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Reversal of Schedule-Induced Self-Injection of Heroin by Naloxone

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OEI, T. P. S. *Reversal of schedule-induced self-injection of heroin by naloxone.* PHARMAC. BIOCHEM. BEHAV. 13(3) 457–459, 1980.—Experimental evidence has shown that an intermittent food delivery schedule interacts with the pharmacological properties of a variety of drugs to produce significant increases in self-injection rates. This self-infusion drug seeking behaviour is further strengthened when body weight reduction is introduced. This experiment studies the effect of the opiate antagonist naloxone upon a strongly established response pattern for heroin self-administration, using naive rats at 80% body weight which were made dependent upon the drug by the schedule-induced self-injection procedure. Results show a clear reversal in responding following naloxone treatment, suggesting that once an interaction between schedule-induced behaviour and a drug is established, blockade of the reinforcing effects of the drug extinguishes the behaviour altogether.

Adjunctive behaviour Heroin Naloxone Schedule Self-administration

RECENT research has demonstrated that although the pharmacological properties of heroin alone were sufficient to induce responding without a schedule, under a fixed-time-1 min (FT1) food delivery schedule, self-injection of heroin increased dramatically [8,10]. Under this schedule-induced self-injection (SISI) paradigm, rats have been shown to self-administer a wide range of other psychoactive drugs such as methadone [8], amphetamine [13], ethanol [9], cocaine [11] as well as drugs such as nicotine [8,12] and Δ^9-THC [14] which have only meagre reinforcing efficacy. These experiments show that drug seeking behaviour and drug dependence are a result, not only of the pharmacological properties of the drug in question, but of the interaction between environmental and physiological factors and the drug [2].

There have been many studies reporting the use of narcotic antagonists, such as naloxone, to eliminate opiate-seeking behaviour in humans as well as animals. The antagonists block the euphoric, analgesic and other effects of the narcotic [4], and thus presumably block the primary reinforcing effects of the narcotic so that the relevant operant response undergoes extinction. However, the use of naloxone for eliminating opiate-seeking behaviour under a SISI paradigm has not been investigated. Recent experiments showed that such behaviour is resistant to extinction [6,15]. The present study was designed to examine whether it would be possible, under optimal response conditions—i.e. at reduced body weight, and utilizing a powerful narcotic reinforcer (heroin) upon which the subjects had become dependent—to reverse such responding solely by blocking the pharmacological effects of the drug with naloxone.

METHOD

Animals

Twenty-seven male Wistar albino rats weighing between 390–450 g were used. They were housed individually in stainless steel cages with water available ad lib. All animals were reduced to 80% at the free feeding body weight prior to surgery and maintained at that weight. The holding room was temperature controlled at 21° ± 1°C and maintained on a 12 hr light/dark cycle.

Apparatus

The apparatus was a modified operant box (35×32×32 cm) of clear Plexiglas, with a food dispenser and a lever on one side. The lever operated a syringe infusion pump (Sage Instrument, Model 341) which delivered 0.07 ml of heroin solution when triggered. A timing device set for a fixed interval of 5 sec was incorporated into the drug delivery system so that any further lever presses by the animals during the 5 sec following an infusion were not reinforced by further infusions. A counter attached to the infusion pump gave a cumulative record of both bar presses and number of infusions. Noyes food pellets (45 mg) were delivered regularly every 1 min throughout the test sessions (i.e. on fixed-time 1-min schedule).

Drugs

Heroin (Victorian Health Department) and naloxone hydrochloride (Endo Laboratories) were each prepared in a solution of 0.9% sterile saline with the heroin at a dose of 0.2 mg/kg/infusion and naloxone at doses of 3 and 10 mg/kg IP injection.

Procedure

Animals were weighed and anaesthetised with an IP injection of sodium pentobarbital and chloral hydrate. They were then implanted with jugular cannulae of SP28 polythylene tubing which were maintained in position by leather jackets and outer protective sheaths which were

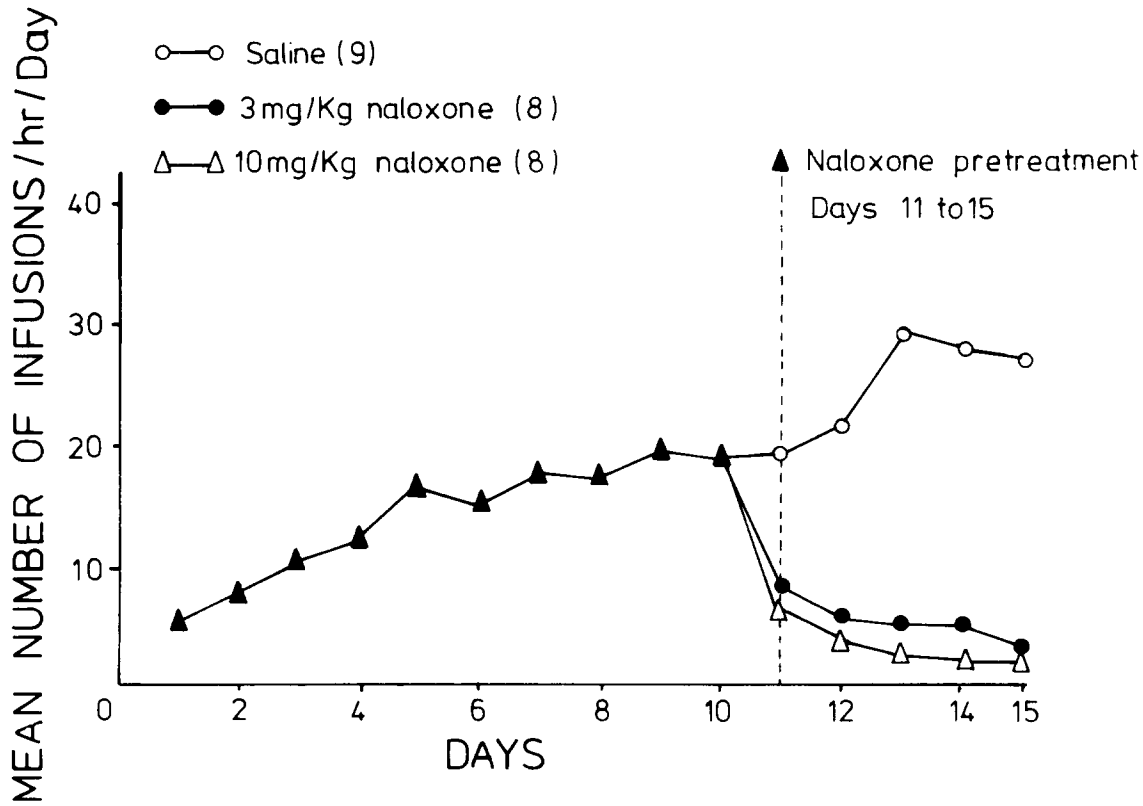

FIG. 1. The mean number of heroin self-infusions (0.2 mg/kg/infusion) with a fixed time food 1 min delivery schedule operating during each session for the three treatment groups. ( ) indicates the number of rats in each group.

worn by each animal. The cannulae were connected to a swivel system to minimize restriction of movement in cages and test chambers.

Following recovery from surgery (3 days), the animals were placed in the test cages for 1 hr/day test sessions for 15 consecutive days at approximately the same time every day. Prior to the test sessions the animals were weighed and the cannulae were flushed with a heparinized saline solution to prevent blood clotting in the cannulae. Each experimental session commenced by priming the animal with an initial dose of drug solution, in order to ensure that the first lever presses of the animals were not reinforced by the infusion of any residual heparinized saline still in the system. Following the test session animals were replaced in the holding cages and fed with a maintenance diet of approximately 8 g of rat chow per day.

After 10 consecutive days of testing [6, 8, 10] by which time the animals were presumed to be dependent upon the heroin (a presumption which was later supported by the observation of withdrawal symptoms such as 'wet-dog shakes' and diarrhea in the naloxone treatment groups), the animals were randomly assigned to the naloxone or saline conditions. For the subsequent five days of testing, the animals were pretreated immediately prior to testing with either 3 or 10 mg/kg IP injection of naloxone hydrochloride, or with an equivalent volume of isotonic saline. Rats with malfunction cannula were discarded from the analysis of the data.

RESULTS

The pattern of heroin self-infusion with an FT1 schedule operating during each session for the three treatment conditions is shown in Fig. 1. Two animals were not included in the final analysis because of blockage in the cannulae. A two-way ANOVA with one repeated measure showed a significant difference in the rates of bar pressing for heroin among the three treatment groups, $F(2,22)=21.185$, $p<0.001$, and a significant interaction between time and treatment groups, $F(8,88)=4.603$, $p<0.001$. Post hoc Scheffe analysis showed that the two naloxone treated groups bar pressed significantly less for heroin than did the saline control animals. However, there was no significant difference in heroin self-infusion between the two naloxone treated groups. In summary, the results show a significant decrease in heroin self-infusion following 3 and 10 mg/kg of naloxone treatment.

DISCUSSION

The findings show that rats which had become dependent on heroin under optimal response conditions, i.e. at reduced body weight (80% of the free feeding weight and fixed-time 1 min food delivery schedule) decreased their heroin self-infusion rates when given 3 and 10 mg/kg IP injection of naloxone. This indicates that naloxone reversed the schedule-induced self-injection of heroin administration. The

results are interesting in view of the suggestion that under schedule conditions and at reduced body weight, a well-established response pattern would be resistant to extinction [6,15]. This, however, was not the case. Naloxone was able to reverse the well-established schedule-induced self-infusion of heroin seeking behaviour. Responding for heroin followed an extinction curve after naloxone treatment (see Fig. 1). Thus, it appears that although schedule-induced behaviour can be developed under a wide variety of conditions, if it is increased through interaction with an additional direct reinforcer (e.g. heroin) then the negating of the reinforcer extinguishes the behaviour.

The present results are not in agreement with the findings of Wallace [16] who showed that naloxone did not depress schedule-induced polydipsia even at a very high dose (30 mg/kg). The discrepancy could be due to the different procedures used and also the addition of heroin in the present study.

Although naloxone had hitherto been considered to have no psychotomimetic properties, Katz [3] reported that the drug may cause dose related declines in motor activity. This could lead to the interpretation that rather than a decrease in bar pressing for heroin being related to the blockage of that drug's reinforcing properties, the decrease was a function merely of the naloxone dosage, and its effect on motor activity. However, this is unlikely. Observation of the rats in the present study and previous experiments in schedule-induced polydipsia [16] showed no observable differences in motor activities between the saline and naloxone treated animals. Previous studies [5] support such observation. Indeed Leander *et al.* [5] reported an increase of operant activity with 3 and 10 mg/kg doses of naloxone.

Further, the animals in the experimental treatment group all exhibited withdrawal symptoms immediately following naloxone administration. In one case the withdrawal was so severe that the animal was unable even to stand on the grid floor without the feet slipping through. These extreme symptoms rarely lasted for more than 20 min, although responding remained low for the whole period.

It has been reported that naloxone-induced withdrawal may be suppressed by the administration of Δ^9-tetrahydrocannabinol (THC) without apparently affecting the blockade of heroin. An extention of the present study with THC and naloxone treatment would be important and that such experiment would have implications not only for better understanding of the SISI paradigm, but also for narcotic detoxification and addiction treatment programmes.

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