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Reinforcing Effects of MDMA ('Ecstasy') in Drug-Naive and Cocaine-Trained Rats

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Key Words

3,4-Methylenedioxymethamphetamine, reinforcing effects · Cocaine · Long-Evans rat

Abstract

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy') is one of the most prevalent illegal drugs of abuse among European adolescents, a population not generally experienced with respect to 'hard' drugs such as cocaine. We, therefore, determined the reinforcing effect of intravenously self-administered MDMA in a fixed ratio 1 time-out 150 s schedule of reinforcement in rats that were truly drug naive and compared it to cocaine-trained rats. The reinforcing effect of MDMA [0.032–10 mg/(kg · injection)] did not differ between drug-naive rats and cocaine-trained ones. MDMA sensitized the animals to its own rate-increasing effect but not to that of cocaine. When MDMA was tested after cocaine, there was no carryover of cocaine's reinforcing effect to that of MDMA, suggesting that MDMA and cocaine produce distinct interoceptive stimuli in rats.

Introduction

3,4-Methylenedioxymethamphetamine (MDMA; 'ecstasy') is a very popular substance of abuse among adolescents. Operant conditioning experiments with MDMA using the intravenous route of self-administration have been performed in nonhuman primates, i.e., rhesus monkeys [1] and baboons [2]. In both species, MDMA proved to be a reinforcer of intermediate strength. However, in none of these did a drug-naive animal receive MDMA as the *first* drug of abuse – even the animals without previous drug history were trained to respond for cocaine before being tested with MDMA. As the drug history of the laboratory subjects may affect their propensity to self-administer drugs [see, e.g., refs. 3–5], experimental data obtained with cocaine-trained nonhuman primates may model the human MDMA abuse pattern for only a fraction of the MDMA-abusing population. Thus, the data obtained in cocaine-experienced laboratory animals indicated the need for a study of the reinforcing effect of MDMA in truly drug-naive individuals and its comparison to the reinforcing effect of MDMA in individuals with a uniform cocaine drug history. By using rats, truly drug-naive subjects can be easily obtained. Furthermore, this rodent species is much more easily accessible and neurochemically much better characterized than the monkey. In rats, MDMA's reinforcing effect had been inferred to from conditioned place preference experiments [6–9] or enhancement of intracranial self-stimulation [10]. Operant conditioning work on MDMA in rats is still missing. Only a minor metabolite of MDMA metabolism in humans, i.e., 3,4-methylenedioxyamphetamine (MDA), which accounts for only about 5–10% of total MDMA ingested [11], was studied and found to serve as a reinforcer in rats [12].

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Thus, in the present study, MDMA's reinforcing effect was determined under controlled laboratory conditions in rats and was compared to the reinforcing effect of cocaine, a drug of abuse with (together with amphetamine) arguably the highest reinforcing strength under controlled laboratory conditions. We also tested whether drug history (i.e., training to respond for cocaine) had any effect on the reinforcing effect of MDMA, i.e., whether individuals without any experience with 'hard drugs' (e.g., cocaine) differ in their susceptibility to the reinforcing effect of MDMA.

Materials and Methods

Subjects and Intravenous Self-Administration Experiments

Nineteen male Long-Evans rats (Harlan-Winkelmann, Borchen, Germany), weighing 280–450 g, were trained to respond for food pellets and for water at a fixed ratio 1 (FR1) schedule of reinforcement (i.e., every single pressing on a lever was rewarded) using the model 259988 RAT operant conditioning setup developed by TSE (Bad Homburg, Germany). The operant chamber dimension was 30 × 24 × 49 cm; two levers – one for food pellets and later for intravenous drugs and one for water – were located on opposite walls of the chamber. The availability of the respective reinforcer was signalled by a red stimulus light above the respective lever; presentation of the reinforcer (i.e., for the intravenous substances, during the injection) was accompanied by a yellow stimulus light; during time-out pressing of the lever did not result in presentation of a stimulus; time-out was marked by yellow lights. The rats were fed once daily and had continuous access to water. Throughout the experiments, no food was available. The criterion for advancing the animals to testing with intravenous drugs was a rate of responding of at least 100 lever presses for food pellets (45 mg, sweet; TSE 259987-PEL-45) in a 23-hour session. Interestingly, rates of food-reinforced responding were remarkably similar across animals, regardless whether the rats reached criterion (i.e., achieved 100 lever presses for food pellets for the first time) in ten sessions (n = 14; mean 2.1 sessions; SEM 0.6 sessions) or needed up to 22 sessions (n = 5; mean 14.4 sessions; SEM 2.0 sessions) to reach the criterion (257 ± 29 responses for those rats that acquired the behavior in ten 23-hour sessions vs. 267 ± 47 responses/23-hour session for the rats that needed more than ten 23-hour sessions). Catheters (Silastic®; inner diameter 0.3 mm, outer diameter 0.6 mm) were then implanted into the right jugular vein under halothane anesthesia (initiation of anesthesia by 4% halothane in oxygen at 4 liters/min, maintenance with 0.5% halothane at 1 liter/min) under sterile conditions. Drug self-administration experiments were started on the following day by intravenous injections of drug available contingent upon presses of the lever that had previously been associated with the presentation of food pellets. Pressing the lever once (FR1) resulted in an injection of 0.3 ml of the drug, delivered steadily over 6 s. The tested drugs were: MDMA 0.032–10 mg/(kg·injection); cocaine 0.75 mg/(kg·injection), or physiological saline (determination of operant level). MDMA HCl and cocaine HCl were dissolved in sterile 0.9% saline. Only one dose was tested per session. The animals were tested in two to four daily sessions, each session lasting 120 min, with an at least 60-min intersession interval. The response requirement of FR1 (as opposed to higher FRs) was chosen to minimize confounding drug effects on locomotor output. The time-out of 150 s was used to avoid accidental overdosing. Lever pressings during time-out were not recorded and had no consequences. Neither drug accumulation nor tachyphylaxis was observed (judging from the absence of any systemic changes in response rates if one and the same dose was tested during several sessions within a single day), regardless of whether the rats were tested during two, three, or four sessions per day (data not shown). Each dose was tested (a) until response rates in three consecutive sessions did not differ by more than 2 responses/2-hour session; (b) until the lowest number of responses per session for a certain dose was at least 67% of the highest number of responses for that dose in three consecutive sessions (e.g., 15-11-13 responses/2-hour session), i.e., until the number of responses did not vary by more than 33% between three consecutive sessions, or (c) until six sessions were completed. Before the start of a session, the rat was given two drug injections by the experimenter. In order to test for (1) drug history, (2) repeated exposure to the drug of abuse, and (3) carryover of cocaine reinforcement to MDMA, the animals were divided into two groups, i.e., (a) 'drug naive' and (b) 'cocaine trained', and were repeatedly given the opportunity to self-administer MDMA or cocaine. The order of drug presentation was: (a) for the 7 drug-naive animals (Nos. 21, 23, 24, 27, 41, 47, and 50) MDMA-saline-cocaine-MDMA-cocaine and (b) for the 12 cocaine-trained animals either (Nos. 12, 14, 16, 18, 19, and 20) cocaine-*saline*-MDMA-saline-cocaine-MDMA-cocaine or (Nos. 40, 43, 45, 46, 52, and 60) cocaine-MDMA-saline-cocaine-MDMA-cocaine. The MDMA dose-response curves were always run in the order 1–3.2–0.32 mg/(kg·injection). If the response rates for 0.32 mg/(kg·injection) MDMA were higher than those for 1 mg/(kg·injection) MDMA, MDMA was tested at 0.1 or even, in 1 rat, 0.032 mg/(kg·injection). In 1 animal, MDMA 10 mg/(kg·injection) was tested. Patency of the catheters was tested every week by injection of 0.3 ml of 25 mg/ml thiopental, immediate anesthesia being the criterion for catheter functioning. The reinforcing effect of MDMA was normalized to responding for 0.75 mg/(kg·injection) cocaine in the following way: % of cocaine responding = [(responses per session for drug) – (responses per session for saline)]/[(responses per session for cocaine) – (responses per session for saline)]·100. The experiments were approved by the Ethics Committee of the Austrian Federal Ministry of Science. The experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals.

Statistics

Unless indicated otherwise, the MDMA dose [mg/(kg·injection)] at which maximum responding occurred was determined for each individual by inspection of the MDMA dose-response curve. The dose producing maximum response rates was then log-transformed before statistical analysis, because only log-transformed doses are normally distributed [13]. Mean values for doses were thus obtained from averaging log-transformed doses and then backtransforming the mean log (dose) value back to its antilog form. Values are given as mean ± SEM of n determinations or animals. Comparisons of group mean values were performed by one-factor analysis of variance (ANOVA) with Huyhn-Feldt correction for repeated measures if necessary. The ANOVA post-hoc test was Student's t test (one- or two-sided, as indicated) or the Newman-Keuls test. Group fractions (i.e., x of y tested animals in group A vs. a of b tested animals in group B) were compared using McNemar's test. Statistical analysis was performed using Prism® software (GraphPad, San Diego, Calif., USA).

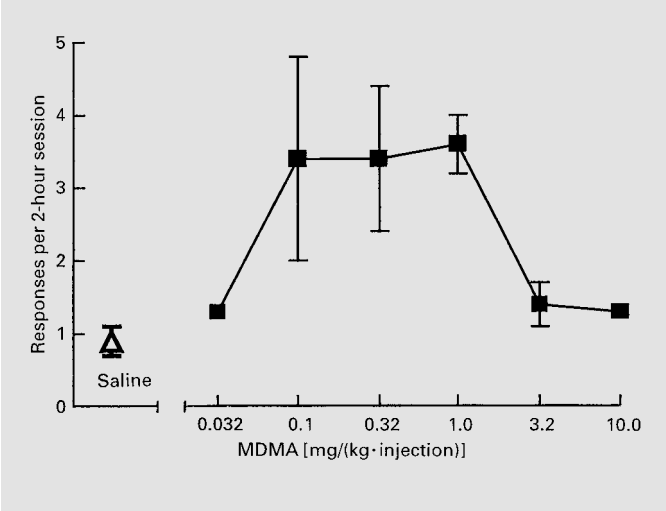

Fig. 1. Overall reinforcing effect of MDMA. Responding for MDMA (unit doses on the abscissa) is expressed as number of responses/2-hour session (ordinate) under an FR1 TO 150 s schedule of intravenous drug self-administration. Response rates (mean ± SEM) were averaged across the following number of animals for each MDMA dose [mg/(kg·injection)]: n = 6 at 0.1, n = 18 at 0.32, n = 19 at 1, n = 18 at 3.2, and n = 1 at 10. Overall response rates for both MDMA and cocaine were significantly different from operant level (saline) and from each other.

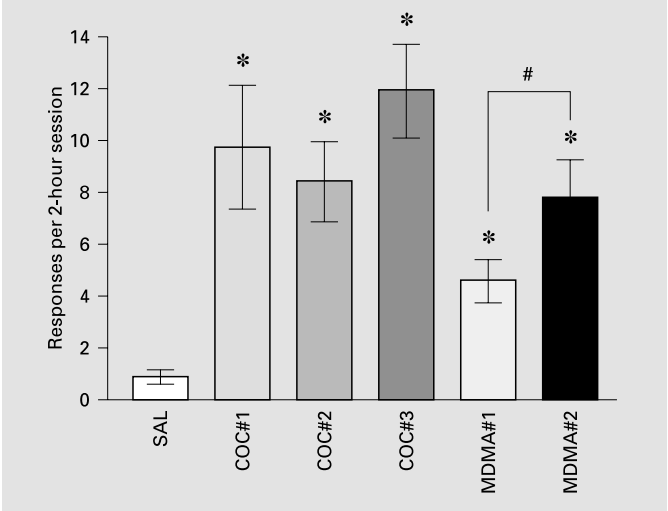

Fig. 2. Reinforcing effects of MDMA and cocaine: effect of repeated exposure. SAL = Overall saline (operant level); COC#1 to COC#3 = first to third cocaine determination; MDMA#1 and #2 = maximum response rate at the first and second MDMA dose-response curve determination. Due to catheter blockade and breakage, not all 19 animals that were entered into the experiment could be tested for its whole length. The numbers of animals completing each session series were 19 for COC#1, 13 for COC#2, 6 for COC#3, 19 for MDMA#1, and 10 for MDMA#2. * Significantly different from SAL; # significantly different from MDMA#1. Response rates between COC#1 to COC#3 and between the first and the second SAL exposure (not shown) were not significantly different from each other.

Drugs

Cocaine and MDMA were generously provided to G.Z. by the National Institute on Drug Abuse (Bethesda, Md., USA). 0.9% saline, halothane, and thiopental were obtained from commercial sources.

Results

MDMA ('ecstasy') proved to be a reinforcer in Long-Evans rats under an FR1 TO 150 s operant conditioning schedule of intravenous drug self-administration. In *none* of the tested parameters did the drug-naive animals differ significantly from the cocaine-trained animals, even at the one-sided Student's t test level (data not shown). Therefore, in the following, the groups are combined (total n = 19 rats).

MDMA maintained responding above operant level in 63% and cocaine in 74% of the tested animals, the difference being not significant (McNemar's test p = 0.1). In 3 of 19 animals (i.e., 16%) both cocaine and MDMA failed to show a statistically significant reinforcing effect. In 2 animals MDMA served as a reinforcer, whereas cocaine did not; in 4 rats cocaine was a reinforcer while MDMA was not.

Figure 1 shows that, averaged across all animals and sessions, the dose-response function for MDMA reinforcement displayed the inverted-U shape that is typical of self-administration experiments [14]: responding to MDMA increased with increasing doses of MDMA, peak responding occurred at 1 mg/(kg·injection), and further increases in the MDMA dose resulted in a decrease of response rates.

When, however, comparing response rates between the first and second MDMA dose-response curve determination and contrasting them to responding for the first, second, and third cocaine exposure, it was found that maximum response rates for MDMA were higher upon the second dose-response determination, while responding for cocaine remained stable across the three exposures (fig. 2). Due to catheter attrition, both MDMA dose-response curves could be completed in only 10 of the 19 animals. To exclude any possible bias (i.e., animals with

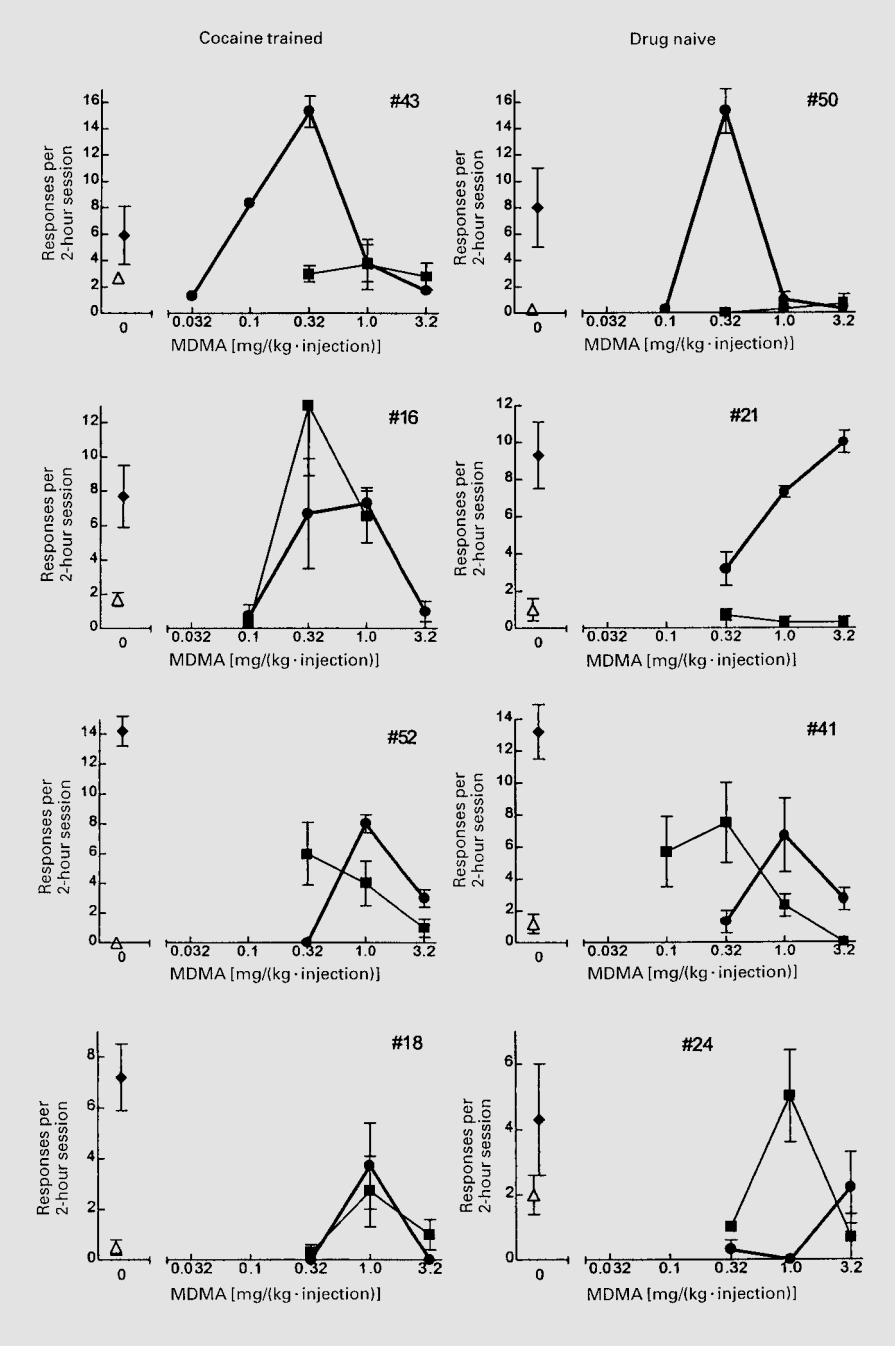

Fig. 3. Reinforcing effects of MDMA and cocaine: individual animals. Shown are response rates of animals in which two MDMA dose-response relationships (MDMA unit doses on the abscissa) could be completed. Animals were either cocaine trained (left row) or drug naive (right row). Open triangles: saline (operant level); filled diamonds: 0.75 mg/(kg · injection) cocaine; filled squares, thin line: first MDMA dose-response determination; filled circles, thick line: second MDMA determination. Rat identities (#) are given in the upper right corner of each panel.

longer-lasting catheters might be differently sensitive to the drugs tested), statistical analyses were performed both for the 10 completers only and for the 19 animals that started experiments. As can be seen below (and in the legend to figure 2), the data were essentially identical.

In contrast to the sensitization of the animals with respect to rates of maximum MDMA responding, repeated MDMA exposure did not increase MDMA's potency, the dose that produced maximum responding for the 10 animals that completed both dose-response curves being: first MDMA dose-response curve 0.7 (0.6–0.9) mg/(kg · injection); second MDMA dose-response curve 1.0 (0.7–1.4) mg/(kg · injection) (range covering 1 SEM in each direction; $p > 0.05$). For all 19 animals tested, the

respective values were 0.8 (0.7–1) mg/(kg·injection) upon the first MDMA exposure and 1.0 (0.8–1.3) mg/(kg·injection) upon the second MDMA exposure ($p > 0.05$). Thus, MDMA's potency remained unchanged upon repeated administration. At the level of the individual animal (fig. 3), all three possible reactions, i.e., sensitization, stability, and tolerance to the reinforcing effects of MDMA, could be seen.

In order to test for a possible carryover of the reinforcing effect of cocaine to the reinforcing effect of MDMA in subsequent sessions, MDMA was tested (a) in drug-naive animals, (b) after a series of saline sessions, or (c) after a series of cocaine sessions. Figure 4 shows the response rates for the first, the second, and the third MDMA session for each group. Anova of each MDMA session showed that none of the group mean values differed significantly from each other.

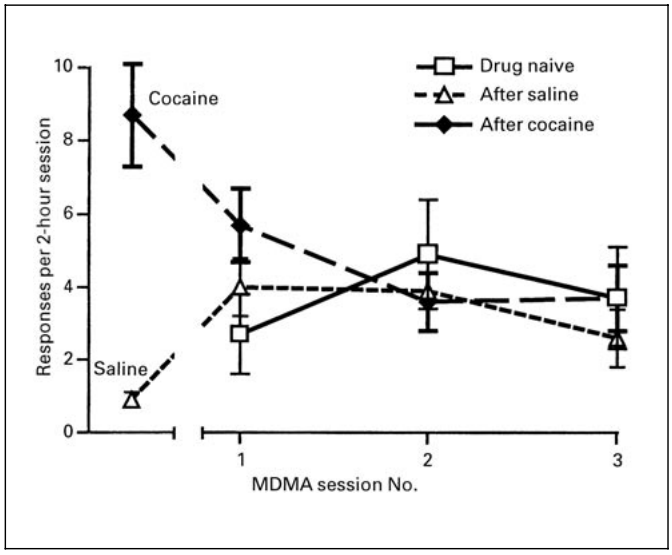

Fig. 4. Lack of cocaine reinforcement carryover to MDMA. MDMA sessions were run either in completely drug-naive animals (open squares, thick solid line; n = 7), after a series of saline sessions (open triangles, dotted line; n = 7), or after a cocaine [0.75 mg/(kg·injection)] series (filled diamonds, broken line; n = 18). Shown are response rates for the first, second, and third MDMA sessions (not significantly different). On the left side of the graph shown are overall means for saline (open triangle) and cocaine (filled diamond).

Discussion

MDMA ('ecstasy') proved to be a reinforcer in Long-Evans rats under an FR1 TO 150 s schedule of intravenous self-administration. MDMA's reinforcing strength was lower than that of cocaine: MDMA served as a reinforcer in a smaller percentage of animals than cocaine and engendered rates of responding that were lower than those for cocaine. The maximum response rates produced by MDMA were, overall, only 35% of a dose of cocaine [0.75 mg/(kg·injection)] that had previously been shown to engender maximum rates of responding in rats under the same experimental conditions [15]. A direct numerical comparison between rates of MDMA and cocaine responding should, of course, be interpreted with care: the different elimination half-lives of cocaine (10–24 min) [16, 17] and of MDMA (2.2–2.5 h) [18] might lead to different rates of drug accumulation and thus to different response rates during the experimental session. However, in accordance with the response rate differences, MDMA proved to be a reinforcer in an – albeit nonsignificantly – smaller proportion (63 vs. 74%) of the tested animals than cocaine. The fact that in 2 rats MDMA served as a reinforcer while cocaine did not indicate that some individuals might be more susceptible to MDMA's than to cocaine's reinforcing effect.

Interestingly, MDMA doses that engendered maximum rates of responding in our experiments in Long-Evans rats under an FR1 TO 150 s schedule [0.32–1 mg/(kg·injection)] are identical to those obtained in baboons [0.32–1 mg/(kg·injection)] under an FR160 TO 3 h schedule [2] and about ten-fold higher than those obtained in rhesus monkeys [0.03–0.1 mg/(kg·injection)] under an FR10 schedule (time-out not mentioned) [1].

In our experiments, cocaine training did not have an effect on MDMA's reinforcing effect, suggesting that the abuse liability of MDMA might be the same in drug-naive and drug-experienced individuals. Furthermore, the finding that cocaine training is not necessary to establish MDMA as a reinforcer in laboratory animals might help to optimize future animal experimental studies on MDMA reinforcement.

While previous exposure to cocaine did not have an effect on the reinforcing strength of MDMA, previous exposure to MDMA did enhance the rate-increasing effect of MDMA itself – without cross-sensitization to cocaine responding. Interestingly, while there was *no* evidence of a cross-sensitization of MDMA to cocaine in the present self-administration experiments, MDMA pretreatment had been shown to increase behavioral responses to cocaine [19], to increase cocaine place preference [20], and to enhance cocaine-stimulated dopamine overflow in the nucleus accumbens [21].

While previous exposure to cocaine did not have an effect on the reinforcing strength of MDMA, previous exposure to MDMA did enhance the rate-increasing effect of MDMA itself. This sensitization did not spread to MDMA's potency: The MDMA dose that engendered maximum response rates remained unchanged upon the second MDMA dose-response curve determination. Our results are in accordance with findings from several groups who found that MDMA produced sensitization to its locomotor effects [19, 22, 23].

We also determined whether previous exposure to cocaine influenced responding for MDMA if we tested a series of MDMA sessions after the cocaine sessions – minimum time interval 1 h; maximum time interval 12 h – between the last cocaine session and the first MDMA session; there was no systemic change in the following response rates for MDMA whether this interval was 1 h, 12 h, or in between (data not shown). We wanted to investigate whether there was a carryover of the cocaine reinforcement to MDMA's reinforcement, because drug discrimination data in cocaine-trained rats had shown that MDMA engendered up to 50–60% cocaine-appropriate responding [24]. Assuming that the interoceptive stimulus of a drug of abuse is relevant to its overall reinforcing effect, these drug discrimination data suggested that, in these animals, the interoceptive stimulus of MDMA resembled that of cocaine. Consequently, MDMA being made available after a series of cocaine self-administration sessions should – at least for the first few sessions after such a cocaine series – engender similar high rates of responding, if it shares some interoceptive stimulus effects with cocaine. Figure 4 shows that this was not the case. There was no significant difference in responding for MDMA regardless whether (a) MDMA sessions were run with drug-naive animals, (b) whether MDMA was tested after a series of saline sessions, i.e., under conditions of complete extinction, or (c) whether MDMA was tested after a series of cocaine sessions. Figure 4 indicates that a reinforcement carryover effect might have been present only during the *first* MDMA session after a cocaine series. However, this slight effect was not significant. Furthermore, from the second MDMA session on, any putative carryover effect disappeared completely. There was also no indication of a cocaine reinforcement carryover to saline responding, i.e., extinction was complete upon the first saline session after a series of cocaine sessions (data not shown).

In summary, MDMA proved to be a reinforcer both in truly drug-naive and in cocaine-experienced animals. While previous exposure to MDMA did enhance the rate-increasing effect of MDMA itself, this sensitization did not spread to cocaine. Vice versa, previous exposure to cocaine did not influence the reinforcing effect of subsequent MDMA challenges. Finally, the lack of any cocaine reinforcement carryover suggests that MDMA and cocaine produce distinct interoceptive stimuli in rats.

Acknowledgements

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