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Long-Term Influence of *d*-Amphetamine on Mesolimbic Brain-Stimulation Reward: Comparison to Chronic Haloperidol and Naloxone Effects

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BOROWSKI, T. B. AND L. KOKKINIDIS. *Long-term influence of* d-*amphetamine on mesolimbic brain-stimulation reward: Comparison to chronic haloperidol and naloxone effects.* PHARMACOL BIOCHEM BEHAV 43(1) 1-15, 1992.— Rate-intensity functions for brain-stimulation reward from the dopamine (DA) A10 cell region of the ventral tegmental area (VTA) were assessed following chronic exposure to *d*-amphetamine (10.0 mg/kg), haloperidol (1.0 mg/kg), and naloxone (20.0 mg/kg). A reward depression developed when animals were tested daily 24 h following injection of amphetamine and haloperidol. In the case of amphetamine, this effect was transitory and a full recovery of intracranial self-stimulation (ICSS) was evident 5 days after drug abstinence. Low-dose (0.5 mg/kg) amphetamine challenge administered 50 days postdrug treatment decreased current thresholds indicating a long-lasting sensitization of mesolimbic reward processes. The reward depression induced by chronic haloperidol exposure showed no signs of recovery during the abstinence period and ICSS rates remained significantly reduced after amphetamine challenge 50 days later. These behavioral observations suggest that under conditions of continued demand the functional aspects of neuroleptic-induced depolarization inactivation of VTA neurons are enduring. Chronic exposure to naloxone did not modify reward thresholds indicating that opioid hypoactivity may not be a factor in the ICSS depression induced by long-term amphetamine and haloperidol treatment. These data were related to the possibility that stimulant-induced sensitization of motivational processes may evolve as a compensatory response to the transitory development of withdrawal depression.

Amphetamine Haloperidol Naloxone VTA Brain-stimulation reward Depression Sensitization Dopamine Opioids

THE mesolimbic dopamine (DA) pathway originating from the A10 cell grouping of the ventral tegmental area (VTA) has received considerable attention as a neural system involved in modulating the rewarding and motivational properties of psychostimulant drugs (13,14,35,58). Human abusers of stimulant drugs typically develop craving and dysphoric symptoms (15,16), and animal studies have shown that withdrawal from chronic exposure to cocaine and amphetamine elicits a depression in central reward functioning (21,22,28,30). It has been suggested that the withdrawal depression can act as a negative reinforcer resulting in increased drug intake as a function of repeated exposure (tolerance) (10,21).

The position that some aspects of tolerance evolve as a consequence of stimulant-induced anhedonia is supported by the observation that chronic exposure to either cocaine or amphetamine does not reduce the sensitivity of central reward mechanisms to the acute rewarding properties of these drugs. In an ICSS paradigm, for example, repeated stimulant preexposure sensitizes brain-stimulation reward when animals are tested under the influence of the drug (21), and in some instances increases in baseline rates of responding have been reported as well (22,39). Reward sensitization also has been shown to develop in a place conditioning paradigm (29) and after intravenous self-administration of cocaine and amphetamine (18,59).

The available evidence suggests that the changes in reward and motivation induced by acute and repeated stimulant exposure are progressive and involve three distinct behavioral states (hedonia, dysphoria, and sensitization). Ultimately, the outcome is dependent upon the dosage level, chronicity of drug treatment, temporal characteristics associated with drug administration and the testing procedure, as well as the drug state of the organism at the time of behavioral evaluation. From the neurochemical perspective, these stages correlate

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well with the stimulant-induced changes in DA neurotransmission. Thus, while the enhancing effects of acute stimulant administration on reward processes are positively related to a drug-induced increase in DA utilization in the nucleus accumbens (17,35), the resulting hypoactivity of DA functioning (8,40,49–51,54) has been implicated in the emerging depression of brain-stimulation reward seen during stimulant withdrawal (21,22). Alterations in presynaptic DA neuronal dynamics possibly reflecting a compensatory mechanism for the stimulant-induced DA hypoactivity (21,22) have been associated with the evolution of behavioral sensitization (41). These include increased neuronal DA release (2,27,42), reduced somatodendritic inhibition of DA neuronal activity in the VTA (1,55), and a reduction of mesolimbic DA reuptake mechanisms following stimulant preexposure (19).

The first objective of this study was to assess the evolution of the postamphetamine reward depression, the time course of the recovery of ICSS from the A10 cell grouping of the VTA, and the longevity of the reward sensitization elicited by amphetamine challenge using a two-hole nose-poke discrimination procedure. The measurement of correct (reinforced) and incorrect (nonreinforced) responses in this discrimination task has proven useful in analyzing and, in some instances, dissociating between reward and performance effects (22). It is known that amphetamine, in high doses, is neurotoxic, destroying DA and serotonin presynaptic terminals (45,47). Since experiments evaluating the dysphoric effects of amphetamine on ICSS have typically employed chronic high-dose drug schedules (26,28), the analysis of reinforced and error responding in the discrimination paradigm might provide a better understanding of the behavioral changes that develop during drug withdrawal, abstinence, and after amphetamine challenge.

A second purpose of this investigation was to compare the behavioral profile of amphetamine withdrawal to that of long-term haloperidol treatment. In animal studies, the anhedonic effects of acute haloperidol injection are well documented (12,56); however, there is little known about the effects of chronic haloperidol preexposure on mesolimbic brain-stimulation reward. This information should prove particularly useful since dysphoria is a reported side effect of chronic haloperidol intake (11). In addition, this approach might shed some light on the functional significance of the development and time course of haloperidol-induced depolarization inactivation of mesencephalic neurons associated with repeated administration of this neuroleptic (9).

The final aim of this study was to determine the long-term consequences of the opiate antagonist, naloxone, on ICSS. It is known that VTA DA plays an important role in opioid reward (57); however, there is little information concerning changes in ICSS after repeated preexposure to opiate antagonists in terms of DA–opioid interactions (44). To this end, the effects of chronic naloxone administration on brain-stimulation reward were evaluated during drug posttest (withdrawal), abstinence, and after amphetamine challenge and compared to the behavioral profiles of amphetamine and haloperidol.

METHOD

Subjects

Male Wistar rats (250–300 g) were individually housed in a temperature-controlled room and provided free access to food and water. Animals were maintained on a 12 L : 12 D cycle, and behavioral testing was conducted during the light portion of the cycle.

Apparatus

The apparatus used for ICSS consisted of four identical black Plexiglas boxes (60 × 50 × 35 cm). Two holes, 4 cm in diameter and 10 cm apart, were located in the center of the Plexiglas floor of each chamber. A ring of lights embedded in the black Plexiglas floor with a white translucent cover (2 cm in width) surrounded the perimeter of each hole. Three infrared photobeam units were mounted in each hole 0.5 cm from the surface, and disruption of the photobeams by a nose-poke response resulted in the delivery of electrical brain stimulation through a mercury-filled commutator. A constant-current stimulator delivered brain stimulation that consisted of a monophasic square wave with a pulse duration of 0.1 ms and frequency of 100 Hz. Once initiated, the stimulation had a duration of 0.5 s. All boxes were interfaced to a Commodore 64 computer whose software controlled the presentation of electrical stimulation and the discrimination procedure that involved alternating the light onset around each hole at predetermined intervals, as well as recording the number of nose-poke responses in each hole during ICSS testing.

Procedure

Surgery. Subjects were anesthetized with sodium pentobarbital (60 mg/kg) and a bipolar electrode (MS-303/1, Plastic Products Co., Roanoke, VA) was stereotaxically implanted in the VTA (AP −2.8 mm from bregma, L ±1.4 mm from midline suture, and V −8.6 mm from the skull surface). Electrodes were implanted perpendicular to the horizontal plane, and the incisor bar was adjusted for each animal such that the horizontal plane was level for anterior and posterior portions of the skull.

Discrimination training. Seven days postoperatively, animals were trained for ICSS. During the daily ICSS sessions, the light around one of the holes always remained on. A nose-poke response into the signalled hole resulted in brain stimulation, whereas responding into the nonsignalled hole was not reinforced. Once stable response rates were established at a current intensity that was adjusted for each individual animal to elicit optimal ICSS rates, discrimination training was initiated. Light onset was alternated between holes every 30 s for a 5-min ICSS test session. Animals were rewarded only when responding was directed into the signalled hole. When subjects performed correctly on at least 90% of the total responses made during the ICSS session, the alternation time for switching light onset between holes was reduced to 20 s and the ICSS test duration was decreased to 4 min. This training procedure was continued until animals showed stable rates of responding with an alternation time of 10 s and ICSS trial duration of 2 min.

Rate-intensity functions. When animals mastered the discrimination paradigm, descending and ascending current-response functions were determined. At the outset of each daily ICSS test session, subjects were allowed to respond for brain stimulation at their individual training current intensity for a 5-min period. Then the descending mode of current presentation was initiated, starting at an intensity level of 40 μA (root mean square), and current intensity was decreased in a stepwise fashion by 4-μA increments every 2 min. Correct (reinforced) and incorrect (nonreinforced) responding were re-

corded for each 2-min test interval at the following current levels; 40, 36, 32, 28,24, 20, and 16 μA. After completion of the descending phase of the ICSS test session, current intensity was increased by 4-μA steps to 40 μA and the number of correct and incorrect responses were recorded for 2 min at each level of the ascending mode of current presentation.

Drug treatments. Once stable rate-intensity functions were achieved, the baseline was determined for each animal using the mean rate of responding at each current level for the last 3 days of ICSS testing. Animals were randomly assigned to one of four drug treatment conditions (n = 10/group) and tested daily for ICSS. Immediately after the ICSS session, subjects in each group received an IP injection of either saline, 10.0 mg/kg *d*-amphetamine sulfate, 1.0 mg/kg haloperidol, or 20.0 mg/kg naloxone hydrochloride. The ICSS test/drug procedure was continued for 12 consecutive days and animals were evaluated for ICSS 24 h following drug administration (postdrug test). Drug treatments were then discontinued for 5 days and daily ICSS testing resumed for the following 16 days. During the abstinence phase of the experiment, no drug treatments were administered. To evaluate sensitization development, rats in the four drug groups were tested for ICSS after low-dose amphetamine (0.5 mg/kg) challenge 50 days postdrug treatment.

Histology. Upon completion of the experiment, animals were anesthetized with an overdose of sodium pentobarbital and perfused intracardially with saline followed by 10% formalin. Brains were removed, sliced in 40-μm coronal sections, and stained with thionine for verification of electrode tracts.

RESULTS

The data from animals that had electrodes located outside the A10 region of the VTA were excluded from the experiment, and animals were replaced such that an n = 10 was maintained for each drug treatment condition. However, because of head-cap loss data from one animal in the saline group is missing from the amphetamine challenge results, and the results of another subject are not included in the haloperidol abstinence and amphetamine challenge phases of the experiment. A schematic representation of electrode placements is depicted in Fig. 1.

ICSS and error rates were averaged over the descending and ascending current presentation modes. Since baseline rate-intensity functions were not congruent between the four treatment groups, drug-induced changes in ICSS rates were analyzed separately for each drug condition relative to the group's baseline function.

Using rate-frequency functions, Miliaressis et al. (31) demonstrated that current thresholds for half maximal (M_{50}) and zero responding (Θ_0) are a good indicator of reward efficacy. Of the two reward indices, the latter was found to be insensitive to experimental manipulations that induced motor deficits. In this study, we manipulated current intensity and electrical brain stimulation was contingent upon a nose-poke response. Since the discrimination ICSS task engenders low levels of responding that are not reinforced (incorrect measure), we modified the zero-responding threshold for this paradigm and determined the minimal current necessary to elicit 5 responses/min (Θ_5). This index of reward was used when a response depression and shift to the right of the rate-intensity function was observed.

With increased ICSS and curve shifts to the left, the half-maximal responding (M_{50}) index of reward was determined. The use of the Θ_5 threshold is problematic in this instance because ICSS was not assessed at current levels lower than 16 μA. Since a number of animals did not achieve maximum response levels, the half-maximal response rate was estimated to be 40 responses/min and current thresholds were calculated using this constant for all animals in the treatment groups.

Separate analyses of variance (ANOVAs) were conducted for the Θ_5 threshold data derived during the withdrawal and abstinence phases of the experiment. The 24-h postdrug ICSS test (withdrawal) current thresholds are depicted in Table 1 and were analyzed using a 4 (drug; saline, amphetamine, naloxone, and haloperidol) × 5 (day; baseline and days 3, 6, 9, and 12) ANOVA with repeated measures on day. This analysis yielded a significant drug × day interaction, $F(12, 144) = 1.85, p < 0.05$. ANOVA of the reward thresholds seen during the abstinence phase of the experiment are shown in Table 2, and involved a 4 (drug; saline, amphetamine, naloxone, and haloperidol) × 8 (day; baseline and days 3, 6, 9, 12, 15, 18, and 21) design with repeated measures on day. This analysis also revealed a drug × day interaction, $F(18, 216) = 2.45$, $p < 0.01$. Newman–Kuels multiple comparisons ($\alpha = 0.05$) were used to assess the simple main effects involved in these interactions, and these results are described below together with the analyses of the rate-intensity function data.

Saline and Naloxone 24-h Postdrug Test (Withdrawal) and Abstinence

Figure 2 depicts the rate-intensity functions of animals injected with saline (left panel) or naloxone (right panel) after each daily ICSS session showing the mean (± SEM) response rates during baseline and days 3, 6, 9, and 12. For the saline withdrawal data, a two-factor repeated measures ANOVA of ICSS rates yielded a significant main effect for current, Fs(6, 54) = 157.15, $p < 0.0001$. As can be seen in Fig. 1, the rate-intensity functions were consistent with little variation from baseline following repeated ICSS testing. Similar results were obtained for the abstinence data with a significant main effect for current, $F(6, 54) = 167.75$, $p < 0.0001$, and no significant curve shifts as a function of repeated ICSS testing were observed.

Θ_5 thresholds for saline-treated animals during the withdrawal and abstinence phases of the experiment are shown in Tables 1 and 2. As was the case for the rate-intensity data, similar threshold values were observed over days with little variability seen after daily ICSS testing.

The bottom panels of Fig. 2 depict the mean (± SEM) error responding into the nonsignalled hole during each 2-min ICSS interval. In agreement with earlier reports from this laboratory (22), error rates were observed to increase with current intensity, Fs(6, 54) = 8.60 and 9.75, $p < 0.001$. It appears that animals have more difficulty terminating responding for brain stimulation as the current intensity increases. While the factors responsible for the increase in nonreinforced behavior need to be elucidated, it is likely that the rate enhancement is related to the sensorimotor arousal associated with brain-stimulation reward.

Analysis of the 12-day naloxone withdrawal results revealed a significant test day × current interaction, $F(24, 216) = 1.83$, $p < 0.05$. As can be seen in Fig. 2, this interaction involved a small depression in ICSS during days 3 and 6, and by day 12 an increase in ICSS rates was evident. These curve shifts were modest and did not translate into significant changes in Θ_5 current threshold over days (see Table 1). Since response increases were seen on day 12, M_{50} current thresholds were determined and one-way ANOVA of these data did not

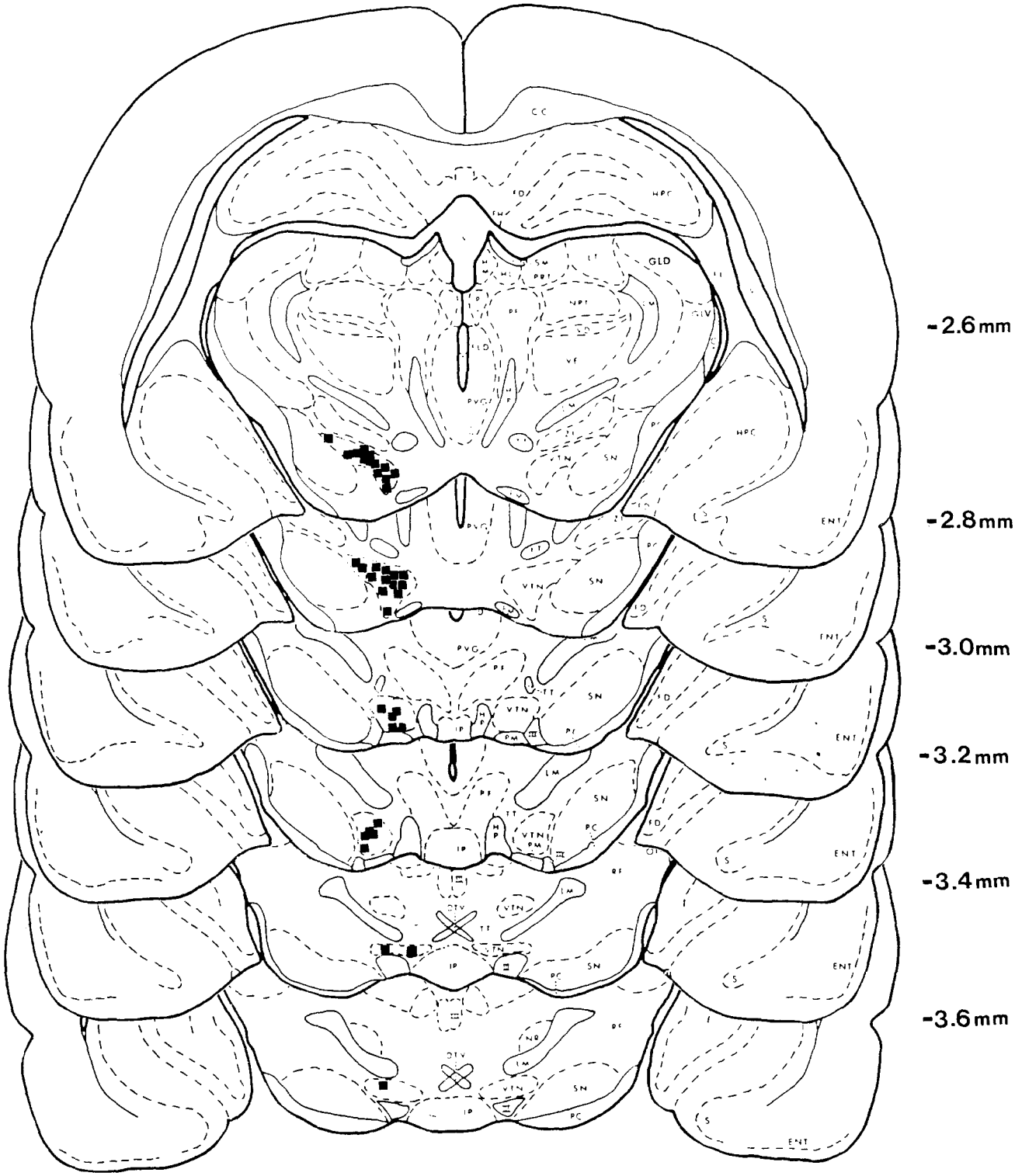

FIG. 1. Schematic representation of the location of electrode placements in the ventral tegmental area (VTA) (34).

TABLE 1

MEAN (±SEM) CURRENT THRESHOLDS (θ_5) DERIVED FROM RATE-INTENSITY FUNCTIONS WITH ELECTRODES SITUATED IN THE VTA AFTER DAILY POSTTEST ADMINISTRATION OF SALINE (Sal), AMPHETAMINE (Amph), HALOPERIDOL (Hal), AND NALOXONE (Nal)

	Chronic Drug Treatment			
	Sal	Amph	Hal	Nal
Baseline	21.6 (±1.1)	21.3 (±0.72)	20.8 (±1.2)	23.0 (±1.4)
Withdrawal Day				
3	22.3 (±1.4)	23.2 (±1.6)	24.8 (±2.0)	20.5 (±0.87)
6	23.3 (±1.7)	25.9 (±2.2)	25.4 (±1.6)	24.2 (±2.4)
9	21.7 (±0.87)	23.7 (±1.8)	27.0* (±1.4)	23.7 (±1.9)
12	22.5 (±1.4)	29.0* (±2.2)	27.1* (±1.4)	21.9 (±1.8)

*$p < 0.05$ from saline values.

yield a significant effect for repeated naloxone treatment, $F(4, 4) = 1.22$, $p > 0.1$. During naloxone abstinence, no significant change over days was evident in the rate-intensity functions and θ_5 thresholds (see Table 2).

d-*Amphetamine 24-h Postdrug Test (Withdrawal) and Abstinence*

An overall two-way repeated-measures ANOVA of the ICSS withdrawal results yielded a significant test day × current interaction, $F(24, 216) = 3.36$, $p < 0.02$. To assess more clearly the progressive changes in postamphetamine behavior, rate-intensity functions for correct and incorrect responding are depicted together with baseline for each test day analyzed (days 3, 6, 9, and 12) in Fig. 3, and ANOVA with repeated measures for current and drug was conducted separately for each ICSS day.

For day 3 results, significant main effects for current, $F(6, 54) = 25.67$, $p < 0.0001$, and drug, $F(1, 9) = 8.74$, $p < 0.02$, were observed. ICSS rates decreased following postamphetamine testing, and there was a small shift in the rate-intensity function to the right. This effect on ICSS was not paralleled by a similar change in the error scores (see Fig. 3). While an increase in responding to the nonreinforced hole developed as a function of increasing current, $F(6, 54) = 5.41$, $p < 0.0002$, drug treatment did not alter error responding.

Essentially the same pattern of results was observed on test days 6 and 9. In both instances, a significant current × drug interaction was observed, $F(6, 54) = 2.91$ and 8.01, $p < 0.01$. ICSS rates were depressed and curve shifts to the right were evident in the rate-intensity functions. Analysis of the error scores found incorrect responding to increase as a function of current, $Fs(6, 54) = 5.80$ and 5.58, $p < 0.0001$; however, this measure of nonreinforced performance was not influenced by amphetamine treatment.

A current × drug interaction, $F(6, 54) = 11.22$, $p < 0.0001$, was found for the day 12 ICSS results. This interaction involved a decrease in ICSS rates and a shift to the right of the rate-intensity function in amphetamine-pretreated animals relative to their baseline curve. In addition to changes in ICSS rates, a significant current × drug interaction, $F(6, 54) = 2.44$, $p < 0.04$, was observed for error responding on day 12. Newman-Keuls posthoc comparisons showed that the in-

TABLE 2

MEAN (±SEM) CURRENT THRSHOLD (θ_5) DERIVED FROM RATE-INTENSITY FUNCTIONS WITH ELECTRODES SITUATED IN THE VTA DURING DRUG ABSTINENCE

	Chronic Drug Treatment			
	Sal	Amph	Hal	Nal
Baseline	21.6 (±1.1)	21.3 (±0.72)	20.8 (±1.2)	23.0 (±1.4)
Abstinence Day				
6	21.0 (±0.92)	25.4 (±2.4)	28.0* (±1.9)	23.4 (±2.0)
9	23.0 (±1.1)	24.4 (±1.8)	28.7* (±1.3)	20.3 (±1.1)
12	23.6 (±1.1)	25.7 (±2.0)	32.1* (±1.6)	21.5 (±1.5)
15	21.8 (±1.2)	25.0 (±2.4)	28.3* (±1.9)	23.9 (±2.2)
18	21.5 (±1.3)	25.7 (±2.7)	28.8* (±1.6)	23.2 (±2.1)
21	23.4 (±1.4)	24.3 (±2.1)	29.4* (±1.3)	24.1 (±2.0)

ICSS testing resumed 5 days after discontinuing saline (Sal), amphetamine (Amph), haloperidol (Hal), and naloxone (Nal) treatment.

*$p < 0.05$ from saline values.

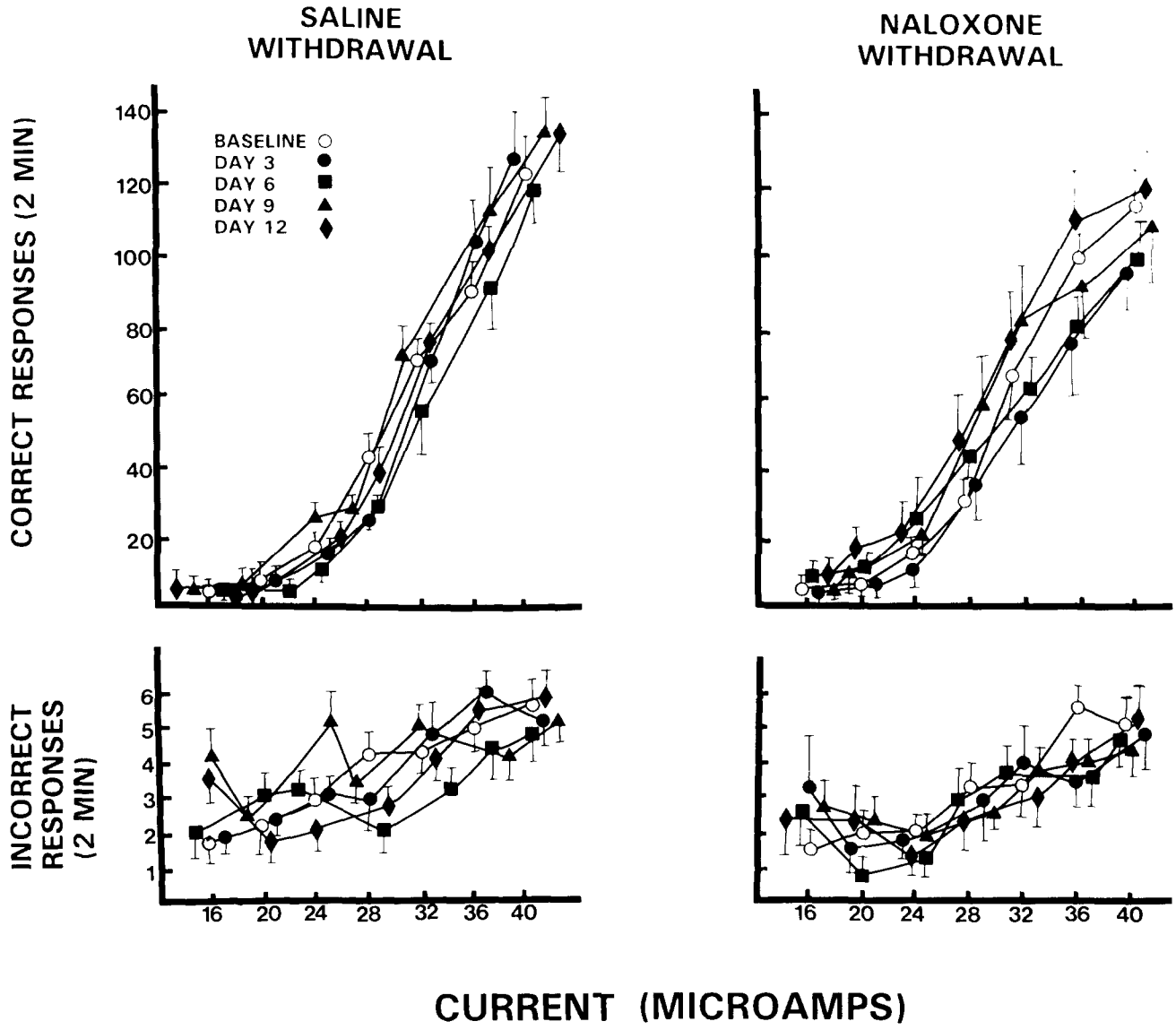

FIG. 2. Mean (±SEM) ICSS rates (correct responses) and error scores (incorrect responses) made during successive 2-min test sessions at each of seven current intensities with stimulating electrodes situated in the VTA following daily posttest administration of saline and naloxone (20.0 mg/kg). ICSS at each intensity level represents the average response rate derived from the descending and ascending modes of current presentation, and the rate-intensity functions show baseline responding and performance on test days 3, 6, 9, and 12 of the withdrawal phase of the experiment.

crease in incorrect responding typically seen as a function of current intensity was not evident in amphetamine-pretreated animals.

The θ_5 reward thresholds for amphetamine withdrawal are shown in Table 1. While there was a small increase in thresholds over days, only the day 12 threshold was significantly higher than the threshold for saline-treated animals ($p < 0.05$).

Rate-intensity and corresponding error functions during the drug abstinence phase of the experiment are depicted in Fig. 4. After a 5-day drug-free period, ICSS testing resumed in the absence of amphetamine treatment, and a repeated-measures two-factor ANOVA of the ICSS data involving current and test day (days 6, 9, 12, 15, 18, and 21) found no significant main or interaction effects involving days.

In contrast to the ICSS results, error responding following amphetamine pretreatment remained lower than baseline throughout the abstinence period and returned to baseline levels by day 21. ANOVA was conducted for each individual day evaluated (days 6, 9, 12, 15, 18, and 21). For day 6, nonreinforced responding was reduced in amphetamine-pretreated animals, $F(1, 9) = 4.52$, $p < 0.065$ (main effect for drug). A similar marginal decrease in error performance was evident on day 9, $F(1, 9) = 3.38$, $p < 0.1$. The perfor-

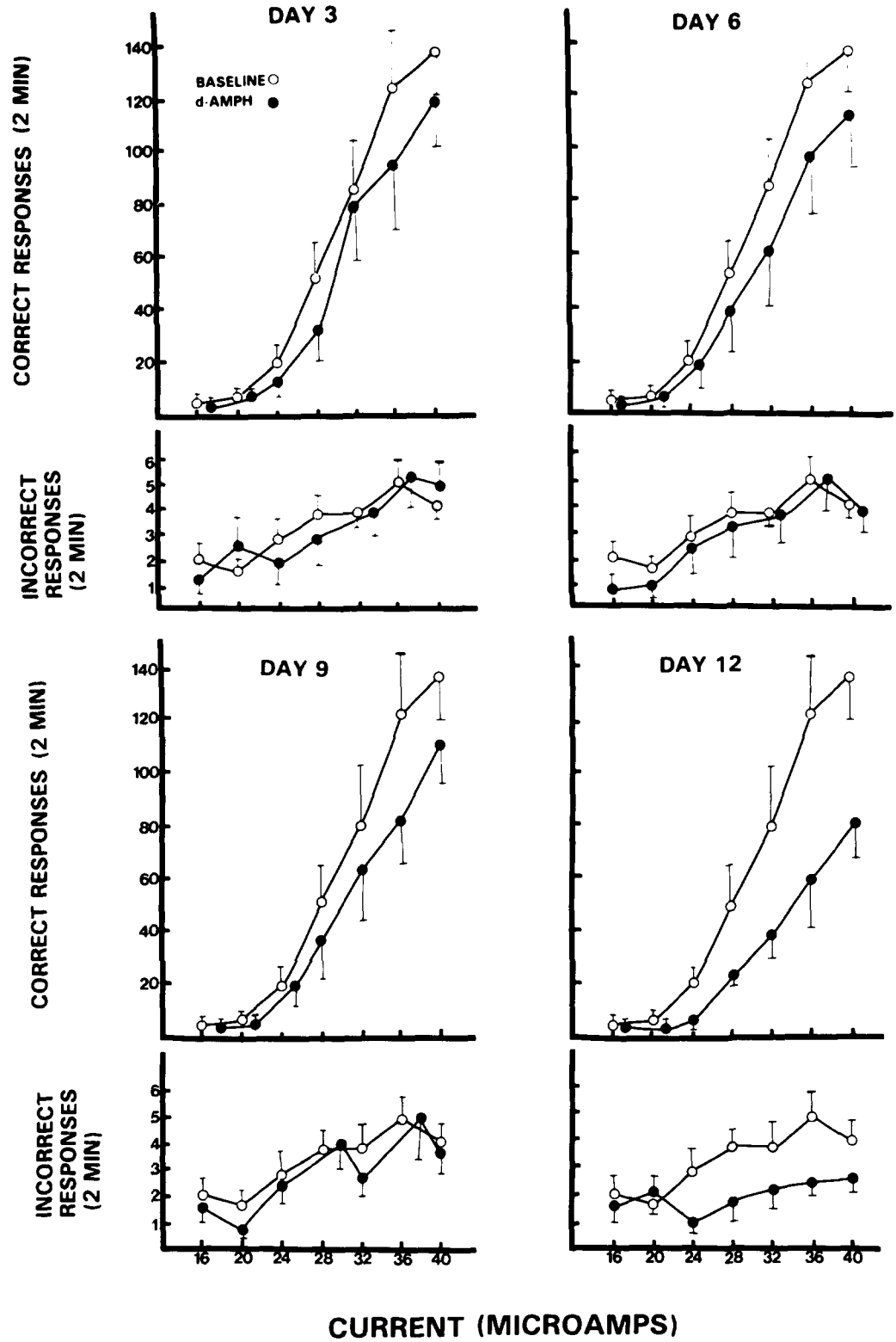

FIG. 3. Mean (±SEM) ICSS and error responding following daily posttest injections of *d*-amphetamine (10.0 mg/kg). Rate-intensity functions for the amphetamine group are shown with the baseline function and depict performance on test days 3, 6, 9, and 12 of the withdrawal phase of the experiment.

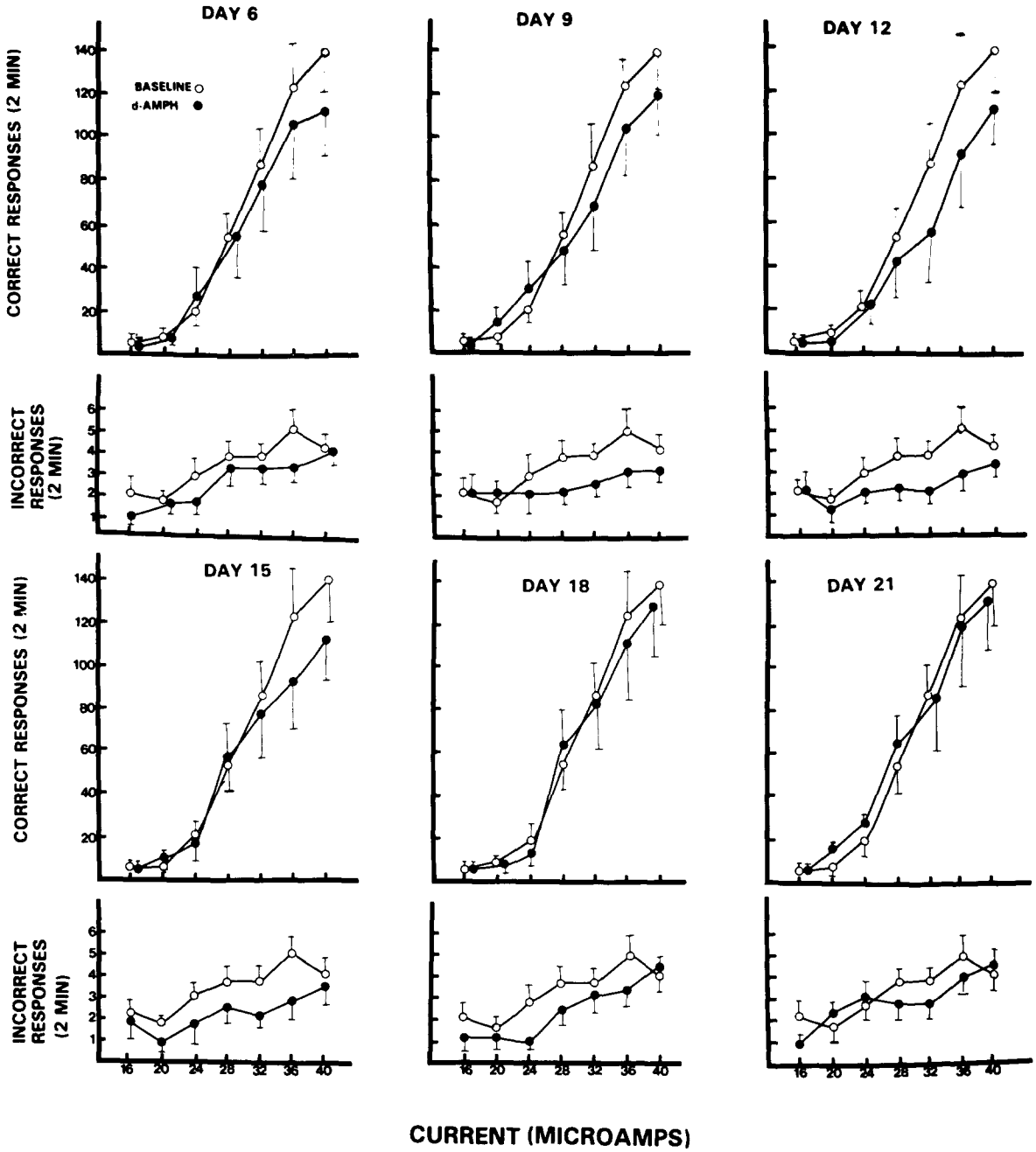

FIG. 4. Mean (±SEM) ICSS and error responding following amphetamine abstinence. Behavioral testing resumed 5 days after the last chronic *d*-amphetamine injection, and rate-intensity functions are shown for baseline and days 6, 9, 12, 15, 18, and 21 of the abstinence phase of the experiment.

mance deficits seen on days 12 and 15 did reach statistical significance, $F(1, 9) = 6.18$ and 6.91, $p < 0.05$, and marginal effect was seen on day 18, $F(1, 9) = 4.33$, $p < 0.07$. Error rates were comparable to baseline values on the last test day of the abstinence phase of the experiment (day 21), $F(1, 9) = 0.83$, $p > 0.1$. Thus in marked contrast to the ICSS recovery, the performance deficits seen in nonreinforced behavior after repeated amphetamine administration were persistent and took more time to dissipate.

Haloperidol 24-h Postdrug Test (Withdrawal) and Abstinence

The chronic effects of haloperidol treatment on ICSS are shown in Figs. 5 and 6. An overall significant test day × current interaction was found for both the withdrawal and abstinence phases of the experiment, $F(24, 216) = 2.08$, $p < 0.004$ (postdrug test), and $F(36, 288) = 3.52$, $p < 0.0001$ (abstinence). ANOVAs of the individual days yielded significant drug × current interactions for each day evaluated dur-

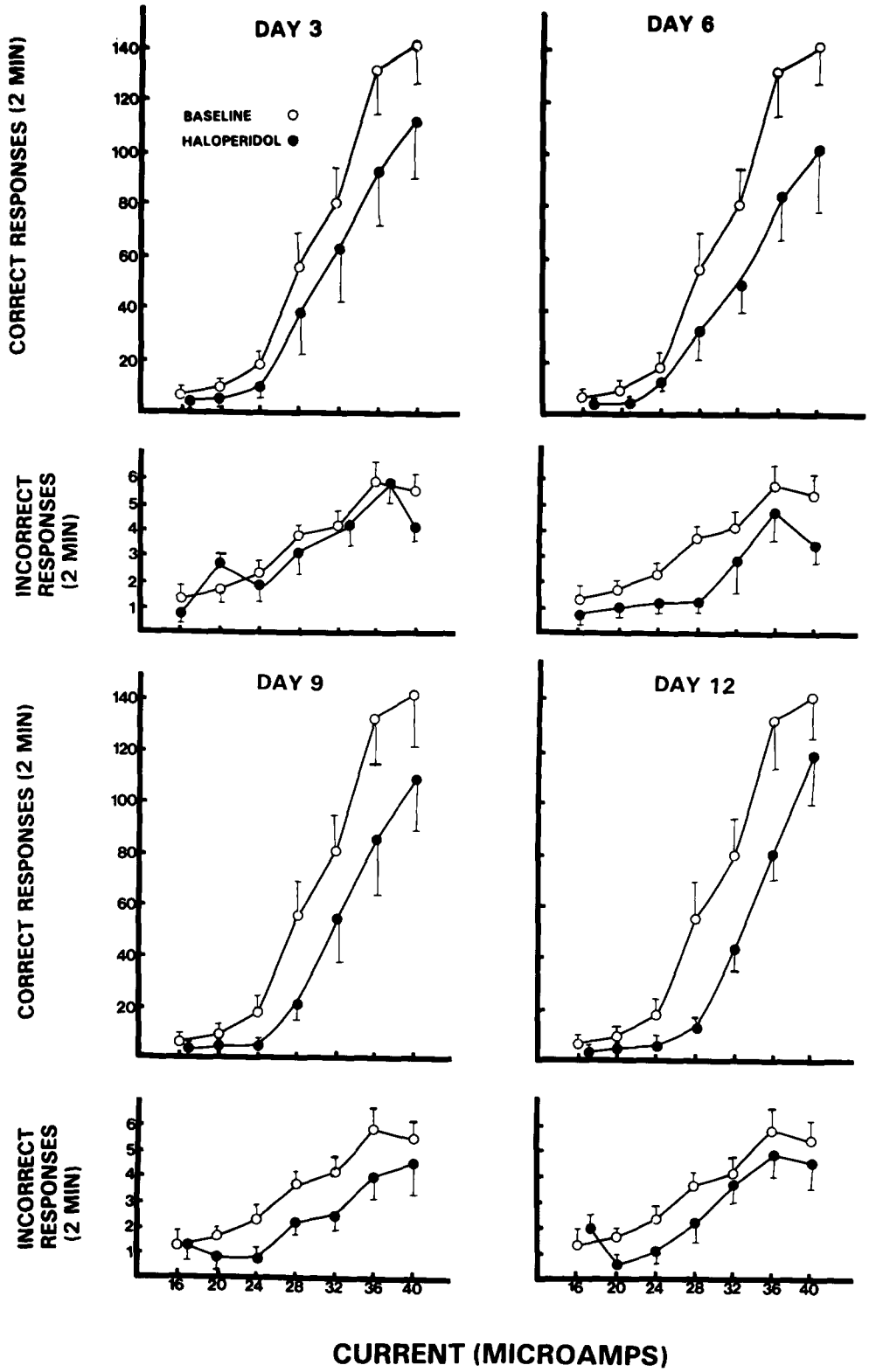

FIG. 5. Mean (±SEM) ICSS and error rates as a function of daily posttest injections of haloperidol (1.0 mg/kg). Rate-intensity functions are shown with the baseline function and depict performance on test days, 3, 6, 9, and 12 of the withdrawal phase of the experiment.

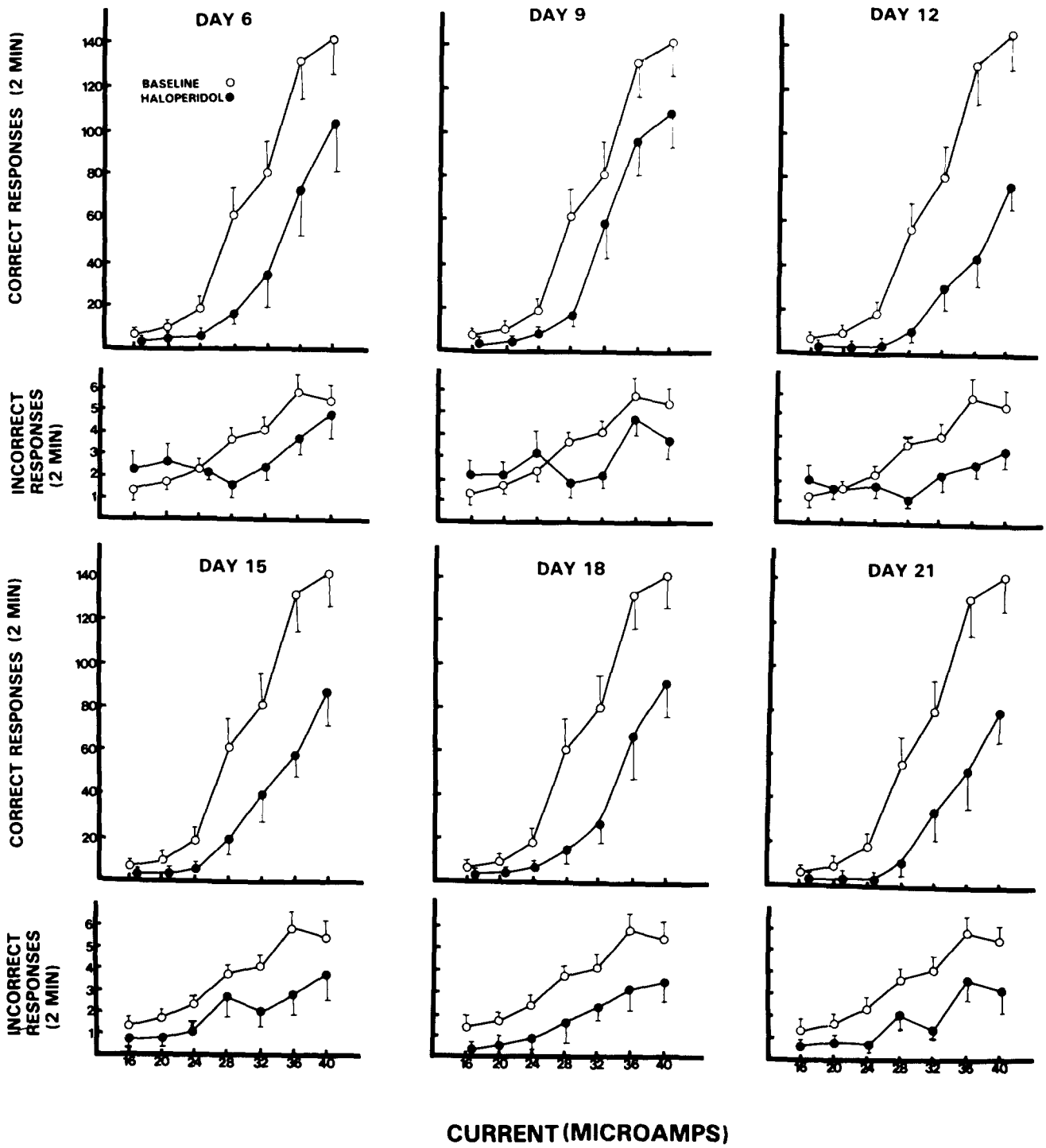

FIG. 6. Mean (±SEM) ICSS and error responding during haloperidol abstinence. Behavioral testing resumed 5 days after the last chronic haloperidol injection, and rate-intensity functions are shown for baseline and days 6, 9, 12, 15, 18, and 21 of the abstinence phase of the experiment.

ing withdrawal (days 3, 6, 9, and 12), $F(6, 54) = 2.47, 3.51, 2.28$, and 6.12, $p < 0.05$, as well as for 21 days of drug abstinence (days 6, 12, 15, 18, and 21), $F(6, 48) = 5.74, 12.17, 5.84, 5.61$, and 9.16, $p < 0.001$. For the day 9 abstinence results, the interaction approached but did not reach statistical significance, $F(6, 48) = 2.14$, $p < 0.07$.

Reward thresholds were higher after haloperidol treatment during both phases of the experiment (see Tables 1 and 2). The Θ_5 index of reward was significantly increased for drug treatment days 9 and 12 as compared to the saline threshold ($p < 0.05$), and current intensities remained significantly higher throughout the abstinence phase of the experiment.

Overall ANOVA of error responding during haloperidol withdrawal yielded significant main effects for current, $F(6, 54) = 25.08$, $p < 0.0001$, and test day, $F(4, 36) = 3.48$, $p < 0.02$. A significant performance effect was evident on test day 6, $F(1, 9) = 7.12$, $p < 0.03$, and day 9, $F(1, 9) = 9.35$, $p < 0.02$. The effects of haloperidol on the incorrect response measure approached but did not reach statistical significance on day 12, $F(1, 9) = 4.32$, $p < 0.07$ (see Fig. 5).

A significant overall test day × current interaction was found for the incorrect response data during haloperidol abstinence, $F(36, 288) = 1.51$, $p < 0.04$. Like the ICSS data, recovery from the haloperidol-induced performance deficits was not evident following cessation of drug treatment (see Fig. 6).

d-*Amphetamine Challenge*

The ICSS rate-intensity functions and corresponding error scores following amphetamine challenge (0.5 mg/kg) for animals in the four chronic drug treatment conditions are shown in Fig. 7.

Individual analyses of the ICSS results for each treatment condition showed that the low dose of amphetamine did not significantly influence ICSS in saline-pretreated animals, $F(1, 8) = 0.08$, $p > 0.1$. However, amphetamine × current interactions were observed when animals were challenged with amphetamine 50 days after the last chronic injection of amphetamine, $F(6, 54) = 3.39$, $p < 0.007$, naloxone, $F(6, 54) = 7.03$, $p < 0.001$, and haloperidol, $F(6, 48) = 8.62$, $p < 0.001$. In the case of amphetamine and naloxone preexposure, these interactions involve a curve shift to the left of the rate-intensity functions. This sensitization effect was not accompanied by significant changes in error responding, indicating specific drug-induced increases in ICSS.

As shown in Fig. 7, rate-intensity functions did not recover from the haloperidol-induced depression following amphetamine administration. In particular, pronounced reductions in ICSS were evident at the 28- to 40-μA current intensities. To some degree, the haloperidol depression might reflect performance deficits given the significant reduction in error responding seen after amphetamine challenge 50 days following the last haloperidol injection, $F(6, 48) = 5.94$, $p < 0.001$ (amphetamine × current interaction).

With respect to M_{50} current thresholds, an overall 4 [chronic (saline, amphetamine, naloxone, and haloperidol)] × 2 [acute (baseline, amphetamine)] ANOVA yielded a significant chronic drug treatment × acute drug treatment interaction, $F(3, 34) = 7.13$, $p < 0.001$. As shown in Table 3, amphetamine challenge did not significantly lower current thresholds relative to baseline in saline-treated animals. In the case of amphetamine pretreatment, a significant decrease in current intensity for half-maximal responding was evident in comparison to the amphetamine threshold in the saline condition ($p < 0.05$). A small sensitization effect was also observed when naloxone-preexposed animals were challenged with a low-dose amphetamine injection. However, in this instance current thresholds were not significantly lower relative to the baseline or amphetamine values ($p < 0.1$). Finally, as shown in Table 3, current intensities of the haloperidol group remained elevated after amphetamine injection. It should be noted, however, that this threshold change was specific to the half-maximal index and was not evident when Θ_5 was determined (21.3 ± 1.2 for saline and 23.2 ± .87 for haloperidol).

GENERAL DISCUSSION

Previous reports have shown that withdrawal from chronic amphetamine treatment elicits a profound reduction in the rewarding value of electrical brain stimulation (21). The postamphetamine depression has been observed from both the substantia nigra (26) and medial forebrain bundle at the level of the lateral hypothalamus (28). The results of this study extend these earlier observations and demonstrate a reward depression in the mesolimbic system following amphetamine withdrawal. Decreased ICSS was evident as early as 3 days of amphetamine exposure; however, the curve shifts in the rate-intensity functions did not translate into increased thresholds until the twelfth postdrug test session.

In contrast to the prolonged nature of the effects of amphetamine withdrawal on substantia nigra ICSS (26), changes in VTA brain-stimulation reward observed in this study were transient with full recovery of ICSS rates and current thresholds within 5 days of drug abstinence. The differential effects of amphetamine preexposure on nigrostriatal and mesolimbic system functioning might involve regional variations in the neurotoxic properties of the drug. Thus, for example, while methamphetamine induces enduring damage to presynaptic DA terminals in the striatum the neurotoxic properties of this drug are less severe on mesocorticolimbic projection sites (38,45).

Low-dose amphetamine challenge to animals with a prior history of amphetamine preexposure resulted in a sensitization of reward system functioning. The findings of a shift to the left of the rate-intensity function and decreased reward thresholds shows that VTA ICSS, like brain stimulation supported from the nucleus accumbens (5,37), medial prefrontal cortex (39), substantia nigra (23), and medial forebrain bundle (25), is increased after repeated amphetamine treatment. Analysis of amphetamine-elicited locomotor activity found behavioral sensitization to evolve following repeated drug microinfusion into the VTA but not the nucleus accumbens (20,53). The regional generality of the ICSS sensitization effects, however, indicates that the enhancement of the incentive-motivational effects of stimulant drugs can be expressed in number of distinct reward sites involving cell bodies and terminal regions of the major DA pathways [see also (33)].

Reward sensitization was evident when animals were challenged with amphetamine 50 days into the abstinence period. These results suggest that although sensitization might evolve as a compensatory mechanism to the withdrawal depression, once reward sensitization is established the neurochemical effects responsible for the ICSS facilitation are persistent and evident well after the postamphetamine depression has dissipated. The longevity of amphetamine sensitization effects are not limited to reward system processes. Paulson et al. (32) recently reported a sensitization of the stereotypic response to amphetamine 1 year after drug withdrawal.

While the conditioning of the locomotor-activating properties of stimulant drugs to environmental stimuli is well documented (6,7), it is unlikely that conditioning factors are involved in the reward sensitization observed after amphetamine challenge in this study. For the conditioning of amphetamine reward to develop, it is necessary for the acute effects of the drug to be associated with the stimulus array of the testing milieu (48). In this experiment, amphetamine injection was not paired with ICSS but rather was repeatedly administered posttest. Thus, the acute actions of amphetamine administration were not expressed in the ICSS environment and could not have become conditioned to the contextual cues associated with the ICSS procedure. Indeed, since daily administration of a high dose of amphetamine resulted in reward system depression it is possible that sensitization development, which is opposite in direction to the withdrawal dysphoria, might represent a conditioned compensatory response (46). While

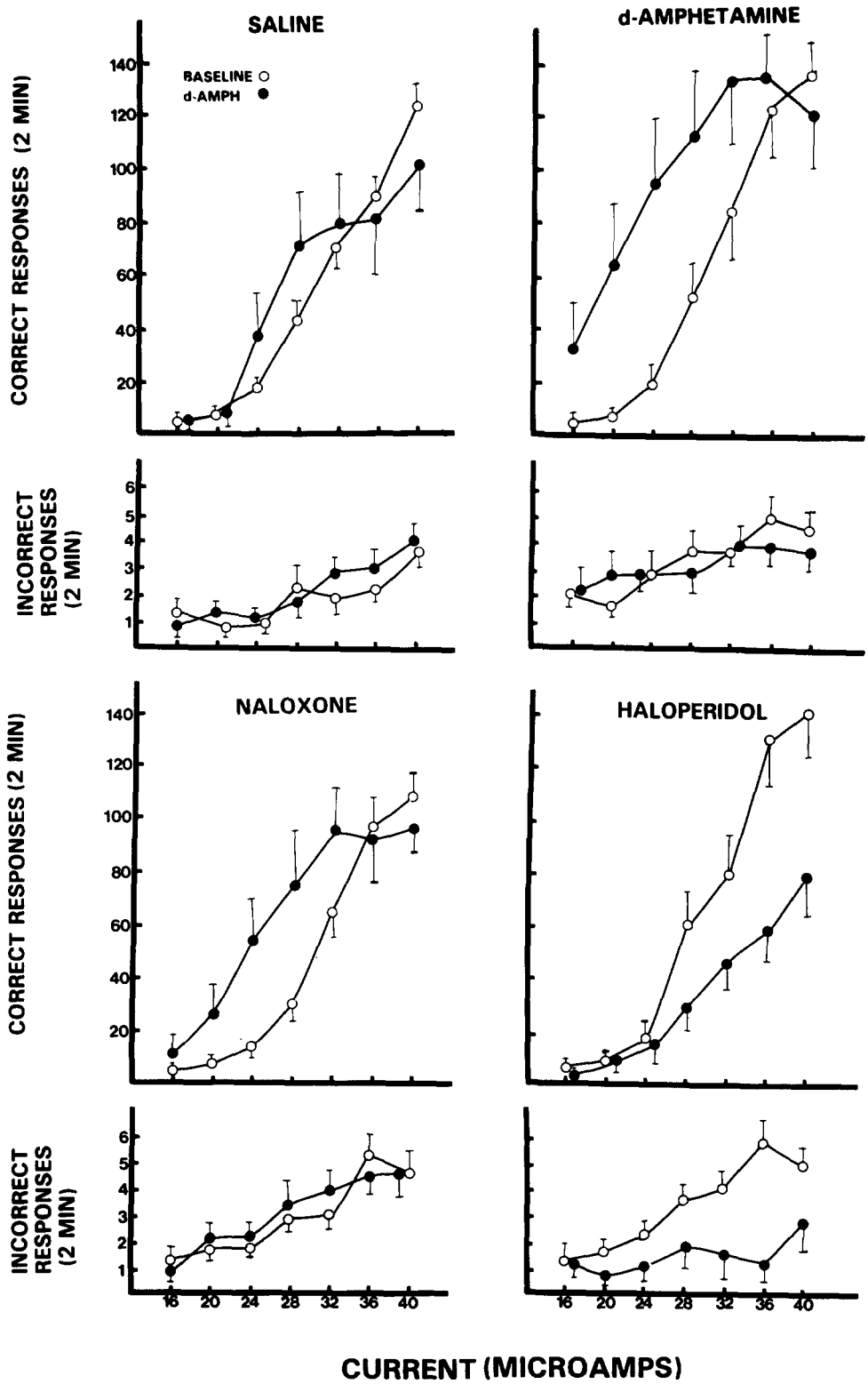

FIG. 7. Mean (±SEM) ICSS and error responding following low-dose *d*-amphetamine challenge (0.5 mg/kg) in animals chronically preexposed to saline, amphetamine, naloxone, and haloperidol. Amphetamine challenge was administered 50 days after the last chronic drug injection, and rate-intensity functions are depicted with each chronic treatment group's baseline curve.

TABLE 3

MEAN (±SEM) CURRENT THRESHOLDS FOR HALF-MAXIMAL RESPONDING (M_{50}) FOLLOWING LOW-DOSE AMPHETAMINE CHALLENGE (0.5 mg/kg) 50 DAYS AFTER THE LAST INJECTION OF SALINE (Sal), AMPHETAMINE (Amph), HALOPERIDOL (HaL), AND NALOXONE (Nal)

	Chronic Drug Treatment			
	Sal	Amph	Hal	Nal
Baseline	34.1 (±1.3)	32.2 (±1.6)	32.0 (±1.3)	34.3 (±1.7)
Amphetamine challenge	34.2 (±2.4)	25.5* (±2.6)	38.0* (±1.3)	30.9 (±2.7)

*$p < 0.05$ from saline values.

we did not test for this eventuality, we have shown previously that conditioning of amphetamine sensitization effects on ICSS developed only after repeated drug/test pairings and not following posttest amphetamine administration (24). Thus, while it is possible that ICSS sensitization might represent a compensatory reaction to the withdrawal depression (21), and can be conditioned to environmental stimuli (24), this does not appear to be a critical mechanism for the genesis of reward sensitization.

The evaluation of error responding in the two-hole discrimination paradigm revealed that the sensitization of VTA brain-stimulation reward seen after amphetamine challenge was not paralleled by rate enhancements to the nonsignalled hole. During the development of the withdrawal depression, however, deficits in incorrect responding were observed, indicating a drug-induced reduction of nonreinforced behavior. A comparison of the ICSS and error functions indicates a variation in the postamphetamine changes in reinforced and nonreinforced responding. Specifically, whereas the postamphetamine depression of ICSS had fully recovered 5 days into the drug abstinence period the reduction in error responding was evident throughout the abstinence phase of the experiment and normalized on the last test day (day 21).

As was the case for amphetamine preexposure, repeated haloperidol administration elicited pronounced effects on ICSS. Decreased ICSS responding and curve shifts to the right were evident following 3 days of haloperidol treatment, and these changes translated into increased thresholds on test days 9 and 12. In contrast to the transient nature of postamphetamine depression of VTA reward, the effects of haloperidol did not recover and were evident throughout the entire abstinence period of the experiment (21 days). Moreover, a pronounced haloperidol-induced reduction of ICSS was evident 50 days after cessation of treatment even after animals were injected with amphetamine prior to ICSS testing.

Biochemical evidence rules out the possibility that our behavioral observations involved pharmacokinetic properties of haloperidol resulting in drug persistence in neural tissue (4). Behavioral sensitization is known to evolve only after intermittent drug administration, and the magnitude of the sensitization effect induced by a particular drug treatment is related to the length of the interval between drug injections during the chronic administration schedule (4,36). As would be expected, a comparison of the ICSS profiles after chronic administration of amphetamine and haloperidol reveals that sensitization following repeated intermittent administration is in the direction of the acute effect of the drug. Thus, amphetamine has positive effects on ICSS (13) and a long-lasting reward sensitization develops after chronic exposure, whereas acute haloperidol treatment decreases ICSS (56) and our results show this reduction to persist and grow in magnitude following haloperidol abstinence. While it is the case that we did not challenge animals with a low dose of haloperidol and determine curve shifts prior to and after the repeated administration of haloperidol, the reduction in baseline ICSS rates was dramatic and it is unlikely that acute drug injection would have had a major influence on the results.

Electrophysiological studies have shown that repeated neuroleptic treatment induces a depolarization inactivation of VTA cells resulting in a cessation of neuronal firing, an effect that has been related to the upregulation of inhibitory DA autoreceptors (9). The results of this study demonstrate the functional importance of depolarization inactivation of VTA neurons on reward performance; however, our behavioral observations are not entirely congruent with the electrophysiological findings. That is, VTA firing rates were shown to normalize after 2 weeks of drug abstinence (9), whereas reward thresholds in this study were lower 21 days following discontinuation of drug treatment and ICSS rates remained depressed 50 days after the last injection of haloperidol. One interpretation of these results is that although neuronal activity recovers following haloperidol abstinence there may exist an underlying drug-induced liability in neuronal functioning that is functionally expressed when demands are placed on VTA neurons, as is the case with brain-stimulation reward.

Van Wolfswinkel et al. (52) reported that systemic injection of naloxone prior to daily self-stimulation testing resulted in a gradual increase in reward thresholds over a 4-week period of repeated drug exposure. In the present study, ICSS was evaluated 24 h after each daily drug treatment and no reliable effects on current thresholds were evident following drug withdrawal and abstinence. Given that the chronic naloxone regimen involved high doses and paralleled the schedule of haloperidol and amphetamine treatment, it would appear that the evolution of the amphetamine- and haloperidol-elicited brain-stimulation reward depression is not related to opioid hypoactivity. However, we did observe a trend toward a sensitization of reward threshold following amphetamine challenge in naloxone-pretreated animals. More specifically, reward threshold was moderately decreased relative to baseline, and the current intensity was lower, albeit not significantly, than that seen for control animals following amphetamine challenge. Amir et al. (3) found that repeated exposure to naltrexone substantially increased the locomotor-stimulating effects of amphetamine, indicating that DA supersensitivity can develop after chronic administration of an opiate antagonist. Since locomotor sensitization was observed 2 and 8 days after naltrexone withdrawal, it is possible that the trend toward a sensitization effect seen in this study might have been more

significant had we challenged animals earlier in the drug abstinence phase of the experiment.

In summary, the results of this study show that in contrast to the enduring effects of haloperidol on ICSS a transitory postamphetamine depression of brain-stimulation reward supported by VTA neurons develops following withdrawal from high-dose amphetamine treatment. Amphetamine challenge to animals with a prior history of stimulant preexposure results in a reward sensitization that is in comparison to the withdrawal depression long lasting. The persistent nature of the reward sensitization complements clinical observations showing that amphetamine psychosis can be reinstated following low-dose drug intake after a prolonged period of drug abstinence (43). Based upon these animal experiments, we speculated previously that stimulant-elicited sensitization of reward and motivational processes might be a mechanism underlying the psychopathology associated with stimulant-induced psychosis (21,22).

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