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### 13. NEUROENDOCRINOLOGICAL EFFECTS OF MDMA IN THE RAT

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#### 1. INTRODUCTION

The amphetamine analogue 3,4-methylenedioxymethamphetamine (MDMA) has attracted public attention, as well as that of the medical community, because of its effects on mood and cognition and the possibility that it is a neurotoxin. Clinical and anecdotal case reports suggest that MDMA elevates mood, relieves dysphoria, and enhances insight that lasts far beyond possible direct effects of the drug [1, 2]. A number of studies in rodents and primates have reported that single and multiple administrations of MDMA selectively deplete brain concentrations of serotonin (5-HT) and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) [3-7]. Since it has been postulated that diminished serotonergic function may increase the vulnerability to depression or actually precipitate it [8], the 5-HT-depleting effects of MDMA and its reputed antidepressant properties appear difficult to reconcile, raising the possibility that current theories of the role of 5-HT in depression or the mechanism of action of MDMA, or both, may need revision.

It has been reported that MDMA releases 5-HT and, to a lesser extent, dopamine (DA), in in vitro preparations, such as whole brain synaptosomes [9] and rat hippocampal slices [10]. MDMA has been reported to block the uptake of [<sup>3</sup>H]-5-HT and [<sup>3</sup>H]-norepinephrine (NE) into synaptosomes prepared from the hypothalamus, hippocampus, and striatum of rat brain [11]. Although a preliminary report suggested that [<sup>3</sup>H]-MDMA bound selectively to membrane preparations prepared from rat brains [12], it was subsequently reported

that [ $^3\text{H}$ ]-MDMA selectively labeled glass fiber filters [13]. These authors concluded that [ $^3\text{H}$ ]-MDMA has limited usefulness in radioligand binding studies. Finally, Lyon et al. [14] found that MDMA had little affinity for 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, or D<sub>2</sub> binding sites. Collectively, these studies suggest that MDMA is not a direct 5-HT or dopamine agonist but rather stimulates the release of endogenous 5-HT and dopamine, as well as blocks the reuptake of 5-HT, dopamine, and norepinephrine.

MDMA has been studied quite extensively in drug discrimination studies. For the most part, these studies clearly support subjective reports in humans that MDMA is not an hallucinogen [15, 16]. For example, in rodents trained to discriminate either LSD or DOM from saline in two-lever drug discrimination paradigms, MDMA did not generalize to either hallucinogen [16, 17]. Moreover, MDMA has been reported to substitute completely for amphetamine in rodents [18, 19], pigeons [20], and primates [21]. These data suggest that MDMA is more amphetamine-like than hallucinogenic, at least with respect to drug discrimination properties.

The most thoroughly investigated effect of MDMA is the ability of single or repeated administration of MDMA to deplete the concentration of 5-HT and 5-HIAA in the brain. Single administration of MDMA produces a dose-dependent depletion of 5-HT and 5-HIAA in 5-HT terminal brain areas, including frontal cortex, striatum, hippocampus, and, to a lesser extent, the hypothalamus [3, 22–24]. In addition, parenteral administration of MDMA produces a dose-dependent reduction in the activity of tryptophan hydroxylase, the rate limiting step in 5-HT synthesis [25, 26], but in vitro, MDMA had no effect on tryptophan hydroxylase activity [25]. The ability of MDMA to deplete biogenic amines has been found to be specific to 5-HT [25, 26]. Complimentary studies have found that single or repeated administration of MDMA reduces the number of 5-HT uptake sites labeled by [ $^3\text{H}$ ]-paroxetine, a marker of 5-HT nerve terminals [27–29]. The most elegant and definitive study of the selective toxicity of MDMA to date is the report of O'Hearn et al. [5]. In this study, immunocytochemistry was used to demonstrate that MDMA selectively damages the axon terminals associated with 5-HT, without affecting 5-HT cell bodies. The ability of MDMA to selectively damage 5-HT axon terminals in rodents and nonhuman primates raises the possibility that this compound could produce similar consequences in humans.

It is well documented that 5-HT plays a role in the secretion of several pituitary hormones [30]. For example, pharmacological studies both in vivo [31] and in vitro [32] support a stimulatory role of 5-HT in the secretion of ACTH and, as a consequence, corticosterone. Similarly, the selective 5-HT uptake inhibitor fluoxetine has been reported to increase corticotropin-releasing factor and vasopressin concentrations in hypophyseal portal plasma [33]. In addition, lesions of the medial basal hypothalamus significantly attenuate p-chloroamphetamine-induced and quipazine-induced corticosterone secretion in rodents [34, 35]. A recent histological study found that serotonergic

fibers originating from the dorsal and medial raphe nuclei synapse directly with CRF synthesizing neurons located in the hypothalamus [36]. Thus, neuroendocrine response patterns have been used to evaluate the mechanism of action of numerous drugs, as well as the functional state of serotonergic mechanisms [37].

The identification of multiple 5-HT binding sites in the brain [38, 39] raises the possibility that different 5-HT receptors control the secretion of pituitary hormones. Koenig et al. [40, 41] reported that both 5-HT<sub>1A</sub> agonists, such as 8-OH-DPAT, buspirone, gepirone, and ipsapirone, and the 5-HT<sub>2</sub> agonists, MK-212 and DOI (Nash et al., unpublished observation), stimulate the secretion of corticosterone in rodents.

The results presented in this chapter are an extension of previous studies conducted in this laboratory [42]. The present studies were conducted to further understand the mechanism by which MDMA stimulates the secretion of corticosterone in rodents.

## 2. NEUROENDOCRINE EFFECTS OF MDMA

Male Sprague-Dawley rats weighting 170–200 g upon delivery were purchased from Zivic Miller Laboratory (Hillson, PA) and were used in all experiments. The animals were housed six per cage in a temperature-controlled room (22–24°C) with a light/dark cycle of 12/12 hours (lights on at 0600). Food (Wayne Lab Blox) and tap water were available *ad libitum*.

The racemic mixture of MDMA was generously provided by Dr. David E. Nichols of Purdue University. Para-chlorophenylalanine (PCPA) hydrochloride was purchased from Sigma Chemical Co., St. Louis, MO. The other drugs were generously provided by the manufacturers: fluoxetine hydrochloride and LY 53857 (Eli Lilly and Co., Indianapolis, IN), ketanserin tartrate (Janssen Pharmaceutica, Beerse, Belgium), and xylamidine tosylate (Wellcome Research Laboratories, Beckenham, England). All drugs were dissolved in distilled water and injected i.p.

On the day before an experiment in which plasma ACTH and corticosterone were determined, the animals were housed six per cage and transferred to the experimental room. All experiments were performed between 0800–1000 hours.

In the dose-response study, MDMA (3, 10, and 20 mg/kg) was administered i.p. 30 minutes prior to decapitation. In the interaction studies, the antagonist was administered at times and doses indicated in the results section, followed by MDMA (3 mg/kg, i.p.) 30 minutes prior to sacrifice. In all cases, trunk blood was collected in chilled plastic tubes containing EDTA/aprotinin. The blood samples were immediately centrifuged (3000 rpm × 20 minutes), and plasma was obtained and transferred to plastic tubes. All plasma samples were stored at –80°C until the time of assay.

In the 5-HT depletion study, PCPA (150 mg/kg, i.p.) or vehicle was administered for three consecutive days. Twenty-four hours following the last

injection, each rat was challenged with saline or MDMA (3 mg/kg, i.p.) and sacrificed 30 minutes later. Trunk blood was obtained for hormone determinations. In addition, the hypothalamus from saline- and PCPA-pretreated animals challenged with vehicle was removed and homogenized in 0.1N perchloric acid for determination of 5-HT and 5-HIAA concentrations.

Plasma concentration of corticosterone was determined by RIA. [ $^3\text{H}$ ]-Corticosterone was purchased from Dupont New England Nuclear, Boston, MA, and the antiserum was purchased from Radioassay Systems Laboratories, Inc., Carson, CA. The unlabeled corticosterone used in preparing the RIA standard was obtained from Steraloids, Inc., Wilton, NH.

ACTH concentration was measured in unextracted plasma samples following the RIA procedure described by Nicholson et al. [43]. Plasma samples were collected in chilled polypropylene tubes containing 0.15 ml of the protease inhibitor aprotinin (Sigma Chemical Co., St. Louis, MO) and 0.1 ml 5% EDTA as an anticoagulant. The reference ACTH was generously provided by Dr. Raiti at the NIDDK and the National Hormone and Pituitary Program (University of Maryland School of Medicine). The primary antiserum used in this assay, IgG-ACTH-1, was purchased from IgG Corporation, Nashville, TN. [ $^{125}\text{I}$ ]ACTH was purchased from Radioassay Systems Laboratories, Inc., Carson, CA. The concentration of plasma ACTH for all samples was measured in the same assay, in duplicate, with an intraassay variation of less than 10% and a sensitivity of 5 pg/ml.

The concentration of 5-HT and 5-HIAA in the hypothalamus was determined by high pressure liquid chromatograph with electrochemical detector using previously described methods [42].

The data were analyzed using one-way and two-way analysis of variance. Differences between treatment groups were assessed with the Student-Newman-Keul's test and were considered significant at  $p < .05$ .

Table 1 presents the effect of MDMA administration on plasma concentrations of ACTH and corticosterone. MDMA produced a dose-dependent increase in the secretion of both hormones. No difference was observed in plasma concentrations of ACTH and corticosterone following the administration of 10 and 20 mg/kg MDMA. MDMA (3 mg/kg) produced a signi-

**Table 1.** Effect of MDMA on ACTH and corticosterone secretion in rodents.

| Txt     | Dose<br>(mg/kg) | N  | Corticosterone<br>(ug/dl) | ACTH<br>(pg/ml)   |
|---------|-----------------|----|---------------------------|-------------------|
| Vehicle | —               | 10 | 7.1 $\pm$ 1.7             | 38.1 $\pm$ 8.8    |
| MDMA    | 3               | 15 | 25.4 $\pm$ 2.0*           | 314.8 $\pm$ 43.0* |
| MDMA    | 10              | 6  | 35.1 $\pm$ 3.5*           | 497.4 $\pm$ 61.8* |
| MDMA    | 20              | 6  | 37.4 $\pm$ 1.8*           | 585.8 $\pm$ 44.0* |

MDMA was administered i.p. 30 minutes prior to decapitation. Each value is the mean  $\pm$  SE of 6–15 rats.  
\* $p < .05$  compared to vehicle treated group.

**Table 2.** Effect of vehicle or PCPA pretreatment on 5-HT and 5-HIAA concentrations in the hypothalamus.

|         | Hypothalamus             |                          |
|---------|--------------------------|--------------------------|
|         | 5-HT                     | 5-HIAA                   |
| Vehicle | 7.39<br>± 0.30           | 5.91<br>± 0.41           |
| PCPA    | 1.77<br>± 0.08<br>(-76%) | 1.07<br>± 0.08<br>(-82%) |

Percent changes are compared to corresponding vehicle group.

Vehicle or PCPA (150 mg/kg) were administered for 3 consecutive days and the animals were sacrificed 24 hours following the last injection. Each value is the mean ± SE of 6 rats. The values are presented as ng/mg protein.

ficant ( $p < .05$ ) increase in plasma ACTH and corticosterone concentration, which was significantly less than that produced by either the 10 or 20 mg/kg dose of MDMA.

The administration of PCPA (150 mg/kg, i.p.) for three days significantly ( $p < .05$ ) reduced the hypothalamic concentration of 5-HT and 5-HIAA by 75% and 82%, respectively (Table 2). PCPA treated rats challenged with vehicle had significantly ( $p < .05$ ) elevated basal plasma corticosterone concentrations, as compared with the rats treated only with the solvent vehicle (Table 3). More importantly, PCPA-pretreatment completely abolished MDMA-induced corticosterone secretion (Table 3).

Table 4 presents the effect of ketanserin and fluoxetine pretreatment on MDMA-induced corticosterone secretion. Administration of ketanserin produced a dose-dependent inhibition of MDMA-induced corticosterone secretion. Similarly, pretreatment with fluoxetine 16 hours prior to MDMA administration significantly ( $p < .05$ ) reduced MDMA-induced corticosterone secretion. Neither ketanserin nor fluoxetine significantly altered basal concentrations of plasma corticosterone (Table 4).

Figure 1 illustrates the effect of the selective 5-HT<sub>2</sub> antagonist LY 53857 on MDMA-induced ACTH and corticosterone secretion. LY 53857 (0.3, 1.0,

**Table 3.** Effect of vehicle or PCPA pretreatment on MDMA-induced corticosterone secretion.

| Txt     | Dose<br>(mg/kg) | Corticosterone (ug/dl)  |                           |
|---------|-----------------|-------------------------|---------------------------|
|         |                 | Vehicle                 | PCPA                      |
| Vehicle | —               | 4.7 ± 0.7               | 11.1 ± 3.0 <sup>a</sup>   |
| MDMA    | 3.0             | 28.8 ± 1.9 <sup>a</sup> | 14.7 ± 2.1 <sup>a,b</sup> |

Vehicle or PCPA (150 mg/kg) were administered for consecutive days and 24 hours following the last injection, each rat was challenged with either vehicle or MDMA (3 mg/kg). Each value represents the mean ± SE of 6 rats.

<sup>a</sup> significantly ( $p < .05$ ) greater than vehicle plus vehicle group.

<sup>b</sup> significantly ( $p < .05$ ) less than vehicle plus MDMA group.

**Table 4.** Effect of ketanserin and fluoxetine on MDMA-induced corticosterone secretion.

| Tst        | Dose<br>(mg/kg) | Corticosterone (ug/dl) |             |
|------------|-----------------|------------------------|-------------|
|            |                 | Vehicle                | MDMA        |
| Vehicle    | —               | 6.7 ± 1.8              | 32.7 ± 3.3  |
| Ketanserin | 0.3             | —                      | 23.1 ± 1.7  |
| Ketanserin | 1.0             | —                      | 13.9 ± 2.0* |
| Ketanserin | 3.0             | 7.0 ± 3.0              | 12.6 ± 2.7* |
| Fluoxetine | 10.0            | 7.1 ± 2.0              | 23.2 ± 2.4* |

Ketanserin (0.3, 1.0, and 3.0 mg/kg) was administered 90 minutes prior to decapitation and 60 minutes before MDMA (3 mg/kg) administration. Fluoxetine (10 mg/kg) was administered 16 hours prior to the administration of MDMA (3 mg/kg); animals were sacrificed 30 minutes later. Each value is the mean ± SE of 6 rats.

\* $p < .05$  versus the vehicle plus MDMA group.

and 3.0 mg/kg) was administered 90 minutes prior to sacrifice and 60 minutes before MDMA (3 mg/kg) was administered. The 1.0 and 3.0 mg/kg dose of LY 53857 significantly ( $p < .05$ ) reduced MDMA-induced ACTH and corticosterone secretion. The 3.0 mg/kg dose of LY 53857 had no effect on basal concentrations of ACTH and corticosterone.

Pretreatment with the peripheral 5-HT antagonist xylamidine had no effect on MDMA-induced ACTH or corticosterone secretion (Figure 2). Xylamidine (1.0 and 5.0 mg/kg) was administered 90 minutes prior to sacrifice and 60 minutes before MDMA (3 mg/kg) administration. The basal concentrations of ACTH and corticosterone were also unaffected by xylamidine (5 mg/kg) pretreatment.

Finally, Table 5 presents the effect of pretreatment with haloperidol (0.3 mg/kg) on MDMA-induced corticosterone secretion. Haloperidol was administered 90 minutes prior to decapitation and 60 minutes before MDMA administration. Haloperidol had no effect on either basal or MDMA-induced corticosterone secretion.

### 3. CONCLUSIONS

The administration of MDMA results in a dose-dependent increase in plasma ACTH and corticosterone concentrations in rodents. Depletion of 5-HT in the hypothalamus by 80% following pretreatment with the tryptophan hydroxylase inhibitor PCPA completely abolished MDMA-induced corticosterone response. Pretreatment with the selective 5-HT uptake inhibitor fluoxetine or the 5-HT<sub>2</sub> antagonists, ketanserin and LY 53857, significantly inhibited MDMA-induced ACTH and corticosterone secretion. Conversely, neither the peripheral 5-HT antagonist xylamidine nor the D<sub>2</sub> antagonist haloperidol significantly affected MDMA-induced neuroendocrine responses. These data suggest that MDMA is taken up by a fluoxetine-sensitive carrier, releases endogenous 5-HT, which interacts with 5-HT<sub>2</sub> receptor mechanisms most likely in the hypothalamus resulting in the secretion of ACTH and corticosterone.

Although a great many studies have been conducted over the past three

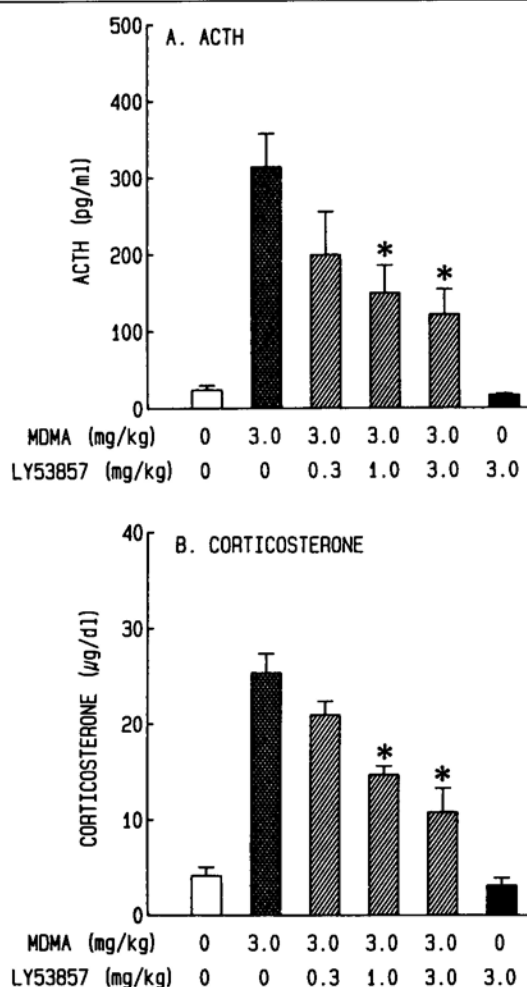


**Figure 1.** Effect of MDMA on concentrations of plasma ACTH (A) and corticosterone (B) in rats pretreated with vehicle or LY 53857. Rats were injected with either vehicle or LY 53857 (0.3, 1.0, and 3.0 mg/kg) 90 minutes prior to sacrifice and 60 minutes before the administration of MDMA (3 mg/kg). All drugs were administered i.p. in a 1 ml/kg volume. Each value represents the mean  $\pm$  SE of 6 rats. The asterisk (\*) represents a significant ( $p < .05$ ) difference as compared with the vehicle + MDMA group.

years designed to further understand the pharmacological/toxicological properties of MDMA, the mechanism of action of this amphetamine analogue remains unsolved. For example, it seems quite clear from our studies that at relatively low doses ( $\sim 3$  mg/kg), MDMA potently stimulates serotonergic systems. This finding agrees with *in vitro* studies that demonstrate the 5-HT releasing properties of MDMA in synaptosomes [9] and hippocampal slice

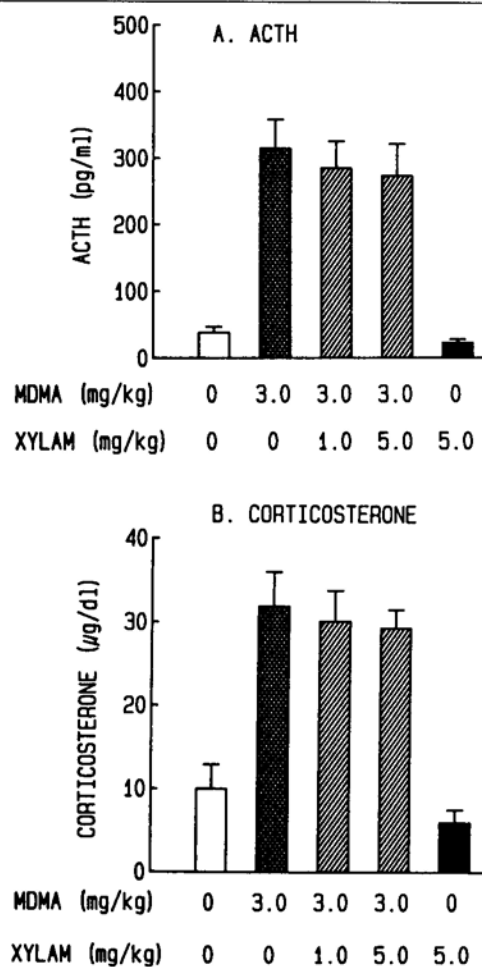


**Figure 2.** Effect of MDMA on plasma concentrations of ACTH (A) and corticosterone (B) in rats pretreated with xylamidine. Rats were injected with xylamidine (1.0 and 5.0 mg/kg) 90 minutes prior to sacrifice and 60 minutes before the administration of MDMA (3 mg/kg). All drugs were administered i.p. in a 1 ml/kg volume. Each value represents the mean  $\pm$  SE of 6 rats.

preparations [10]. Yet drug discrimination studies suggest that MDMA possesses amphetamine-like stimulus properties [44], which inferentially supports a dopamine-mediated response. Moreover, the lack of stimulus generalization with hallucinogens argues against the involvement of 5-HT<sub>2</sub> receptor mechanisms by which MDMA acts, based on studies suggesting that these hallucinogens are potent 5-HT<sub>2</sub> agonists [45–47]. Finally, with the notable exception of the studies of Steele et al. [11] and Johnson et al. [26], little attention has been directed towards examining the effect of MDMA on other neurotransmitter systems.

**Table 5.** Effect of haloperidol on MDMA-induced corticosterone secretion.

| Txt         | Dose<br>(mg/kg) | Corticosterone (ug/dl) |               |
|-------------|-----------------|------------------------|---------------|
|             |                 | Vehicle                | MDMA          |
| Vehicle     | –               | 6.4<br>± 1.8           | 19.9<br>± 2.0 |
| Haloperidol | 0.3             | 5.0<br>± 1.6           | 20.4<br>± 1.8 |

Haloperidol (0.3 mg/kg, i.p.) was administered 90 minutes prior to decapitation and 60 minutes before MDMA (3.0 mg/kg, i.p.). Each value is the mean ± SE of 5–6 rats.

The ability of ketanserin and the more selective 5-HT<sub>2</sub> antagonist LY 53857 [48, 49] to block MDMA-induced ACTH and corticosterone secretion suggests that a part of the effect of MDMA is mediated by this 5-HT receptor subtype. Although it has been reported that the 5-HT<sub>2</sub> antagonist pirenpirone fails to attenuate the disruptive effects of MDMA on operant responding in mice [50], there have been reported differences between rats and mice in response to MDMA [51, 52], which could account for this discrepancy. It is probable that the action of MDMA is dependent upon both serotonergic and catecholaminergic mechanisms. The drug discrimination cue and neuroendocrine responses may arise from catecholaminergic and serotonergic mechanisms, respectively. This explanation is supported by the fact that the 5-HT agonists MK-212 and quipazine elevate serum corticosterone via 5-HT<sub>2</sub> receptor mechanisms [40, 53] without producing visual hallucinations or perceptual distortions in humans [54, 55].

Pretreatment with fluoxetine significantly antagonized MDMA-induced corticosterone secretion. This finding is consistent with reports in which fluoxetine pretreatment blocked the 5-HT depleting effects of MDMA [3]. These data suggest that MDMA is taken up into axon terminals via a fluoxetine-sensitive uptake carrier. These studies suggest that MDMA releases endogenous 5-HT, which interacts with postsynaptic 5-HT<sub>2</sub> receptors, since pretreatment with PCPA, ketanserin, or LY 58357 abolished MDMA-induced Corticosterone secretion. An indirect effect of MDMA on serotonergic mechanisms is supported by the weak affinity of MDMA for 5-HT<sub>2</sub> and 5-HT<sub>1</sub> binding sites [14].

The inability of the peripheral 5-HT antagonist xylamidine [56] to block MDMA-induced ACTH and corticosterone secretion suggests that this response is centrally mediated. The doses of xylamidine used in this study have been reported to block peripherally-mediated responses to 5-HT agonists [57] and thus could not account for the negative findings. Similarly, in the present study, haloperidol had no effect on MDMA-induced increase in plasma corticosterone concentration even though the dose used previously had been reported to block the corticosterone response to the D<sub>2</sub> agonist pergolide [58]. Collectively, these findings argue against an involvement of either peripheral

5-HT or central mechanisms in MDMA-induced activation of the hypothalamic-pituitary-adrenocortical axis.

As mentioned in the introduction, 5-HT has been suggested to play a role in the etiology of depression. Specifically, it has been postulated that a decrease in central 5-HT function may increase the susceptibility to depression [8]. Based on this hypothesis, drugs that enhance serotonergic neurotransmission should be effective antidepressants. For example, drugs that block the reuptake of monoamines, such as the tricyclics, imipramine, and amitriptyline, as well as newer more selective 5-HT uptake inhibitors, (e.g., fluoxetine), appear to enhance 5-HT transmission and are effective antidepressants [59, 60]. Similarly, electroconvulsive shock (ECS) reduces 5-HT uptake and increases postsynaptic receptor function [60]. Chronic administration of the 5-HT precursors tryptophan or 5-hydroxytryptophan have been reported to be effective antidepressants when administered alone, or with much greater efficacy when administered in combination with tricyclic antidepressants [61, 62]. Collectively, these data support the hypothesis that serotonergic function is diminished in depression and that drugs that enhance serotonergic neurotransmission effectively alleviate the symptoms of depression.)

The acute administration of MDMA elevates mood. Based on the preceding discussion, a probable explanation for the mood-elevating properties of MDMA is the release of 5-HT. In support of this hypothesis is the study of Ward et al. [63] in which the 5-HT releaser fenfluramine was reported to significantly improve the mood of subjects with major depression following acute administration. The authors concluded that the acute effect of fenfluramine mimicked long-term antidepressant effects in these subjects. It is tempting to speculate that the chronic administration of MDMA may effectively enhance 5-HT neurotransmission by releasing endogenous 5-HT and blocking its reuptake.

In this regard, *p*-chloroamphetamine (PCA) has previously been reported to be an effective antidepressant [64, 65]. In these studies, the daily administration of 75 mg of PCA (~1.0 mg/kg) significantly improved the mood of depressed patients. The antidepressant effect of PCA was suggested to be the result of enhanced serotonergic transmission. It is interesting to note that, like MDMA, both PCA and fenfluramine have been previously reported to produce long-term depletion of 5-HT and 5-HIAA in rodents [66, 67]. Finally, although the administration of fenfluramine, PCA, and MDMA potentially release 5-HT from nerve terminals, all of these amphetamine analogues interact with other neurotransmitter systems, such as dopamine and norepinephrine, which may contribute to their complex pharmacological effects.

The study of the 5-HT depleting properties of MDMA in primates [7] clearly illustrates the potential neurotoxic effects of this agent in humans. However, determining the consequences of MDMA-induced 5-HT depletion in laboratory animals is needed. We plan to study whether MDMA administration affects serotonergic function, using neuroendocrine challenge studies.

As reviewed by Meltzer and Nash [37], the secretion of hormones, including prolactin, ACTH, and cortisol, is dependent, in part, upon serotonergic stimulation. These studies are believed to provide inferential data regarding the functional status of 5-HT systems. For example, the i.v. infusion of the 5-HT precursor tryptophan stimulates the secretion of prolactin and growth hormone. Several studies have found that tryptophan-induced prolactin and growth hormone secretion is blunted in depressed patients as compared to normal volunteers [68, 69]. These blunted responses have been attributed to an abnormality in serotonergic function. Several studies have found that the cortisol response following the administration of 5-HTP is enhanced in depressed patients as compared to normal volunteers [70–72]. These results were interpreted as an enhancement of postsynaptic receptor sensitivity as a result of diminished presynaptic 5-HT function. We propose that if MDMA destroys axon terminals, then a compensatory change of postsynaptic 5-HT receptor function may occur, resulting in an enhanced cortisol response to direct-acting 5-HT agonists such as MK-212. Studies such as these will provide valuable information about the potential prolonged effects of MDMA on serotonergic function.

In conclusion, the neuroendocrine responses to MDMA administration appear to be mediated by endogenous 5-HT via 5-HT<sub>2</sub> receptor mechanisms. Since 5-HT<sub>2</sub> antagonists inhibit MDMA-induced hormone secretion, it would be interesting to determine whether a 5-HT<sub>2</sub> antagonist, such as ketanserin or ritanserin, would block the subjective effects of MDMA in humans. Studies such as this would provide extremely important data regarding the role of 5-HT<sub>2</sub> receptors in the regulation of mood. MDMA may possess antidepressant properties, but this should be rigorously tested in preclinical studies in comparison to established antidepressants.

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