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The Effect of Schedule Removal on the Maintenance of Heroin Self-Injection

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MADDEN, C., T. P. S. OEI AND G. SINGER. *The effect of schedule removal on the maintenance of heroin self-injection.* PHARMAC. BIOCHEM. BEHAV. 12(6)983–986, 1980.—The present study investigated the effect of schedule removal on the maintenance of heroin self-injection in 80% reduced body weight Wistar rats. During the acquisition phase, 42 animals were subjected to a fixed time 1 min food delivery schedule and were allowed to self-inject either heroin or saline for 10 days. During the maintenance phase (Days 11–15), animals in both the heroin and saline conditions were randomly allocated to schedule, no schedule, and no schedule plus food groups. Infusion rates, hot plate response latencies, and food intake were used as dependent measures to monitor differences between groups. The results revealed that schedule removal disrupted, but did not extinguish, heroin-seeking behaviour.

Schedule Heroin Self-injection Analgesics

EXPERIMENTAL findings with naive rats confirm the importance of physiological and environmental factors in the acquisition of drug self-injection behavior. A three-factor model of schedule-induced self-injection (SISI) behavior has been demonstrated, which is applicable across a range of drugs, including nicotine, alcohol, methadone and heroin [3, 5, 8, 9, 10].

The SISI procedure maximizes drug intake due to a combination of food deprivation to 80% of free-feeding body weight (physiological state), and a fixed time 1 min (FT1) food delivery schedule (environmental factor). The rate of self-injection is marginal when either of these factors is omitted. Alternatively, when the pharmacological factor is omitted, as in saline self-injection, animals will not acquire a reliable level of self-injection, regardless of the presence or absence of the physiological and/or environmental factors previously mentioned.

Further indication of the relative pharmacological affects of different drugs is evident when various drugs are made available to animals which have been subjected to identical physiological and environmental conditions. For example, naive rats will attain a higher rate of self-injection when heroin is available than will rats having access to methadone [8,9].

While the acquisition of self-injection behavior has been shown to be enhanced by physiological and environmental variables, the influence of these variables on the maintenance of drug intake is not clear. The present experiment was designed to investigate the effect of schedule removal on the maintenance of heroin self-injection in naive rats. Recent findings [8, 9, 10] suggest that heroin dependence has occurred within a ten day acquisition period, using the SISI procedure. Thus schedule removal after this acquisition period ought not to effect drug intake.

METHOD

Animals

Forty-two naive male albino Wistar rats were reduced to 80% of free-feeding body weight (340–390 g) and housed individually in temperature controlled conditions (23±1°C) with a 12 hour light-dark cycle.

Each animal was anaesthetized with an IP injection of pentathesin, and a polythene (SP 28) catheter was surgically implanted into the right jugular vein. Catheters were held in position by leather jackets.

Apparatus

The apparatus was identical to that described in Oei *et al.* [8,9]. Briefly, an operant box, containing a bar as well as a food pellet dispensing unit with FT 1 min delivery, comprised the drug-taking environment. The bar triggered the delivery of 0.07 ml solution via a syringe infusion pump (Sage Instruments, Model 341) into a polythene catheter. The catheter was connected to a flexible swivel system which allowed the animals free movement in the operant box. The infusion system allowed only one infusion per 5 sec interval. Infusion frequency was recorded on a continuous graph recorder. Food delivery consisted of Noyes (45 mg) food pellets.

Procedure

On recovery from surgery (2 days post-operative), animals were given a daily 1 hour session in the operant box. An initial priming dose was administered prior to each experimental session.

Freshly prepared diacetylmorphine hydrochloride (0.1 mg/kg) (Victoria Health Department) was available to 21

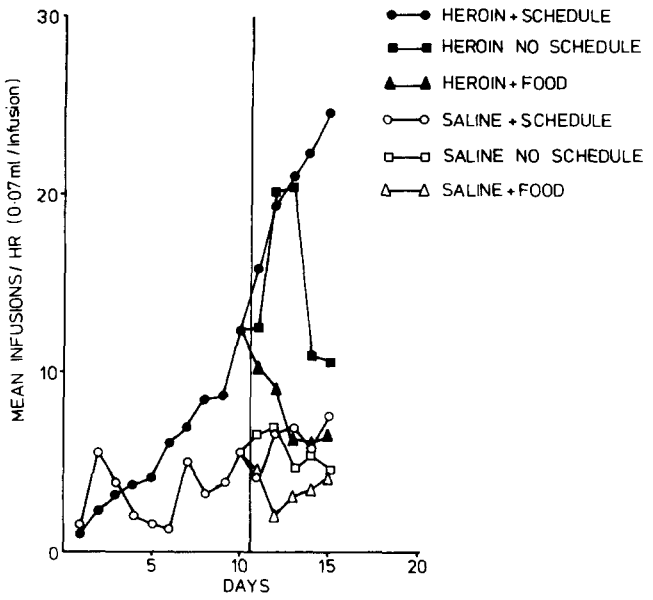

FIG. 1. Mean number of self-infusions/hr for the control and experimental animals during acquisition and maintenance periods.

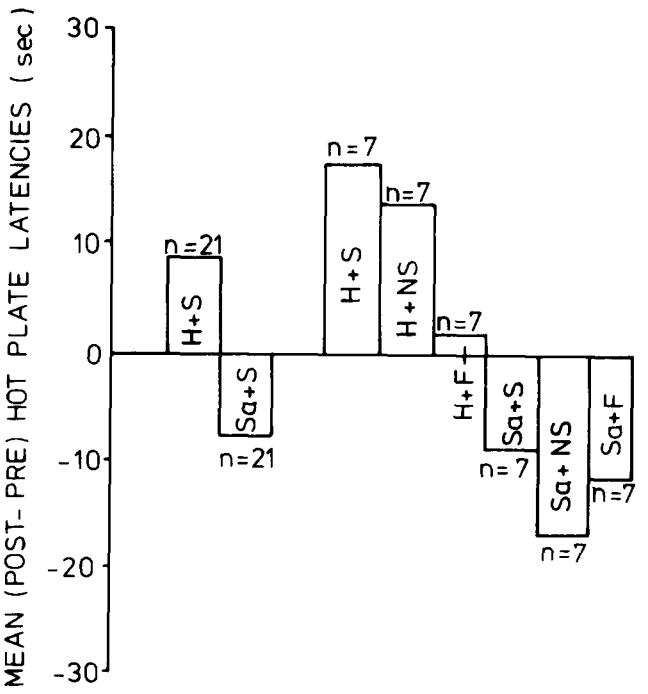

FIG. 2. Mean (Post-Pre) hot plate latencies in seconds for the control and experimental animals for Days 1, 3, 5, 7, 9 during the acquisition period and for Days 11, 13, 15 during the maintenance period. (H=Heroin; Sa=Saline; S=Schedule; NS=No Schedule; F=Food).

animals and 0.9% saline was available to the remaining 21 animals. All animals were exposed to the FT-1 food delivery schedule during the acquisition stage of the experiment (Days 1–10).

During the maintenance stage (Days 11–15), animals in both the heroin and saline conditions were randomly allocated to the following 3 groups: schedule; no schedule; no schedule plus food. In the schedule groups, 60 Noyes pellets were delivered to the animal at the rate of 1-min. Food pellets were not available to animals in the no schedule groups. For animals in the no schedule plus food groups, 60 pellets were placed in the food bowl prior to each session. All three groups in both conditions were maintained at 80% of free-feeding body weight.

All animals were given the hot plate (paw-lick) latency test (45°C) immediately before and after each alternate experimental session. The number of food pellets remaining in the bowl at the end of each session was recorded.

RESULTS

Infusions

The overall means of infusions/hr for the animals self-injecting heroin and saline over the 15 days are shown in Fig. 1. A two-way ANOVA, with repeated measures on days, was applied to the data for Days 1 to 10. The results revealed significant main effects for drug treatment, $F(1,40)=6.809$, $p<0.001$; for Days, $F(9,360)=8.633$, $p<0.001$; and for the interaction of Drugs and Days, $F(9,360)=4.161$, $p<0.001$; indicating that the rate of self-injection for heroin was significantly faster than that of saline.

A two-way ANOVA with repeated measures was applied to the saline data for Days 11 to 15. The results showed no significant differences between the three groups. Since there was no significant differences between the saline groups, the data were combined for comparison with the heroin groups. The results of a two-way ANOVA with repeated measures revealed significant main effects for treatment groups, $F(3,38)=6.321$, $p<0.01$; for the interaction of treatment groups and Days, $F(12,152)=2.587$, $p<0.01$; indicating that the rate of self-infusion for the treatment groups was significantly different. Figure 1 shows that the rate of heroin infusion for the animals in the heroin plus food condition fell to almost the control levels. Post hoc Scheffe analysis at Days 14 and 15 showed that only the animals in the heroin and schedule condition self-injected significantly more heroin than the saline controls.

Hot Plate

The mean (Post-Pre) hot plate latencies are presented in Fig. 2. A student t-test was applied to the data of the first 10 days. The result showed that heroin animals took longer to respond to the hot plate test than the saline animals ($t=9.606$, $p<0.001$). A one-way ANOVA for Days 11–15 also revealed significant differences between groups, $F(5,36)=4.256$, $p<0.01$. Post hoc Scheffé analysis showed that only animals in the heroin plus schedule and heroin with no schedule groups took longer than the saline groups to respond to the hot plate test.

Food Intake During Experiment

Behavioral observations indicated marked differences in activity between the heroin and saline groups during the acquisition stage of the experiment. Unlike the saline group, animals in the heroin group demonstrated immobility and 'freezing', often in mid-posture, for up to ten minutes after initial self-injections during the first 2-3 days of the experiment. The consequent lack of food intake during these periods of immobility can be seen in Fig. 3.

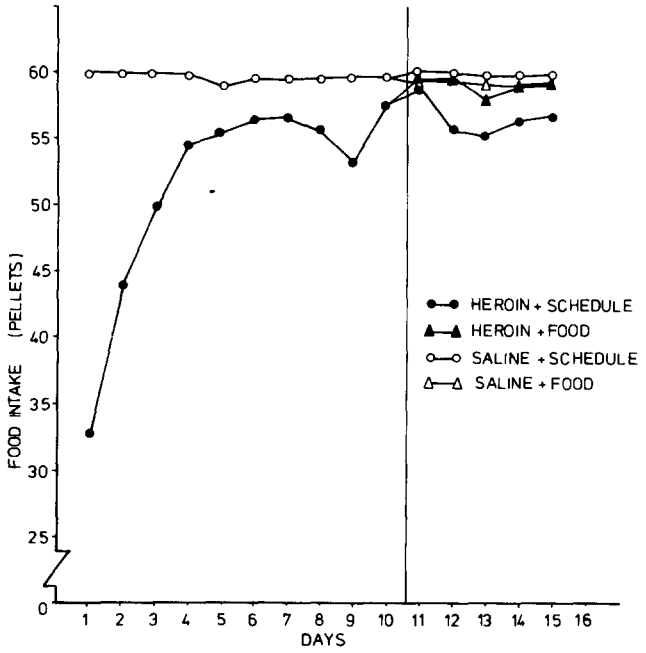

FIG. 3. Mean number of food pellets consumed for the control and experimental animals during acquisition and maintenance periods.

A two-way ANOVA with repeated measures was applied to the data for Days 1–10. Significant main effects for drugs, $F(1,40)=20.501$, $p<0.001$; for days, $F(9,360)=7.410$, $p<0.001$; and for the interaction of drugs and days, $F(9,360)=7.986$, $p<0.001$; were found, showing that heroin animals consumed less food pellets than the saline animals.

No significant difference between heroin and saline groups was found for Days 11–15.

DISCUSSION

The gradual daily increase in infusion rate for the heroin group during the 10-day acquisition period (Fig. 1) complies with the pattern of chronic opiate intake reported in previous studies [8, 9, 11, 12].

Once the pattern of heroin-seeking behavior had been established, schedule removal, either with or without food, led to a decrease in heroin intake. Indeed, on Days 11–15, drug intake for the heroin plus food group was only marginally higher than the saline control groups. This finding appears to be due to food availability competing with drug reinforcement, since the animals in the heroin plus food group were observed to consume all the pellets in the food bowl prior to exhibiting drug-seeking behavior. In contrast to the animals in the heroin plus food group, animals in the heroin plus schedule and heroin with no schedule groups, bar-pressed for drug immediately on being placed in the operant box. However, heroin with no schedule animals, unlike the heroin plus schedule animals, demonstrated a fluctuating pattern of drug infusion (Fig. 1). This effect may well be due to cessation of food (pellet) delivery. For, just as food provides a competing reinforcer to an animal, removal of food places the animal in a situation of extinction. In short, heroin-seeking behavior may be confounded with food-seeking behavior.

It is also evident from the hot plate data that a learning effect is present. Mean post-pre latencies for the saline groups reveal negative scores (Fig. 2). It is likely that an association (classical conditioning) between the paw-licking response and removal from the hot plate allowed operant avoidance behavior to develop. That learning factors, and in particular, environmental cues, can influence hot plate latencies is well established [1, 2, 4]. In an attempt to minimize the influence of learning during the current study, hot plate testing was restricted to every second test session. Notwithstanding this, positive latency scores for the heroin groups revealed an analgesic effect. Only the heroin plus food group (during schedule removal) showed no analgesic effect.

The pattern of food (pellet) ingestion (Fig. 3) suggests development of tolerance to the depressant effects of heroin on motor activity. The development of tolerance to the depressant effects of opiates has been well documented [6,7]. In the first 2–3 days of the acquisition stage of the current experiment, animals in the heroin groups demonstrated reduced motor activity following drug infusion. However, motor activity and infusion rate increased over the ten-day acquisition period. This depression of motor activity during the first 3 days resulted in reduced pellet ingestion. However, tolerance to the depressant effects of heroin, and the concomitant increase in pellet ingestion, was evident from Days 4–10.

Collectively, the results of the current study show that the environmental conditions in which heroin dependence is established are important in maintaining a consistent pattern of heroin self-injection. Schedule removal disrupts but does not extinguish drug intake. However, while such environmental conditions (schedule effects) may be of paramount importance in the acquisition of heroin-seeking behavior, others (conditioned stimuli) may be salient for the maintenance of heroin-seeking behavior.

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