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(±)3,4-Methylenedioxymethamphetamine ('Ecstasy')-Induced Serotonin Neurotoxicity: Clinical Studies

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Key Words

(±)3,4-Methylenedioxymethamphetamine · Amphetamines · Serotonin · Neurotoxicity · Neuroendocrine function

Abstract

(±)3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') is a brain serotonergic neurotoxin in experimental animals, including nonhuman primates. It is also an increasingly popular recreational drug of abuse, and doses of MDMA that are used recreationally overlap with those that produce serotonin (5-HT) neurotoxicity in animals. Studies in human MDMA users probing for evidence of brain serotonergic neurotoxicity indicate that some MDMA users may incur MDMA-related 5-HT neural injury and, possibly, functional sequelae. In particular, MDMA users have selective decrements in cerebrospinal fluid 5-hydroxyindoleacetic acid and brain 5-HT transporters, similar to nonhuman primates with documented MDMA-induced neurotoxicity. Functional abnormalities seen in MDMA users that may be related to 5- HT injury include cognitive deficits, altered sleep architecture, altered neuroendocrine function, altered behavioral responses to 5-HT selective drugs, and increased impulsivity. Additional studies in animals, as well as longitudinal and epidemiological studies in MDMA users, are required to confirm and extend the present data, and to determine whether MDMA users are at increased risk for developing neuropsychiatric illness as they age.

Introduction

There is compelling evidence that the popular recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') is toxic toward brain serotonin (5-HT) neurons in animals and that in nonhuman primates, MDMA-induced 5-HT neurotoxic injury may be permanent. Further, as discussed in the preceding article [1], doses of MDMA used by humans fall squarely into the range of dosages that are toxic in animals, when dosages are adjusted to account for interspecies differences. As such, animal models of MDMA-induced neurotoxicity suggest that human MDMA users are at high risk for incurring 5-HT neurotoxicity.

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In order to determine whether MDMA also produces 5-HT neurotoxic effects in humans, and to ascertain whether animal models accurately predict the effects of MDMA on 5-HT neurons in the human brain, we and others have conducted studies over the last decade involving individuals with a history of MDMA use. Some of these studies probed for neurobiological evidence of brain 5-HT neurotoxicity, while others probed for evidence of behavioral changes in MDMA users that might be attributed to 5-HT dysfunction. In this paper, we review findings from these studies, highlighting areas of agreement, as well as areas where there is a lack of consensus and where more research is needed.

Cerebrospinal Fluid Studies

Nonhuman primates with documented MDMA-induced 5-HT neurotoxic lesions have been shown to have selective deficits of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), with no alterations in CSF homovanillic acid (HVA) or 3-methoxy 4-hydroxyphenylglycol (MHPG), the major metabolites of dopamine and norepinephrine, respectively [2]. As such, CSF monoamine metabolites can be used as an index of MDMA-induced 5-HT injury, although decrements in CSF 5-HIAA underestimate the extent of damage seen in the brain [2]. To date, there have been four studies that have used lumbar CSF 5-HIAA measurements to screen for possible MDMA-induced neurotoxicity in humans. The first two of these were conducted in an outpatient setting. One of the studies reported reductions in CSF 5-HIAA in MDMA users [3], while the other did not [4]. Given that neither of these initial studies controlled for a large number of factors that have been found to influence CSF 5-HIAA, such as diet, activity, age, gender, presence of diagnosis of an affective disorder, concurrent use of psychoactive drugs, season and volume of the sample withdrawn [5–7], it is not surprising their results were disparate. Two subsequent inpatient studies that controlled for these factors found selective reductions in CSF 5-HIAA in MDMA users compared to control subjects who had never used MDMA [8, 9]. Notably, no differences between the two groups were found in CSF HVA or MHPG, a pattern reminiscent of that found in monkeys with MDMA-induced 5-HT injury [2]. In these two studies (and indeed, in all controlled studies of MDMA users from our laboratory), MDMA users had used MDMA on at least 25 separate occasions.

Positron Emission Tomography Studies

Like studies of CSF 5-HIAA, PET studies with [^{11}C]McN-5652, a 5-HT transporter ligand, also appear capable of detecting MDMA-induced 5-HT neurotoxicity in nonhuman primates [10], although they too may underestimate the true extent of MDMA-induced 5-HT neurotoxicity [11]. Recent PET imaging studies indicate that humans with a history of MDMA abuse show evidence of decreased [^{11}C]McN-5652-labeled 5-HT transporter sites, and that this decrease is correlated with the degree of MDMA exposure [12]. These PET data, in conjunction with data from CSF studies, provide strong evidence that at least some MDMA users incur brain 5-HT injury as a result of MDMA use.

Pharmacological Challenge Studies

Pharmacological challenge is the most effective method in animals for detecting subclinical neurotoxic injury secondary to neurotoxic amphetamines [13], suggesting that this tool might be particularly appropriate for studies in human MDMA users. The pharmacological challenge strategy takes advantage of the important role of 5-HT in the hypothalamic-pituitary-adrenal axis [14]. Although its precise role is not entirely understood, 5-HT is involved in the normal regulation of prolactin, cortisol and growth hormone secretion [15], and alterations in the 5-HT system can sometimes be detected through disturbances in homeostatic regulatory mechanisms of these hormones. For example, rats with 5-HT lesions have been shown to have an altered prolactin response to 5-hydroxytryptophan [16].

Four studies have utilized pharmacological challenges to evaluate the status of brain 5-HT neuronal function in MDMA users [8, 17–19]. Two of these studies [8, 17] used the 5-HT precursor, *L*-tryptophan. One [17] found suggestive evidence of altered neuroendocrine function in MDMA users, while the other [8] did not. Although the lack of consistency in neuroendocrine findings might be related to insufficient sensitivity of the tryptophan challenge technique, it might also be related to reinnervation of hypothalamic 5-HT neurons that has been observed to occur over time in nonhuman primates following MDMA-induced 5-HT injury [20, 21].

Gerra et al. [18] conducted neuroendocrine challenges in male MDMA users with the amphetamine analog, fenfluramine, which is thought to act principally by releasing 5-HT from presynaptic neurons. These investigators found that, compared to control subjects, MDMA users

had blunted prolactin responses following fenfluramine. These findings indicate that MDMA users have alterations in hypothalamic 5-HT function, suggestive of MDMA-induced 5-HT neurotoxicity.

Recently, our group used meta-chlorophenylpiperazine (*m*-CPP) to conduct pharmacological challenges in MDMA users and control subjects with no previous history of MDMA use [19, unpubl. data]. Pretreatment with 5-HT neurotoxins has been shown to alter the neuroendocrine and behavioral responses to *m*-CPP in animals [22–24]. In humans, *m*-CPP reliably induces increases in plasma cortisol and prolactin, effects that have been primarily attributed to actions at postsynaptic 5-HT2C receptors [25], although there is now evidence that *m*-CPP also releases 5-HT [26]. In addition to its neuroendocrine effects, *m*-CPP also induces behavioral changes, and different psychiatric populations respond differentially to the behavioral effects of *m*-CPP. For example, healthy controls typically report mild increases in anxiety following *m*-CPP [27]. In contrast, patients with obsessive-compulsive disorder report increased obsessions following *m*-CPP infusion [28], while patients with panic disorder report panic attacks [27]. We found that, following intravenous infusion of *m*-CPP, MDMA users had blunted plasma prolactin and cortisol responses compared to control subjects. In addition, MDMA users reported greater levels of 'positive' symptoms, such as happiness and lesser levels of 'negative' symptoms, such as anxiety during the 90-min period following infusion, and were significantly less likely to have a panic attack than controls. It is possible that these behavioral results reflect the fact that MDMA users in the study, as compared to controls, had used more recreational drugs, and were therefore less anxious about states of altered consciousness. However, past recreational drug use (but no MDMA use) was permitted in the control group, in an effort to avoid this potential confound.

Cognitive Studies

Several research groups have evaluated cognitive function in MDMA users in an effort to probe for persistent functional sequelae of MDMA use [9, 29–33]. The bulk of these studies utilized classic neuropsychiatric testing methods, and found that MDMA users, compared to controls, had deficits in verbal memory [29–33] and visual memory [32]. More recently, MDMA users were evaluated using a computerized performance assessment battery designed to evaluate a wide range of psychomotor tasks [9]. MDMA users showed impaired performance on a sustained attention task requiring arithmetic calculations, a task requiring visual discrimination and working memory, a short-term memory task, and a task of semantic recognition and verbal reasoning. In two of the studies [9, 32], MDMA users were also found to have significant selective decrements in CSF 5-HIAA. Further, cognitive deficits on some tasks were directly correlated with extent of past MDMA use, and in one study [32], inversely correlated with CSF 5-HIAA levels.

Sleep Studies

It is widely accepted that 5-HT plays a role in sleep regulation, although the nature of that role is unclear. Animals with experimentally induced lesions of 5-HT cell bodies develop near total insomnia [34]. Similarly, pharmacological depletion of brain 5-HT typically leads to dramatic decreases in non-rapid eye movement (NREM) sleep with less dramatic decreases in rapid eye movement (REM) sleep [34]. However, studies in humans have been less consistent. For example, treatment with the 5-HT precursor *L*-tryptophan has been found to decrease [35], increase [36] or produce no changes [37] in REM sleep time. Further complicating the picture is the fact that 5-HT neurons have progressively decreased firing rates as sleep progresses from stage 1 to stage 4 sleep, becoming nearly silent in the deepest stages of NREM [34]. Thus, although it is not clear how brain 5-HT neurons modulate sleep, they are widely viewed to be one of several neuron types that are involved in normal sleep regulation.

There has been one published study evaluating the sleep of MDMA users compared to control subjects [38]. MDMA users were found to have decreased total sleep time compared to controls. When further analyzed, it became apparent that the decrease in total sleep time was nearly entirely due to a decrease in stage 2 sleep, or an early phase of NREM sleep.

In attempt to confirm and extend previous data, we recently conducted all-night sleep studies in an independent cohort of MDMA users [unpubl. data]. As before [38], sleep architecture in MDMA users was found to be different from that of control subjects, although the differences found in the present study were not identical to those in our earlier study. In particular, MDMA subjects were found to spend significantly more time asleep, a finding that could be attributed to increases in stage 3 and stage 4 sleep. Further, MDMA users were found to have significantly greater sleep efficiency than controls.

It is not clear why results from the more recent sleep studies are not identical to those from our earlier study, but differences between the two study cohorts in the extent of MDMA use, the amount of time since last MDMA use, and the duration of time since first MDMA use could, in part, underlie the apparent discrepancy between studies. Nevertheless, the present results provide further evidence for alterations in a serotonergic-mediated function.

Personality Studies

Decreased CSF 5-HIAA levels have been found in individuals with impulsive and hostile personality traits [39, 40]. Because of the putative link between 5-HT and impulsivity, in our first controlled study of MDMA users, we sought to determine whether decreases in CSF 5-HIAA in MDMA users were associated with increases in impulsivity [8]. Contrary to expectations, we found that MDMA users, as a group, had lower scores on two hostility measures (i.e. assaultiveness and hostility) on the Buss Durkee Hostility Inventory [41] compared to controls. Further, female MDMA users reported increased harm avoidance and increased constraint on the Multidimensional Personality Questionnaire [42] compared to female control subjects. There was no relationship between CSF 5-HIAA values and measures of impulsivity or hostility.

Since our initial study, two additional reports have evaluated impulsivity in MDMA users [18, 43]. Results from these two studies were in direct contrast to our earlier study, with both studies showing increased, rather than decreased, impulsivity in MDMA users compared to controls. Although neither study involved measurement of CSF 5-HIAA, the study by Gerra et al. [18] found MDMA users to have blunted prolactin and cortisol responses to fenfluramine, suggesting reductions in brain 5-HT activity associated with increased impulsivity. Consistent with these two reports, in our most recent study of MDMA users and controls, we once again assessed personality variables, particularly impulsivity, and MDMA users were found to report greater levels of impulsivity than controls [unpubl. data].

The difference between our earlier personality findings and those of all subsequent studies may be related to the extent of MDMA use reported by the various study cohorts. During the 10 years since we first began evaluating MDMA users, the typical use patterns have dramatically changed [44]. In particular, in the 1980s, MDMA use was typically sporadic, most often on weekends, once to twice monthly at most. More recently, MDMA is most often used in the setting of raves, where individuals may take several doses of MDMA per night and may use MDMA more than once weekly. The type of individual who attends raves may be more likely to be sensation-seeking and impulsive than the average person, whereas those who use MDMA sporadically may have entirely different motives for their drug use. Thus, it is possible that increased impulsivity seen in most studies of MDMA users is unrelated to MDMA use, but represents the type of individual who is attracted to raves or who seeks out and continues to use MDMA. On the other hand, it is possible that MDMA use leads to increased impulsivity in a group already prone to impulsive behaviors. Prospective studies in MDMA users as well as individuals who attend raves but do not use MDMA are necessary to adequately address this question.

Conclusions

MDMA is a selective brain serotonergic neurotoxin in animals, and doses of MDMA that produce injury in animals overlap those used by humans, once adjustments for body mass and surface area have been made. Although it has not been ascertained with certainty that humans are also susceptible to MDMA-induced 5-HT injury, an increasing body of data suggests that they are, and that there may be direct functional consequences. Data from several laboratories, using a variety of techniques (PET studies of the 5-HT transporter; CSF studies of monoamine metabolites; neuroendocrine challenge studies; cognitive, personality and sleep evaluations) are all indicative of alterations of brain 5-HT structure or function in MDMA users.

Despite these converging lines of evidence indicating persistent alterations in 5-HT systems in MDMA users, it is important to acknowledge the limitations of previous studies probing for MDMA neurotoxicity in humans. All of the studies have been retrospective, and thus, preexisting abnormalities in 5-HT systems cannot be ruled out. However, no known neuropsychiatric condition has been associated with a loss in 5-HT transporters. Also, the patterns of CSF and PET changes seen in MDMA users parallel those seen in MDMA-treated primates, suggesting that changes are indeed produced by MDMA rather than due to preexisting conditions. Nevertheless, it is possible that some of the features that have been associated with MDMA use, such as impulsivity, are preexisting condi-

tions rather than a result of MDMA-induced 5-HT neurotoxicity. A second limitation of previous studies is that drug histories were obtained retrospectively. Thus, subjects' recall regarding drug use may be inaccurate, or drugs that were thought to be MDMA may have contained other substances. Similarly, most studies of MDMA users have involved subjects who had been exposed to multiple recreational drugs, not exclusively MDMA. These limitations notwithstanding, only MDMA and some structurally related amphetamine analogs are known to produce selective serotonergic neurotoxic injury. As such, it would be difficult to attribute decrements in CSF 5-HIAA and loss of 5-HT transporters to use of other classes of recreational drugs.

Further research is needed to validate other measures, such as pharmacological challenges, for their usefulness in detecting MDMA-induced neurotoxic injury. It will be important to determine whether animal models accurately predict the development of neurotoxicity in humans with regard to the minimal dose required to induce 5-HT injury. Also, longitudinal studies in larger cohorts of subjects will be useful in confirming existing data and determining whether disturbances in neuropsychiatric functioning develop over time, with age. These studies should be aimed at determining whether individuals exposed to MDMA are at increased risk for developing neuropsychiatric dysfunction in behavioral spheres thought to involve 5-HT, such as mood, anxiety, cognition, impulsivity, sleep and sexual function.

In sum, existing data indicate that some MDMA users incur brain serotonergic damage, as indicated by reductions in CSF 5-HIAA and loss of brain 5-HT transporters. A growing body of evidence suggests that MDMA-induced 5-HT neural injury is associated with functional consequences, including cognitive abnormalities (particularly memory), neuroendocrine abnormalities, sleep abnormalities and, possibly, impulsivity. Future studies are needed to confirm and extend currently available data, and to better define the relationship between MDMA exposure and development of neurotoxicity (i.e., determine the minimal dose necessary to produce neurotoxicity in humans). It will also be important to conduct longitudinal epidemiological studies in an effort to determine whether individuals exposed to MDMA are at a higher risk for developing neuropsychiatric problems as they age.

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