and other tissues of mice pretreated with CPZ [34] has been previously attributed to the membrane stabilizing effect of CPZ [26]. CPZ-induced marked hypothermia could affect the amine metabolism in vivo [11]. There is evidence that CPZ effects the membrane permeability to various amines [6, 14, 20]. Either or both of these effects could account for small increases in DMT levels following CPZ administration. These possibilities are currently being investigated both in vitro and in vivo studies.

Biochemically CPZ evokes a multitude of effects on various metabolic pathways and on membrane permeabilities. Pharmacologically, it exerts antagonism to both catecholamine and indoleamine hallucinogens. The fact that CPZ blocks the pharmacological effects of structurally unrelated hallucinogens suggests that either the hallucinogens may have a common site of action in the CNS or that the action of CPZ may be nonspecific so far as pharmacologic antagonism of hallucinogens is concerned.

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