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Concurrent Heroin Self-Administration and Intracranial Self-Stimulation in Rats

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GERBER, G. J., M. A. BOZARTH, J. E. SPINDLER AND R. A. WISE. *Concurrent heroin self-administration and intracranial self-stimulation in rats.* PHARMACOL BIOCHEM BEHAV **23**(5) 837–842, 1985.—In a two-lever testing chamber, rats lever pressed for lateral hypothalamic brain stimulation or intravenous heroin reinforcers on a concurrent FR1 FR1 schedule of reinforcement. Responding for stimulation did not alter the rate of heroin self-administration, and responding for heroin caused increased responding for stimulation. Discontinuing heroin injections, or administering 3 mg/kg of naloxone, disrupted responding for both reinforcers, while changing the unit dose of heroin did not appreciably affect response rates for stimulation. This experiment demonstrates that rats are able to lever press during the period between successive self-administered heroin infusions, suggesting that the pausing normally seen between infusions is not due to debilitation, stereotyping, or sedation.

Intracranial self-stimulation Intravenous self-administration Concurrent schedules Heroin Naloxone Drug reinforcement

OVER the range of unit doses that is usually studied, rats self-administer intravenous injections of psychomotor stimulants and opiates at rates which are inversely proportional to the unit drug dose [11,13]. Yokel and Pickens [17,18] have demonstrated that rats closely regulate hourly drug intake in a manner which is predictable from the kinetics of amphetamine metabolism. Rats respond for d-amphetamine when the blood level of the drug falls below 0.2 μg/ml. This finding applies across variations in unit dose, response requirements, and rate of stimulant metabolism [18]. One possibility is that rats respond to obtain amphetamine whenever the blood level of the drug falls below some threshold concentration, presumably at a central site of stimulant action.

Two other possibilities have been suggested. First, responding for drug reinforcers may be limited by aversive or motor effects of high blood levels of drugs. Oral stereotypes are seen in rats during stimulant and opiate self-administration [17]. Perhaps these drug-induced head-wagging, licking, and chewing movements are incompatible with lever pressing, and perhaps they, rather than drug satiation, limit drug intake. In the case of psychomotor stimulants, this explanation of the control of drug intake can be ruled out, because rats have been shown to be capable of lever-pressing at high rates for brain stimulation reinforcement during the period between normally spaced drug-reinforced responses [15]. The slow, regularly spaced pattern of responding for opiate reinforcers may, nonetheless, be the result of response debilitation; perhaps the frequency of opiate self-administration is limited by sedative or other side effects of the opiates which are not shared by stimulants.

This issue is resolved in the present study by the same strategy used in the case of psychomotor stimulants. Rats with concurrent access to opiate reinforcement and brain stimulation reinforcement were found to lever press at higher than normal rates for brain stimulation while responding for normally spaced opiate injections.

METHOD

Animals

Male Sprague-Dawley rats weighing 350 g were implanted with 0.25 mm monopolar stainless steel electrodes in the lateral hypothalamus using stereotaxic procedures. The incisor bar was 3.2 mm above the interaural line; the coordinates were 0.8 mm posterior to Bregma, 1.5 mm lateral to the sagittal suture, and 8.5 mm ventral to the skull surface. Electrode placements were verified histologically. After stabilization of self-stimulation responding (see below), standard procedures were used to catheterize the jugular vein using a silastic and polyethylene catheter [14] which passed subcutaneously to the electrode assembly on the animal's head.

Training Procedure

Following recovery from surgery, the rats were tested for self-stimulation in a two-lever box with the right lever covered. Each response on the left lever delivered a 0.5 sec train of 60 Hz sine wave stimulation. Each rat was tested at a stimulation intensity sufficient to maintain steady responding for 1 hr. This current intensity was used in all subsequent testing and ranged between 20 and 40 μA (mean=30 μA). Rats were tested daily in six-hour sessions until the day-to-day variation in responding was less than 20% (about one

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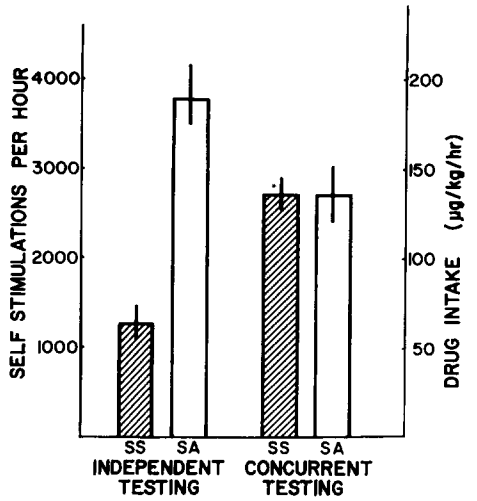

FIG. 1. Histograms showing means and standard errors of the mean (N=9) for rates of lateral hypothalamic self-stimulation (SS) and intravenous heroin self-administration (SA) under independent and concurrent testing conditions. Current intensities ranged between 22 and 40 μA. The heroin unit dose was 30 μg/kg/injection. Self-stimulation rates increased during concurrent testing ($p<0.001$). The decrease in self-administration during concurrent testing is not statistically significant ($p>0.20$).

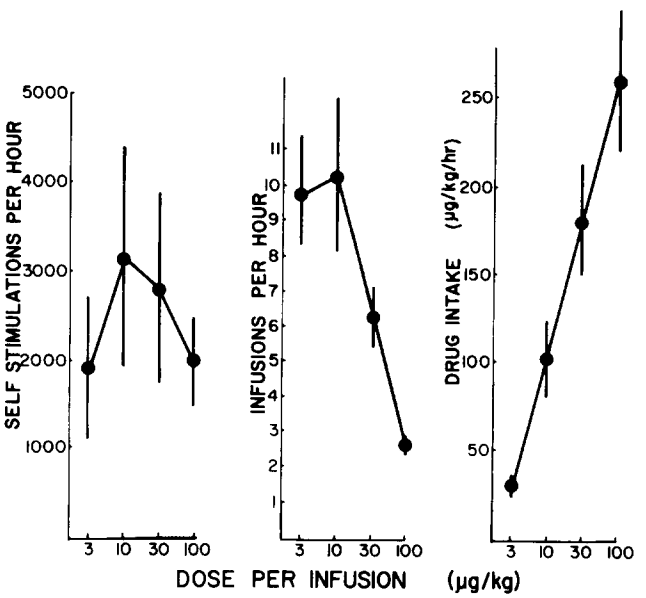

FIG. 2. Means and standard errors of the mean, for 5 sessions, are shown for each unit dose of heroin tested. Self-stimulation results are shown on the left panel, infusions on the center panel, and drug intake on the right panel (N=7). Stimulation intensity was constant throughout testing.

month). Chronic catheters were then implanted into the jugular vein.

Procedures

Experiment 1. Self-stimulation testing continued for several weeks during which a non-contingent injection of heroin (10–300 μg/kg) was delivered during each fourth session. Results of this non-contingent injection procedure were reported previously [6].

Heroin self-administration training was conducted in 6-hr sessions. The rats were first trained to press the right lever in order to self-administer a 30 μg/kg unit dose of heroin in a volume of 0.25 mg delivered over 28 sec. The self-stimulation lever was covered for the duration of self-administration training. Heroin self-administration testing was continued for at least five sessions until day-to-day variation in intake was less than 20%. Rats that failed to meet stability criteria for both self-stimulation and self-administration were discarded.

Rats were then tested in 6-hr sessions with concurrent access to brain stimulation on the left lever, and to 30 μg/kg of heroin on the right lever. A schedule of continuous reinforcement was in effect at all times. Testing continued until the day-to-day variation in responding was less than 20% for both brain stimulation and heroin. Data were collected for 9 rats from the last 5 days of self-stimulation alone, heroin self-administration alone, and concurrent self-stimulation and self-administration.

Experiment 2. A second group of 7 rats was trained on the concurrent self-stimulation and self-administration procedures as in Experiment 1. For these rats, heroin was available in doses of 3, 10, 30 and 100 μg/kg/injection for five sessions each. The sequence of dose testing was 30, 100, 10 and 3 μg/kg/injection for each rat. Saline was substituted for heroin for one session between successive heroin doses. Stimulation intensity remained constant throughout testing.

Experiment 3. Five rats that had been used in Experiment 2 were restabilized for 3 sessions of concurrent self-stimulation and self-administration in which the heroin unit dose was 30 μg/kg. They were then tested in sessions during which the stimulator or the heroin pump were inactivated after 2 hr of the 6-hr sessions had elapsed. Results from the last 4 hr of the sessions were used as data for this experiment.

Experiment 4. Five rats from Experiment 3 were restabilized for three sessions on the concurrent self-stimulation and heroin self-administration schedule (30 μg/kg unit dose) and were challenged with an IP injection of saline or naloxone after 2 hr of the 6-hr session had elapsed. Naloxone was tested at doses of 0.1, 0.3, 1.0 and 3.0 mg/kg.

Experiment 5. Six rats were restabilized on the concurrent self-stimulation and self-administration schedule at a unit dose of 30 μg/kg of heroin. The mean of the last 3 days of testing was used as the restabilization baseline. Either the heroin unit dose or the stimulation current was then changed after 2 hr of the 6-hr session had been elapsed. In separate sessions, current was increased 10 μA above, or decreased 10 μA below the maintenance current, or the unit dose of heroin was doubled (to 60 μg/kg) or halved (to 15 μg/kg) for the last 4 hr of the test session. Each procedure was repeated 3 times and the mean of the 3 determinations was used. Data from the last 4 hr of the restabilization baseline performance were compared to data obtained from the dosage and current intensity change procedures.

Drugs

Heroin hydrochloride (Bureau of Dangerous Drugs of Health and Welfare, Canada), and naloxone hydrochloride

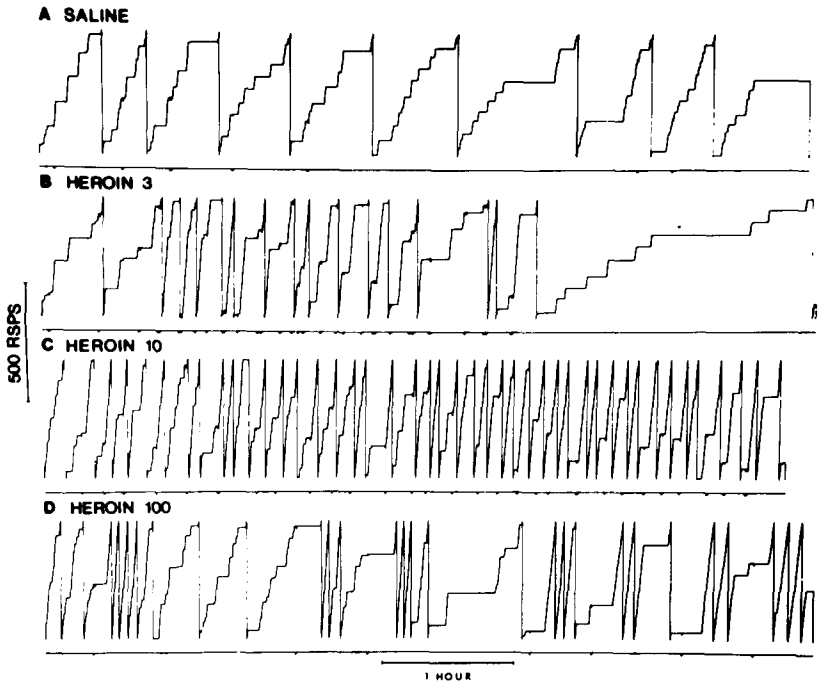

FIG. 3. Cumulative-response records for 6-hr sessions for a rat tested on concurrent self-stimulation and self-administration of saline or three doses of heroin. The unit dose of heroin in μg/kg is indicated on each panel. The response pen was stepped upward by lever presses for stimulation, and deflected downward by lever presses for heroin. The event pen was deflected downward for the duration of each infusion. The response pen reset to the bottom of the excursion after each 500 responses.

(Endo Laboratories) were dissolved in normal saline solution, and were sterilized by filtration. All drug doses are expressed in terms of the salt.

RESULTS

Experiment 1

Given concurrent access to brain stimulation and heroin reinforcement, rats alternated between the two levers and maintained regular patterns of responding for both. Rates of heroin self-administration decreased relative to those occurring under baseline single-lever conditions but the change was not statistically reliable, $t(8)=1.122$, $p>0.20$. Self-stimulation rates were increased more than two-fold, $t(8)=5.56$, $p<0.001$. Results from the last 5 test sessions are shown in Fig. 1.

Experiment 2

Changes in the heroin unit dose produced compensatory changes in drug-reinforced responding. As the unit dose was increased over a 33-fold range, heroin intake increased eight-fold, while the number of infusions per hour decreased four-fold. Self-stimulation rates did not change significantly as a function of these changes in heroin unit dose (Fig. 2). A repeated measures analysis of variance of each rat's 5-session mean self-stimulation response rate under each heroin unit dose condition was not significant, $F(3,18)=2.64$. Response rates decreased markedly on both levers during the saline substitution tests. Cumulative response records from one rat illustrating concurrent self-stimulation and self-administration responding for saline and three doses of heroin are shown in Fig. 3.

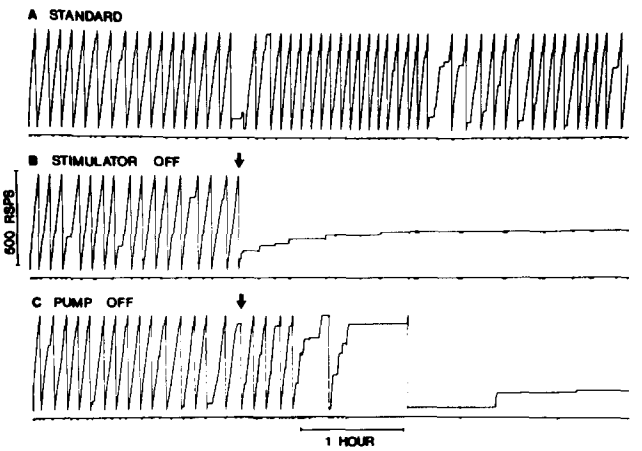

FIG. 4. Cumulative-response records for 6-hr sessions for a rat tested on concurrent self-stimulation and self-administration of 30 μg/kg heroin. Panel A shows a standard session for this rat, Panel B shows the effect of shutting off the stimulator (arrow), and Panel C shows the effect of shutting off the infusion pump (arrow). Details for each record are the same as described for Fig. 3.

Experiment 3

Turning off the stimulator after 2 hr of the 6-hr session had elapsed produced rapid cessation of self-stimulation and

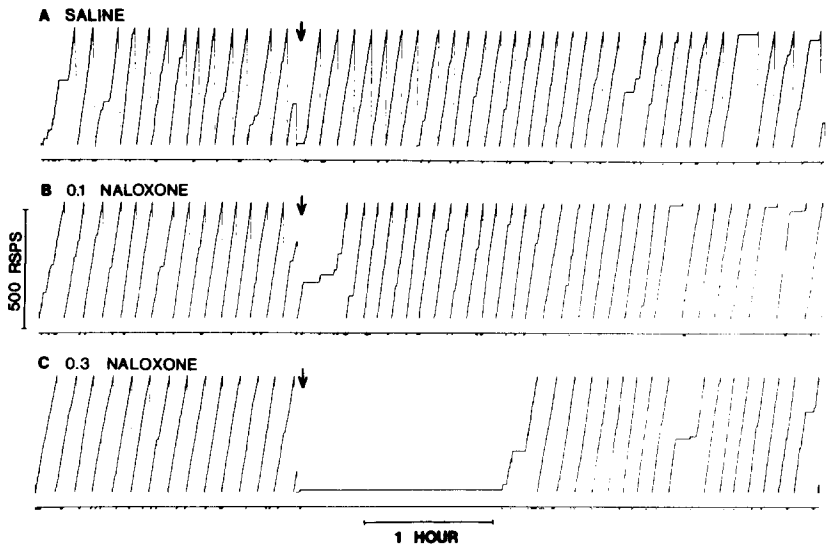

FIG. 5. Cumulative-response records for 6-hr sessions for a rat tested on concurrent self-stimulation and self-administration of 30 μg/kg heroin. IP injections of saline (Panel A), 0.1 mg/kg naloxone (Panel B), and 0.3 mg/kg naloxone (Panel C) were given at the times indicated by the arrows. Higher doses of naloxone suppressed responding for the 4-hr period following injection. Details for each record are the same as described for Fig. 3.

produced a mean 3-fold increase in heroin self-administration. Turning off the syringe pump resulted in an immediate increase in responding on the drug-reinforced lever, with no immediate change in responding on the stimulation lever. Turning off the syringe pump produced cessation of responding on both levers with 30–60 min. This was seen in all animals tested. The cumulative response record for one rat is shown in Fig. 4.

Experiment 4

Naloxone injections given after 2 hours of the 6-hr session, produced disruption of responding for both reinforcers. This is the same effect found when the infusion pump was turned off in Experiment 3. The duration of the response disruption varied as a function of naloxone dose: high doses produced longer periods of response disruption than low doses. The cumulative response record for one rat is shown in Fig. 5.

Experiment 5

Increases or decreases in stimulation current produced no effect on heroin self-administration rates, but a 10 μA increase in the stimulation current produced a 37% increase in self-stimulation rate. Doubling or halving the heroin unit dose, did not appreciably affect rates of self-stimulation. Rates of heroin intake increased 85% when the unit dose was doubled, but were unchanged when the unit dose was halved. Mean percentage changes from baseline performance for the 6 rats in each phase of this experiment are presented in Table 1.

DISCUSSION

The present findings clearly demonstrate periods of non-responding between successive self-administered heroin injections which cannot simply be attributed to drug-induced motor impairment. Motor impairment may be responsible for a portion of the observed pauses in both self-administration and self-stimulation when the 100 μg unit dose of heroin was tested. However, in the cases of the 3 and 10 μg unit doses, pauses in self-administration were usually associated with periods of active self-stimulation. In these cases, pauses in self-administration cannot be attributed to drug-induced impairment of lever pressing. In the 3 and 10 μg conditions, animals are capable of lever pressing for more drug but fail to do so. While high doses of opiates appear to cause some degree of motor impairment, this cannot explain all the behavior occurring between responses for drug. In the 100 μg unit dose condition as many as 3000 responses for stimulation were made in periods between responses for drug. While periods of non-responding may reflect motoric incapacitation, these periods of non-responding were shorter for brain stimulation than they were for drug injections. Thus some factor above and beyond incapacitation must account for the spacing of drug responses.

Concurrent access to intravenous heroin and intracranial stimulation increased self-stimulation rates, as would be expected from previous findings with experimenter-administered opiates [3, 6, 8, 10]. Opiates generally have a biphasic effect on self-stimulation, inhibiting responding for the first hour or more, and subsequently facilitating it. The inhibiting and facilitating actions are independent of one another, and are produced through receptor populations localized in different brain regions [2]. The sedative effect dominates at high doses, but disappears as drug is metabolized to levels that produce reliable facilitation of self-stimulation [5,7]. In the present study, the usual high dose effects were seen only at the 100 μg dose. These effects usually have a short latency, and in the present study, the latency should have been even shorter since the drug was administered IV rather than IP. The pauses in self-

TABLE 1

EFFECTS OF CHANGING INTENSITY OF STIMULATION CURRENT OR HEROIN UNIT DOSE ON CONCURRENT SELF-STIMULATION AND SELF-ADMINISTRATION RESPONDING* (EXPRESSED AS PERCENTAGE OF BASELINE PERFORMANCE)

Stimulation Intensity		Heroin Dosage	
Increased 10 μA	Decreased 10 μA	2 × Unit Dose‡	0.5 × Unit Dose‡
Self-Stimulation Rate			
137	6	96	123
Self-Administered Heroin†			
119	102	185	111

*Mean of 6 rats.

†Calculated as change in total dose of heroin self-administered during the time that current intensity or unit dose parameters were changed.

‡Baseline heroin unit dose was 30 μg/kg/injection.

stimulation seen in the 10 μg condition in the present records do not occur immediately after the drug is self-administered, but at some later time. This unexpected finding requires further study.

Concurrent self-stimulation did not increase heroin self-administration; rather, self-administration was unchanged or perhaps even decreased (although the effect was not statistically reliable). Given the evidence that opiates activate the same reinforcement substrate that is activated directly by rewarding brain stimulation [1, 2, 16], there might be a question about why the two reinforcers were not redundant when given concurrently, and why one did not "substitute" for the other. A definite answer cannot be given at this time, but a partial answer comes from consideration of the factors that control rate of responding for each reinforcer. The rate of responding for brain stimulation reinforcement is directly proportional to stimulation current or stimulation frequency over a wide range of parameters [9].

The rate of responding for drug reinforcement, in contrast, seems to be controlled by the duration, rather than the magnitude, of activation of brain reinforcement mechanisms. The time required for drug to be metabolized determines when the next drug-reinforced response will be made. The presence or absence of brain stimulation reinforcement does not alter the duration of drug action in any obvious way. Thus it is not surprising that stimulation does not alter the rate of drug self-administration. One explanation for the rate-altering effects of opiates on self-stimulation responding is that opiates amplify the reinforcing magnitude of stimulation, and since self-stimulation responding depends on reinforcing magnitude, response rates increase. Stimulation fails to alter the rate of responding for drug because this rate depends on the duration of drug action, and stimulation is not capable of altering this duration. For the same reason, increasing or decreasing the intensity of stimulation current produced the expected increase or decrease in self-stimulation rates, but did not appreciably affect heroin intake.

Another major question concerns why the discontinuation of heroin reinforcement or the administration of naloxone should cause cessation of responding for brain stimulation reinforcement. This seems to be a behavioral contrast phenomenon; animals are less likely to work for a given reinforcer if testing follows a period of access to greater reinforcement [4]. The cessation of self-stimulation after naloxone treatment is unlikely to be the result of naloxone on brain stimulation reinforcement itself, since naloxone has not been found to have robust effects on brain stimulation involving similar electrode placements in experiments that did not involve opiates [12]. Thus the loss of self-stimulation when heroin was available for the first part of a session and then either discontinued or blocked with naloxone, seems due to the contrast between the effectiveness of brain stimulation reinforcement with and without drug. That self-stimulation did not cease for 30 to 60 min after cessation of drug injections is consistent with the time course of facilitation of responding by heroin.

The most important observation in the present study was that animals would lever-press for brain stimulation during periods when lack of responding might otherwise be taken as a reflection of an inability to respond. Rats are clearly capable of lever-pressing during much of the period between regularly-spaced responses for opiate or stimulant reinforcers, indicating that it is a temporary loss of the reinforcing value of the drug, and not simply a temporary loss of the response capacity of the animal, that is largely responsible for normal pattern of pauses between self-administered drug infusions. The fact that the animal can respond earlier, but fails to do so, suggests that animals lever-press for heroin until a particular blood level is reached; during the inter-infusion pauses additional heroin does not appear to be sufficiently reinforcing to maintain addition lever pressing.

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