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Oral Self-Administration of N-Allylnormetazocine (SKF-10,047) Stereoisomers in Rhesus Monkeys: Substitution During Phencyclidine Self-Administration and Withdrawal

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CARROLL, M. E. *Oral self-administration of N-allylnormetazocine (SKF-10,047) stereoisomers in rhesus monkeys: Substitution during phencyclidine self-administration and withdrawal.* PHARMACOL BIOCHEM BEHAV **30**(2) 493–500, 1988.—Orally-delivered N-allylnormetazocine (NANM) and its isomers were tested for their ability to function as reinforcers by substituting them for phencyclidine (PCP). Two monkeys were trained to self-administer PCP (0.25 mg/ml) and water under concurrent fixed-ratio (FR) 16 schedules during 3-hr sessions. Liquid deliveries were contingent upon lip-contact responses on solenoid-operated drinking devices. When the *dextro* (+)-isomer of NANM (0.062–1 mg/ml) was substituted for PCP, response rates increased and then decreased in an inverted U-shaped concentration-response function with peak response rates comparable to those maintained by PCP. Drug intake ranged from 2.8 to 25.7 mg/kg across the two monkeys and five concentrations. Water-maintained responding was considerably lower than drug-maintained behavior indicating that NANM was functioning as a reinforcer. As previously reported for PCP, almost all of the (+)-NANM was self-administered during the first half of the session. Substitution of the *levo* (−)-isomer of NANM resulted in an immediate decline to low response rates that were not distinguishable from those maintained by water. The racemic form (±) of NANM was also not self-administered in excess of concurrent water. In the second experiment concurrent PCP- and water-maintained responding were reestablished under FR 8 schedules during three 6.5-hr sessions daily. Food (6 g/pellet) was available under FR 64 and FR 80 schedules during three 1-hr sessions immediately preceding the liquid components. Water was then substituted for PCP for four days and PCP, (+)-, (−)- or (±)-NANM were reinstated in subsequent replications of the experiment. During PCP withdrawal food-maintained responding was substantially disrupted, especially during the first two days. Reinstatement of PCP or (+)-NANM resulted in a rapid recovery of food maintained behavior, and the number of (+)-NANM deliveries was comparable to the baseline PCP deliveries. Food- and drug-maintained responding did not reliably recover when (−)- or (±)-NANM was introduced after four days of water substitution. However, after 5 days when (−)- or (±)-NANM was replaced by PCP, food and liquid-maintained responding immediately returned to baseline rates. These results agree with previous findings from intravenous self-administration studies that only the *dextro* (+)-isomer of NANM functions as a reinforcer. Neither taste factors nor PCP withdrawal altered these reinforcing effects.

Behavioral dependence Phencyclidine PCP Oral route N-Allylnormetazocine NANM
Rhesus monkeys Self-administration SKF-10,047 Stereoisomers

N-ALLYLNORMETAZOCINE (NANM), a benzomorphan opioid with psychotomimetic effects, has been considered to be the prototypical agonist of the putative *sigma* opiate receptor [19] and has received considerable experimental attention due to its similarity to the dissociative anesthetics phencyclidine (PCP) and ketamine. N-Allylnormetazocine and PCP have similar pharmacological activity; they both produce mydriasis, tachycardia, hyperthermia and depression of the flexor reflex in the chronic spinal dog [19,33]. Sigma agonists and PCP have comparable effects on complex operant behavior in monkeys [23,24] and radial maze performance in rats [18], and they result in the same subjective effects in humans [11, 13, 20]. There is evidence of cross tolerance between the two drugs [31] as well as neurochemical data suggesting common receptor mechanisms [12, 17, 26, 32, 37]. N-Allylnormetazocine has also been shown to share discriminative stimulus properties with PCP and cyclazocine in rats, pigeons, rhesus monkeys and squirrel monkeys [2, 3, 15, 16, 27, 34, 37]. The shared stimulus properties between racemic NANM and PCP appear to be specific to the pharmacological activity of the *dextro* (+)-isomer [2].

Although racemic NANM and PCP share a wide spec-

trum of pharmacological effects, they are not similar in their reinforcing effects. Self-administration of NANM appears to be stereoselective. The racemic (±) form of the drug was not self-administered by rhesus monkeys when it was substituted for ketamine, codeine [35] or cocaine [29], nor was the *levo* (−)-isomer self-injected; however, the *dextro* (+)-isomer was self-administered at rates that far exceeded saline and were equal to or greater than rates maintained by cocaine and PCP [29]. Self-administration of PCP has been reliably established using both the intravenous [1,29] and oral [7] routes. Previous work with oral self-administration of PCP in monkeys [6] and etonitazene in rats [8] indicates that taste stimuli contribute significantly to the acquisition and maintenance of drug-reinforced behavior. The purpose of the present research (Experiment 1) was to determine whether orally-delivered NANM and its stereoisomers would readily substitute for PCP as reinforcers.

An additional objective of this experiment (Experiment 2) was to examine the effect of presenting racemic (±)-NANM and its pure isomers during PCP withdrawal. Recent studies have shown physiological changes [1] and disruptions in food-maintained behavior [4,29] when PCP access or administration was terminated, suggesting a PCP withdrawal syndrome. The behavioral disruptions have been reported to last 7 or 8 days [4,29]. In these studies, behavioral disruptions were immediately reversed when PCP was reinstated. There are two reasons why the various forms of NANM would be self-administered during PCP withdrawal. First, they may substitute for PCP in alleviating the withdrawal symptoms. There is evidence that NANM suppresses a PCP withdrawal syndrome in rats produced by terminating subcutaneous injections of PCP [31]. Second, recovery from withdrawal illness may become associated with the taste of NANM and result in a conditioned taste preference. Others have shown increased intake of sweetened solutions during recovery from morphine withdrawal [25] and vitamin deficiency [27]. In the present experiment, after stable rates of PCP-reinforced behavior were obtained, water was substituted for the drug. Phencyclidine or NANM stereoisomers and the racemic mixture were presented after four days to determine whether or not the disruptions in food-maintained responding could be reversed.

METHOD

Animals

Two adult male rhesus monkeys (*Macaca mulatta*) served as subjects. The number of subjects used in this oral self-administration experiment was small because large amounts of drug (up to 50 mg/kg/day in Experiment 2) were consumed and the supply was limited. The monkeys had prior experience with self-administration or orally-delivered PCP on a daily basis for several years. Monkey M-C also had experience with oral *d*-amphetamine self-administration, and M-M1 had previously self-administered orally-delivered methohexital, phencyclidine analogs and saccharin. Both monkeys had recently participated in a parametric study of PCP dependence [4] that employed procedures that were identical to those used in Experiment 2. In Experiment 1 each monkey was maintained at 85% of its free-feeding body weight by restricting access to food (Purina High Protein Monkey Chow). The 85% weights were 8.1 (M-C) and 8.7 (M-M1) kg. In Experiment 2 food intake was controlled by the monkeys' responding, and body weights increased to 13 and 13.5 kg for M-C and M-M1, respectively. The monkeys were housed individually in their experimental chambers in a room maintained at 24°C with the lights on between 7:00 and 19:00 hr.

Apparatus

Each monkey was housed in a stainless steel Hoeltge (No. H-108) primate cage with a work panel mounted on one wall. Two drinking devices were mounted on the panel, 30 cm apart and at eye level for the monkey, and a response lever and food receptacle were located in the center of the panel. The brass drinking spouts were 2.7 cm long and 1.2 cm in diameter. A drinkometer circuit was completed each time the monkey put his mouth on the spout. Two white lights mounted behind a Plexiglas panel that supported the spout were illuminated during each lip contact when water was available, and two green lights were illuminated during each lip contact when drug was available. A large green light 12 cm above the drinking device was illuminated when water was available and the light flashed (10 cycles/sec) on the side where a drug solution was available during the session. Liquids were contained in covered stainless-steel reservoirs, and there was no measureable evaporation. In Experiment 2 when food was available, responses on the lever operated a Universal feeder (Ralph Gerbrands Co., Arlington, MA) that delivered a Purina High Protein Monkey Chow (No. 5045) pellet that weighed approximately 6 g. When food was available, a large red light above the lever was continuously illuminated. Experimental sessions were recorded automatically by microcomputers located in an adjacent room. Complete details of the control and recording equipment, drinking devices and experimental chambers have been reported earlier [10, 14, 22].

Drugs

Phencyclidine HCl and the stereoisomers and racemate of NANM were obtained from the National Institute on Drug Abuse (Research Triangle Institute: Research Triangle Park, NC). Solutions were prepared with room temperature tap water at least 20 hr before use.

Experiment 1. Substitution of Orally-Delivered NANM for Phencyclidine in a Self-Administration Paradigm

Procedure. The monkeys had been trained to self-administer orally-delivered phencyclidine (0.25 mg/ml) and water under concurrent FR 16 schedules during daily 3-hr sessions (9:30 a.m. to 12:30 p.m.). Each session was preceded and followed by a 1-hr timeout when solutions were changed and data were recorded. During the timeout, stimulus lights were not illuminated and responding had no programmed consequences. During the 19-hr intersession periods, water was available from both drinking spouts under an FR 1 schedule. The monkeys were fed at the end of the 3-hr session. Their food (Purina High-Protein Laboratory Chow No. 5045) was limited to maintain them at 85% of their free-feeding weight.

A baseline consisting of 10 sessions of stable behavior was obtained with PCP and then the *dextro* (+)-isomer of NANM was substituted for PCP. Concentrations were varied in the following order: 0.25, 0.5, 1.0, 0.0625, and 0.125 mg/ml, allowing behavior to stabilize for at least five sessions after each concentration change. This experimental design was similar to those used previously with other drugs [21], with the exception that due to a very limited supply of the

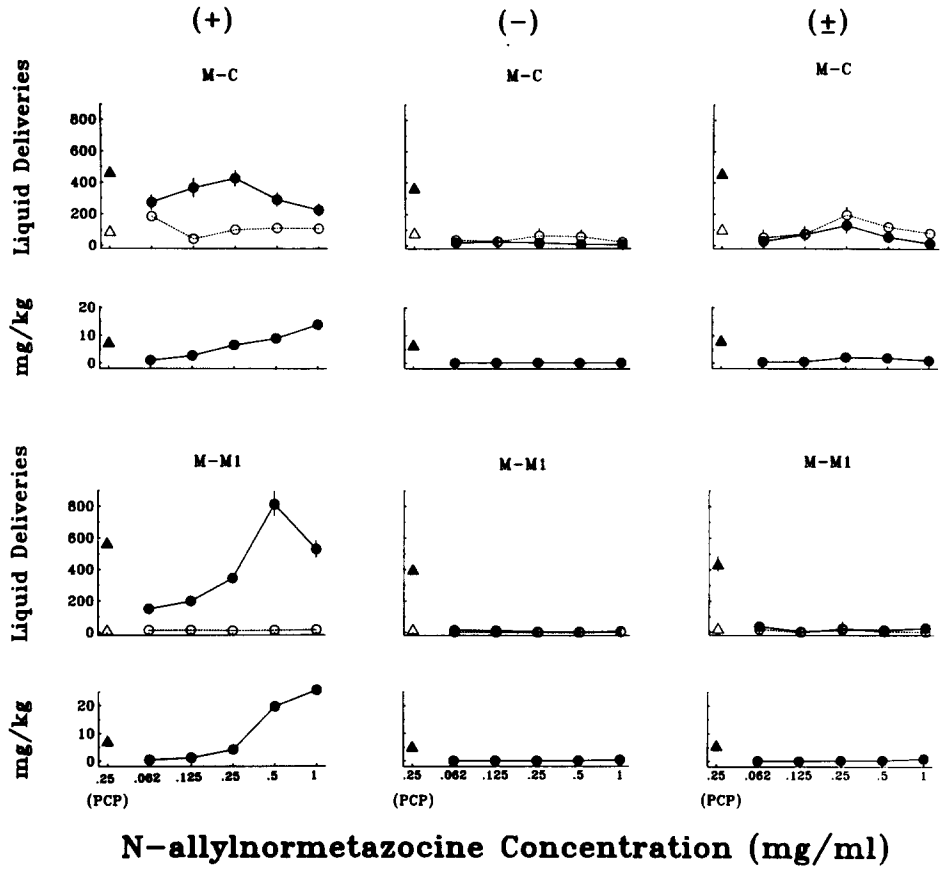

FIG. 1. Mean liquid deliveries and drug intake (mg/kg) are presented as a function of N-allylnormetazocine (NANM) concentration (mg/ml) for two monkeys (M-C and M-M1). The three panels (+), (−) and (±) refer to the *dextro* and *levo* isomers and the racemate, respectively. NANM was substituted for phencyclidine (PCP), and concentrations were presented in the following order 0.25, 0.5, 1, 0.062 and 0.125 mg/ml. Water was concurrently available, and side positions were reversed daily. Both drug and water were available under FR 16 schedules. *Filled triangles* refer to PCP (0.25 mg/ml) deliveries and intake (mg/kg). In the upper frames for each monkey, *open triangles* indicate the concurrent water deliveries during the control period. The *filled circles* refer to NANM deliveries and intake (mg/kg), and the *open circles* represent concurrent water deliveries. Each point is a mean (±S.E.) of the last five sessions of stable behavior at each concentration. Absence of S.E. bars indicates the lines fell within the plotted point.

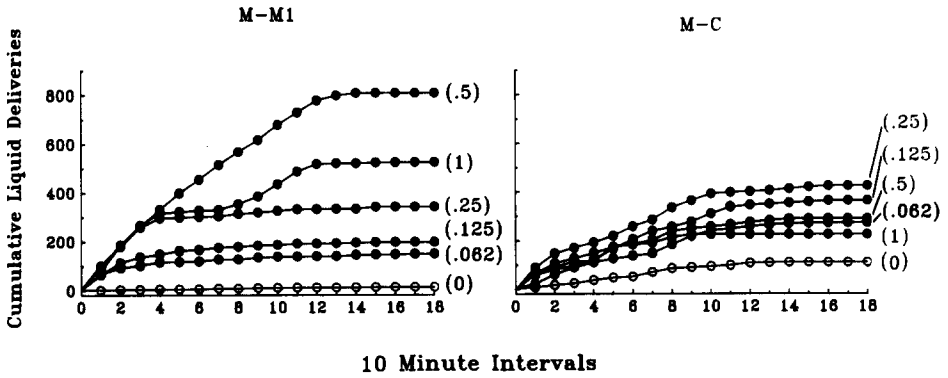

FIG. 2. Mean liquid deliveries cumulated at 10-min intervals over 3-hr sessions are presented for a range of (+)-NANM concentrations (mg/ml). *Filled circles* represent NANM deliveries and *open circles* indicate water deliveries. The curve shown for water deliveries represents the median (of the five drug conditions tested) concurrent deliveries. Each point refers to the mean of the last five sessions of stable behavior under each condition.

drug, a retest value was not obtained using the 0.25 mg/ml concentration. In earlier studies with other drugs, retest values have always been nearly identical to those obtained in the original condition. Water was always concurrently available and side positions were reversed daily. Stability was defined as no steadily increasing or decreasing trend in the number of liquid deliveries and no change in the overall pattern of responding over five consecutive sessions. Typically, there were about 5 to 7 sessions at each concentration since behavior changed rapidly with changes in drugs and concentrations, and the number of sessions required to meet stability criteria did not vary systematically with concentration. After completion of the first concentration series, PCP (0.25 mg/ml) was reinstated, and behavior was again allowed to stabilize for at least five sessions. Subsequently, the concentration series was repeated with the *levo* (−)-isomer of NANM. A third PCP baseline was then obtained and the racemic (±)-form of NANM was tested with the same concentration series, followed by reinstatement of PCP.

RESULTS

Figure 1 shows that PCP (0.25 mg/ml) deliveries exceeded water deliveries indicating that the drug was functioning as a reinforcer. When the (+)-isomer of NANM was substituted for PCP at a moderate concentration (0.25 mg/ml) responding was maintained at rates comparable to those shown for the PCP baseline. Self-administration behavior was maintained over a range of concentrations in an inverted U-shaped curve with a peak at the 0.25 mg/ml concentration for monkey M-C and at 0.5 mg/ml for M-M1. Drug intake steadily increased to a maximum of 10–25 mg/kg as concentration increased. Figure 1 also shows that when the (−)-isomer of NANM was substituted for PCP liquid deliveries were very low and not substantially different than water deliveries. When the racemic (±)-form of NANM was substituted for PCP, monkey M-M1's responding returned to low rates as it was for (−)-NANM; however, M-C maintained higher rates of drug- and water-reinforced responding although drug deliveries did not exceed water deliveries. When 0.25 mg/ml was reinstated after each concentration series, liquid deliveries were very similar to the initial baseline condition.

Figure 2 shows the mean time course of liquid deliveries over the 3-hr sessions for the (+)-NANM concentrations and concurrent water. Drug deliveries followed a negatively accelerated pattern with almost all drinking ending by the first half of the session. Water deliveries were evenly distributed throughout the 3-hr session. The curve shown was the median (total deliveries) of the five concurrent conditions that were tested. There were no consistent differences in the time course of water deliveries across all of the NANM concentrations.

Experiment 2. Substitution of NANM Isomers During PCP Abstinence

Recent research has documented physical [1] and behavioral dependence [4,29] on PCP in rhesus monkeys. Marked physical [1] and behavioral [4,29] disruptions were noted after access to self-administered [1,4] and experimenter-administered [29] phencyclidine was terminated, and these disruptions were readily reversed by restoring PCP infusions or self-administration. The purpose of the present experiment was to examine the possibility that NANM isomers would reverse disruptions produced by PCP withdrawal. A second goal was to determine whether introduction of these isomers in this context would lead to self-administration of the (−)-isomer and racemate (±), as these compounds were not reliably self-administered when directly substituted for PCP. The subjects and apparatus used in these experiments were identical to those described in Experiment 1.

Procedure. After Experiment 1 was completed, PCP (0.25 mg/ml) was substituted for (±)-NANM and behavior was allowed to stabilize for at least ten sessions. The FR requirement for PCP and water was reduced to 8 to generate greater drug intake and to be consistent with previous work [4]. Drug and water became available three times daily (10:30 a.m., 6:00 p.m. and 1:30 a.m.) for 6.5 hr each time. Side positions of drug and water continued to be reversed daily. The monkeys were also trained to respond for Purina monkey chow pellets (6 g each) on a lever located in the center of their cage. Food was available three times daily (9:30 a.m., 5:00 p.m. and 12:30 a.m.) for 1 hr each time. The response requirement for pellet deliveries was increased until all food was consumed and not discarded (e.g., FR 1, 2, 4, 8, 16, 32, 64 and 80). For Monkey M-C the final food FR was 80 and for Monkey M-M1 it was 64. The mean number of food pellets consumed during the baseline conditions (when PCP was available) was 47.5 for M-C and 49.2 for M-M1 or approximately 285 and 295.2 g, respectively. Each day there was a 1.5 hr timeout (8:00–9:30 a.m.) when data were recorded and solutions were changed. After behavior stabilized for at least ten days under these conditions, water was substituted for PCP for four days. This procedure was identical to that described in a previous experiment in which M-C and M-M1 served as subjects [4], and baseline data were nearly identical across the two experiments. Phencyclidine then replaced water for at least five days or until behavior stabilized, and this entire sequence was then repeated with the NANM isomers and the racemate (±). The order of presentation for M-C was (+)-, (−)- and (±)-NANM, and for M-M1 it was (±)-, (+)- and (−)-NANM.

RESULTS

The monkeys readily adapted to the change from the 3-hr concurrent PCP and water sessions to the 19.5-hr sessions with three 1-hr food components and three 6.5-hr liquid components. The mean total number of pellets (approximately 6 g each) earned daily during the 5-day control periods across monkeys ranged from 41.4 to 63.4, and body weights increased to 13 and 13.5 kg for M-C and M-M1 respectively. Figure 3 shows that when water was substituted for PCP for four days, pellet deliveries were reduced to less than half of control levels for four days in M-C and two days in M-M1. When PCP was reinstated, pellet deliveries returned to control levels. When (+)-NANM was substituted for water during PCP withdrawal, pellet deliveries were restored to control levels immediately in M-M1 and after two days in M-C. The (−)-isomer and racemic form of NANM did not effectively restore the suppression in pellet deliveries to control levels after PCP withdrawal; however when PCP was reinstated after five days of NANM access, response rates rapidly returned to control levels. As noted previously [4] the monkeys were irritable, but other than the disruption in pellet deliveries, there were no other physical or behavioral signs of withdrawal.

Figure 4 shows water and drug deliveries for each substitution condition. Baseline PCP deliveries were greater than water deliveries indicting that the drug was functioning as a reinforcer. When water was substituted for PCP the total

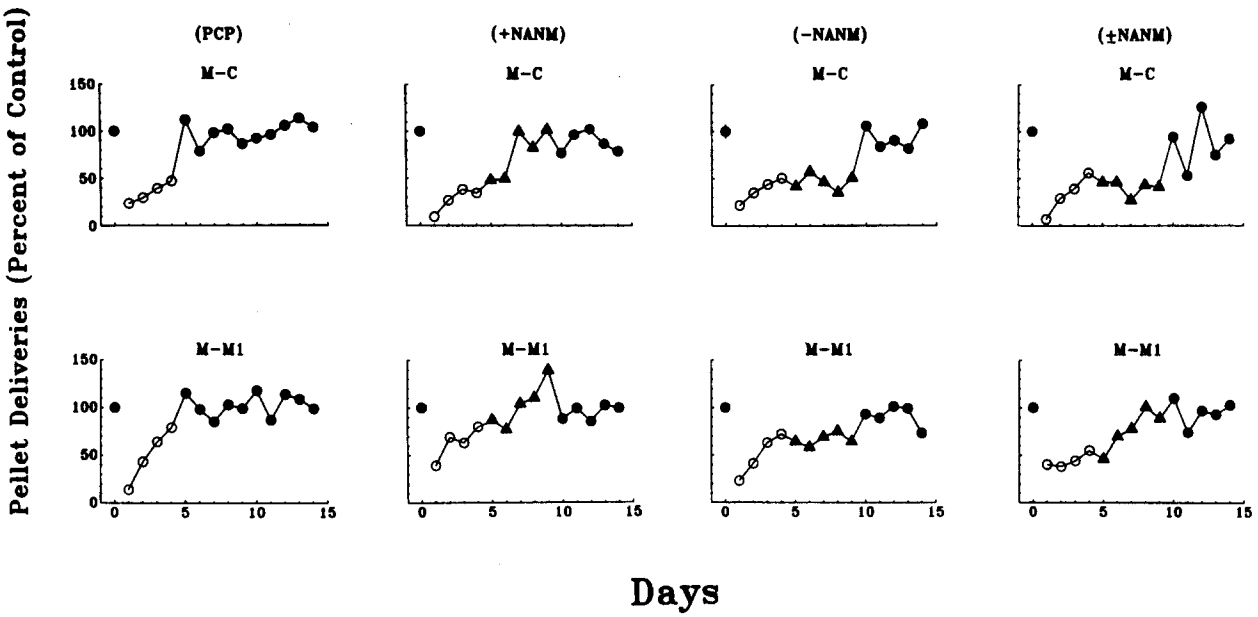

FIG. 3. Pellet deliveries (expressed as a percent of the mean of the 5-day control period) are presented for each of two monkeys as a function of the drug (indicated in parentheses) that was substituted after four days when water replaced phencyclidine. All drug concentrations were 0.25 mg/ml. *Filled circles* indicate that phencyclidine was concurrently available with water, *open circles* refer to days when water was available from both drinking spouts, and *filled triangles* represent the first five days after water substitution, when NANM was concurrently available with water. The first point (100%) serves as a control and represents a mean (±S.E.) of the last five days of stable behavior before water substitution. Connected points refer to the number of pellet deliveries (as a percent of control) each day during water substitution and drug reinstatement. Absence of S.E. bars indicates the lines fell within the plotted point.

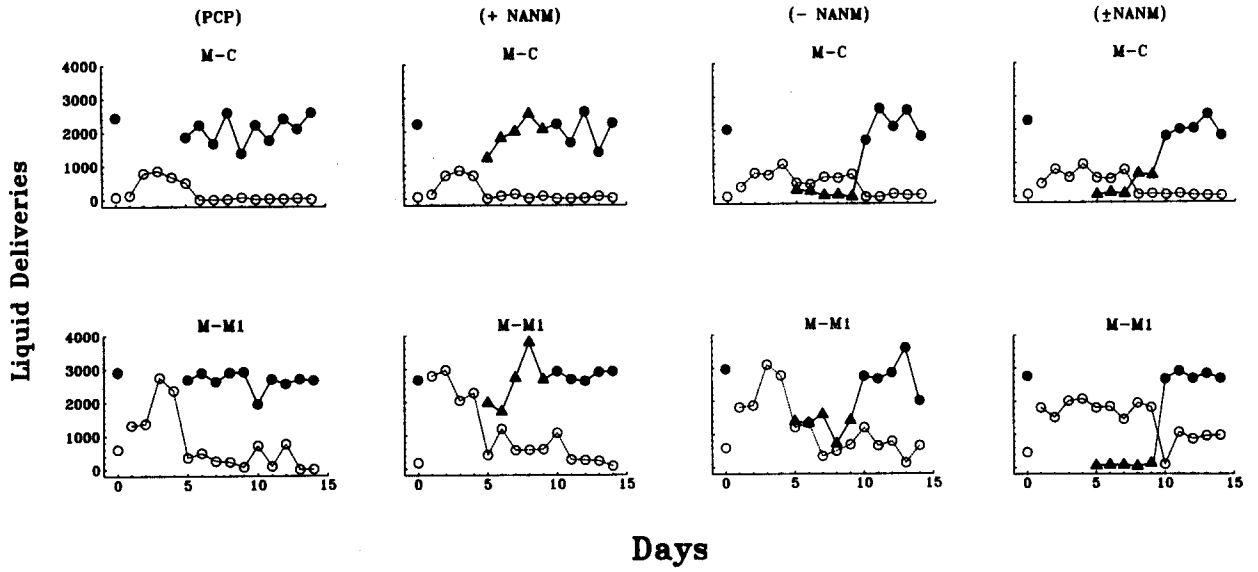

FIG. 4. Liquid deliveries are presented for each of two monkeys as a function of the drug (indicated in parentheses) that was substituted after four days when water replaced phencyclidine. *Filled circles* represent phencyclidine PCP deliveries, *open circles* refer to water deliveries and *triangles* indicate NANM deliveries. The first point represents a mean (±S.E.) of the last five days of stable behavior before water substitution. Connected points are the number of liquid deliveries during water substitution and drug reinstatement. Standard error bars fell within the plotted points.

number of liquid deliveries decreased to amounts that were lower than when the drug had been available. When PCP or (+)-NANM were then substituted for water, drug deliveries immediately returned to control rates, except (+)-NANM-maintained responding was suppressed the first two days it was available for monkey M-M1 and on the first day for M-C. Responding maintained by (−)- and (±)-NANM was low and not consistently above water levels. However, substituting PCP for these compounds resulted in an immediate return to control levels of liquid deliveries.

DISCUSSION

Orally-delivered PCP was self-administered far in excess of water when both liquids were available under concurrent FR 16 schedules indicating that the drug was functioning as a reinforcer. When racemic NANM and its pure isomers were substituted for PCP, only the (+)-isomer maintained responding above water levels. Orally-delivered (+)-NANM was readily self-administered in amounts that were equal to or greater than the amount of 0.25 mg/ml PCP consumed. Maximum daily intakes (approximately 20 mg/kg/day) were considerably greater than the amounts self-administered via the intravenous route (approximately 1 mg/kg/day) [29]. The stereoselectivity of NANM's reinforcing effects was consistent with previous findings from intravenous self-administration studies [29,35]. When the (−)-isomer and racemic form of NANM were substituted for PCP, responding declined to nearly negligible levels on the first day suggesting that these orally-delivered drugs were not functioning as reinforcers.

The results of the present oral drug self-administration study agree with previous results from IV self-administration experiments in other laboratories [29], and with a number of other reports from this laboratory in which a variety of drugs were substituted for PCP [21]. In these studies as well as the present one, the substituted (new) drug was immediately self-administered at a rapid rate during the first session it was presented, before the onset of postingestional effects, suggesting that its initial acceptance was based on taste stimuli that were similar to those of PCP and/or highly palatable taste properties. Since most of these drugs are weak bases, thus bitter tasting, it is not likely that they were highly palatable. Instead, the prolonged self-administration of these substances is likely to be due to their reinforcing effects since self-administration of a nonpsychoactive substance (quinine) that was similar to PCP in taste extinguished after 1–28 sessions [6]. In fact, in the earlier study quinine maintained responding was above water levels for only 6 sessions in M-M1 [6]; M-C was not tested with quinine. The negatively accelerated time course of (+)-NANM self-administration may have been another indicator of its reinforcing effects, as it is characteristic of the self-administration of several other drugs such as *d*-amphetamine and alcohol [21]. Nondrug substances such as water and saccharin [5] are typically consumed at a steady rate throughout a 3-hr session. The failure of the monkeys in the present experiment to self-administer (−)- and (±)-NANM may have been due to taste properties that were unlike those of PCP and/or aversive taste since these compounds maintained little responding from the start of the first substitution session. It is also possible that the rejection of (−)- and (±)-NANM was due to a conditioned taste aversion resulting from the paring of aversive effects of PCP withdrawal with the novel taste of these compounds. It has been shown that withdrawal disruptions occur when daily 3-hr access to PCP is terminated [4]. If this were the case, however, a similar avoidance of other novel tastes such as quinine, saccharin and other drugs would have been expected, but these substances were readily consumed when substituted for PCP [21].

When PCP was available concurrently with water for 19.5 hr daily, it was self-administered in large quantities and clearly functioned as a reinforcer. In fact, the differences between drug and water deliveries were more striking than those reported for Experiment 1, especially for M-M1, even though water intake was also higher in Experiment 2. Water intakes were generally higher than (−)- and (±)-NANM intakes because the water concurrently available with drug during 19.5 sessions was the only other daily source of liquids. As reported previously [4], when PCP was replaced by water, food-maintained responding was severely disrupted for at least two days, and it gradually recovered over the remaining two days of the 4-day water substitution period. In an earlier study water was substituted for 8 days and the pellet deliveries for M-C and M-M1 remained below 50 percent of baseline during that period. In the present experiment as well as the earlier one [4] there was an immediate return to control levels of food- and liquid-maintained responding when PCP was reinstated. The (+)-isomer of NANM (0.25 mg/ml) was self-administered at relatively high rates after PCP had been removed, but it increased even more after two days. This hesitancy to consume the (+)-isomer was not evident in Experiment 1, and it may have been related to the preceding 4-day abstinence phase or the longer (19.5 hr) sessions. Pellet deliveries returned to baseline rates after 2 days of (+)-NANM substitution. This may have been due to the smaller (+)-NANM intakes that occurred on those first two substitution days, or it may have been characteristic of the normal course of recovery when (+)-NANM is presented during PCP withdrawal.

When (−)- and (±)-NANM were available after four days of PCP withdrawal, intakes were negligible as they had been in Experiment 1, except for M-M1's (−)-NANM deliveries. Furthermore, pellet deliveries were not restored to baseline rates, as they had been with (+)-NANM. Monkey M-M1 did show a gradual increase in pellet deliveries after (±)-NANM substitution, but since liquid deliveries were negligible, that was probably the normal course of recovery. Thus, it is not known whether or not these forms of NANM would have alleviated the suppression in food-reinforced behavior due to PCP withdrawal. Further work with injection of the (−)- and (±)-isomers would be needed to answer this question. Food and drug-reinforced responding immediately returned to control rates when PCP replaced (−)- and (±)-NANM, indicating that the suppression in response rates during NANM access was not due to a nonspecific decline in operant levels.

The intersubject variability across the series of concentrations and substitution conditions in Experiments 1 and 2 was generally low, as has been the case in most of the oral drug self-administration [21] and dependence [4] studies that have been conducted in this laboratory. The present results indicate a stereoselectivity in the reinforcing and dependence producing properties of NANM; however more work is needed with other species and routes of administration to extend these findings. For several reasons, the generality of the present results is probably not limited by the small number of subjects tested. Within-subject comparisons were made, and conditions were counterbalanced. The subjects were highly-trained, and they had exhibited results that were very similar to each other as well as other monkeys in prevous studies of drug self-administration [21] and behavioral

dependence [4]. Finally, the results of Experiment 1 were in agreement with those reported on three rhesus monkeys that self-administered intravenously-delivered NANM isomers [29], and there were few intersubject differences among these subjects.

In summary, these results suggest that (+)-NANM is effective as an orally-delivered reinforcer as it is an intravenously-delivered reinforcer [29]. The drug was self-administered across a range of concentrations and according to a time course that was similar to PCP-reinforced behavior. The (−)-isomer and racemic (±)-form of NANM did not function as orally-delivered reinforcers. The present findings also indicate that PCP withdrawal was not a sufficient condition to induce self-administration of the NANM isomers that did not function as reinforcers.

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