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# Opposite Effects of PCA and Chlorimipramine on ICSS and on Its Facilitation by Amphetamine

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OLDS, M. E. *Opposite effects of PCA and chlorimipramine on ICSS and on its facilitation by amphetamine.* PHARMACOL BIOCHEM BEHAV 47(4) 803–817, 1994.—The long-term effects of chloramphetamine (PCA) and chlorimipramine (CHLOR) on intracranial self-stimulation (ICSS) were investigated in sessions lasting 13 h. PCA, 5 mg/kg given IP, led first to an attenuation of ICSS lasting 3 h, then to a slow recovery to baseline rates, and then to a facilitation of ICSS lasting 6 h. Repeating the treatment 7 days later resulted in less attenuation of ICSS, more rapid recovery, and longer-lasting facilitation. Again, repeating the treatment with PCA 7 days later but injecting simultaneously amphetamine (AMPH) 2 mg/kg IP, altered the response seen with PCA alone. The attenuation phase was missing but the facilitatory phase remained except that it occurred early and was of shorter duration than after PCA given alone. Pretreatment with haloperidol (HALO) 0.5 or 1.0 mg/kg IP before PCA blocked the facilitatory phase of the response. CHLOR injected at a dose of 15 mg/kg IP attenuated ICSS. The combined administration of CHLOR and AMPH led to the CHLOR-attenuation of ICSS being replaced by a modest facilitation. These results are discussed in terms of the biochemical actions of PCA and CHLOR on the serotonin and dopamine systems.

Amphetamine Chlorimipramine Dopamine 5-Hydroxytryptamine p-Chloramphetamine Self-stimulation

CHLORAMPHETAMINE (PCA) releases serotonin (5-hydroxytryptamine, 5-HT) short-term, thus enhancing serotonergic transmission in that period, and depletes central 5-HT levels long term as a result of damage to 5-HT terminals, thus depressing serotonergic transmission (13,17,18,21,29,46,49, 52,53). In addition, PCA also acts on the dopamine (DA) system where it is reported to induce the release of the transmitter short term but without causing damage to DA neurons. The absence of toxic damage here prevents the long-term depletion of central levels, in sharp contrast to the depletion of 5-HT induced by PCA (8,12,25,29,49,52). The consequence of increased levels of synaptic DA is to enhance dopaminergic activity. Whereas the functional significance of the actions of PCA on the serotonin system is beginning to be understood, the functional significance of its action on the DA system remains to be elucidated.

Chlorimipramine (CHLOR) is a serotonergic compound with a capacity to inhibit 5-HT reuptake, resulting, therefore, in enhanced serotonergic transmission (6,14). Such action is of relatively short duration, and because CHLOR is reported to be devoid of significant action on dopaminergic activity, the effects of this compound on ICSS could represent the purely serotonergic action, whereas in the case of PCA, the effects might represent the concurrent actions on serotonergic and dopaminergic activity.

Intracranial self-stimulation (ICSS) is generally viewed as a behavior that depends on the integrity of the DA neurons giving rise to the mesolimbic and mesocortical systems on evidence showing that enhanced DA transmission results in the potentiation of reward and depressed DA transmission in its reduction (55,57). It was assumed early on that the 5-HT neurons played a role in reward on the basis of findings showing a capacity of the 5-HT systems to influence ICSS. The view proposed was that the catecholamine system was responsible for the activation of the reward pathways and the 5-HT system for keeping that activation within bounds (41–43,50,56). Over time, information about the role of the DA neurons in reward has grown, but precise information about the regulation exerted by the 5-HT neurons has failed to keep up in spite of increased evidence that the two systems work intimately in their regulation of behavior.

We previously investigated the effects on ICSS of fenfluramine, a compound belonging to the same family as PCA (40). These had been investigated by others (31), but not with the

intention of correlating the long-term effects on ICSS with the prolonged depletion of central 5-HT levels the drug induces in animals after chronic treatment with high doses, and not with the intention of explaining whether its neuroleptic-like actions on DA transmission might have played a role in its effects on ICSS (3,15,16,22–24). Our own interest in fenfluramine does not derive from its capacity to reduce feeding but from its capacity to influence 5-HT transmission via release, to deplete central 5-HT levels (1,17,20,27,28,35,48,51,54), to influence DA transmission (3,15,16,22–24), and to alter the normal serotonin/dopamine interactions that may be relevant to an understanding of its behavioral effects. Of particular interest was evidence showing that fenfluramine had the capacity to antagonize the motor behaviors induced by amphetamine and apomorphine (2,44), two agents known to enhance DA transmission in the CNS (5,7,36,59), and to induce neuroleptic-like biochemical effects on DA metabolism as shown by increased levels of DA metabolites similar to those seen after treatment with haloperidol (HALO) (3,15,16,22–24). Interestingly, the behavioral significance of the neuroleptic-like action of fenfluramine is not known (44).

In our previously reported study in which we tested for the effects of fenfluramine on ICSS (40), we focused on the acute and chronic effects of the drug. The aim was to determine whether the release of 5-HT by the drug induced early on but lasting briefly and in that period resulting in enhanced 5-HT transmission, led to different behavioral effects from those seen when stores were depleted because of overutilization or damage of 5-HT terminals leading to depressed reuptake and synthesis. We also wanted to find out whether the depressed 5-HT activity in animals treated chronically with fenfluramine modified the facilitation of ICSS seen in drug-naive subjects treated with amphetamine (AMPH). The results of that study show that fenfluramine, given at a dose of 20 mg/kg IP, suppressed ICSS for 24 to 48 h. Partial recovery was observed only 5 to 6 days later. Repeating the treatment a second time on the seventh day after the first treatment potentiated the effects seen in the drug-naive subject. Repeating the treatment a third time, 7 days after the second treatment and combining it with AMPH, 2 mg/kg, dramatically shortened the duration of the suppression of ICSS seen with fenfluramine, but dramatically prolonged the facilitation of ICSS seen with AMPH. These findings raised two questions. One was whether the neuroleptic-like action of fenfluramine was responsible for the blockage of ICSS occurring immediately after treatment and lasting many hours. The second was whether the long-term depletion of central 5-HT levels induced by fenfluramine given at a dose of 20 mg/kg was responsible for the protracted recovery of ICSS or whether even here, the neuroleptic-like action of the drug had a role in its behavioral effect.

In the present study, these same questions were addressed but with a different strategy. Here, PCA was tested for its effects on ICSS because its actions on serotonergic transmission were similar to those of fenfluramine but its actions on DA transmission appeared to lack the neuroleptic-like properties, perhaps substituting for them agonist-like properties. We also tested for the effects of chlorimipramine (CHLOR) because of its capacity to enhance 5-HT transmission without inducing long-term depletion of central levels and without significantly affecting DA transmission in the short or long term.

## METHOD

The methods and behavioral protocols used in the present study were the same as those used in the study of the effects of fenfluramine on ICSS (40).

### *Subjects*

The subjects of the experiments were adult male, Sprague-Dawley-derived rats weighing 300 to 350 g at the time of electrode implantation. Before electrode implantation, and for 1 week after surgery allowed for recovery, the animals lived in groups of three in rodent colony cages with food and water available on demand. Training to ICSS began in individual operant chambers, and from then on, the subjects lived in these cages, with food and water available on demand. Eight subjects were tested concurrently in a room in which the temperature was set at 23°C, and the lights went off at 1800 h and came on 13 h later. The lights coming on signaled the beginning of the rest and recuperation period, and the lights going off signaled the availability of brain stimulation, provided the subject made the proper response, which was depressing a level placed on one of the walls of the operant chamber.

### *Electrodes and Implantation Procedures*

The type of electrode used and the implantation procedures have been described (40). One bipolar electrode was implanted in each subject, being aimed at the medial forebrain bundle (MFB), at the level of the ventromedial hypothalamus by using stereotaxic coordinates (30) (3.5 mm posterior to bregma, 1.5 mm lateral to the midline, and 8.3 mm from the top of the skull). The surgery was performed under pentobarbital anesthesia, 50 mg/kg given IP. Seven days later, each subject was placed in its operant cage, where it lived during training and drug testing.

The electrode was made from a pair of stainless steel wires (250 $\mu$m in diameter), factory insulated, twisted together, and terminating in a small nylon pedestal anchored on the skull (39). A customized connector was available to connect the electrode to the leads from the stimulator.

### *Behavioral Training and Testing*

The operant chambers were made from Plexiglas. Each had a metal level on the front wall, a counterbalanced overhead arm fitted with a commutator, a trough in which regular rodent chow was available, a water bottle to deliver drinking water, and a plastic floor with holes in it sitting over a pan filled with wood shavings.

With the connector attached to the electrode and the stimulator turned on, each depression of the lever delivered a brief stimulus to the MFB. Lever presses during the delivery were ineffective. Each brain stimulus was a train of 60 Hz sine waves of 0.25-s duration, with the intensity selected for each animal to yield high response rates. Different current intensities were made available in different experiments, depending on the protocols selected, but for a given animal, only one protocol was used.

Training consisted of a series of daily sessions, each starting at 1800 h and terminating 13 h later. In the first session, the current for subjects trained concurrently (8) was 60 $\mu$A peak to peak. The subjects were left to train themselves during the protracted session. In the morning, the connector was removed and stimulation was not available until that evening. In the second session, the current intensity was increased by 20 $\mu$A for those subjects whose total number of responses (made available on hard copy in the morning at the end of the session) had not reached 10,000. The same procedure was followed in the subsequent sessions until a maximum of 160 $\mu$A had been reached for subjects not making 10,000 or more

responses in the last session. The subjects meeting the requirement were continued at that current or the current was raised by 10 μA until responding was increased and distributed evenly throughout the lengthy session. At the end of 8 to 10 days the subjects not meeting the requirement were removed from the study, and the others either underwent more elaborate training or were tested for drug effects.

The animals tested for drug effects were then given two consecutive sessions each preceded by an IP injection of 0.9% saline. The absence of significant effects led to the data from these two sessions being pooled with the data from the two to three preceding sessions to compute baseline rates in drug-naive subjects tested with the current intensity selected to produce optimal and stable ICSS throughout the series of drug tests each animal underwent.

The animals undergoing more elaborate training received daily sessions in which the current intensity varied repeatedly within each session, in cycles. During each cycle, the brain stimulus was a descending train, starting with the optimal intensity selected from the first phase of training, and being stepped down from there each 10 min by 20 μA until 10 min of no stimulation (extinction, zero current) had elapsed, at which point a new cycle began. Data at the end of each session showed the operant rate (during extinction), the threshold current eliciting ICSS, and the ICSS rate at the optimal intensity. The animals selected for this training learned the task in two to three sessions but were given five sessions, with the fourth and the fifth preceded by an injection of 0.9% saline before the session began.

Stimulation, data acquisition, and analysis were under the control of a PDP-11 34 A computer. At the end of each session, the response rates of each animal were made available on hard copy in blocks of 10 min and 60 min and as totals for the full session. For the animals tested with the descending trains, the response rates were in blocks of 10 min. Additional scores made available represented the total number of responses made at each current intensity during the session. The scores for the two sessions preceded by saline injections and the two sessions without these injections (total of four) were used to compute baseline ICSS rates in the drug-naive animals at each current intensity. Drug tests started in the session following the second saline injection.

### *Treatments*

DL-p-PCA was injected IP at a dose of 5 mg/kg. This dose was selected on the basis of evidence in the literature that it was effective in releasing 5-HT from central stores, in causing long-term depletion of central 5-HT levels, in affecting dopaminergic activity, and in altering behavior (8,12,13,21, 25,41,46,49,53). The schedule for PCA was identical to the schedule of treatment in our previous study with fenfluramine (40). This schedule included a minimum of three treatments with the 5-HT releasing drug, the first two separated by 1 week, and the third separated from the second treatment by 1 week and coadministered with d-AMPH injected IP at a dose of 2 mg/kg. AMPH was selected on the basis of its releasing action on central DA stores (7,23,59) and of our results in fenfluramine-experienced subjects coadministered fenfluramine and AMPH, in which the normal facilitation of ICSS induced by AMPH was dramatically prolonged (40). PCA and AMPH were dissolved in 0.9% saline immediately before being injected, and they were injected in a volume of 1 ml/kg body weight.

Two doses of haloperidol (HALO) were tested for their effectiveness in blocking the actions of PCA. In one experiment, the dose of HALO injected IP was 1 mg/kg and in the other experiment, 0.5 mg/kg. The pretreatment was given 30 min before PCA, and during that period ICSS was not available. HALO was dissolved in two drops of acetic acid and then brought up to appropriate volume with 0.9% saline.

CHLOR was injected IP at a dose of 15 mg/kg, selected on the basis of evidence in the literature that it was effective as a 5-HT reuptake blocker (6,14,17,45). The drug was dissolved in 0.9% saline. The effects of CHLOR were also tested when coadministered with AMPH at a dose of 2 mg/kg.

### *Analysis of Data*

Group data were computed differently for the animals tested at the single current intensity and for the animals tested with the descending trains. For the group of animals tested with the single intensity, group scores (mean, SD) were computed from the individual hourly scores. For the first treatment, the baseline scores represented the average hourly response rates in the four sessions preceding the treatment. If a second treatment was given, the control scores represented the average response rates in the fifth and sixth sessions after the first treatment and 1 day before the second treatment given on the seventh day. If a third treatment was given, the baseline score represented the average hourly response rates in the fifth and sixth sessions after the second treatment and 1 day before the third treatment. The group response rate achieved under drug treatment (test rates) was compared with the appropriate baseline score for determination of treatment effect. The Student's *t*-test (two-tailed) was used to determine the significance of the changes, with 0.05 taken as the minimal level of significance.

For the animals tested with descending trains, the group data were computed from the individual scores representing the total number of responses made at each current intensity in the 13-h session. Because the number of cycles varied from animal to animal, depending on the optimal intensity selected for a given animal to achieve stable responding within a session and from session to session, the scores for the last five highest current intensities were used to compute the group score. Thus, the peak score from one animal was added to the peak score from another animal, the next highest score to the next highest score, and so on. Typically, the threshold for ICSS was either one or two levels before the peak current intensity. For the first treatment, the baseline score represents the response rates in the last four sessions before the treatment, and for the subsequent treatments, the baseline score was computed from the scores achieved in the fifth and sixth day after the previous treatment and one day before the subsequent treatment. The test scores were compared to these baseline scores for evaluation of change in ICSS threshold and in ICSS rates at the higher intensities. Here also, the Student's *t*-test was used to determine significance of the changes.

### *Histology*

After completion of each experiment, the animals were killed with an overdose of pentobarbital. The brains were removed, placed in formalin, and sectioned with the frozen technique 8 to 10 days later. Placement of the probe was determined from cresyl violet-stained sections.

## RESULTS

### *PCA: Time Course and Residual Effects*

The treatment of drug-naive self-stimulators with PCA attenuated ICSS during the first 3 h compared to control ICSS

(Fig. 1, Top, $n = 7$, PCA I). However, by the fifth hour of the session, the ICSS rate was back to the control level for that hour in the session, remaining at that level for the next 3 h. Afterwards, ICSS increased to a level significantly above the control level and remained there until the end of the session (PCA I vs. controls, last 7 h, $p < 0.001$). PCA had, thus, a delayed facilitatory effect on ICSS. In the two sessions that followed the drug session, the ICSS rate was depressed, being more so 2 days after the treatment than the next day (PCA I day 1 post vs. PCA I drug day $p < 0.003$; PCA I day 2 post vs. PCA I drug day $p < 0.0001$).

A second treatment with PCA, 7 days after their first treatment with PCA, again led to a facilitatory response (PCA II vs. new controls, which now represented ICSS rates in sessions 5 and 6 after PCA I, all 13 h, $p < 0.0001$). This response was greater than the response to the first treatment with PCA (Fig. 1, Middle, PCA II). In sessions on days 5 and 6 after the first treatment with PCA, the ICSS rate had not recovered to the initial control levels (top). In these subjects now self-stimulating at lower rates than before the PCA I treatment, PCA given a second time (PCA II) induced a more robust facilitatory response than PCA I had. The facilitatory effect of PCA II had disappeared in the next session when the ICSS rate was only slightly above the control rate. In the second session after PCA II, the ICSS rate was attenuated, indicating a carry over of the effect of PCA into this session.

Coadministering PCA a third time and AMPH for the first time 7 days after the second treatment with PCA also induced a facilitatory response when the scores in the drug sessions were compared to controls, the control scores representing the mean ICSS rate in sessions 5 and 6 after PCA II (Fig. 1, bottom, PCA III + AMPH, drug test scores vs. controls, days 5 and 6 after PCA II, $p < 0.0004$). With the combined treatment, the response was different from the responses seen after PCA I and PCA II. After the combined treatment, the peak effect occurred during the first and second hour; thereafter, ICSS gradually decreased to control levels in the 11th and 12th hour after the injection. In contrast, peak effect after PCA I was delayed until the ninth hour and after PCA II, until the fourth hour.

*PCA: Thresholds and Stimulus Discrimination*

The schedule of treatments given the subjects trained with the descending trains was the same as for the subjects trained with the single current intensity.

PCA given to drug-naive subjects (PCA I) lowered the ICSS threshold and increased the response rate at the intensities above threshold, except for the highest and next to the highest current intensity (Fig. 2, top, $n = 3$, PCA I, $p < 0.05$). There were no residual effects of the treatment in the next two sessions given 24 and 48 h later (Fig. 2, top, PCA I). In these sessions, the ICSS threshold was now the same as in the drug-naive animals, and the response rate was not significantly different from the control rate (Fig. 2, top).

PCA given a second time, 7 days later (PCA II), lowered the ICSS threshold to that seen after PCA I but with higher response rates at that level than after PCA I. The treatment also led to larger increases in the ICSS rate at the intensities above threshold than after PCA I (Fig. 2, middle, PCA II; $p < 0.001$, note difference in the y-axis). The controls for PCA II represent the ICSS rate on days 5 and 6 after PCA I and 1 day before PCA II injected on day 7 after PCA I. The ICSS rates at the highest intensity showed a slight decline compared to the rates at the next lower intensity, as had been the case after PCA I.

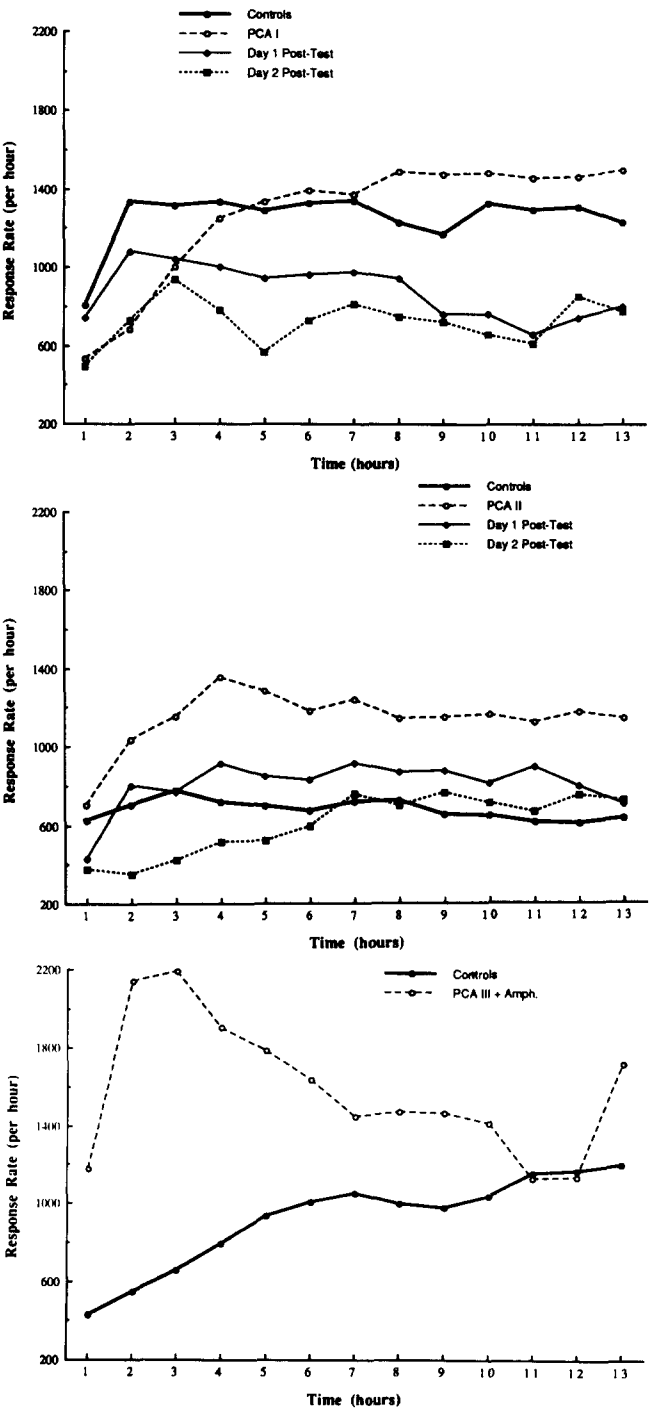



FIG. 1. Acute and chronic P-chloramphetamine (PCA), 5 mg/kg given IP, influence self-stimulation (SS) rates tested at peak current intensity ($n = 4$). Top: first treatment with PCA. Middle: second treatment with PCA given 7 days after the first treatment. Bottom: third treatment with PCA with the IP coadministration of amphetamine (AMPH), 2 mg/kg, given 7 days after the second treatment with PCA. Controls in the top panel represent the mean SS rate in the last 4 days of training, with saline injected in the last two sessions. Controls in the middle panel represent the mean SS rate on days 5 and 6 after the first injection of PCA. Controls in the bottom panel represent the mean SS rate on days 5 and 6 after the second injection of PCA.

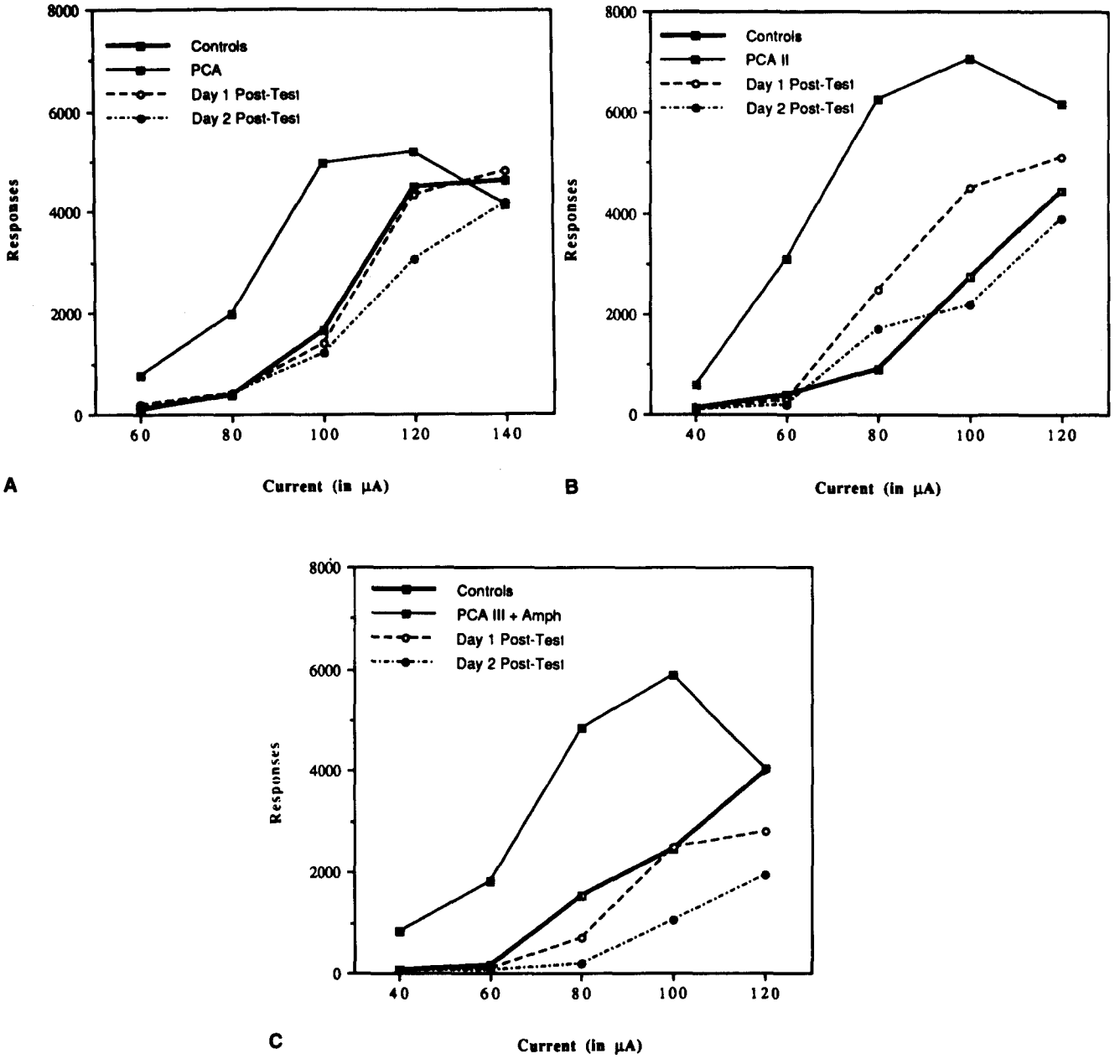
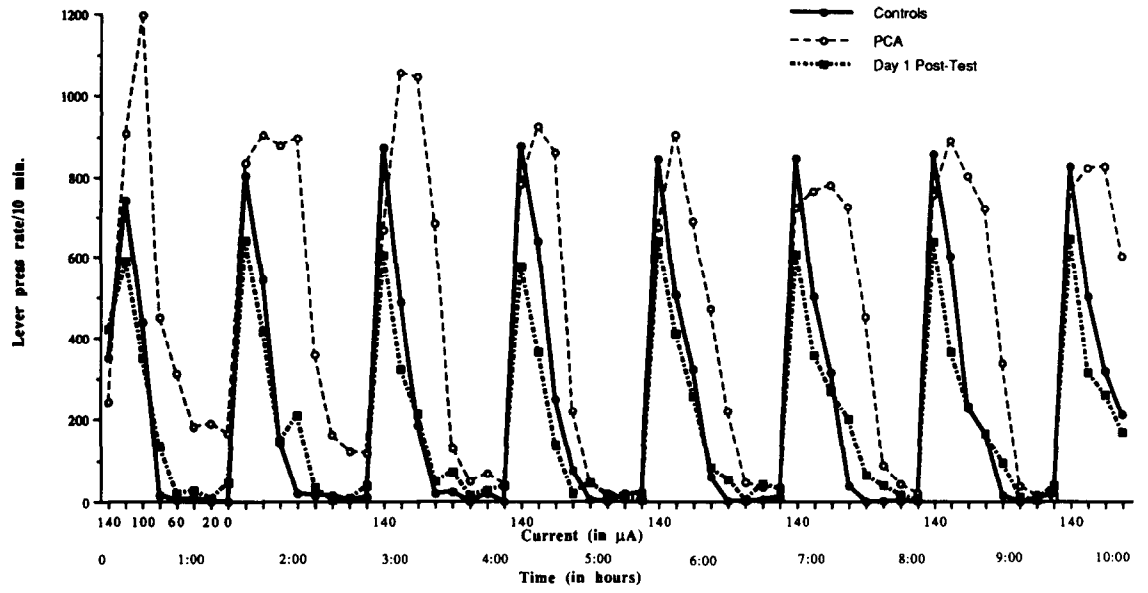


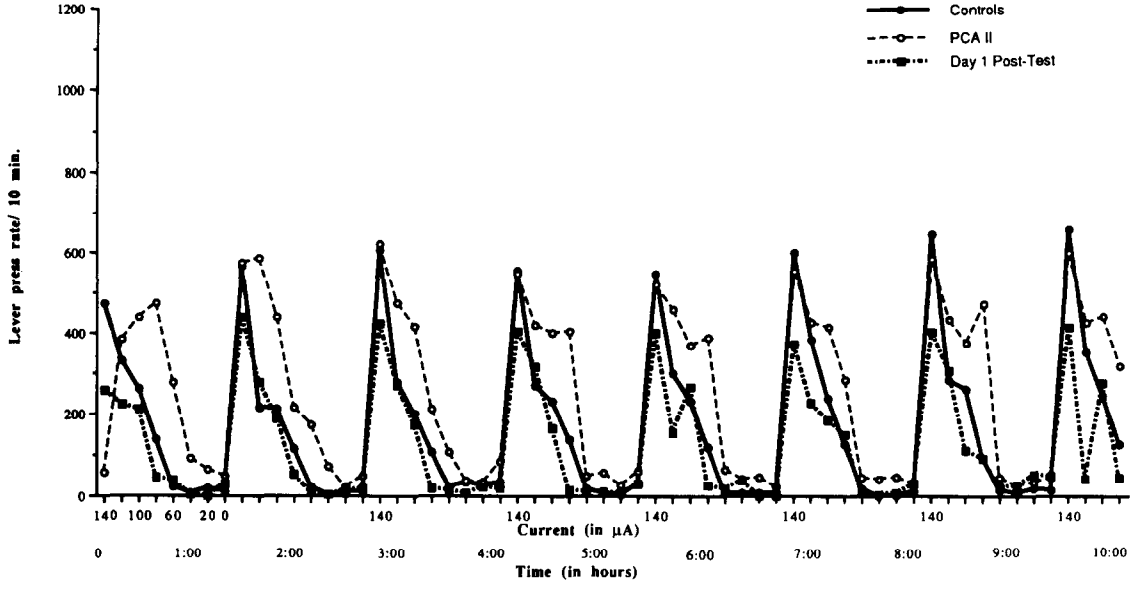

FIG. 2. Acute and chronic administration of P-chloramphetamine (PCA), 5 mg/kg given IP, influence self-stimulation (SS) tested with descending stimulus trains to determine changes in the SS threshold. The last five current levels made available are shown, starting with the peak current level. (A) first treatment with PCA ($n$ = 5). (B) second treatment with PCA given 7 days after the first treatment ($n$ = 5). (C) third treatment with PCA combined with amphetamine (AMPH), 2 mg/kg given IP ($n$ = 3).

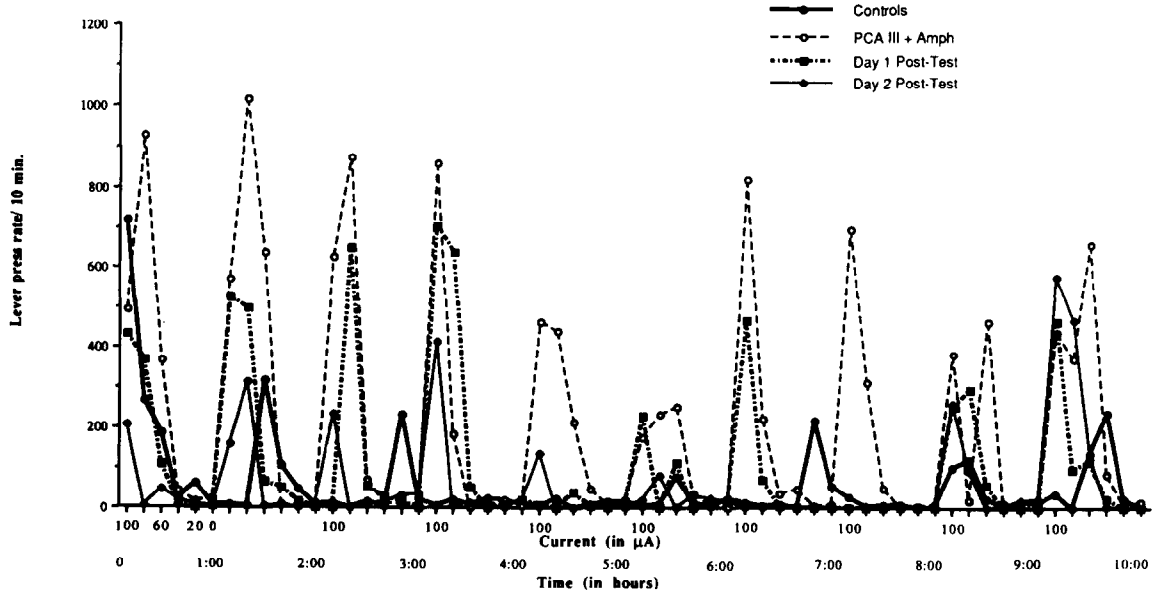
There were some residual effects of PCA II 24 h after the treatment on the ICSS rates, which were still higher than the controls at the current intensities above threshold, but not on the ICSS threshold, which now was the same as in controls (Fig. 2, middle). There were no residual effects of PCA II 48 h after the treatment.

PCA given a third time and coadministered with AMPH (PCA III + AMPH) essentially resulted in a replication of the effects seen after PCA II (Fig. 2, bottom; $p < 0.001$). Here, again, the ICSS threshold was lowered, and the ICSS rates increased at each intensity compared to the control rates, except at the highest intensity at which the rates returned to the control level. The control scores here represents the ICSS rates on days 5 and 6 after PCA II and 1 day before the treatment with PCA III + AMPH. The addition of AMPH to the treatment did not increase the facilitatory effect of PCA. This third treatment seemed to have had residual effects, as shown by the decreased ICSS rates 24 and 48 h after the treatment.

An example of the effects of PCA on threshold and current intensity discriminating is shown in Fig. 3. The intensities and the corresponding times are shown on the x-axis, and the ICSS


Controls
PCA
Day 1 Post-Test
Lever press rate/10 min.
1200
1000
800
600
400
200
0
140 100 60 20 0
140
140
140
140
140
Current (in µA)
0
1:00
2:00
3:00
4:00
5:00
6:00
7:00
8:00
9:00
10:00
Time (in hours)


Controls
PCA II
Day 1 Post-Test
Lever press rate/ 10 min.
1200
1000
800
600
400
200
0
140 100 60 20 0
140
140
140
140
140
Current (in µA)
0
1:00
2:00
3:00
4:00
5:00
6:00
7:00
8:00
9:00
10:00
Time (in hours)


Controls
PCA III + Amph
Day 1 Post-Test
Day 2 Post-Test
Lever press rate/ 10 min.
1200
1000
800
600
400
200
0
100 60 20 0
100
100
100
100
100
100
100
100
Current (in µA)
0
1:00
2:00
3:00
4:00
5:00
6:00
7:00
8:00
9:00
10:00
Time (in hours)

rates per 10 min for each step of the descending train are shown on the y-axis. This example shows that PCA I and II (top and middle) had facilitatory effects on ICSS that lasted throughout the sessions, and that the ICSS rates showed increases that extended the duration of peak effect. Furthermore, the results show that the ICSS threshold was lower after the treatments but not as a result of an increase in gross motor activity because the subject continued to discriminate the current intensities as shown in the sharp decrease in the response rate during extinction.

The combination of PCA and AMPH led to higher ICSS rates and a lower ICSS threshold (Fig. 3, bottom) but did not increase the duration of peak effect as PCA I and II had done. Furthermore, the period of maximum facilitation lasted only about 3 h during which four descending stimulus trains had been made available, in sharp contrast to the effects of PCA I and II in which the facilitation remained of the same magnitude throughout the session. The facilitatory response lasting 2 to 3 h produced by the combined treatment was followed by a gradual decline of the ICSS rate. As illustrated in Fig. 3, the residual effect of the combined treatment was more pronounced than after PCA I and II, resulting in sharply lower ICSS rates.

*Pretreatment With Haloperidol: Time Course*

Pretreatment of subjects with HALO, 1 mg/kg IP, 30 min before the IP injection of PCA, 5 mg/kg IP, suppressed ICSS throughout the session and, thus, blocked the facilitatory effect of PCA given alone (Fig. 4, top). In the two sessions that followed the treatment with HALO and PCA, 24 and 48 h later, the ICSS rate had returned but at depressed levels.

Pretreatment with HALO at a dose of 0.5 mg/kg 30 min before PCA also suppressed ICSS, but the effect now lasted 9 h, with partial recovery of ICSS appearing in the last 3 h of the session (Fig. 4, bottom).

*Chlorimipramine: Thresholds and Stimulus Discrimination*

The IP injection of CHLOR at a dose of 15 mg/kg led to a slight attenuation of the ICSS rate but did not alter the ICSS threshold (Fig. 5, top, $n = 5$). The lowered ICSS rates were not significantly different from controls, but their occurrence at each intensity above threshold indicates that the effect was consistent.

The coadministration IP of CHLOR 15 mg/kg and AMPH 2 mg/kg reversed the effect of CHLOR given alone (Fig. 5, bottom). The ICSS rates now increased, and the ICSS threshold decreased, but the effect on each measure was small although consistent at each current intensity. The addition of AMPH to the treatment prevented the depressant effect of CHLOR given alone.

The effects of CHLOR alone and of the combined treatment with AMPH are illustrated in Fig. 6. When the serotonin uptake inhibitor was injected by itself (top), it depressed the ICSS rate and increased the ICSS threshold, but it did not interfere with the discrimination of the current intensities. The effect was most pronounced in the first 4 h after the injection, with recovery almost complete at 10 h after the injection.

When CHLOR was injected in combination with AMPH, there was a slight attenuation of ICSS in the first h after the treatment, occurring concurrently with a deterioration of stimulus discrimination, but this was followed by an increase in the ICSS rate and a lowering of the ICSS threshold (Fig. 6, bottom). The ICSS rate increase was at peak effect 3 to 4 h after the injection, but discrimination of stimulus intensities was not affected. The effects of the combined treatment had worn off 8 h after the injection; at that time there was a slight decrease in the rate at the peak current intensity.

*AMPH: Time Course, Threshold, Stimulus Discrimination*

Although the facilitation of ICSS by AMPH in drug-naive subjects is well established, it seems important to test for the facilitatory effects of the stimulant alone, given that it was combined with the serotonergic agents in some of the tests.

The time course of the effects of AMPH, 2 mg/kg IP, was determined in drug-naive subjects self-stimulating for a single, optimal current intensity. The first treatment with the stimulant resulted in a three- to fourfold increase in the ICSS rate, with a peak effect observed 2 h after injection (Fig. 7, top). After the peak effect, the ICSS rate declined rapidly, reaching control levels at 4 h after injection, declining still further during the next 4 h, and then returning to the control level 10 h after the injection and remaining at that level until the session ended. The stimulant had a biphasic effect, with each phase of approximately equal duration.

A second treatment with AMPH, at the same dose and given 7 days later, replicated the biphasic effect (Fig. 7, bottom). Now, however, the increase in the ICSS rate seen in the first phase was not as large as after AMPH I, possibly because the control rate for AMPH II was higher than the control rate for AMPH I, and the attenuation in the ICSS rate in the next phase was deeper and longer lasting than after AMPH I. AMPH II produced a biphasic response, like AMPH I, but the magnitude and duration of the second phase were potentiated. AMPH II had residual effects as shown by the depressed ICSS rates at 24 and 48 h after injection (Fig. 7, bottom).

The effects of AMPH on the ICSS threshold and stimulus discrimination were investigated in subjects tested with the descending stimulus strains. In these subjects, AMPH lowered the ICSS threshold during the first 3 h of the session (Fig. 8, top left, $p < 0.001$, $n = 7$) but not during the last 6 h of the session (Fig. 8, top right). The ICSS rates increased at threshold and at all the intensities above threshold, although peak effect was seen at the next to the highest intensity (Fig. 8, top left).

An example of the effects of AMPH on ICSS behavior tested with descending trains shows that in the first 2 h after the injection, gross motor activity increased as reflected by abnormally high response scores during extinction and when the current intensity was low (Fig. 8, bottom). Furthermore, AMPH increased the ICSS rate at the highest intensity, but

FIG. 3. Example of acute and chronic administration of P-chloramphetamine PCA 5 mg/kg given IP, on self-stimulation (SS) in a subject trained to respond for hypothalamic stimulation made available in the form of descending current intensities, starting with peak intensity and stepping down by 20 $\mu$A each 10 min until 10 min at zero intensity had elapsed (extinction), when a new cycle with a descending train started. The data are shown for the first 10 h of the 13 h session. The control values for PCA I represent the mean SS response rate in the four sessions preceding the drug treatment; for PCA II, the mean response rate in sessions 5 and 6 after PCA I (PCA II injected on day 7 posttest); and for PCA III coadministered with amphetamine (AMPH), 2 mg/kg given IP, the mean SS rate in sessions 5 and 6 after PCA II (PCA III injected on day 7).

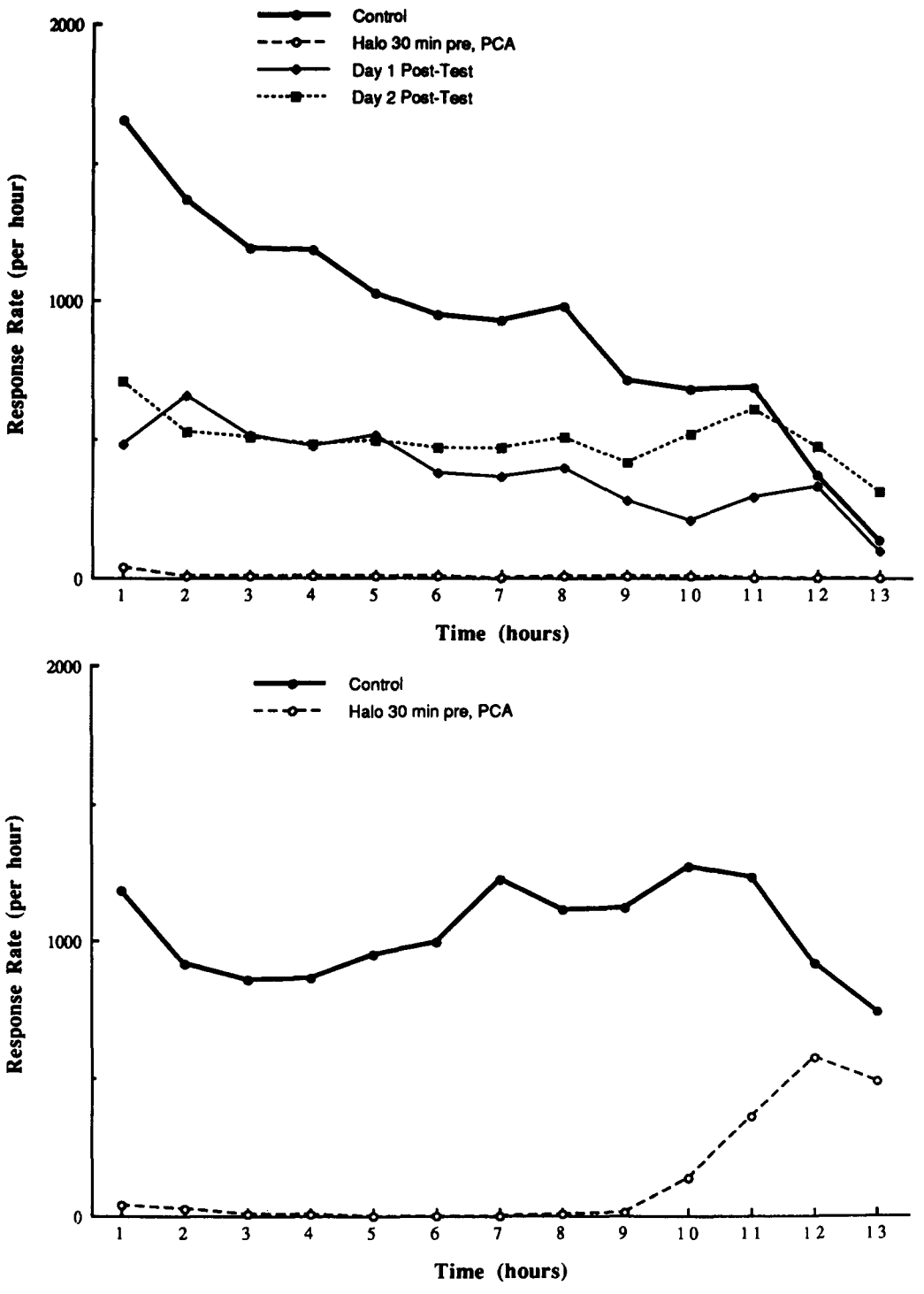



FIG. 4. Haloperidol (HALO) pretreatment affects the response to P-chloramphetamine (PCA) in subjects tested at the peak current intensity. Top: HALO was injected IP at a dose of 1 mg/kg 30 min before PCA, 5 mg/kg given IP ($n$ = 5). Bottom: HALO was injected IP at a dose of 0.5 mg/kg 30 min before PCA, 5 mg/kg given IP ($n$ = 3). Pretreatment with the neuroleptic blocked the facilitation induced by PCA (compare with Fig. 2) and, in addition, suppressed self-stimulation (SS). This effect was long lasting, as shown by the SS rates being depressed on days 1 and 2 posttest.

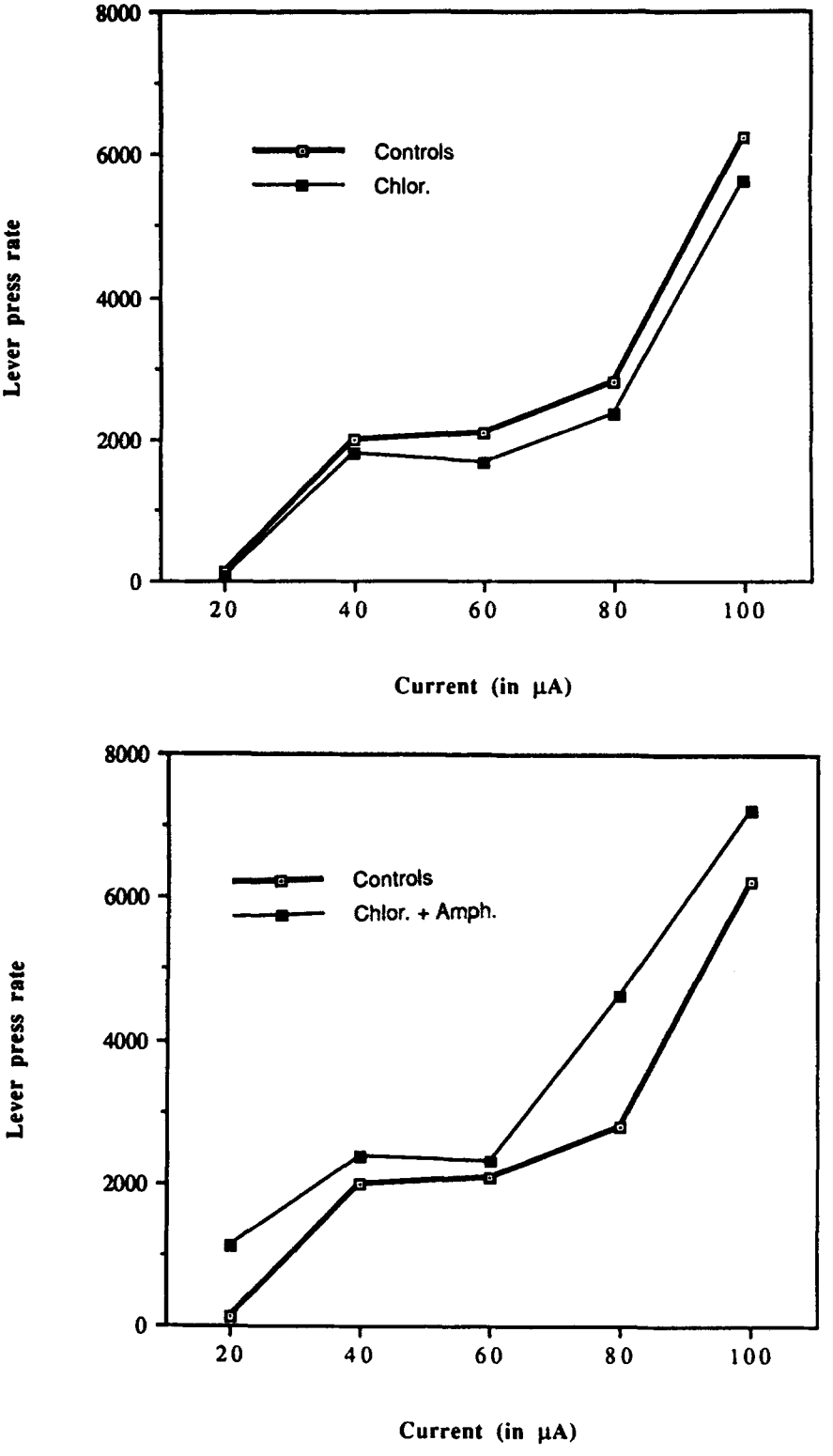



FIG. 5. Chlorimipramine (CHLOR), 15 mg/kg given IP, influences self-stimulation (SS) in subjects tested with descending stimulus trains. Top: CHLOR for the last five current levels did not alter the SS threshold but slightly depressed the SS rate at the current intensities above threshold ($n$ = 5). Bottom: coadministration IP of CHLOR 15 mg/kg and amphetamine (AMPH) 2 mg/kg ($n$ = 5) counteracted the effect of CHLOR: the SS response was above control at each current intensity and the threshold of SS was lower than in the control sessions. However, the dramatic increases seen with AMPH alone were not seen.

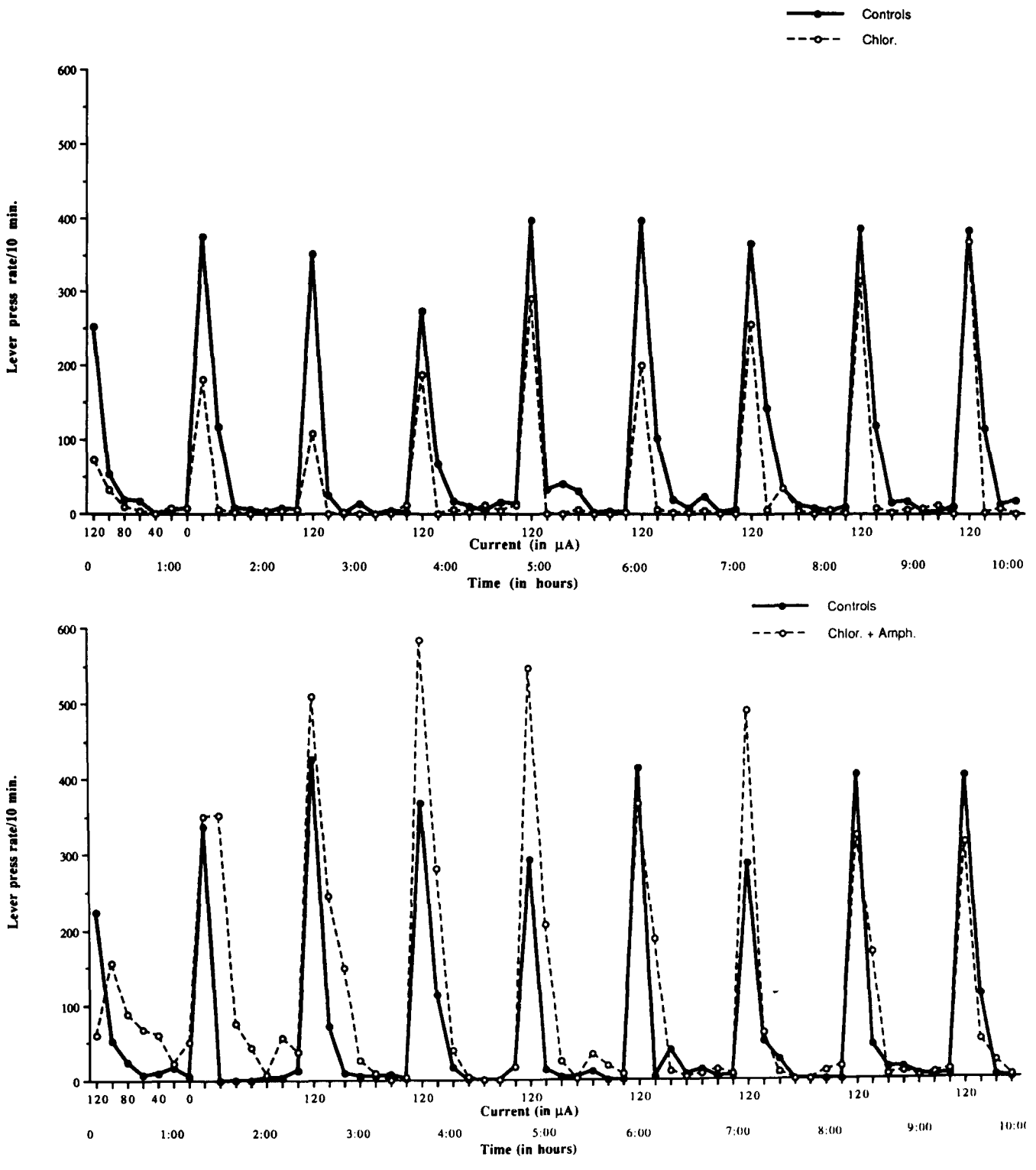



FIG. 6. Example of chlorimipramine (CHLOR), 15 mg/kg given IP, and CHLOR coadministered with amphetamine (AMPH), 2 mg/kg given IP, in a subject tested with descending stimulus trains. Top: CHLOR attenuated self-stimulation (SS) at the intensities above threshold and raised the SS threshold. Bottom: combination of CHLOR and AMPH reversed the effect seen with CHLOR, lowering the SS threshold, increasing the SS rate at the peak intensity, and inducing an increase in motor activity (during extinction) the first hour after injection.

only during the first hour. Discrimination of current intensity had returned to the control level 3 h after the injection of the stimulant, but at that time, the ICSS rate at the higher intensities was depressed and remained so until the end of the session. The ICSS rate was also depressed in the next session, but 72 h after the injection, the ICSS threshold, rate, and current discrimination were at the control level.

## DISCUSSION

PCA produced a facilitation of ICSS that lasted longer than the facilitation induced by AMPH and was in sharp contrast to the mild attenuation induced by CHLOR or to the long-term blockade of ICSS induced by fenfluramine which we reported previously (40). The findings also show that the facilitation was blocked by treatment with the neuroleptic HALO whose depressant effect on ICSS is ascribed to its capacity to block the DA receptor (55,57). The results with HALO are interpreted to mean that the PCA facilitation of ICSS depended on the activation of the DA receptor.

The findings with PCA also show that the facilitation was delayed for a few hours with the first treatment, that the delay was shorter with the second treatment, and absent with the third treatment given in combination with AMPH. Thus, chronic PCA administration potentiated the facilitation seen after acute PCA and at the same time reduced the latency of the facilitatory response. PCA also had effects that extended beyond the drug session, as shown by ICSS rates below control rates 24 and 48 h after the treatment.

Chronic PCA injections, at a dose of 5 mg/kg, had effects that were opposite to those seen after chronic fenfluramine injected at a dose of 20 mg/kg (40). With fenfluramine, ICSS was blocked during the drug session and the session that followed 24 h later, and it was still profoundly depressed in most subjects in the sessions given 48 and 72 h after the injection. The long-term effect of acute PCA and chronic PCA was not an absence of recovery and, thus, a permanent cessation of ICSS but, instead, a slightly attenuated ICSS rate compared to the control rate in the drug-naive subject. This is in sharp contrast to the long-term effect of chronic fenfluramine, which was a cessation of all ICSS (40). But this slight attenuation bears some similarity to the long-term effect of AMPH given alone. Here the drug resulted in a facilitatory response seen within the first 2 h of the treatment, then in a gradual return to the baseline ICSS rate over the next few hours, and then in a further decline that was still seen at 24 and 48 h after the treatment. Finally, the results obtained with CHLOR show an attenuation of ICSS that was reversed into a modest facilitation when CHLOR and AMPH were combined. Thus, AMPH blunted the effect of CHLOR, and CHLOR blunted the response to AMPH.

These results, taken together, support the notion that enhancing serotonergic activity (by release of 5-HT with PCA or, as previously reported, with fenfluramine (40) or by inhibiting reuptake with CHLOR) depresses ICSS. The results also support the notion that the facilitation of ICSS seen after PCA but not fenfluramine (40) was, in large measure, due to the agonist-like action of PCA on dopaminergic activity because it could be prevented by pretreatment with HALO and was absent after fenfluramine even though the effects of the two amphetamine substitutes on serotonergic activity were similar. Although PCA is reported to induce the release of DA concurrently with the release of 5-HT, as does fenfluramine, it does not have the neuroleptic-like action of fenfluramine that leads to increased levels of DA metabolites, an effect that can be prevented by pretreatment with DA agonists but not 5-HT antagonists (3,11,12,15,16,19,23,58). Furthermore, PCA does not appear to have the capacity to block AMPH and apomorphine-induced stereotypies, whereas fenfluramine does have such a capacity (44). Therefore, the evidence reported by us earlier (40) that fenfluramine suppressed ICSS during the period of 5-HT release and continued to suppress ICSS during the prolonged period when 5-HT levels in frontal cortex, hippocampus, and caudate were depleted must be viewed as favoring the view that the PCA-induced facilitation of ICSS reflected its agonist-like action on dopaminergic activity.

It seems likely that the modest attenuation of ICSS by PCA immediately after the injection, lasting several hours and delaying the facilitation, was due to enhanced serotonergic activity because it was similar in magnitude to the attenuation seen with CHLOR, a compound inhibiting 5-HT reuptake and, thus, prolonging its synaptic action (14). The fact that the delay became shorter and that the attenuation of ICSS was further reduced after the second treatment with PCA, may have been due to lower amounts of 5-HT being released after the second injection of PCA, the first given 1 week earlier having been highly effective in reducing central 5-HT levels. It, thus, seems that the 5-HT neurons have a capacity to influence the reward function, but apparently that influence is modest.

The facilitation of ICSS by PCA given alone may represent, at the biochemical level, a situation not unlike that described for fenfluramine given in combination with AMPH to twice-treated fenfluramine subjects (40). In that situation, the treatment produced an attenuation of ICSS of short duration followed by a dramatic facilitation that lasted much longer than the normal AMPH response in drug-naive animals. The attenuation of ICSS was interpreted as resulting from enhanced activity in the 5-HT system because fenfluramine treatment leads to 5-HT release. The reason for ICSS now being merely attenuated instead of suppressed and of short duration in the fenfluramine-experienced subjects was interpreted to mean that abnormally low levels of 5-HT were released in these subjects. And in these animals, the prolonged facilitation induced by AMPH was interpreted to mean that the activation of the DA receptor by AMPH (7,36,59) occurred in an environment in which the normal tonic inhibitory modulation of dopaminergic activity by the 5-HT system (33,41–43,56) was deficient.

A somewhat similar situation may have been present after a single treatment with PCA. It is reported that this compound causes widespread damage in the 5-HT pathways even after a single treatment of the rat with a low dose (5 mg/kg) (21, 29,52–54). On the other hand, a low dose of fenfluramine (5 mg/kg) may not be toxic unless given chronically, moderate to high doses (10 to 20 mg/kg) being required to induce damage in the 5-HT pathways (1,20,35). It is possible, therefore, that differences in the extent of damage induced by the two drugs explain the different effects of the two drugs on ICSS, PCA producing a biphasic response when injected alone, whereas fenfluramine producing a blockade of ICSS in all subjects during the same time course. Treatment with PCA may have resulted in a situation in which 5-HT levels were more rapidly and more drastically depleted than in the situation induced by fenfluramine. In the PCA situation, DA released endogenously by hypothalamic stimulation would be less stringently regulated by the behaviorally inhibitory regulation of the 5-HT pathways and, thus, DA would now be as efficacious as if AMPH had been coadministered.

It is also possible that the prolonged facilitation seen with

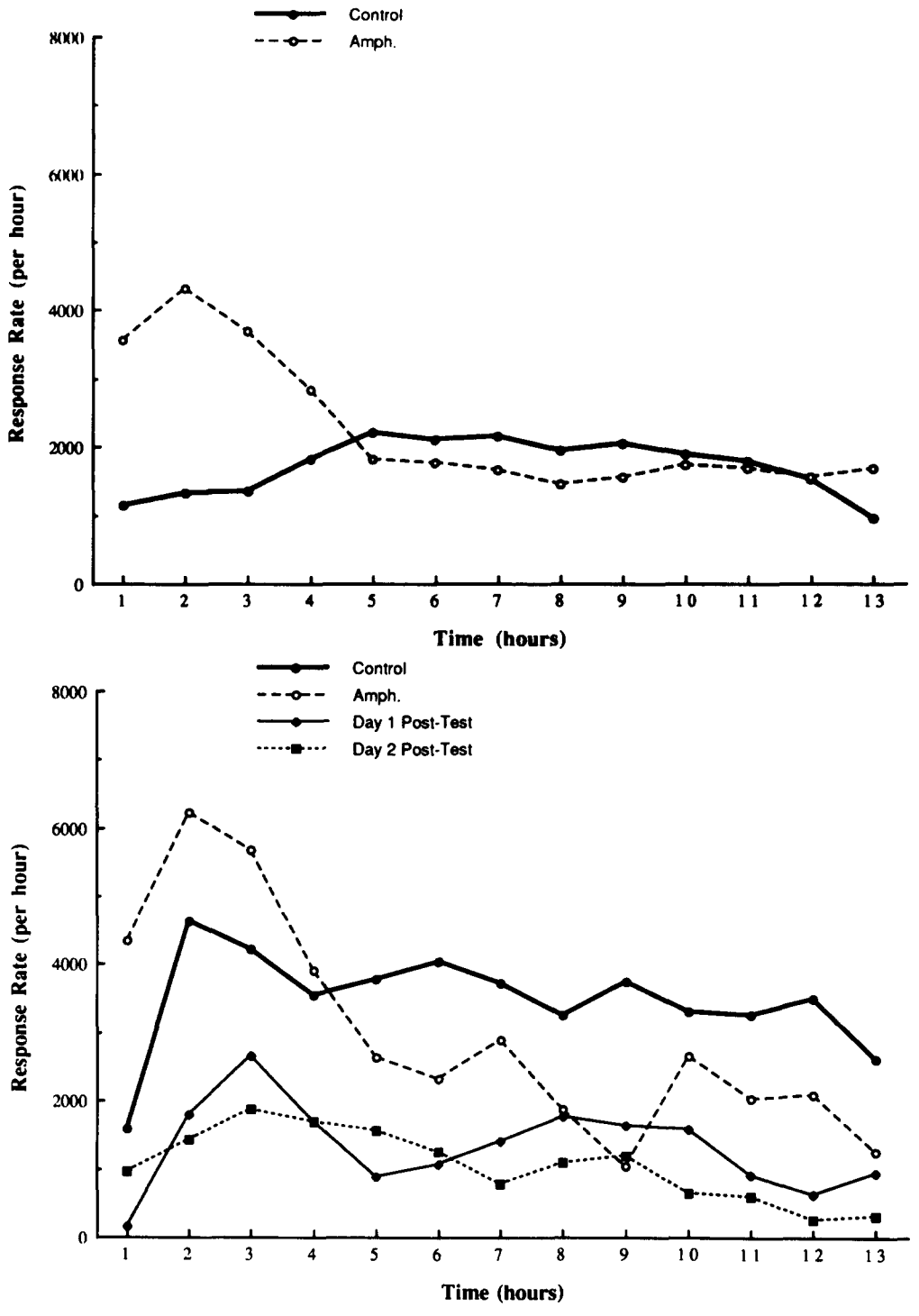



FIG. 7. Amphetamine (AMPH), 2 mg/kg given IP, influenced self-stimulation (SS) in subjects tested at peak current intensity. Top: AMPH facilitated SS in the first 1 to 2 h after injection, then depressed SS during the next 5 h ($n$ = 7). Bottom: example of AMPH in the drug test session and in sessions given on days 1 and 2 posttest. AMPH facilitated SS early in the session, then depressed it. The response rate was still depressed 48 h after the injection.

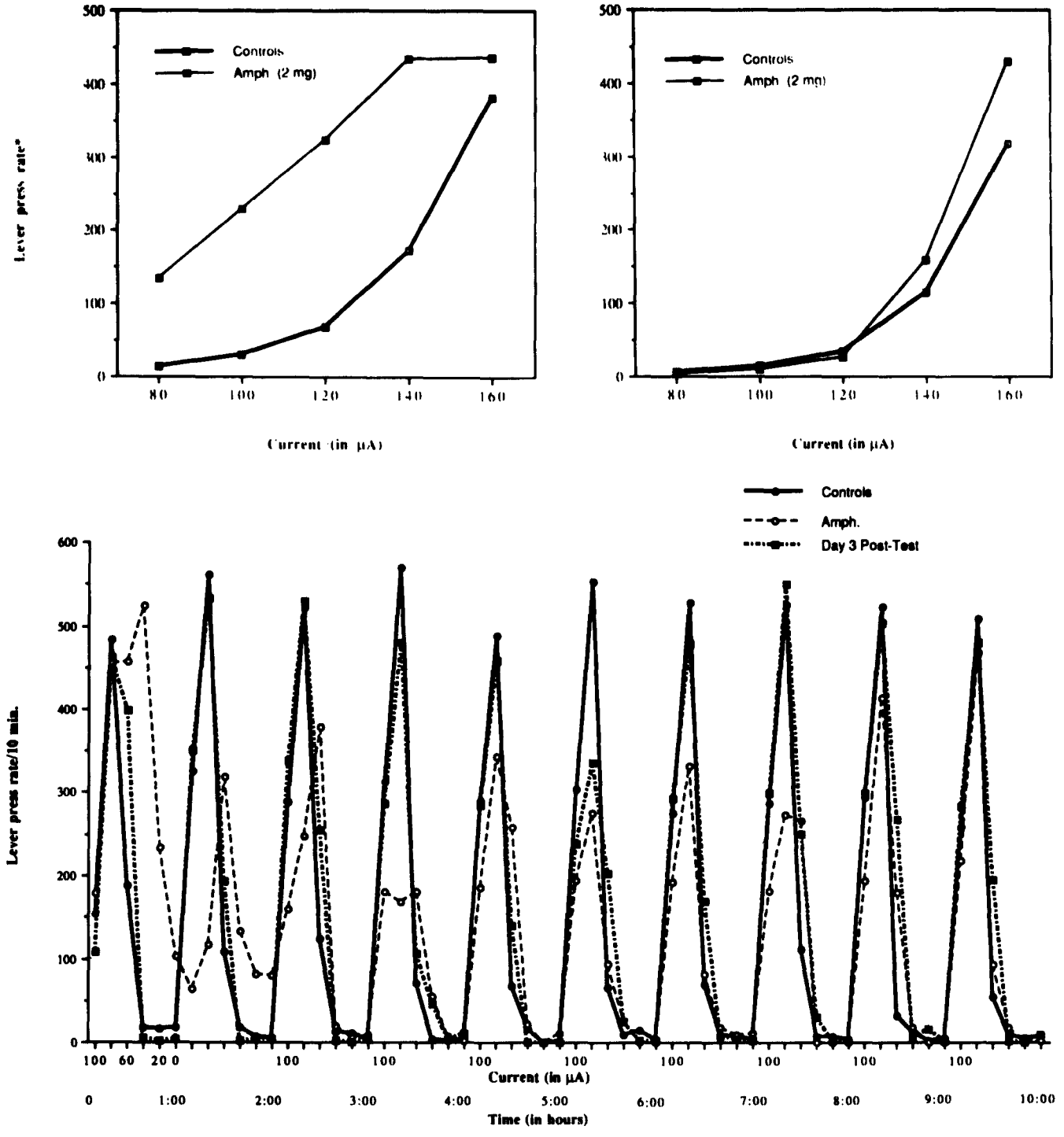



FIG. 8. Amphetamine (AMPH), 2 mg/kg given IP, influenced self-stimulation (SS) in subjects tested with descending stimulus trains. Top left: in the first 3 h of the 13-h session the treatment lowered the SS threshold and increased the SS rate at each current intensity ($n$ = 7). Top right: in the last 6 h of the 13-h session, the threshold had returned to the control level but the SS rate was still facilitated at the peak current intensity made available ($n$ = 7). Bottom: example of the effect of AMPH shows the early facilitation of SS, the lower threshold, and the increase in motor activity (responses during extinction and at intensities below threshold). Full recovery had not occurred by day 3 posttest.

PCA injected alone, even the first time, was due to its having agonist-like actions on DA transmission in addition to serotonergic inhibitory regulation of the reward function being impaired as a result of the toxicity of the treatment. By the same token, the lack of facilitation after fenfluramine alone (40) must have reflected the neuroleptic-like action of the drug on DA transmission rather than its capacity to damage the 5-HT pathways.

The rate of ICSS at 24 and 48 h after the first and the second treatment with PCA was lower than the control rate, yet in the drug session, ICSS was facilitated. This long-term effect of PCA was similar to the attenuation of ICSS seen 24 and 48 h after treatment. The attenuation of ICSS that followed the facilitatory response induced by AMPH might be viewed as expressing the low levels of DA present 24 and 48 h after treatment owing to the massive release of DA produced by the combined actions of the drug (59) and brain stimulation in the medial forebrain bundle. With PCA, a similar situation might have been induced by the massive release of DA, this time induced by the combined actions of PCA and rewarding brain stimulation. In both situations, and perhaps because the ICSS sessions were of such long duration, synthesis of DA could not keep up with utilization and, therefore, ICSS was attenuated in the session 24 h after the drug treatment. Perhaps if the subjects had not been given a ICSS session at 24 h after the treatment, regardless of whether the treatment was AMPH or PCA, recovery to ICSS might have been complete.

In conclusion, the results of this study indicate that the 5-HT and the DA systems interact over the long term. The degree of regulation exerted by either system seems to depend on several factors, with the actions of the drugs determining the availability of the transmitter and the availability for binding to the receptor being of primary importance. For brain stimulation reward, activation of the DA system seems to take precedence over the activation of the 5-HT system.

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