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Oral Administration of 3,4-Methylenedioxymethamphetamine (MDMA) Produces Selective Serotonergic Depletion in the Nonhuman Primate

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ALI, S. F., G. D. NEWPORT, A. C. SCALLET, Z. BINIENDA, S. A. FERGUSON, J. R. BAILEY, M. G. PAULE AND W. SLIKKER, JR. *Oral administration of 3,4-methylenedioxymethamphetamine (MDMA) produces selective serotonergic depletion in the nonhuman primate.* NEUROTOXICOL TERATOL 15(2) 91-96, 1993.—MDMA (3,4-methylenedioxymethamphetamine) has been reported to produce serotonergic depletion in nonhuman primates at doses as low as 2.5 mg/kg (1-2 times the typical human dose). The current study evaluated the dose-response relationships of MDMA (1.25-20.0 mg/kg) using regional concentrations of serotonin (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and home cage behavior as endpoints. Adult female rhesus monkeys (n = 16) were treated orally with 0, 1.25, 2.5, or 20.0 mg/kg MDMA twice daily for 4 consecutive days. Eighteen behaviors were measured in the home cage prior to, during, and after MDMA treatment. One month after the last dose, the animals were sacrificed and brains dissected into several regions for neurochemical analyses. 5-HT and 5-HIAA were analyzed via HPLC/EC. The lower doses of MDMA (1.25 and 2.5 mg/kg) did not significantly alter 5-HT or 5-HIAA concentrations in any brain region except hippocampus in which 5-HT concentrations were decreased after 2.5 mg/kg. MDMA at 20.0 mg/kg significantly decreased 5-HT and 5-HIAA concentrations in several cortical and midbrain structures. However, 5-HT and 5-HIAA concentrations in brain stem and hypothalamus were not significantly altered after any dose of MDMA. Combined with previous data from this laboratory, these results indicate that the decreased concentrations of 5-HT and 5-HIAA in selected brain regions show a selective dose-response relationship for MDMA-induced neurotoxicity as measured by serotonergic depletion in the nonhuman primate.

Methylenedioxymethamphetamine (MDMA) Nonhuman primate Monkey Serotonin 5-HIAA
Macaca mulatta Home cage behavior

METHYLENEDIOXYMETHAMPHETAMINE (MDMA) is an amphetamine analog that has been used by some professionals in the field of psychotherapy (11). Despite reports of its neurotoxicity and potentially long-lasting neuropsychiatric alterations (13), it continues to be abused recreationally. Noted neuropsychiatric alterations may be related to its apparent selective and long-lasting effects on the serotonergic system.

Rodent and nonhuman primate studies indicate that MDMA exerts selective effects on the serotonergic system with little, if any, effects on the dopamine systems (2,19,20,14,15, 12). After subcutaneous administration in the rat, MDMA decreased tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis) activity, but not tyrosine hydroxylase (dopamine synthesis) activity in hippocampus, frontal cortex, and striatum (10,16). Regional concentrations of 5-HT and/or 5-HIAA were decreased in caudate nucleus, hippocampus, hypothalamus, thalamus, and cortex of MDMA-treated rhesus and squirrel monkeys (12,14). Such decreases were reflected in concentrations of biogenic amines or metabolites

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in cerebrospinal fluid. MDMA decreased 5-HIAA concentrations while concentrations of the dopamine metabolite, homovanillic acid (HVA), and the norepinephrine metabolite, 3-methoxy-4-hydroxyphenethyleneglycol (MHPG), were relatively unaltered (12,14).

In order to more closely model typical human intake, recent studies in this laboratory have shown that MDMA selectively depletes serotonin and metabolite concentrations following oral administration in rats and rhesus monkeys. These studies indicated similar regional depletions of 5-HT and 5-HIAA as well as MDMA-induced neuropathological alterations (19,20). In addition, these studies demonstrated that the monkey is more sensitive to MDMA-induced serotonergic depletion than the rodent. For example, 80 mg/kg MDMA decreased 5-HT by 55% and 5-HIAA by 40% in the frontal cortex of the rat, whereas 10 mg/kg MDMA in the rhesus monkey produced nearly a 70% decrease of 5-HT and 5-HIAA concentrations in the same area (18).

The current study is an extension of previous work (18,20) in which the depletion of serotonin and its metabolites was examined after orally administered MDMA (5.0–10.0 mg/kg) in nonhuman primates. In the current study, the dose-response relationship of MDMA was evaluated by measuring regional 5-HT, 5-HIAA, dopamine (DA), HVA, and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations. Greater definition of the MDMA dose-response curve was obtained by administering a wider range of doses (1.25–20.0 mg/kg) than previously used. In addition, because behaviors of nonhuman primates have been reported to be sensitive to MDMA-induced alterations (12), home cage behaviors were measured before, during, and after MDMA dosing.

METHOD

Chemical

MDMA was supplied by the National Institute on Drug Abuse, (Rockville, MD). Its structure was confirmed by mass spectrometry and its purity (>99%) and stability were confirmed as previously described (8).

Experimental Design

The subjects were 16 individually-housed adult female rhesus monkeys (*Macaca mulatta*) maintained as previously described (18). Subjects were assigned to one of four treatment groups such that mean body weights (kg, ±SE) prior to treatment were 6.45 ± 0.74, 7.30 ± 0.37, 7.73 ± 0.68, and 6.63 ± 0.43 for the 0.0, 1.25, 2.5, and 20.0 mg/kg groups, respec-

TABLE 1

Behavioral Categories	
Locomotion	Ambulation or brachiation in which the torso moves at least one-half body length through space.
Environmental exploration	Manual, oral or pedal manipulation of the physical environment.
Self-motion play	Play activity (e.g., hopping in place, exaggerated locomotion, swinging from mesh).
Inactivity	A static posture in which there is an absence of all other activity with the exception of vocalizations.
Stereotypy	Patterned movement maintained in a rhythmic and repetitive fashion.
Huddle	A fetal-like posture in which the back is hunched and the head is at or below the shoulders.
Self-sex	Oral or manual manipulation of the genital area.
Self-bite	A specific vigorous bite to any part of the body.
Self-groom	Discrete picking and/or spreading of the fur.
Self-aggression	Aggressive behavior consisting of biting, hair pulling, or other self-punishing behavior.
Self-directed behaviors	Oral, manual or pedal self-manipulation that does not fit one of the defined self-directed behaviors.
Threat	An aggressive facial expression directed toward another monkey in the room.
Fear grimace	A submissive facial expression directed toward another monkey in the room.
Vocalization	Coo, bark, screech, or other vocalization.
Hostility to tester	Hostile behavior directed toward the tester.
Submissiveness to tester	Submissive behavior directed toward the tester.
Orientation to tester	Visual orientation directed toward the tester.
Collar manipulation	Manual, oral, or pedal manipulation of the monkey's restraining collar.

tively. Monkeys were treated with vehicle (water), 1.25, 2.5, or 20.0 mg/kg MDMA via gastric intubation twice/daily (9 a.m. and 4 p.m.) for 4 consecutive days. One month after the last MDMA dose, each monkey was sacrificed by a lethal IV injection of pentobarbital.

Brain Dissection

Cortical. Each brain was dissected on an ice-cold plate employing a minor modification of the method of Brown et al. (4) using the atlas of Szebenyi (21). First, the brain was sliced mid-sagittally with a brain knife. The cortex was then removed in four large pieces. The prefrontal cortex was dissected as described by Brown et al. (4). Then, a slice through the posterior extent of the sulcus cinguli defined a second portion. This portion was further dissected mid-coronally into an anterior part (corresponding to Brown's premotor cortex/pre-central gyrus) and a posterior sample of preoptic/parietal cortex. The remaining cortical segment was occipital cortex.

Subcortical. The basal ganglia, thalamus, hypothalamus, and brain stem were removed as described by Brown et al. (4), except that the basal ganglia were further dissected into the caudate nucleus and putamen and the hippocampi were rolled out from the surrounding temporal gyrus and frozen as two separate pieces, one from each hemisphere. The cortex underlying the hippocampus was also separated as entorhinal cortex. As individual regions were removed, each was immediately frozen on dry ice and the dissection was completed within 5 min of brain removal.

Neurochemical Analyses

Concentrations of 5-HT and 5-HIAA were quantitated using high performance liquid chromatography (HPLC) combined with electrochemical detection (EC) as described previously (1). Briefly, each brain region was weighed and diluted with a measured volume (10% w/v) of 0.2 *N* perchloric acid containing 100 mg/ml of the internal standard 3,4-dihydrobenzylamine (DHBA). Brain tissue was then disrupted by ultrasonication, centrifuged (×15,000 g; 7 min) and 150 μl of the supernatant was removed and filtered through 0.2 μM nylon-66 microfilters [MF-1 microcentrifuge filter, Bioanalytic System (BAS), W. Lafayette, IN]. Aliquots of 25 μl (representing 2.5 mg of brain tissue) were injected directly onto the HPLC/EC system for separation of 5-HT and 5-HIAA.

The analytical system included a Waters Associates 510A pump (Milford, MA), a Rheodyne 7125 injector (Rheodyne Inc., Cotati, CA), a Supelco Supelcosil LC-18, 3 μM (7.5 cm × 4.6 mm) analytical column, a LC-4B amperometric detector and LC-17 oxidative flow cell (BAS) consisting of a glassy carbon electrode (TL-5) versus Ag-AgCl reference electrode maintained at a potential of 0.75 V. The mobile phase consisted of 0.07 M potassium phosphate, pH 3.0, 8% methanol, and an ion pairing reagent of 1.02 mM 1-Heptane sulfonic acid and 0.12 mM EDTA. Chromatograms were recorded and integrated on a Perkin-Elmer LCI-100 integrator (Perkin-Elmer Corp., Norwalk, CT). Concentrations of 5-HT, 5-HIAA, DA, HVA, and DOPAC were calculated using standard curves generated by determining, in triplicate, the ratio between three different known amounts of each amine or its metabolite and a constant amount of the internal standard.

Behavioral Assessments

Home cage behavior was assessed following the method of Ferguson et al. (7). An experienced tester who was blind to the experimental treatment of the monkeys conducted all sessions. Test sessions for each subject were 300 s in duration and each monkey was tested once daily (Monday-Friday) at the same time of day for a total of three consecutive weeks (the week prior to MDMA dosing, the four days of dosing, and the week following dosing). Test sessions during the four dosing days began approximately 30 min after the morning administration of MDMA. A focal animal scoring technique was used (3). The 18 behavioral categories are listed in Table 1. For each subject, weekly means were calculated for each of the 18 behaviors.

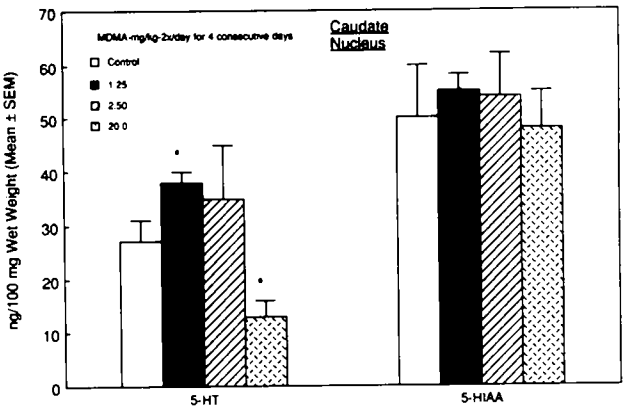

FIG. 1. Effects of MDMA on the concentrations of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the caudate nucleus of the rhesus monkey. Each value represents the mean ± SEM for 4 monkeys in each dose group.

Statistical Analysis

Concentrations of each neurotransmitter or metabolite were analyzed by separate analyses of variance (ANOVAS), and, where appropriate, by Duncan's Multiple Range Test (5). Behavioral categories which occurred with enough frequency to warrant analysis were analyzed via separate repeated measures ANOVA. Body weights were analyzed via a repeated measures ANOVA. A p value of <0.05 was taken as significant.

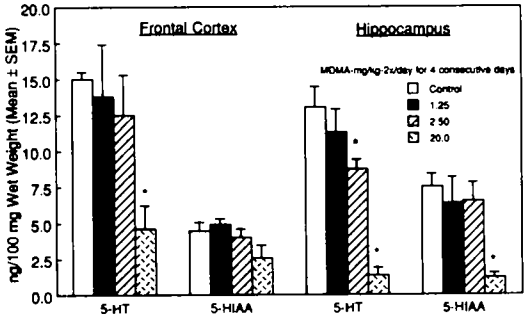

FIG. 2. Effects of MDMA on the concentrations of 5-HT and 5-HIAA in the frontal cortex and hippocampus of the rhesus monkey. Each value represents the mean ± SEM for 4 monkeys in each dose group.

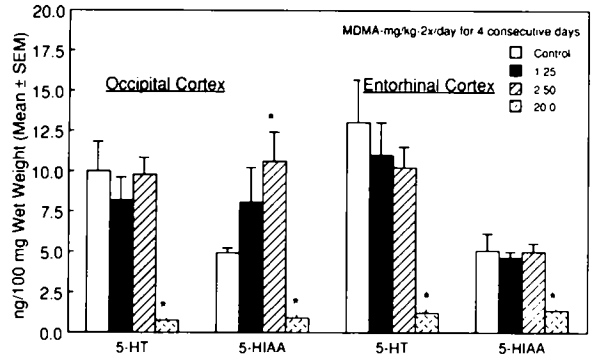

FIG. 3. Effects of MDMA on the concentrations of 5-HT and 5-HIAA in the occipital and entorhinal cortices of the rhesus monkey. Each value represents the mean ± SEM for 4 monkeys in each dose group.

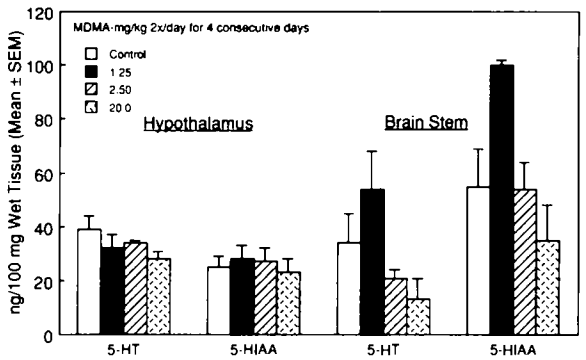

FIG. 4. Effects of MDMA on the concentrations of 5-HT and 5-HIAA in the hypothalamus and brain stem of the rhesus monkey. Each value represents the mean ± SEM for 4 monkeys in each dose group.

RESULTS

Neurochemical Analysis

5-HT and 5-HIAA concentrations.

Caudate nucleus. At 20.0 mg/kg, MDMA produced a significant depletion of 5-HT in caudate nucleus. At 1.25 and 2.5 mg/kg, however, MDMA increased 5-HT concentrations with this effect being statistically significant at the lower dose. Concentration of 5-HIAA was not significantly affected by any dose (Fig. 1).

Frontal cortex. At 20.0 mg/kg, MDMA significantly decreased 5-HT concentrations in the frontal cortex whereas 5-HIAA concentration was not significantly altered at any dose (Fig. 2).

Hippocampus. 5-HT concentrations in the hippocampus were significantly decreased after both the 2.5 and 20.0 mg/kg doses of MDMA whereas 5-HIAA concentration was significantly decreased only after the 20.0 mg/kg dose (Fig. 2).

Occipital cortex. The low doses of 1.25 and 2.5 mg/kg increased 5-HIAA concentration, with the increase being significant after the 2.5 mg/kg dose. 5-HT concentration was not affected at either of these doses. At 20.0 mg/kg, MDMA produced, as seen in other brain regions, significant depletions of 5-HT and 5-HIAA concentrations in the occipital cortex (Fig. 3).

Entorhinal cortex. At 20.0 mg/kg, MDMA produced significant depletions of both 5-HT and 5-HIAA in the entorhinal cortex. The lower doses of 1.25 and 2.5 mg/kg had no significant effects (Fig. 3).

Hypothalamus and brain stem. MDMA produced no significant changes in the concentrations of 5-HT and 5-HIAA in the hypothalamus and brain stem at any dose tested. However, there was a trend of increased levels of 5-HT and 5-HIAA in brain stem after the 1.25 mg/kg dose (Fig. 4).

DA, DOPAC, HVA concentrations. Concentrations of DA, DOPAC, and HVA did not change significantly in caudate nucleus after MDMA administration. However, there was a trend that the lower doses of 1.25 and 2.50 mg/kg caused some increases in HVA concentration (Fig. 5). When these results are combined with those obtained in previous rat and monkey studies conducted in this laboratory, a more complete dose-response relationship for MDMA and neurotransmitter concentrations is obtained. This is especially interesting for 5-HT concentrations in the hippocampus. At daily doses of 40 mg/kg (2 × 20 mg/kg), MDMA can deplete up to 90% of the 5-HT concentrations from monkey hippocampus; however, in rat hippocampus the depletion was never more than 58% with daily doses as high as 160 mg/kg (19).

Behavioral assessments. Two monkeys were excluded from behavioral analyses: one control monkey was found to be

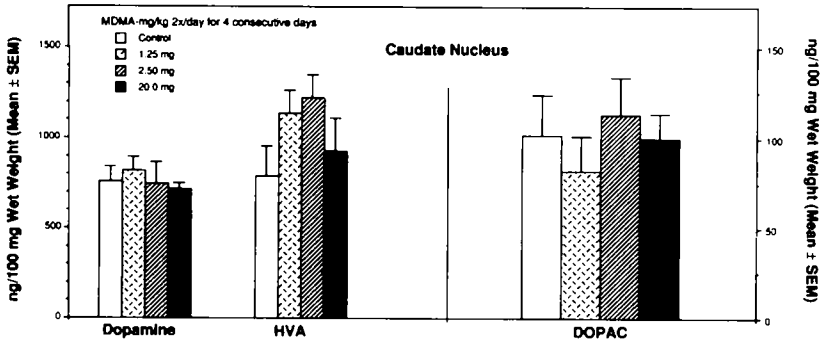

FIG. 5. Effects of MDMA on the concentrations of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in different regions of the rhesus monkey brain. Each value represents the mean ± SEM for 4 monkeys in each dose group.

pregnant at the time of sacrifice and one monkey in the 2.5 mg/kg group suffered from chronic endometriosis and was sacrificed 2 weeks after the last MDMA dose due to a moribund condition. Thus, behavioral data were based on 14 of the 16 experimental subjects.

Of the 18 behavioral categories monitored, only four occurred with enough frequency to be useful in an ANOVA. These 4 behaviors were inactivity, environmental exploration, self-directed behavior, and locomotion (Table 1). There were no significant effects of MDMA administration on the duration of any of these behavioral categories (data not shown). Anecdotal observations indicated that monkeys treated with MDMA at 20.0 mg/kg 2 times per day engaged in prolonged visual fixations and/or nystagmus, however, these behaviors were not quantified.

DISCUSSION

In combination with data previously obtained in this laboratory, the present findings further elaborate the dose-response relationship between oral MDMA administration and its selective effects on serotonergic systems in the rhesus monkey. The selective toxicity of MDMA (at doses >2.5 mg/kg given twice a day) was demonstrated by the marked and significant depletions of 5-HT and 5-HIAA that were seen in brain areas containing 5-HT axons and nerve terminals (e.g., hippocampus and cortical regions) but not in those areas supporting 5-HT cell bodies (e.g., brain stem) or areas close to regions containing cell bodies such as the hypothalamus. Increases in 5-HT and/or 5-HIAA levels after the administration of the lower doses were noted in several brain areas, suggesting increased activity in the serotonin system at doses below those that generally cause significant depletions in these neurochemicals.

Although there were significant depletions of 5-HT and 5-HIAA in most brain regions after the 20.0 mg/kg doses and some selective depletion at the lower doses used in the present study, there were no significant alterations in the home cage behaviors monitored at any dose. Fixed gazes and nystagmus were noted in most subjects receiving the 20 mg/kg dose, but the frequency and duration of these phenomena were not quantified. In male rhesus monkeys, MDMA has been reported to increase inactivity and decrease environmental exploration, particularly during the dosing period (12). In general, the control female monkeys in the current study were inactive for approximately the same amount of time as that reported for the control male monkeys of the Insel et al. study (190 vs. 222 per 300 s session, respectively). However, baseline data from their study indicated that the male monkeys in the MDMA-treated groups were somewhat less inactive prior to MDMA treatment than their control counterparts while the female monkeys in the three MDMA-treated groups of the current study were somewhat more inactive than the controls. Thus, in the current study, duration of inactivity was approaching a ceiling prior to MDMA treatment. Whether gender is a factor which interacts with the behavioral alterations produced by MDMA is not yet known.

The lack of effect of MDMA on home cage behavior in monkeys is consistent with earlier work in rodents in which there were also no significant MDMA effects on several behavioral measures with the exception of an acute *serotonergic motor syndrome* which was pronounced only on the first day after treatment (20). Thus, whether the depletion of 5-HT and/or 5-HIAA mediates any of these behaviors in monkeys or in rats is unclear. Additionally, home cage behaviors may simply not be as sensitive as other behavioral measures. For example, rhesus monkey home cage behaviors have been shown to be less sensitive to lead treatment than other types of behavioral assessments (6,7).

At the highest dose of 20.0 mg/kg, MDMA produced significant depletions of 5-HT and 5-HIAA in most regions of the monkey brain. In addition, this effect was nicely dose-dependent in the hippocampus. The lowest dose in this study (1.25 mg/kg) is approximately that used in humans (17). Therefore, the effects noted after administration of this and the 2.5 mg/kg dose are likely to be important for human risk assessment. After repeated administration of these lower doses, 5-HT and/or 5-HIAA levels actually increased or did not change in most brain areas. Only in the hippocampus was a significant reduction in 5-HT noted after repeated administration of the 2.5 mg/kg dose. Thus, doses in the 1.25 to 2.5 mg/kg range appear to be at a pivotal point on the dose-response curve for neurochemical effects in the serotonin system. Clearly, however, at doses just 3 to 4 times the approximate human dose, long-lasting decreases in 5-HT do occur in the hippocampus. Recently, Gaylor and Slikker (9) reported a relatively new approach toward risk assessment for neurotoxicity. The neurochemical, neurohistological, and behavioral effects of MDMA were used as biomarkers (endpoints) in the calculation of the risk(s) associated with given exposures (doses).

To our knowledge, this is the first study in which a dose of 1.25 mg/kg MDMA was administered to a monkey. This dose is equal to, or in some cases, lower than reported human doses (11). At this dose we found no significant depletion of 5-HT or 5-HIAA in any regions of the monkey brain. In some regions (e.g., CN and brain stem), we found an increase which did not reach statistical significance. At the next higher dose (2.5 mg/kg), we found a significant depletion of 5-HT and 5-HIAA in several brain areas but no changes in dopamine, which concur with the report of Ricaurte et al. (15). Based on the results from our 1.25 and 2.5 mg/kg dose groups, we are in agreement with the report of Ricaurte et al. (15) that the margin of safety of MDMA in humans may be narrow.

The data presented here, when combined with previous work from this laboratory (1,18,19), serve to confirm the observation that nonhuman primates (rhesus monkeys) are more sensitive to the 5-HT depleting effects of MDMA than are rodents. The Gaylor and Slikker (9) risk assessment model confirms this apparent difference in sensitivity by demonstrating that MDMA produces more significant neurochemical effects at lower doses (as low as 2.5 mg/kg) in monkeys than in rats. Additionally, MDMA's serotonin-depleting effects in rats are never as great as those seen in the monkey, even at doses as high at 160 mg/kg/day.

In conclusion, these data clearly show that MDMA produces a dose-related serotonergic depletion in the rhesus monkey and help to confirm that the monkey is more sensitive to MDMA-induced serotonin depletion than the rat. Furthermore, these data demonstrate that oral administration of MDMA in the monkey produces significant depletions of 5-HT and 5-HIAA in selected brain regions at doses very close to those reportedly used by humans. The lack of effects of MDMA administration on monkey home cage behavior suggests that these behaviors are not particularly sensitive to alteration by psychotropic agents and/or that serotonin systems are not critical for their expression. The observation that low doses of MDMA tend to increase, whereas higher doses decrease 5-HT and/or 5-HIAA concentrations suggest a biphasic dose-response function.

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