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Intracranial Self-Stimulation as a Technique to Study the Reward Properties of Drugs of Abuse

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BOZARTH, M. A., G. J. GERBER AND R. A. WISE. *Intracranial self-stimulation as a technique to study the reward properties of drugs of abuse.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1, 245–247, 1980.—Rats allowed concurrent access to intravenous heroin and intracranial self-stimulation (ICSS) showed facilitation of ICSS while maintaining stable self-administration of heroin. The facilitatory action of heroin on ICSS was indexed by an increase in response rates and a lowering of intensity thresholds. Both measures showed dose-dependent changes, but only threshold tracking allowed a reliable determination of the time-dependent effect of self-administered heroin on ICSS.

Threshold tracking Intracranial self-stimulation Heroin self-administration
Effect of heroin on intracranial self-stimulation

THE notion that drugs owe their abuse potential to their ability to activate brain reward mechanisms has gained considerable interest in the past few years (see [6]). Among the various methods of studying the interaction of drugs with this reward system, the intracranial self-stimulation (ICSS) paradigm seems to be one of the most promising. Many drugs of abuse enhance ICSS as reflected in increased response rates for fixed-intensity stimulation [5] and in a reduction of the stimulation intensity needed to maintain some fixed behavioral response (i.e., intensity threshold; [1]).

Not all drugs of abuse have been shown to reliably facilitate ICSS [6]. Variability in drug absorption and the administration of only high drug doses may have produced results which are only partially concordant with the hypothesized relationship between a drug's effect on ICSS and its intrinsically rewarding properties. The use of insensitive behavioral measures and the failure to assess the full time-course of drug action may also contribute to equivocal drug effects on ICSS.

The hypothesis that facilitation of ICSS by drugs of abuse reflects the intrinsically rewarding properties of these drugs predicts that the facilitation effect should be evident across a wide range of reinforcing doses of drug. Measures of drug-induced facilitation of ICSS should also be dose-dependent and correspond to the pattern of drug intake seen during tests of self-administration. Furthermore, the facilitation effect should be immediate and evident from low drug doses which maintain self-administration.

We report here the development of a more sensitive paradigm which allows determination of the effects of intravenously administered drugs on ICSS rates and thresholds. Since the facilitatory action of opiates on ICSS is well established [2, 4, 5], we have assessed the utility of this paradigm first using heroin.

METHOD

Under sodium pentobarbital anesthesia, rats received a jugular catheter and were implanted with a stimulating electrode in the lateral hypothalamic area. After at least five days of recovery from surgery, rats were trained to press a lever for electrical brain stimulation.

In the first experiment, rats were allowed concurrent access to two levers, one of which produced an intravenous infusion of heroin (0.25 ml volume delivered over 28 sec) while the other produced a 0.5-sec train of 60 Hz sine wave stimulation. The rats were tested for six-hour sessions at a fixed current intensity, and unit doses of heroin were varied from 3 to 300 μg/kg/infusion across sessions.

In tests of the current intensity threshold for ICSS, 100 Hz square wave stimulation was used with a train duration of 0.3 sec and a pulse width of 0.3 msec. Every 10th stimulation train, the intensity decreased by 0.05 log units until the rat pressed another lever to reset the intensity to its initial value. Thresholds, prior to drug testing, were stable over four- and six-hour sessions, seldom fluctuating more than 5%. In some tests, rats had access to a third lever which produced an intravenous infusion of heroin.

RESULTS

We have previously reported that acute intravenous injections of rewarding heroin doses (as judged in independent self-administration tests) produced facilitation of ICSS rates across a 10 to 100 μg/kg dose range [3]. The duration of the

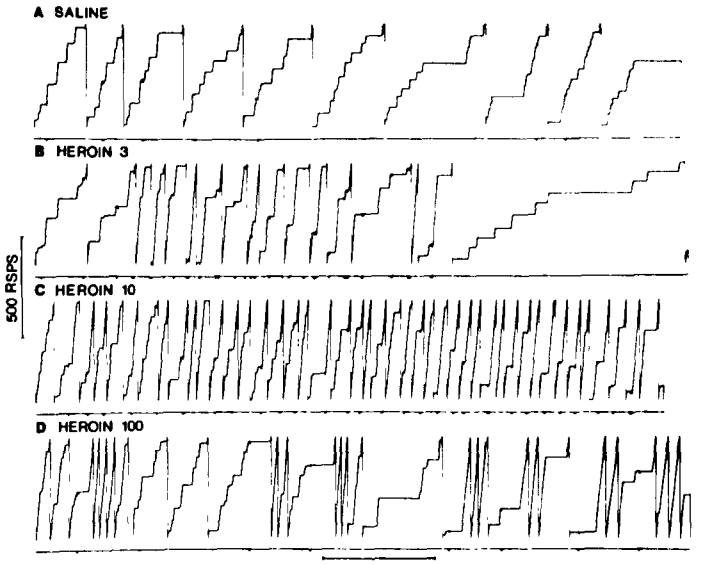

FIG. 1. The effect of heroin on rates of pressing for brain stimulation reward. Doses are given in μg/kg/infusion and self-administration is marked on the event channel. The horizontal bar represents one hour.

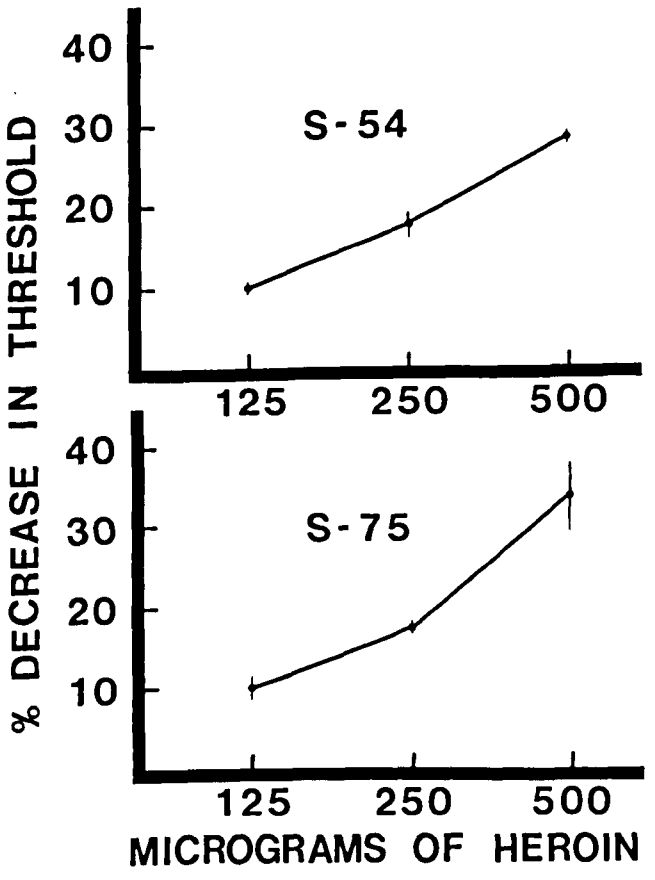

FIG. 2. The effect of subcutaneous injections of heroin on ICSS threshold. Each point represents the mean ± SEM of three determinations. The entire time-course of drug action was assessed during three hours of continuous testing and the data are from the time of peak-effect (15 to 30 min post injections).

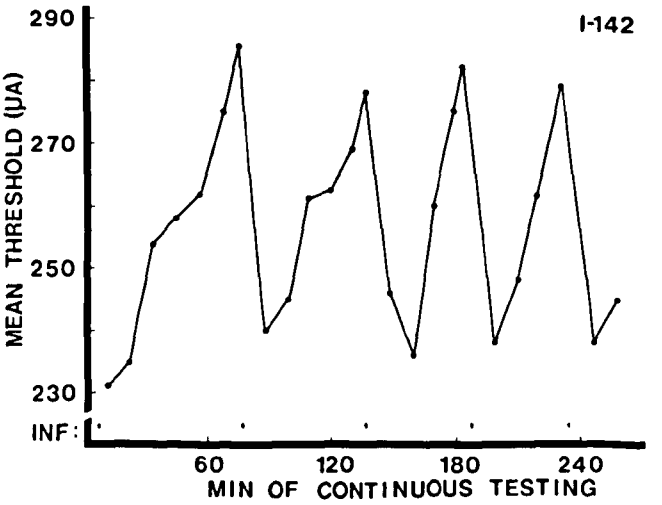

FIG. 3. The effect of self-administered heroin (100 μg/kg/infusion) on ICSS threshold. Arrows indicate drug self-administration. Heroin infusions cause an immediate lowering of threshold and the time of the next self-administered infusion can be predicted from the higher thresholds preceding each infusion.

facilitatory action was dependent on drug dose, corresponding to the independently determined reward duration (self-administration inter-response intervals).

During concurrent access to intravenous heroin and ICSS, rates of lever-pressing for ICSS were elevated while heroin self-administration paralleled that seen in tests of self-administration alone. Although the cumulative records in Fig. 1 clearly show facilitation of ICSS, response rates were variable, making comparisons of ICSS immediately before and after infusions difficult.

Figure 2 illustrates the effect of subcutaneous heroin in-

jections on ICSS thresholds. There is a dose-dependent lowering of thresholds which is similar to that reported by others using different methods of measuring thresholds [2,4]. By tracking the entire time-course of drug action (not illustrated), we can easily discern the appropriate time period to compare peak drug effects and ensure that the facilitatory action is not missed by discrete testing at the wrong time after injections.

The effect of self-administered heroin on ICSS thresholds is depicted in Fig. 3. There is a pronounced lowering of threshold immediately after each self-administered infusion of heroin and each infusion is preceded by a period where threshold approaches (but does not reach) predrug levels. It is significant that thresholds immediately before a drug request are appreciably above those following drug infusions since this suggests that threshold tracking accurately reflects the rewarding properties of the self-administered heroin.

Thresholds immediately preceding each heroin self-administration can be averaged within a session to determine the mean threshold prior to self-administration. The thresholds following each heroin infusion can be averaged across the session to yield the mean effect of heroin on threshold. The result of this procedure is represented in Fig. 4. As can be seen in the figure, there is a dose-dependent lowering of threshold which shows little variation across four hours of continuous testing.

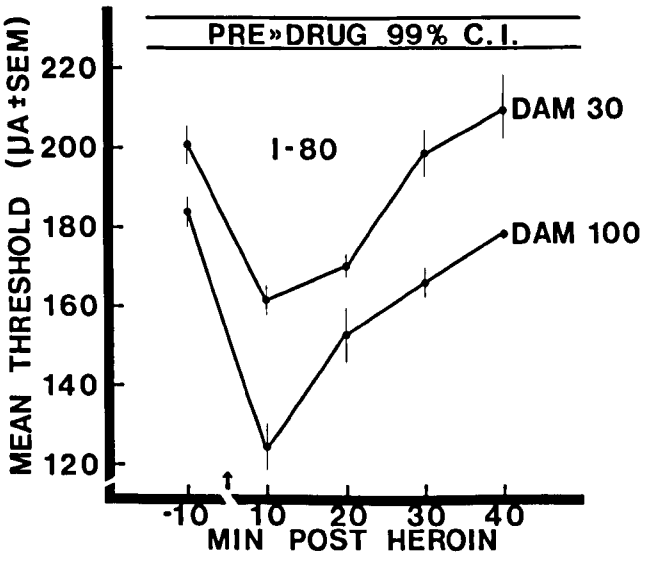

FIG. 4. The mean ± SEM threshold 10 min before and 10, 20, 30, and 40 min after heroin self-administration. DAM 30=30 μg/kg/infusion, heroin; DAM 100=100 μg/kg/infusion, heroin; 99% C.I.=99% confidence interval of threshold prior to testing with concurrent heroin self-administration.

DISCUSSION

The threshold tracking paradigm provides a very sensitive measure of heroin's effect on ICSS. The use of intravenous delivery simplifies the evaluation of the effect of rewarding drug doses on ICSS and probably minimizes variability due to differences in drug absorption. Furthermore, concurrent self-administration identifies the time-course of the rewarding drug effect and threshold tracking provides a reliable measure to determine corresponding changes in ICSS. The data regarding the immediacy of action, dose-dependency, and time-course for the effect of self-administered heroin on ICSS are concordant with the notion that threshold tracking can accurately reflect the rewarding properties of drugs of abuse. Whether or not a common substrate is involved can only be established after determination of the neural substrate mediating these behaviors.

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