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Time-Dependent Alterations in ICSS Thresholds Associated With Repeated Amphetamine Administrations

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LIN, D., G. F. KOOB AND A. MARKOU. *Time-dependent alterations in ICSS thresholds associated with repeated amphetamine administrations*. PHARMACOL BIOCHEM BEHAV **65**(3) 407–417, 2000.—The time interval between successive injections of psychostimulant drugs, such as amphetamine, plays an important role in the development of neuroadaptive responses to these drugs. Changes in reward function were quantified using a discrete-trial current-intensity paradigm to determine thresholds for lateral hypothalamic electrical self-stimulation after experimenter-administered amphetamine injections (4 mg/kg, IP) at 1- and 5-day intervals. Repeated administration of amphetamine produced progressive changes in ICSS behavior that were dependent on the time interval between injections. The acute effects of amphetamine on ICSS thresholds were potentiated, and threshold elevations associated with withdrawal from the drug diminished after repeated drug challenges at 5-day intervals. By contrast, daily injections of the same dose of amphetamine did not alter the acute threshold-lowering effect of the drug, but resulted in progressive increments in thresholds at later time points. Notably, the decreases in response latency produce by acute amphetamine administration were potentiated by both exposure regimens, which indicates a dissociation of drug effects on motor performance and brain stimulation reward. Thus, the distinct components of changes in reward function associated with acute amphetamine administration and subsequent withdrawal were differentially altered by the two exposure regimens, suggesting that the pattern of exposure is an important determinant of neuroadaptive responses to the drug. © 2000 Elsevier Science Inc.

Self-stimulation Amphetamine Withdrawal Reward

REPEATED administration of psychostimulant drugs, such as amphetamine and cocaine, alters subsequent responsiveness to these drugs on a range of behaviors such as locomotor activation (27,45,52), feeding suppression (59), and reward potentiation (5,44). The magnitude of some psychostimulant-induced behavioral responses diminishes with repeated exposures to the drugs, a phenomenon called tolerance (16), whereas others intensify with repeated exposures, a process termed sensitization (45,48). The changes in behavioral responsiveness with repeated drug exposures reflect neuroadaptations, which continue to be expressed long after the drug is cleared from the body (22,24,51). These adaptive processes have been postulated to play an important role in the development of drug dependence in humans, and may contribute to the maintenance of drug use among long-term drug users (22,23).

Several factors are critical for the expression of behavioral and neuronal changes in response to repeated psychostimulant exposure. Notably, the drug-exposure regimen and the time of behavioral assessment relative to the drug exposure are important determinants of the direction and magnitude of drug-induced changes. For example, continuous exposure to cocaine produced behavioral and neurochemical changes that were opposite in direction to those observed after intermittent administration of the drug (17,18). Locomotor activation after an acute cocaine challenge was diminished (i.e., tolerance) in animals pretreated with continuous cocaine via osmotic minipumps, but increased (i.e., sensitization) in animals pretreated with intermittent subcutaneous injections (17). Furthermore, cocaine-induced dopamine efflux from striatal slices was diminished after continuous exposure to the drug,

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but increased after intermittent administration (18). The importance of the time of behavioral assessment was demonstrated in a study in which the expression of sensitization to the locomotor-activating effect of amphetamine was observed on the 28th day, but not on the third or seventh days of withdrawal from chronic intermittent administration (39). These behavioral changes were paralleled by changes in drug-induced increases in striatal dopaminergic transmission, which also became evident 28 days after the end of the chronic exposure period but not at earlier time points.

In contrast to the well-characterized effects of psychostimulant drugs on locomotor behavior, the effects of repeated exposures on the reward-potentiating properties of these drugs are less clear. Tolerance (28,30), sensitization (20,21,44), or no change (57) have been reported regarding the facilitating effects of amphetamine on intracranial self-stimulation (ICSS) reward after repeated amphetamine administration. This variability in results may be due in part to methodological differences, such as differences in anatomical placement of the electrode, as well as to differences in drug exposure and test sequence.

Although the effects of repeated psychostimulant drug administration on the acute drug-induced potentiation of brain stimulation reward are variable, there is consistent evidence of decrements in the reward value of the stimulation after cessation of chronic drug administration. Withdrawal from self-administered (33,34,36) or experimenter-administered (19) cocaine, or high-dose experimenter-administered amphetamine (8,28,29,50,57), all produced decrements in ICSS behavior. These findings suggest that the neuronal substrates mediating both brain stimulation and psychostimulant drug reward undergo adaptations after chronic exposure to the drugs. The characterization of changes in reward processes that occur after different patterns of drug exposure may be particularly important for understanding the factors that contribute to the escalation of drug use in humans and for the development of potential therapies for drug dependence. It is possible that different drug exposure regimens would have divergent effects on reward processes, analogous to those observed in studies of locomotor activity (17).

In the experiments described below, a discrete-trial ICSS procedure was used to provide a sensitive threshold measure of drug-induced changes in reward function (11,26,35). Decreases in ICSS thresholds are interpreted to reflect an increase in the reward value of electrical stimulation, whereas increases in thresholds are interpreted to reflect a reduction in the reward value of the stimulation. Thus, in the case of reward potentiation, an animal will make operant responses for electrical brain stimulation at current intensities that previously did not support responding. Conversely, in the case of reward impairment, animals will be less likely to make operant responses for stimulation at current intensities that supported responding under baseline conditions. Importantly, the discrete-trial threshold procedure used in the present studies is relatively insensitive to the potentially confounding rate-altering effect of psychostimulant drugs because reward thresholds are determined independently of response rate (11,26,35). This procedure also provides measures of performance on the self-stimulation task with regard to response speed and stimulus control over behavior, thus allowing concurrent assessment of amphetamine-induced changes in performance capacity (35). The purpose of the present study was to characterize changes in reward processes as a function of two distinct amphetamine exposure regimens; namely, repeated high-dose administrations at 1- and 5-day intervals. The 4-mg/kg dose of amphetamine used in this study was determined from preliminary experiments, which indicated that this dose, but not lower doses, produced a sequence of behavioral changes that allowed analysis of both acute drug effects and longer latency effects associated with withdrawal from the drug. Self-stimulation behavior was assessed at multiple time points after each injection to determine how the behavioral sequence of responses to a drug challenge changed across repeated exposures. This detailed time-course analysis may provide valuable information about the reward processes during the transition from a drug-naive state to a drug-experienced state, and finally to a withdrawal state.

METHOD

Subjects

The subjects were 30 male Wistar rats from Charles River (Hollister, CA) or from Beckman Laboratories of The Scripps Research Institute. Rats from Beckman Laboratories are from a stock originally derived from Charles River (Kingston, NY), and were bred using a circular pair random system of breeding to maintain genetic heterogeneity. New breeders were obtained from Charles River as determined by our Genetics Advisory Board. Animals weighing 250–300 g upon arrival in the laboratory were housed in pairs in a temperature-controlled environment (21°C) with a 12 L:12 D cycle (lights on at 2200 h). Food and water were available ad lib in the home cages. For the first week after arrival, animals were allowed to habituate to their new environment without handling. Training and testing occurred predominantly during the dark cycle, but some test sessions took place during the light cycle in the time-course phases of the experiments. All procedures were in accordance with the National Institutes of Health's guidelines regarding the principles of animal care. The animal facilities and protocols were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute, and assessed by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Apparatus

The experimental apparatus consisted of eight Plexiglas chambers (30.5(L) × 30(H) × 17(W) cm), each housed in a sound-attenuating box (Med Associates, VT). The operant chamber consisted of a metal grid floor and a metal wheel manipulandum (5 cm wide) centered on a side wall, which required approximately 0.2 N to rotate it a quarter turn. Brain stimulation was delivered by constant current stimulators (Stimtech model 1200, San Diego Instruments, San Diego, CA). Subjects were connected to the stimulation circuit through bipolar leads (Plastics One, Roanoke, VA) attached to gold-contact swivel commutators (model SL2C, Plastics One) that were mounted above the chamber. The stimulation parameters, data collection, and all test session functions were controlled by a microcomputer.

Surgical Procedure

Stainless steel bipolar electrodes (model MS303/2, Plastics One) were surgically implanted when rats reached a weight of at least 300 g. The subjects were anesthetized with an halothane/oxygen vapor mixture (1.0–1.5%), and placed in a Kopf stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set 5 mm above the interaural line. The electrode, cut to 11 mm in length, was implanted into the posterior lateral hypothalamus according to the coordinates: AP −0.05; ML ± 1.7; DV −8.3 mm from dura (41). Dental

acrylic was applied around the base of the electrode and four stainless steel screws to affix the assembly permanently to the skull. Half of the subjects were prepared with electrodes on the right side and the remainder on the left side of the brain to counterbalance for possible brain asymmetries (15,32). At least 7 days elapsed between the surgical procedure and the start of behavioral training.

Drugs

d-Amphetamine sulfate, obtained from the National Institute on Drug Abuse (Washington, DC), was dissolved in sterile 0.9% saline and administered intraperitoneally (IP) in a volume of 1 ml/kg. Doses were expressed in terms of the salt.

ICSS Behavioral Procedure

The subjects were initially trained to turn the wheel manipulandum on a fixed ratio 1 (FR1) schedule of reinforcement. Each quarter turn of the wheel resulted in the delivery of a 500-ms train of 0.1-ms cathodal square-wave pulses at a frequency of 100 Hz. After the successful acquisition of responding for stimulation on this FR1 schedule, defined as 100 reinforcements within 10 min, the rats were trained gradually on a discrete-trial current-threshold procedure (see below).

The discrete-trial current-threshold procedure used was a modification of a task developed by Kornetsky and Esposito (25), and is described in detail by Markou and Koob (35). Each trial began with the delivery of a noncontingent electrical stimulus, followed by a 7.5-s response window within which the animal could make a response to receive a second contingent stimulus identical to the initial noncontingent stimulus. A response during this 7.5-s response window was labeled a positive response, while the lack of a response was labeled a negative response. During a 2-s period immediately after a positive response, additional responses were recorded as extra responses, but had no consequence. Extra responses often reflect the vigor with which the subjects rotate the wheel, because a strong turn can set the wheel in motion for more than a quarter turn (35). The intertrial interval (ITI), which followed either a positive response or the end of the response window (in the case of a negative response), had an average duration of 10 s (ranging from 7.5 to 12.5 s). Responses that occurred during the ITI were recorded as time-out responses, and resulted in a further 12.5-s delay of the onset of the next trial. During training on the discrete-trial procedure, the duration of the ITI and delay periods induced by time-out responses were gradually increased until animals performed consistently for a fixed stimulation intensity at standard test parameters. The subjects were subsequently tested on the current-threshold procedure in which stimulation intensities were varied according to the classical psychophysical method of limits (10). A test session consisted of four alternating series of descending and ascending current intensities starting with a descending series. Blocks of three trials were presented to the subject at a given stimulation intensity. The intensity was altered systematically between blocks of trials by 5-μA steps. The initial stimulus intensity was set at 40 μA above the baseline current threshold for each animal. A descending series was terminated after two consecutive blocks of trials, during which the animal failed to make positive responses on at least two out of the three trials or after 15 successive decrements were presented. An ascending series was terminated after two consecutive blocks of trials during which the animal made positive responses on at least two out of three trials or after 15 successive increments were presented. Each test session typically lasted 30–40 min, and provided four dependent variables for behavioral assessment:

Thresholds. The current–threshold for a descending series was defined as the midpoint between stimulation intensities that supported responding (i.e., positive responses on at least two of the three trials), and current intensities that failed to support responding (i.e., positive responses on fewer than two of the three trials for two consecutive blocks of trials). The current–threshold for an ascending series was defined as the midpoint between stimulation intensities that did not support responding and current intensities that supported responding for two consecutive blocks of trials. Thus, four current–threshold estimates were recorded, and the mean of these values was taken as the current–threshold for each subject on each test session.

Response latency. The time interval between the beginning of the noncontingent stimulus and a positive response was recorded as the response latency. The response latency for each test session was defined as the mean response latency on all trials during which a positive response occurred.

Extra responses. Extra responses for each test session were defined as the mean number of extra responses per trial on which a positive response occurred, and were calculated in the following manner: total number of extra responses/number of positive response trials.

Time-out responses. Time-out responses for each test session were defined as the mean number of time-out responses per trial, and were calculated in the following manner: total number of time-out responses/total number of trials.

Experiment 1: The Effects of Repeated Amphetamine Administration at 5-Day Intervals on ICSS Behavior

After establishment of stable baseline thresholds (±10% across five consecutive daily sessions), animals received an injection of either 4 mg/kg *d*-amphetamine ($n = 10$) or saline IP ($n = 6$) between 1000–1100 h, and were tested at 2, 4, 8, 12, 24, 48, 72, and 96 h after the injection. Because high doses of amphetamine lead to stereotyped behaviors that interfere with the performance of the ICSS task, the present study used longer pretreatment times than those in previous studies. This injection and test sequence was repeated three times, resulting in an injection of 4 mg/kg amphetamine or saline every 120 h.

Experiment 2: The Effects of Repeated Daily Administration of Amphetamine on ICSS Behavior

After establishment of stable baseline thresholds, animals received seven daily injections of either 4 mg/kg amphetamine ($n = 7$) or saline ($n = 7$) IP between 1100–1200 h. ICSS thresholds were determined at 3, 12, and 23 h after each injection. In this experiment, the pretreatment interval was extended to 3 h to minimize the potentially disruptive effects of stereotypy observed after high dose amphetamine administration, particularly after repeated exposures at shorter interinjection intervals. After this first series of seven daily injections, ICSS thresholds were assessed once daily between 1000–1100 h for 6 days without any drug injections. A second sequence of seven daily injections followed by ICSS testing at 3, 12, and 23 h after each injection was repeated after the 6-day drug-free period.

Data Analyses

Threshold and latency data for Experiment 1 were expressed as percentages of the last baseline value prior to each of the three injections. The extra and time-out response data

were expressed as difference scores, which were calculated by subtracting values obtained after an injection from their respective preinjection baseline values. Difference scores were used for these last two measures because scores of zero were frequently obtained, making the use of percentage calculations unfeasible. All data were subjected to repeated measures ANOVAs, with challenges and time as the within-subjects factors, and the four ICSS measures described above as the dependent measures. When the overall analyses indicated a significant effect of time or time × treatment interaction, separate analyses of the 2 h time point data (challenge as the within-subjects factor) and 8–96-h time points (challenge and time as the within-subjects factors) were conducted to characterize the acute actions of the drug and subsequent adaptive responses to the drug, respectively. Additional analyses were performed to characterize the dynamic range of changes in ICSS thresholds observed after successive amphetamine administrations. The first analysis assessed the amplitude of acute amphetamine-induced changes in ICSS threshold, which was defined as the difference between threshold values obtained immediately prior to an injection and those obtained 2 h after an injection. The second analysis assessed the amplitude of change in ICSS threshold between maximal lowering and peak elevation, which was defined as the difference between ICSS thresholds determined at the 2- and 12-h time points. These data were subjected to repeated-measures ANOVAs with challenge as the within-subjects factor. The above analyses were followed by Newman–Keuls post hoc

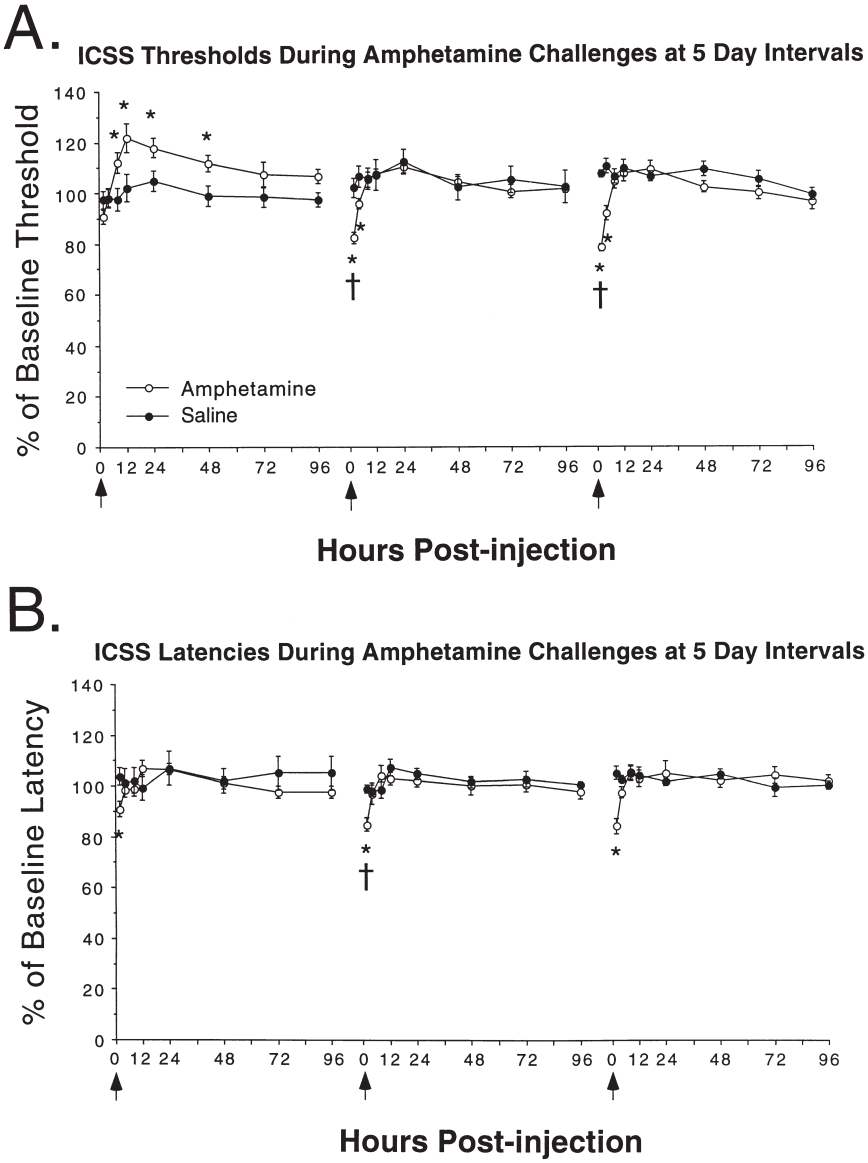

FIG. 1. ICSS thresholds (A) and response latencies (B) 2, 4, 8, 12, 24, 48, 72, and 96 h after administration of amphetamine (4 mg/kg, IP) (n = 10) or saline (n = 6) at 5-day intervals. Arrows below the ordinate indicate the time of each injection. The asterisks indicate statistically significant differences ($p < 0.05$) between control and experimental groups with Newman–Keuls tests. Daggers denote a significant lowering of thresholds, or shortening of latencies ($p < 0.05$) in amphetamine-treated animals after the second and third injections relative to the first injection.

tests whenever the ANOVAs indicated statistically significant main or interaction effects (55).

Threshold and latency data for Experiment 2 were expressed as percentages of the last baseline value prior to each of the two series of injections. All data were first subjected to repeated-measures ANOVAs with series, challenge, and time as the within-subjects factors and the four ICSS measures as the dependent measures. When statistically significant series × challenge × treatment interactions were observed, data for the two series of challenges were analyzed separately to characterize the time course of drug effects in greater detail. When the analyses revealed statistically significant time × treatment interactions, separate analyses were performed on data for the 3-h time point (challenge as the within-subjects factor) and data for the 12- and 23-h time points (challenge and time as the within-subjects factors) to assess the acute actions of the drug and early withdrawal effects, respectively. Data from the 6-day drug-free periods (i.e., 12- to 144-h time points after the last injection of a series) were analyzed separately for each series, with time as the within-subjects factor in a repeated-measures ANOVA to characterize the time course of withdrawal from amphetamine injections. Additional analyses characterizing the dynamic range of changes in ICSS thresholds associated with an amphetamine challenge were performed, similar to those described above for Experiment 1. The first analysis assessed the amplitude of acute amphetamine-induced changes in ICSS thresholds, which was defined as the difference between threshold values obtained prior to an injection and those obtained 3 h after an injection. The second analysis assessed the amplitude of change in ICSS thresholds at later time points; namely the 3- and 23-h time points after an injection. Again, the amplitude was defined as the difference between ICSS thresholds taken at the 3- and 23-h time points. These data were subjected to repeated-measures ANOVAs, with challenge as the within-subjects factor.

RESULTS

Experiment 1: The Effects of Repeated Amphetamine Administration at 5-Day Intervals on ICSS Behavior

Electrode placements were not verified histologically. Nevertheless, the behavioral profiles of the animals used in this study were consistent with those of previous studies [e.g., (36)] utilizing the same stereotaxic coordinates for the stimulation electrodes where histological analyses were conducted.

Thresholds. Figure 1A shows the time course of effects on ICSS thresholds of repeated amphetamine or saline injections at 5-day intervals. For reference, Table 1 shows the values for the four dependent measures obtained for the ICSS session immediately prior to an injection that were used to calculate changes in ICSS behavior after the respective injection. Analysis of variance of baseline values for the four ICSS measures revealed no significant group differences [threshold, $F(1, 14) = 1.61$, NS; latency, $F(1, 14) = 0.01$, NS; extra responses, $F(1, 14) = 2.26$, NS; time-out responses, $F(1, 14) = 0.67$, NS]. Analysis of variance of thresholds at the 2-h time point revealed a significant effect of treatment, $F(1, 14) = 91.67$, $p < 0.0005$, and a significant treatment × challenge interaction, $F(2, 28) = 8.78$, $p < 0.005$. At the 2-h time point, thresholds for amphetamine-treated animals decreased from 90.75 ± 2.67% of preinjection baseline after the first injection to 78.12 ± 1.49% after the third injection. Analysis of ICSS thresholds at the later time points (8–96 h postinjection) indicated no overall effect of treatment, $F(1, 14) = 2.40$, NS, but a significant treatment × challenge interaction, $F(2, 28) = 4.06$, $p < 0.05$. Separate analyses of the 8–96 h time points for the three challenges revealed significant threshold elevations in amphetamine-treated animals relative to saline-treated controls after the first challenge, $F(1, 14) = 6.83$, $p < 0.05$, but no significant differences after the second $F(1, 14) = 0.05$, NS, or third, $F(1, 14) = 1.04$, NS, challenges. ICSS threshold elevations decreased from 121.67 ± 5.67% of preinjection baseline after the first challenge to 108.87 ± 3.36% after the third challenge. Analysis of the data characterizing the amplitude of threshold change after an acute injection revealed a significant effect of treatment, $F(1, 14) = 74.14$, $p < 0.005$, and a significant treatment × challenge interaction, $F(2, 28) = 4.01$, $p < 0.05$. This interaction was due to a greater acute response in amphetamine-treated animals across repeated challenges, $F(2, 18) = 7.80$, $p < 0.005$. Analysis of the data characterizing the amplitude of change in ICSS thresholds between peak lowering and peak elevation also revealed a significant overall effect of treatment, $F(1, 14) = 27.98$, $p < 0.0005$, but no significant change across repeated challenges in either series [treatment × challenge: $F(2, 28) = 0.35$, NS].

Latencies. Response latencies (Fig. 1B) were shorter in amphetamine-treated animals relative to saline controls at the 2-h time point as indicated by a main effect of treatment, $F(1, 14) = 19.24$, $p < 0.001$. Repeated injections produced progressively shorter latencies in amphetamine-treated animals, $F(2, 18) = 3.97$, $p < 0.05$. Response latencies in these animals decreased from 90.8 ± 3.1 percent of preinjection baseline after the first injection to 84.2 ± 3.0 after the third injection. In contrast to the pattern observed with thresholds, no significant differences in latencies were observed between amphetamine and saline-treated animals at the later time points, $F(2, 28) = 0.19$, NS.

No significant group differences were detected for the measures of extra responses or time-out responses at any of the time points (data not shown).

TABLE 1

PRE-INJECTION VALUES FOR THE FOUR ICSS MEASURES IN EXPERIMENT 1: AMPHETAMINE CHALLENGES AT 5-DAY INTERVALS

Treatment Group	Challenge	Mean Baseline Threshold Current Intensity (μA) ± SEM	Mean Baseline Latency (s) ± SEM	Mean Baseline Extra Responses ± SEM	Mean Baseline Time-Out Responses ± SEM
Amphetamine	1	135.50 ± 16.84	3.39 ± 0.12	0.50 ± 0.19	0.14 ± 0.06
	2	142.92 ± 17.29	3.35 ± 0.12	0.43 ± 0.15	0.11 ± 0.03
	3	144.08 ± 17.37	3.27 ± 0.15	0.45 ± 0.14	0.05 ± 0.02
Saline	1	116.74 ± 10.65	3.30 ± 0.09	0.17 ± 0.04	0.11 ± 0.04
	2	113.06 ± 9.78	3.33 ± 0.10	0.13 ± 0.04	0.04 ± 0.02
	3	116.4 ± 12.5	3.34 ± 0.10	0.15 ± 0.05	0.06 ± 0.03

Experiment 2: The Effects of Repeated Daily Administration of Amphetamine on ICSS Behavior

Thresholds. Figure 2 shows the time course of effects on ICSS thresholds of repeated amphetamine or saline injections at 1-day intervals. Table 2 shows the values for the four dependent measures from the ICSS session immediately prior to each of the two series of injections, which were used to calculate changes in ICSS behavior across the respective series. Analysis of variance of baseline values for the four ICSS measures revealed no significant group differences [threshold, $F(1, 12) = 0.23$, NS; latency, $F(1, 12) = 0.87$, NS; extra responses, $F(1, 12) = 0.02$, NS; time-out responses, $F(1, 12) = 0.23$, NS]. Analysis of variance of threshold data at the 3-h time point indicated a significant effect of treatment, $F(1, 12) = 7.32$, $p < 0.05$, which reflected a lowering of thresholds in amphetamine-treated animals relative to saline controls. However, daily amphetamine injections altered thresholds at the 3-h time point differentially between the two series of challenges as indicated by a significant series × challenge × treatment interaction, $F(6, 72) = 2.77$, $p < 0.05$. In the first series, threshold values for amphetamine-treated animals at the 3-h time point did not change significantly across challenges, $F(6, 36) = 1.57$, NS, but increased gradually across the second series, $F(6, 36) = 4.84$, $p < 0.005$. Thresholds at the later time points (i.e., 12 and 23 h after the injection) were significantly elevated in animals treated with amphetamine relative to saline controls, $F(1, 12) = 5.47$, $p < 0.05$. A strong statistical trend in the series × challenge × treatment interaction, F 6, 72) = 2.08, $p = 0.066$, suggested that thresholds at the later time points tended to vary differentially between treatment

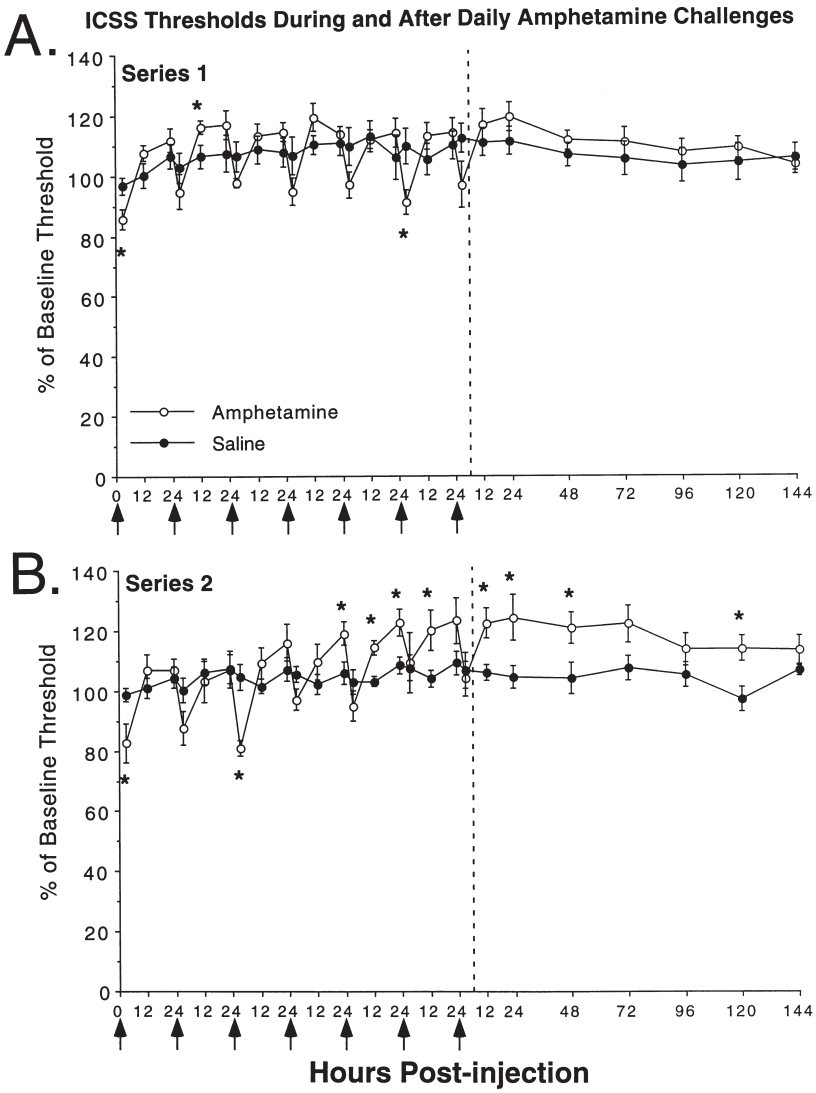

FIG. 2. ICSS thresholds across two series (series 1—top panel, series 2—bottom panel) of seven daily amphetamine (4 mg/kg IP) ($n = 7$) or saline ($n = 7$) injections with 6 drug-free days following each series. Arrows below the ordinate indicate the time of each injection. Threshold determinations were made 3, 12, and 23 h after each injection and once daily during the 6 drug-free days. The vertical lines denote the start of the 6-day drug-free period. Asterisks denote statistically significant differences ($p < 0.05$) between control and experimental groups with Newman–Keuls tests.

TABLE 2

PRE-INJECTION VALUES FOR THE FOUR ICSS MEASURES IN EXPERIMENT 2: DAILY AMPHETAMINE CHALLENGES

Treatment Group	Series	Mean Baseline Threshold Current Intensity (μA) ± SEM	Mean Baseline Latency (s) ± SEM	Mean Baseline Extra Responses ± SEM	Mean Baseline Time-Out Responses ± SEM
Amphetamine	1	102.74 ± 8.25	2.99 ± 0.13	1.71 ± 0.70	0.34 ± 0.10
	2	105.53 ± 7.86	2.95 ± 0.12	1.35 ± 0.53	0.23 ± 0.09
Saline	1	111.07 ± 15.24	3.17 ± 0.14	1.87 ± 0.86	0.40 ± 0.08
	2	116.61 ± 16.05	2.96 ± 0.10	2.12 ± 0.99	0.41 ± 0.24

groups across the two series of amphetamine challenges. Whereas no systematic change in thresholds at later time points was detected in amphetamine-treated animals across the first series of challenges, $F(6, 36) = 1.63$, NS, thresholds became progressively higher across the second series, $F(6, 36) = 3.07$, $p < 0.05$.

Analysis of the data characterizing the acute amphetamine-induced lowering of ICSS thresholds revealed a significant overall effect of treatment, $F(1, 12) = 31.7$, $p < 0.0005$, but no systematic change across repeated challenges in either series [series × challenge × treatment, $F(6, 72) = 0.91$, NS]. Thus, the acute effect of amphetamine on thresholds did not change significantly with repeated challenges. Analysis of the data characterizing the magnitude of change in ICSS thresholds between peak lowering and peak elevation (i.e., 3 h and 23 h postinjection, respectively) also revealed a significant overall effect of treatment, $F(1, 12) = 33.05$, $p < 0.0005$, but no significant change across repeated challenges in either series [series × challenge × treatment, $F(6, 72) = 0.93$, NS].

Thresholds for self-stimulation were assessed during 6 drug-free days after each series of injections, which are demarcated by the vertical lines in Fig. 2. Analysis of variance of these data indicated an overall effect of treatment, $F(1, 12) = 8.87$, $p < 0.05$, but no significant series × treatment interaction, $F(1, 12) = 1.09$, NS.

Latencies. Data characterizing the amphetamine-induced changes in response latency are shown in Fig. 3. Analysis of variance of latency values at the 3-h time point indicated that amphetamine-treated animals made responses more quickly than saline controls [treatment, $F(1, 12) = 16.61$, $p < 0.005$]. Response latencies at the 3-h time point, however, were differentially affected by the two series of injections, as indicated by a significant series × challenge × treatment interaction, $F(6, 72) = 4.16$, $p < 0.005$. Latencies at the 3-h time point progressively decreased across repeated challenges in the first series, $F(6, 36) = 3.91$, $p < 0.005$, but remained constant across challenges in the second series, $F(6, 36) = 1.41$, NS, albeit at the potentiated level seen at the end of the first series. No significant differences in latencies were observed between the amphetamine- and saline-treated groups at the 12- or 23-h time points.

Analyses of the extra response and time-out response data did not reveal significant group differences at any time point (data not shown).

DISCUSSION

The results of the present study indicate that repeated administrations of amphetamine produced progressive changes in ICSS behavior, which were dependent on the time interval between injections. The acute effect of amphetamine on ICSS thresholds was potentiated after repeated injections at 5-day intervals, as indicated by greater decreases in thresholds. Concomitantly, the threshold elevations observed at later time points after an amphetamine injection diminished with repeated challenges. By contrast, daily injections of the same dose of amphetamine did not alter the acute threshold-lowering effect of the drug, but tended to produce progressively greater elevations in thresholds at later time points. Notably, the acute amphetamine-induced increase in operant response speed was potentiated after amphetamine injections at 5-day intervals and after the first series of daily amphetamine challenges, which indicates a dissociation of drug effects on motor performance and brain stimulation reward.

The present data demonstrate that a single high-dose administration of amphetamine was sufficient to produce a transient elevation in ICSS thresholds. This finding resembles the phenomenon of acute withdrawal observed with other drugs, such as opiates (1,37) and benzodiazepines (3,4,6), but differs in a number of regards from previously reported instances. First, the acute withdrawal effects were observed after injection of the indirect agonist (i.e., amphetamine) only, and were not precipitated by subsequent antagonist administration. Second, withdrawal symptoms were manifested as changes in ICSS thresholds only, in contrast to the observation of both somatic and reward symptoms characterizing opiate (47) and benzodiazepine withdrawal (6). Abstinence from psychostimulant drugs in humans is not typically associated with gross somatic disturbances, yet affective symptoms of anhedonia or reduced reward are commonly reported during the early "crash" phase of withdrawal (13,54). These clinical reports are paralleled by findings in the present study in which acute withdrawal from amphetamine was associated with diminished reward without overt signs of physical distress or impairments in indices of performance capacity such as response latency, extra- or time-out responses.

Current conceptualizations of the motivational processes that underlie drug-seeking behavior emphasize two major hypotheses. The first posits that the euphorigenic properties of a drug provide a powerful incentive to seek further exposure (53,56), and the second that drug-taking behavior is driven by the need to alleviate the aversive consequences of prior drug exposure (22). The expression of both acute reward potentiation and diminished reward at later time points after a high dose of amphetamine suggests that both motivational processes may be engaged by the drug. The dose-dependent potentiation of brain stimulation reward by acute amphetamine administration has been clearly demonstrated in previous studies [e.g., (12,46)]. It is possible that the degree to which amphetamine administration leads to both positive and negative affective states may depend on the dose of the initial drug exposure and time since drug administration. Findings from a recent study indicate that the initial dose of amphetamine or cocaine available to the subjects is an important determinant

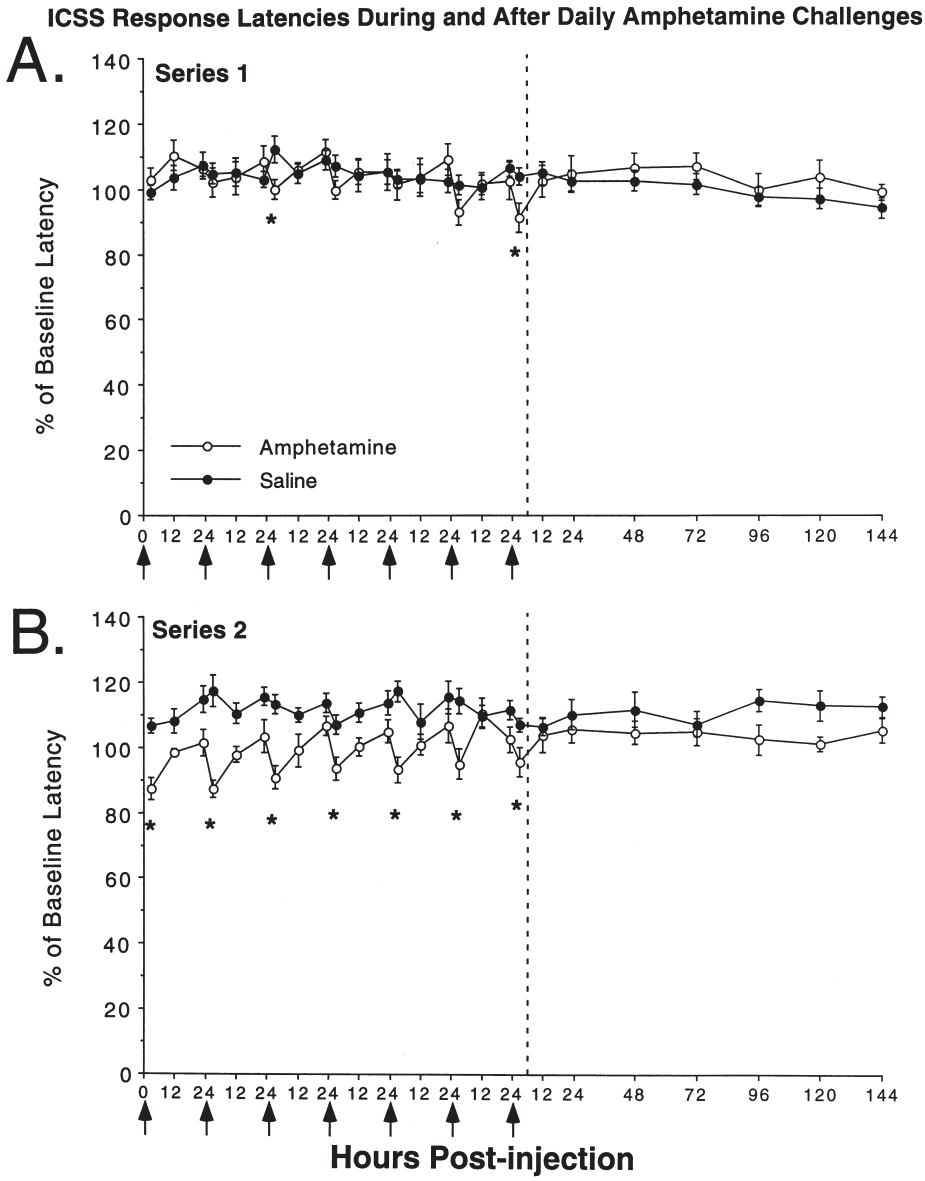

FIG. 3. Response latencies for ICSS across two series (series 1—top panel, series 2—bottom panel) of seven daily amphetamine (4 mg/kg IP) or saline injections with 6 drug-free days following each series. Asterisks denote statistically significant differences ($p < 0.05$) between control and experimental groups with Newman–Keuls tests.

of the acquisition of self-administration behavior (7). Thus, the motivation to seek subsequent drug administration may be influenced by the intensity of positive and/or negative affective states associated with initial exposure to the drug.

The present findings complement those from another study in which discriminated responding between three levers previously associated with amphetamine, saline, or haloperidol, a D_2 dopamine receptor antagonist, shifted from the amphetamine-appropriate lever at time points immediately after an injection of amphetamine (5 mg/kg, IP), to the haloperidol-appropriate lever 24 h after the injection, and subsequently to the vehicle-appropriate lever at later time points (9). This shift to haloperidol-appropriate responding during acute withdrawal from amphetamine suggests the development of an internal cue state that resembles decreased dopaminergic function. Notably, the acute withdrawal effects observed in the present study followed a similar time course with threshold elevations between 12 and 24 h postinjection, and a gradual return to preinjection levels at later time points. It is interesting to note that acute systemic administration of antagonists relatively selective for D_2 receptors, such as haloperidol (31) and pimozide (38), and D_1 receptors, such as SCH23390 (38) and SKF81297 (2), also decrease brain stimulation reward. Taken together, these data suggest that a transient decrease in dopaminergic function may be associated with acute withdrawal from amphetamine.

The elevations in ICSS threshold after a single exposure to amphetamine were qualitatively similar, albeit of smaller

magnitude, to those observed during withdrawal from more severe and prolonged treatment regimens (8,28,58). The relatively greater magnitude and longer duration of threshold elevations observed after withdrawal from chronic amphetamine and administration may reflect, at least in part, an amplification of neuroadaptive processes that oppose the acute euphoric effects of the drug (22). It should be noted that withdrawal-associated ICSS threshold elevations are relatively transient, even after 42 days of a multiple daily injection regimen with escalating doses (1–10 mg/kg) (58), or two series of seven daily injections (present study). Nonetheless, the return of ICSS thresholds to preexposure baseline levels does not necessarily represent a restoration of neuronal function to the predrug state. For example, preexposure to amphetamine and to other psychostimulant drugs, such as cocaine, has been shown to produce persistent changes in locomotor response to subsequent drug challenges long after the behavioral effects of the initial exposure have dissipated (43,45). Repeated exposure to psychostimulant drugs may alter the neuronal substrates that mediate the acute actions of the drugs, and thus, subsequent challenges may produce greater effects (series 1 vs. series 2 in the present study).

The amplitude of acute amphetamine effects on ICSS thresholds, defined as the difference between thresholds values determined immediately prior to and shortly after an injection, was potentiated after repeated injections of the drug at 5-day intervals, but did not change after daily drug challenges. The differential effects of the two treatment regimens indicate that the time interval between injections is an important determinant of neuroadaptive responses. In this regard, the present findings are consistent with those from other studies that showed that the interval between successive administrations of amphetamine is a critical determinant of the expression of sensitization to the locomotor-activating effect of the drug. Injections of amphetamine spaced widely in time produce more robust sensitization of drug-induced motor activation than injections given close together (38,40,42). It is possible that the neuronal adaptations mediating sensitization to the threshold-lowering action of amphetamine also may require time to become maximally expressed. Reexposure to the drug before these adaptations are developed may interfere with the development of sensitization.

Contrary to our initial predictions, the ICSS threshold elevations associated with withdrawal from amphetamine diminished with repeated challenges at 5-day intervals. The Opponent Process theory postulates that the drug-induced enhancement of reward (a-Process) engages adaptive processes that oppose (b-Process) the positive hedonic state (22,51). The current findings indicate that decreases in the rewarding value of stimulation associated with withdrawal from amphetamine, which may reflect activation of b-Process, were not augmented proportionally with sensitization of the a-Process. It should be noted, however, that the b-Process is hypothesized to develop slowly and to increase in strength gradually (22,51). Thus, a transient and infrequent activation of the a-Process may not be sufficient to potentiate the expression of the b-Process, and perhaps may promote adaptations that mitigate the consequences of b-Process activation. This possibility raises an interesting question about the dynamics of counteradaptive responses, whether they are governed by passive processes or actively regulated.

The findings of the second experiment point to an important distinction between estimates of acute drug-induced changes in ICSS threshold and global estimates of threshold change relative to a pretreatment value. If analyses of threshold changes at the 3 h postinjection time point were determined from a pretreatment value, one might conclude that the ability of amphetamine to potentiate brain stimulation reward diminished with cumulative drug history. Analyses based on local estimates of threshold change, however, revealed that the acute potentiation of brain stimulation reward by amphetamine did not change across daily drug challenges. Thus, the gradual elevation of the threshold function in response to daily amphetamine challenges reflected a progressive decrease in the rewarding efficacy of stimulation onto which a constant acute drug effect was overlaid. It should be noted, however, that this progressive increase in threshold elevations was observed only during the second of two series of daily injections. It is currently unclear whether the drug-induced changes observed in the second series of challenges were due to cumulative drug history (i.e., if the same changes would have been observed if injections were administered for 14 consecutive days), or whether the intervening drug-free period was a contributing factor.

The results of the second experiment are particularly interesting in light of the affective changes associated with chronic psychostimulant exposure in humans. Over the course of repeated psychostimulant drug exposures, human users often report a gradual decrement in the acute euphorigenic effect of the drug (14). Subsequent administrations of the drug may serve to alleviate negative affective symptoms that are manifested when the acute effects of the drug subside. In the present study, an analogous pattern was observed during the second series of amphetamine injections in which initial injections of the drug acutely lowered ICSS thresholds below pretreatment values, but by the last injections of the second series only transiently restored thresholds to pretreatment values from an elevated level.

In contrast to the divergent effects of daily vs. 5-day interval injections of amphetamine on ICSS thresholds, the drug-induced potentiation of motor performance was augmented by both treatment regimens. This finding is in concurrence with previous studies of sensitization to the motor activating effects of amphetamine (45,49). Nevertheless, unlike the effects observed with ICSS thresholds, response latencies in amphetamine-treated animals did not show a biphasic function, and were not significantly different from saline controls at later time points. The absence of impairments in motor performance at later time points is interesting in light of findings that show subtle motor deficits during withdrawal from chronic psychostimulant administration (39,49). The conditions under which motor behavior was assessed may have been a critical difference between the present and previous studies. In the present study, motor behavior was assessed on a positively motivated task, whereas the previous studies assessed spontaneous locomotor activity.

The progressive shortening of response latencies after both amphetamine injection regimens indicates a dissociation of drug effects on motor performance and reward. A similar dissociation was observed in an earlier study, which showed that the acute potentiation of brain stimulation reward is unaltered by repeated administrations of amphetamine, but drug-induced locomotor activation is sensitized (57). These findings, taken together, suggest that motor and reward processes may be mediated by a different set of neuronal substrates that are differentially altered by chronic amphetamine exposure. Notably, other measures of performance on the ICSS task, namely extra and time-out responses, were not sensitive to the drug treatment at any time point. Therefore, the drug-induced changes in ICSS thresholds could not be attributed to

nonspecific effects of the drug, such as response preservation or impaired attention to the self-stimulation task.

In summary, the current findings indicate that distinct patterns of amphetamine exposure can differentially activate adaptive responses in the neuronal substrates mediating reward processes. It is likely that similar differences in adaptive responses arise from the wide range of psychostimulant administration patterns observed in humans. "Recreational" or infrequent psychostimulant drug use may induce neuroadaptions quite different from those produced by compulsive "binge" use. Therefore, the history of drug exposure in humans should be taken into consideration in the development of treatment strategies.

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