1. HISTORY OF MDMA

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1. INTRODUCTION

There can never be a complete history of any intensely controversial topic whose proponents and skeptics state their beliefs with equal confidence. Some historical facts will rest uncontested. Many facts will be clothed in opinions that will color the way the facts are to be interpreted. Other facts will never be publicly known, for reasons of legality or privacy. And some facts may simply be irretrievably lost.

Most important, no history can be complete if it concerns a topic that is alive and developing. The subject of MDMA is very much alive and developing today. The story of its neurochemical effects is still unfolding and is being widely published. The story of its psychotherapeutic value is also unfolding and, although not being published, is nonetheless being widely distributed. This very volume is part of the developing history of MDMA in that it brings together spokesmen for all aspects of this history. In this opening chapter, I will attempt to present a number of historical facts with as little interpretation as possible and with available documentation.

The organization of this review largely follows the historical record. The chemical synthesis of MDMA (1912) was followed by the Army-sponsored toxicological studies (1953). The initial therapeutic exploration of MDMA in humans (1976) was followed by its popularization outside of the medical area (1981) and by the initial legal moves by the DEA to establish control (1984). The current flood of animal study (biochemistry, pharmacology, and especially neuotransmitter research) had its start in 1985.

2. CHEMICAL HISTORY

2.1. Chemical nomenclature

MDMA are the initials of the synthetic base 3,4-methylenedioxymethamphetamine. It has a number of correct chemical synonyms. With amphetamine as a stem, the principal name is N-methyl-3,4-methylenedioxyamphetamine. With the benzene ring itself as the target of naming, MDMA can be called either N, alpha-dimethyl-3,4-methylenedioxyphenethylamine or N,alpha-dimethyl-homopiperonylamine. Named as an aliphatic amine, it is either N,alpha-dimethyl-beta-(3,4-methylenedioxyphenyl)-ethylamine or N-methylbeta-(3,4-methylenedioxyphenyl)-isopropylamine. The hydrocarbon name is 2-methylamine-1-(3,4-methylenedioxyphenyl)-propane. And finally, named as a heterocycle, there is N,alpha-dimethylbenzodioxole-5-ethylamine (ethanamine in present Chemical Abstracts).

There are many code names and popular terms for MDMA. The shortened MDM stands for methylene-dioxy-methamphetamine. An early street name, "Ecstasy," has given rise to the initials XTC. In Europe it is often called, simply, "E." In the area of clinical psychology, the name "Adam" is common, having been created by the psychologist who first introduced MDMA into psychotherapy. The U.S. Army in its studies assigned it the code EA-1475, wherein EA stands for Edgewood Arsenal.

2.2. Chemical origin

Neither the chemist nor the date of the first synthesis of MDMA is known. The first public recording of the preparation and properties of MDMA was a German patent filed for in 1912 and issued in 1914, assigned to the firm E. Merck [1]. Although the popular press has stated that the compound had been developed as an appetite suppressant, the only claims in the patent are that this compound (among others) can serve as important intermediates for the production of therapeutically active compounds. A second German patent appeared a few years later describing a chemical modification of MDMA [2]. Again, there is no pharmacology mentioned.

2.3. Chemical synthesis

All known synthetic schemes leading to MDMA start with materials that contain the preformed methylendioxyphenyl ring. The principal sources are piperonal, isosafrole, safrole, and piperonylacetone [3]. These sources are, to some extent, interconvertible, in that isosafrole can be made from safrole, and piperonylacetone can be made from any of the other three.

2.3.1. Synthesis via piperonal

Piperonal may be used as a source of piperonylacetone. There are reports that describe a Darzans reaction with ethyl bromopropionate followed by hydrolysis [4], an intermediate glycol followed by hydrolysis [5], or reaction

with nitroethane to form an intermediate nitrostyrene followed by reduction with elemental iron [6]. The conversion of piperonylacetone to MDMA is discussed in section 2.3.4.

The last mentioned intermediate, the nitrostyrene, can be reduced by a number of methods to produce 3,4-methylenedioxyamphetamine (MDA). This centrally active base has served as a synthetic starting point for the preparation of MDMA by the addition of the one-carbon methyl group to the amine nitrogen. This has been done via the formate [7] followed by reduction with LAH. This process has been used for the preparation of the optical isomers of MDMA [8]. The intermediate urethane (from ethylchloroformate) can be reduced with Red-Al [9]. The direct methylation with methyl iodide is complicated by the formation of di- and tri-methylated contaminants [10].

2.3.2. Synthesis via isosafrole

All procedures that employ isosafrole require its conversion to piperonylacetone. The usual oxidant is hydrogen peroxide and formic acid [11], although the use of peracetic acid has been encountered [12]. This ketone can be reductively aminated to MDA, which can be methylated to MDMA, as discussed in section 2.3.1. Again, the conversion of piperonylacetone to MDMA is outlined in section 2.3.4.

2.3.3. Synthesis via safrole

The addition of HBr to safrole followed by reaction with methylamine is the original method described for the preparation of MDMA [1]. This same process was published almost a half century later by two Polish chemists [13], several years following the U.S. Army's first contracted studies on its toxicology. A second procedure employing safrole requires its base isomerization to isosafrole followed by this product's oxidation to piperonylacetone, as described in 2.3.2.

2.3.4. Synthesis via piperonylacetone

The reductive methylamination of piperonylacetone can be achieved with sodium cyanoborohydride [7] or amalgamated aluminum [14]. The cyanoborohydride method has been used for the preparation of tritium-labeled MDMA [15]. The conversion has also been reported using N-methylformamide in a Leuckart reaction with hydrolysis of the intermediate amide to provide MDMA [16].

2.4. Chemical analysis

It was through careful analytical work that the first clues arose that a new drug, MDMA, was coming into general availability. The first reports were in the Midwest, with observations in the early 1970s in Illinois [17, 18] and Indiana [19]. The initial screening tests for methamphetamine are positive for MDMA as well, so the two can be initially confused. Even the presumptive

microcrystalline tests give very similar results for the two drugs [20]. The confirmatory analyses of recent "at risk" samples, both from street submissions [21] and the urine of suspected users [22], have shown that the vast majority of these are indeed methamphetamine.

Many of the analytic procedures for MDMA are incorporated as experimental data in papers that are largely directed to another aspect. Below are the major papers that are concerned primarily with analytical procedures per se, with a primary emphasis on MDMA and closely related compounds.

2.4.1. Thin-layer chromatography

Two studies have been made employing TLC techniques. A group of N-methylated amphetamine derivatives was synthesized and characterized spectroscopically [16]. Six distinct TLC systems were evaluated. Another study evaluated two systems and a variety of visualization procedures [10]. A study of a number of phenethylamines had included by misprint the drug MDMA in its title, but the drug actually studied was MMDA [23].

2.4.2. Gas chromatography

The early studies of Bailey and his coworkers [16] covered a number of column materials and conditions for the separation of MDMA from close chemical allies. The use of GC has been used for the establishment of purity of MDMA in toxicology studies [14]. A number of papers have reported studies of large collections of drugs, including MDMA. These papers are intended for screen purposes and are not included here.

2.4.3. Immunoassay

MDMA and its two close homologues, the primary amine MDA and the N-ethyl counterpart MDE, have been compared with each other and with amphetamine or methamphetamine in immunological analyses designed to detect amphetamine. In the homogeneous EMIT assay, all three showed positive crossreactivity but with reduced response [24]. Studies with RIA (Abuscreen) and TDX (a fluorescent polarization immunoassay), as well as EMIT, showed similar crossreactivity but with extremely variable results, depending on the specific assay employed [25].

2.4.4. High-pressure liquid chromatography

Two reports have appeared describing a study of retention characteristics of MDMA and its close relatives MDA and MDE by HPLC [26, 27].

3. TOXICITY

The first report that described any research other than chemistry was a large toxicological study done at the University of Michigan under a classified contract with the U.S. Army [28]. The study was performed in the 1953–54 period, declassified in 1969, and finally published in 1973. It embraced eight phenethylamine bases that had been synthesized at Edgewood Arsenal; all

were structural variations of mescaline involving ring substitution patterns and chain length. MDMA was the only N-methyl compound studied. Five laboratory animal species were employed, and the study evaluated toxicity and behavioral effects.

The results of this study, along with more recent animal toxicity data, are presented below, arranged by the specific animal used. A recent review emphasized a close toxicological resemblance between MDMA and MDA [29].

3.1. Mouse

The Army studies by Hardman et al. [28] included toxicity measurements on five laboratory animal species, including the mouse. MDMA was found to have an LD-50 of 97 mg/Kg following i.p. administration. Recent studies [9] have shown almost exactly the same values (106 mg/Kg i.p. in six hours, 98 mg/Kg in 24 hours). The aggregate toxicity phenomenon, well established for amphetamine [30], is still present for MDMA, but to a lesser extent (aggregate LD-50 30 mg/Kg at six hours, 20 mg/Kg at 24 hours). A study of activity cage behavior of mice (crowding conditions not reported) showed an LD-50 of about 20 mg/Kg [31].

3.2. Rat

The Hardman study [28] found an acute i.p. LD-50 for MDMA in Sprague Dawley rats of 32 mg/Kg. Chronic studies employing oral dosages of up to 100 mg/Kg [32] were conducted to assess pathology at necropsy. No treatment-related brain lesion could be found, although some clinical measurements were noted. This study reported no deaths, and coupled with chronic oral studies by Slikker et al. [33] of up to 80 mg/Kg and chronic subcutaneous studies by O'Hearn of 20 mg/Kg [34], it seems that MDMA has relatively low toxicity by these routes in the rat. Another study [35] employed oral chronic administration of MDMA to rats at dosages of up to 300 mg/Kg, with complete blood chemistry and microscopic and histological workup. Kidney changes and possible testicular tubular changes were noted, but there was no evidence of brain damage. Acute oral LD-50 was estimated to be 325 mg/Kg and chronic oral LD-50 about half of this.

3.3. Guinea Pig

The Hardman study [28] reports an i.p. acute LD-50 of 98 mg/Kg in the guinea pig.

3.4. Dog

The acute i.v. LD-50 of MDMA in the dog is 14 mg/Kg [28]. Chronic studies at dosages of up to 15 mg/Kg were conducted [32] with clinical chemistry measurements made during and a complete pathology workup done at the end of the highest dosage exposure. There were signs of testicular atrophy and gross prostatic enlargement in some of the animals at the higher levels of drug

administration. Weight loss was also observed, but there were no indications of neuropathological changes.

3.5. Monkey

The Hardman study [28] reports an LD-50 of 22 mg/Kg for the i.v. administration of MDMA to the rhesus monkey *Macaca mulatta*. Several other primate species have been employed in neurotoxicity and behavioral studies.

3.6. Man

The lethal level of MDMA in man can only be inferred from anecdotal data in the published literature. A report describes five deaths in Dallas associated with MDMA or MDE use, with one stated to be due to MDMA specifically [36]. Hayner and McKinney describe two toxic episodes [37], one of which has been presented in detail [38]. A toxic interaction with MDMA use in association with a monoamine oxidase inhibitor has been described [39]. The association between human plasma levels of MDMA and clinical state is unclear, in that levels of 7 ug/ml [38] and 0.1 ug/ml [40] have been associated with non-lethal usage, whereas levels of 1.4 ug/ml [41] and 1.1 ug/ml [36] have been seen in fatalities. No experimental procedures are provided for any of these numbers. A review of the medical literature has been assembled for use by the physician in the emergency room [42]. One investigation of human CSF for evidence following MDMA use reported no abnormalities in the levels of neurotransmitter metabolities [43].

4. HUMAN PHARMACOLOGY

The first report of the pharmacological action of MDMA in humans appeared in 1978 [44], but it made no mention of the exploratory therapy role that had been initiated by clinical psychologists some two years earlier. The written description of the action of MDMA compared it with that of MDA when used at low levels.

MDMA is described as evoking an easily controlled altered state of consciousness with emotional and sensual overtones. "Within the effective dosage range, 75–150 mg orally, the effects are first noted very quickly, usually within a half-hour following administration. With most subjects, the plateau of effects is reported to occur in another half-hour to one hour. The intoxication symptoms are largely dissipated in an additional two hours, except for a mild residual stimulation..."

These properties, the openness of emotional expression and the unusually short duration, established the unique character of MDMA, which made it so promising to therapists and tempting, eventually, to the curious public as well.

4.1. Therapy studies

MDMA was first introduced into clinical practice on the West Coast in the latter part of 1976 and was being used by therapists on the East Coast within a

few months. It is impossible to determine accurately the size of the medical following it commanded. By far, the largest body of published clinical work with MDMA has been authored by George Greer, M.D. (see Chapter 2). His first publication [45] describes sessions with 29 patients in a therapeutic setting. He described its value in the treatment of alcohol and drug-abuse problems, in the facilitation of communication and intimacy between people involved in emotional relationships, and as an adjunct to insight-oriented psychotherapy. Further detail and some retrospective evaluation of these 29 patients has been given [46], as well as a recommended protocol for MDMA sessions [47]. A second report [48] presents a discussion of a training experiment designed to familiarize a group of 13 potential clinicians with a first-hand experience of MDMA so that they might evaluate its differences from earlier therapeutic tools, such as LSD.

Two extensive clinical studies are reported from Germany, one involving 11 MDMA-assisted group therapy meetings with a total of 52 patients [49]. There were some positive changes described, and in some cases there was no improvement observed. One extensive report has appeared in considerable detail of a clinical application [50], and several surveys have appeared of MDMA users. These include retrospective psychological interviews [51] and an evaluation of sexual aspects of the drug's effects [52]. A small volume was published containing a collection of several dozen first-hand reports of personal experiences [53].

Another large study [54] employed 21 normal volunteers, who underwent continuous physiological measurement, blood chemistry analyses, and (for some) neurological and electrocardiogram tests. These latter tests were continued for 24 hours. All subjects experienced an elevation of blood pressure and pulse rate, peaking at about one hour, and all experienced loss of appetite, to some degree. Other changes (jaw clench, reflex enhancement, and physical incoordination) were seen in some subjects. At the psychological level, all subjects reported a heightened sensual awareness and three subjects experienced sexual arousal. One retrospective survey has failed to note signs of neurotoxocity in humans [55].

4.2. Public controversy

The first promotional publications concerning MDMA were geared to the drug-oriented population. An anonymous article appeared in the counterculture magazine *Wet* in 1981 [56], and shortly thereafter appeared two privately published tracts that attempted to answer questions concerning the use of MDMA [57]. In 1985 the entire issue became a public controversy, with the appearance of news articles in *Newsweek* [58] and, just after MDMA's proposed emergency scheduling, in *Time* [59]. In the following weeks, all major magazines and newspapers carried articles and editorials that ranged from strong support to open-mindedness to outright condemnation. Reference to writings in *Life* [60], *C&E News* [61], *Harvard Medical School Mental Health*

Letter [62], *Harpers Bazaar* [63], *Alcohol and Addiction* [64], *New Age* [65], *Psychology Today* [66], *Rolling Stone* [67], and the comic strip "Doonesbury" [68] gives a good cross-section of this onslaught of information and opinion.

The controversy intensified. On the medical use side, a small but dedicated group of professional psychologists and psychiatrists maintained that MDMA was too valuable in therapy to simply have it disappear into legal oblivion. Groups such as the Earth Metabolic Design Laboratories formed to champion the cause [69]; a national conference was held in Oakland, California [70]; and several days of testimony were presented at the DEA hearings that addressed the scheduling problem. On the abuse and illegalization side, the Government issued anonymous position papers that emphasized the public health considerations [71], and extended emergency funding to researchers to quickly provide information that dealt with the neurotoxicity subject.

4.3. Future research

Two factors regarding future research into drugs that might have use in psychotherapy are immediate outgrowths of the MDMA controversy.

First, clinical studies with MDMA have come to a complete halt. The recommendations from the HHS (Health and Human Services) to the DEA, which accompanied the emergency scheduling of MDMA, encouraged the facilitation of research with the drug. However, the FDA has yet to approve an IND (Investigational New Drug) license that permits a study in humans. None have been conducted since the effective scheduling by the DEA. The abrupt invocation of the Emergency Scheduling Act in controlling MDMA, even while hearings were underway to examine the very question of scheduling itself, had a chilling effect on research in this area in the pharmaceutical houses [72] and the academic world [73]. The Analogue Substane Act of 1986 specifically outlaws any human research with drugs that have actions or structures substantially similar to MDMA (or any other Schedule I or II drugs) unless permission is received from the FDA (in the form of an IND).

A second aspect that may bear on future research deals with the pharmacological classification of MDMA. Although legally it is classified together with hallucinogenic drugs, it is not similar in action to the usual psychedelic drug. A new classification seems needed [74], and the term "entactogen" has been proposed [75] to emphasize the unique nature that MDMA has shown in therapy. A search for examples of drugs that are psychologically enabling but not hallucinogenic has been started [76].

5. LEGAL HISTORY

This review of history (as with the neurotransmitter story presented in 6. below) will be quite brief, as specific chapters in this volume will cover these subjects in intimate detail.

The first administrative acknowledgment of MDMA was a request from the World Health Organization (WHO) to the Food and Drug Administration

(FDA) for information and comments concerning the abuse potential, actual abuse, and medical usefulness of some 28 stimulants and/or hallucinogens [77]. Just one week later [78], the DEA filed a pro forma request for comments, objections, or requests for hearings, in connection with its intent to place MDMA into Schedule I of the Controlled Substances Act.

A petition requesting hearings on this listing was sent to the DEA [79] and an initial procedural hearing was scheduled [80]. At this time, the law judge assigned to this matter recommended that, as there is no place in the scheduling structure for a drug with no accepted medical use but with less than a high abuse potential, MDMA should either not be scheduled or it should be placed in less severe schedule [81]. The hearings were set to take place in Los Angeles on June 10, in Kansas City on July 10–11, and in Washington D.C. on October 8,9,10, and 11, 1985. On May, 31, 1985, just ten days before the first hearing was to be held, the DEA unilaterally invoked the Emergency Scheduling Act regarding MDMA and effected its placement on a temporary basis into Schedule I, effective July 1, 1985 [82].

The judicial recommendation that followed the hearings was that MDMA had some accepted medial use and should be placed in Schedule III [83]. The DEA took exception to the facts that were presented [84] and maintained that the placement of MDMA in Schedule I was appropriate. The temporary emergency status was extended as required on the first anniversary of the original invocation [85] and then made permanent four months later, effective November 13, 1986 [86]. It has become apparent [87] that the emergency scheduling invoked during this period by the DEA (mid-1985 to late 1986) was not valid, as Congress had invested this authority in the Attorney General, who had never subdelegated it to the DEA.

This final action by the DEA, which was contrary to the opinion and recommendation of the law judge, was appealed by Dr. Grinspoon, and one specific claim concerning the currently accepted use of MDMA in the United States was found valid. It was found [88] that FDA approval was not the sole criterion for determining the acceptability of a drug for medical use, and the DEA was ordered to remove MDMA from Schedule I, pending reconsideration of its medical status. The DEA removed MDMA from Schedule I, effective December 22, 1987 [89], but upon reconsideration replaced it into Schedule I, effective three months later [90].

MDMA now rests soundly as a Schedule I drug. In light of the removal from Schedule I ordered by the Court for documented reasons, the Department of Justice stated [91] that valid challenges may be made to any legal action that had been taken prior to the eventual permanent scheduling (which became final on March 23, 1988).

6. PHARMACOLOGY

Under the general heading of pharmacology are gathered all references to pharmacological studies including behavior and discrimination studies, and at

least a brief outline of the development of the serotonin story. Again, as with the legal history section, there are several contributions in this volume that will deal specifically and at length with these matters. Only the historic sequence of findings will be outlined here.

There are a few reports on animal behavior and drug discrimination studies that were in the literature prior to the proposed legal scheduling in 1985, but with this government action there was urgent solicitation of supporting pharmacological data from a number of academic researchers. Several reports were promptly provided and sent in unpublished form directly to the DEA for its use at the hearings. These reports were introduced directly into evidence by the DEA attorneys, as they contained conclusions (MDMA has neurotoxicity [92], MDMA is self-administered in baboons similarly to cocaine and phencyclidine [93], MDMA action in monkeys suggests a high abuse potential [31]) that were felt to support the government's position. Some of these findings have subsequently appeared in the published literature.

6.1. Behavior studies and pharmacological responses

The first studies of animal behavior changes induced by MDMA were included in the original toxicity studies done at the University of Michigan in 1953 [28]. Observations were made in both the dog and monkey of motor activity, including convulsions, rigidity, and tremor, and indications of central activity, such as bizarre body attitudes and fright displays that were interpreted as hallucinations. These studies did, however, employ i.v. dosages that incorporated levels in excess of three times the observed LD-50s for both animals.

Observers of operant behavior of primates have reported interference with grooming and social interactions [94] and the loss of conditioned behavior [95] due to MDMA, and mice studies with the optical isomers have involved specific behavioral regimens [96, 97]. Studies have been made of rotational activity [98], changes in reward thresholds [99, 100], and the voluntary self-administration of MDMA in both rhesus monkeys [101] and baboons [102].

Specific pharmacological responses that have been observed with MDMA administration have included analgesia [103, 104] and hyperactive stimulation [105, 106].

6.2. Discrimination studies

Animals (usually the rat) that are trained to discriminate between a test drug and a saline control have been used to help classify drugs into specific pharmacological categories. The Glennon group at Virginia has worked extensively with MDMA and has generally found that MDMA is "seen" by the test animal more as a stimulant than as a hallucinogen. The earliest studies were conducted before the proposed scheduling of MDMA [107, 108], and their findings were generally consistent with the reported human effects. Other discrimination tests compared MDMA to drugs involved in specific neurotransmitter function [109], and other groups used animals trained to MDMA

itself to attempt to classify its optical isomers [110, 111]; the *S* isomer (the isomer effective in man [8]) was the more potent.

Both pigeons [112] and monkeys [113] have also been used as test animals in discrimination studies. In a study with both rats and monkeys trained to discriminate amphetamine from saline, MDMA mimicked amphetamine [114].

6.3. Biochemical studies

The first biochemical studies on MDMA (1986) have shown an interference with the enzyme TPH, tryptophan hydroxylase [115, 116], which is involved with the biosynthesis of the neurotransmitter serotonin. The corresponding enzyme in the biosynthesis of dopamine, TH, (tyrosine hydroxylase), which is disturbed by pretreatment with methamphetamine, is unchanged with MDMA administration [116]. However, the inhibition of the enzyme that deaminates gamma-aminobutyric acid (GABA) protects the rat from toxic doses of methamphetamine and also protects the rat from neurotoxicity due to MDMA [117]. The TPH loss is spared by the prior removal of the adrenal glands [118].

The metabolism of MDMA has been briefly studied. N-demethylation to form 3,4-methylenedioxyamphetamine (MDA) is a minor pathway in humans [41] and in microsome studies [119]. The abstract of a study [120] reports the identification of seven metabolites (including MDA) in the rat.

6.4. In Vitro studies

The first in vitro study of MDMA appeared in 1982, and this was also the first report that serotonin might play some role in the action of MDMA [121]. Both serotonin and dopamine release from striatal slices have been reported [122], and specific binding to receptors has been studied in tissue homogenates and with radioligand assays [15, 123, 124]. The releasing potencies of MDMA for the dopamine-labelled caudate nucleus [125] and striatum [126] have been determined. Using the optical isomers of MDMA, the receptor sites in various regions of the brain have been recorded [127]. MDMA was compared with several close structural analogues in rat brain-slice studies, with dopamine release reflecting a greater dependence on chemical structure than does serotonin release [128]. A warning has been issued concerning binding of radioactive MDMA to non-biological components in these assays [129].

The observed contraction in ilium strips induced by MDMA [130] apparently does not involve serotonin receptors.

6.5. Neurotoxicity

The initial study that was used to support the government placing MDMA into Schedule I of the Controlled Substances Act was conducted by researchers at the University of Chicago. This was an investigation into the serotonin nerve terminal damage caused by MDA (methylenedioxyamphetamine) [131].

Just prior to the effective date of the DEA's emergency scheduling of MDMA (July 1, 1985) and during the period of intense publicity that MDMA was receiving in the popular press, there was a television forum, *the Phil Donahue Show*, which brought together several prominent figures in the controversy. Mr. Gene Haislip (a representative of the DEA), Dr. Charles Schuster (the director of the University of Chicago Drug Abuse Research Center), and Dr. Rick Ingrasci (a psychiatrist with broad clinical experience with MDMA) were on the program. After the show, Dr. Schuster mentioned his unpublished study on MDA, which showed nerve damage [132].

A preprint of that paper was obtained by Mr., Haislip, who used it in justifying the proposed emergency scheduling. The draft, states that other ring-substituted amphetamines (MMDA, TMA, and DOM are specified) are widely abused and that their toxicity need be evaluated. When this paper finally appeared in September, 1985, the drug MMDA had been replaced with the drug name MDMA, and the DEA justified the public health hazard, saying, "research with a similar drug (MDA) showed that a single dose may cause permanent brain damage" [133].

The torrent of serotonin-related research involving MDMA which followed these events will be only outlined briefly below, as this topic is addressed specifically in several chapters in this volume.

6.5.1. Mouse studies

The few studies that have investigated the potential neurotoxicity of MDMA in the mouse have agreed that there is very little serotonin involvement — certainly less than that seen in the rat [134]. Chronic treatment of high doses for several days showed, following a seven day rest, no serotonin loss and no nerve damage [135]. A single large dose showed transient effects, but there was no further change following additional exposure [136].

6.5.2. Rat studies

By far the most research on the neurotoxicity of MDMA has been conducted on the rat. The studies have employed a wide range of doses administered chronically or acutely by any of several routes, and in general all agree that there is a depletion of serotonin and a long-term axon damage, both of which are dose-dependent [33, 134–144]. The homologue of MDMA with an ethyl group on the nitrogen (MDE) has also been found to be neurotoxic [145, 146].

One study has reported that the administration of MDMA intracerebrally produces no neurotoxicity [147], suggesting that some peripherally formed metabolite might be responsible for the apparent neurotoxicity of MDMA. A study with a number of potential metabolites, however, shows all to be of reduced toxicity [148]. Also, one study involving the chronic administration of MDMA where each application was preceded by the serotonin uptake blocker citalopram showed a complete blockade of all neurodegenerative effects of MDMA [138].

Two studies have found evidence for the involvement of dopamine with MDMA. An effort to explain the rewarding aspect of MDMA, using brain electrodes and specific neurotransmitter inhibitors, has indicated that the reinforcing values may be mediated by dopamine D-2 receptors rather than serotonin 5-HT-2 receptors [149]. And with 6-hydroxydopamine-induced lesions, there was less motor activity following MDMA administration [150].

6.5.3. Guinea pig studies

Two studies have compared the guinea pig directly with the rat [135, 140]. In both, there was a drug-induced decrease in serotonin and in the density of uptake sites.

6.5.4. Cat studies

A single study in the cat [151] covered the dosage range of 0.25 to 5.0 mg/Kg. There was a decrease in serotonin level observed, and this was suppressed by pretreatment with p-chloroamphetamine, suggesting that the action of the two drugs is similar.

6.5.5. Primate studies

The serotonin depletion and neural damage, so well established in the rat for MDMA, appears to occur in primates as well [152, 153]. Subcutaneous administration of MDMA to three species of monkey at dosages of between 2.5 and 5 mg/Kg, twice daily for four consecutive days produces a dose-related depletion of serotonin and its principal metabolite 5-hydroxyindole acetic acid. Also, there was evidence of structural damage to serotonergic nerve fibers. The most recent study by this group has shown that the oral route is less effective than the subcutaneous and that single dosages are less effective than multiple dosages in the depletion of serotonin. However, even a single oral dose of 5 mg/Kg MDMA is effective in producing a long-lived depletion of serotonin [154].

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