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Heroin and Morphine: Aversive and Analgesic Effects in Rats[1]

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SWITZMAN, L., T. HUNT AND Z. AMIT. *Heroin and morphine: Aversive and analgesic effects in rats.* PHARMAC. BIOCHEM. BEHAV. 15(5) 755–759, 1981.—Although a number of studies demonstrate morphine-induced taste aversions, no such reports exist for heroin. In a conventional taste aversion paradigm, rats were injected with one of six heroin doses (0.5–12.0 mg/kg) after consuming a novel saccharin solution (Experiment 1). When the saccharin was reintroduced a second time no significant reduction in consumption occurred at any of the doses tested. It was therefore concluded that heroin does not readily induce a taste aversion. In Experiment 2, morphine was tested in an identical taste aversion paradigm and, as expected, a significant taste aversion did result at two of the doses tested. Experiment 3 demonstrated that heroin produced analgesia equal to or greater than morphine when comparing dosages of heroin which failed to induce a CTA with CTA-inducing morphine dosages. Thus, whereas heroin is more potent than morphine as an analgesic, heroin is less potent than morphine as a CTA-inducing agent.

Heroin Morphine Conditioned taste aversion Analgesia Temporal properties

VIRTUALLY all drugs self-administered by laboratory rats also induce conditioned taste aversion (CTA) in these animals [19]. The nature of CTA induced by self-administered drugs continues to be investigated in order to attain a more comprehensive understanding of drug-reinforced behavior. There is no simple explanation to account for the fact that self-administered drugs can induce CTAs. Neurochemical interventions which attenuate or block drug self-administration also attenuate or block the formation of CTA induced by self-administered drugs [22]. Moreover, the same amphetamine or morphine injections can induce a CTA as well as positively reinforce operant behavior [17, 20, 21, 25, 28]. In order to account for these effects, a number of investigators proposed, in various terms, that the positively reinforcing and CTA-inducing properties of self-administered drugs are functionally related [7, 22, 25]. If this is so, then any positively reinforcing drug should induce a CTA.

Although a number of reports exist that demonstrate morphine-induced CTAs [2, 6, 20, 22, 25, 28], there seems to be no report in the literature on CTA induced by heroin. The present investigation examines the CTA-inducing potential of heroin, a drug readily self-administered by rats [26].

EXPERIMENT 1

In this experiment, heroin was tested using a one-bottle CTA paradigm consisting of a single conditioning trial. In this situation, morphine is known to induce a CTA [22].

METHOD

Subjects

Subjects were 52 male Wistar rats (Canadian Breeding Farms and Laboratories Ltd., Quebec) weighing 225–260g. The animals were individually housed in stainless steel cages with free access to standard laboratory chow and tap water prior to the onset of the experiment. The laboratory was maintained on a 12 hr light/dark cycle.

Drugs

Heroin (Merck, Sharp and Dohme Canada Ltd.). was dissolved in injectable Ringer's solution (Abbott Laboratories Ltd.).

Procedure

After at least 7 days adaptation to laboratory housing conditions, the animals were placed on a 23 hr 40 min water deprivation schedule. For the following 7 consecutive days, tap water was available to the rats for a 20 min period between 1000 and 1100 hr each day in the home cage. The water was presented in stoppered glass test tubes fitted with stainless steel ball-bearing spouts inserted through the wire mesh in the front of the cage. Fluid intake over the first 10 min was measured to the nearest ml.

On day 8 (conditioning day) the animals were presented with a 0.1% (w/v) saccharin solution for a 10 min period.

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Within a minute after termination of the drinking period, animals were intraperitoneally (IP) injected with either Ringer's solution (0 mg/kg heroin, n=6) or one of six dosages of heroin. The following dosages of heroin were administered: 0.5 mg/kg (n=8), 1.0 mg/kg (n=8), 2.0 mg/kg (n=7), 4.0 mg/kg (n=7), 8.0 mg/kg (n=8), and 12.0 mg/kg (n=8). The injection volume for all of the groups was 1 ml/kg body weight.

For 5 days following the conditioning day, tap water continued to be available for 20 min daily drinking periods. On the sixth day after conditioning, the saccharin solution was once more presented to the animals for a 10 min period (test day).

RESULTS AND DISCUSSION

Conditioning and test day saccharin intakes at each heroin dose are presented in Fig. 1. A two-way ANOVA was carried out on the saccharin intake scores across all of the dosage groups over the two saccharin days (conditioning and test days). The two-way ANOVA [29] yielded a significant interaction between dose and days, $F(6,45)=2.40$, $p<0.05$. A simple main effects test [29] was used to compare baseline saccharin intakes across groups. The baseline saccharin intakes on the conditioning day did not differ significantly across groups, $F(6,79)=1.77$, $p>0.10$. Thus, conditioning and test day means within each dose were compared to each other with simple main effects tests. Significant test day increases in saacharin intake were observed in the 0.0 mg/kg group, $F(1,45)=6.64$, $p<0.05$, the 0.5 mg/kg group, $F(1,45)=14.09$, $p<0.05$, the 2.0 mg/kg group, $F(1,45)=5.69$, $p<0.05$, and the 12.0 mk/kg group, $F(1,45)=5.44$, $p<0.05$.

A significant increase in saccharin intake on test day resulted for three doses of heroin (0.5, 2.0 and 12.0 mg/kg). This increase probably reflected a loss of neophobia [4] as the Ringer's control group also increased saccharin intake on test day. Saccharin intake did not change significantly from conditioning to test day for the three remaining heroin groups (1.0, 4.0 and 8.0 mg/kg). This would suggest that the CTA-inducing potential of heroin is low. That is, the effect of heroin did not meet the criterion for a CTA when defined as a significant decrease from baseline intake of a novel-tasting flavor. It would be important to reconfirm that the criterion set out above is met by morphine in this paradigm prior to accounting for the results obtained with heroin.

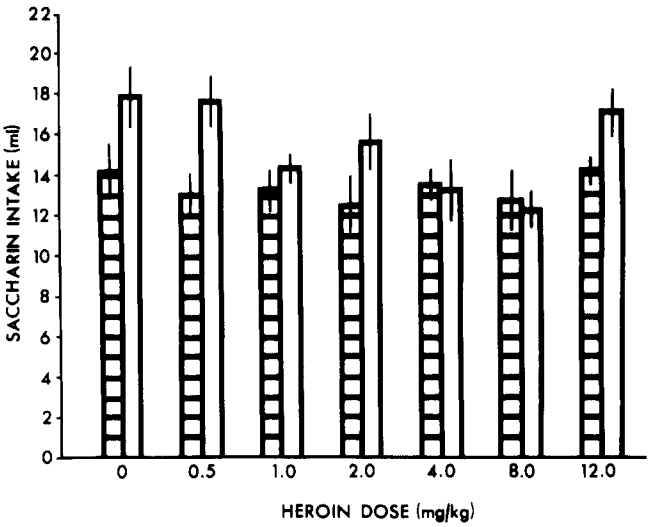

Fig. 1. Conditioning day (horizontally-striped bars) and test day (clear bars) saccharin intake as a function of the heroin dose administered.

EXPERIMENT 2

In Experiment 1, it was observed that heroin did not readily induce a CTA. The present experiment assesses whether or not morphine induces a CTA in the same paradigm.

METHOD

Animals

Subjects were 40 male Wistar rats (Canadian Breeding Farms and Laboratory Ltd.) weighing 225–260 g. Housing conditions were the same as those in Experiment 1.

Drugs

Morphine hydrochloride (Merck, Sharp and Dohme Canada Ltd.) was dissolved in injectable Ringer's solution.

Procedure

The procedure was identical to that of Experiment 1. On conditioning day (day 8), the rats were dividied into 4 equal groups (n=10/group) receiving IP injections of either Ringer's or morphine after the 10 min saccharin presentation. The dosages of morphine were 4 mg/kg, 8 mg/kg and 12 mg/kg. The injection volume for all groups was 1 ml/kg body weight. As in Experiment 1, the test day occurred 6 days after the conditioning day.

RESULTS AND DISCUSSION

Figure 2 illustrates conditioning and test day saccharin intakes at each morphine dose. A two-way ANOVA was carried out on the saccharin intake scores across all of the dosage groups over the two saachrin days (conditioning and test days). The two-way ANOVA yielded a significant interaction between dose and days, $F(3,36)=9.29$, $p<0.0002$. A simple main effect test [29] was used to compare baseline saccharin intakes across groups. The baseline saccharin intake on the conditioning day did not differ significantly across groups, $F(3,62)=1.81$, $p>0.10$. Thus, conditioning and test day means within each dose were compared to each other with simple main effects tests. Significant decreases in saccharin intake occurred for the 8 mg/kg morphine group, $F(1,36)=9.54$, $p<0.05$ and the 12 mg/kg morphine group, $F(1,36)=4.35$, $p<0.05$. The only other change in saccharin intake was a significant increase on test day for the Ringer's control group, $F(1,36)=14.32$, $p<0.05$.

At the two higher doses tested, morphine induced a CTA as evidenced by a significant reduction in saccharin intake on test day. No significant change in saccharin intake was observed at the 4 mg/kg dose of morphine although the 0 mg/kg group (Ringer's) demonstrated the typical test day increase in saccharin intake. Thus, whereas heroin did not induce a significant CTA in this paradigm (Experiment 1), morphine did induce a significant CTA.

TABLE 1

MEAN±SEM PAW LICK LATENCIES (SEC) OF GROUPS INJECTED WITH EITHER RINGER'S, HEROIN OR MORPHINE OVER FOUR POST-INJECTION TEST TRIALS

Injection Group	Time Lapsed Post-Injection 5 min	30 min	80 min	180 min
Ringer's	11.3 ± 1.1	12.6 ± 1.1	9.1 ± 1.0	10.5 ± 1.1
Heroin 2 mg/kg	15.4 ± 1.4	15.4 ± 3.2	6.4 ± 0.8	8.6 ± 1.1
Heroin 4 mg/kg	32.8 ± 9.3	42.2 ± 9.8	15.8 ± 9.0	9.9 ± 1.2
Morphine 8 mg/kg	11.6 ± 1.0	21.8 ± 6.3	8.2 ± 0.4	8.0 ± 1.1
Morphine 12 mg/kg	11.8 ± 1.4	24.9 ± 7.5	17.4 ± 8.6	8.8 ± 1.0

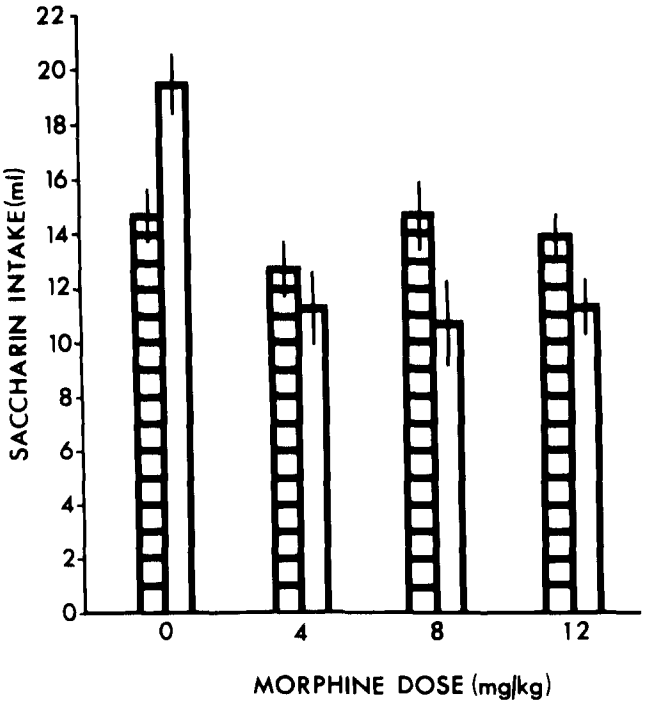

FIG. 2. Conditioning day (horizontally-striped bars) and test day (clear bars) saccharin intake as a function of the morphine dose administered.

EXPERIMENT 3

A number of studies demonstrate that heroin is as potent or more potent than morphine. These two drugs are equally active in the guinea-pig ileum preparation [11] and in the isolated dog intestine [13]. In humans, heroin is reported to be more potent than morphine as indicated by a wide range of behavioral and physiological measures [12, 18, 23, 24]. A similar picture arises in rats where a lower unit dose of heroin produces similar rates of self-administration to that of morphine at a higher dose [26]. Heroin is also a more potent analgesic than morphine in rats [16]. In view of the fact that results obtained in Experiments 1 and 2 of this paper demonstrate a greater potency of morphine over heroin in the CTA paradigm, the present experiment employs a different behavioral measure to assess the relative effectiveness of the drugs. Heroin dosages that did not induce significant CTAs were compared with morphine dosages that did induce CTAs in a test of analgesia. The two middle doses of heroin administered in Experiment 1 (2 and 4 mg/kg) were compared with the two CTA-inducing doses of morphine in Experiment 2 (8 and 12 mg/kg) using a hot-plate procedure [5, 10, 14, 16, 30].

METHOD

Subjects

Subjects were 36 naive male Wistar rats (Canadian Breeding Farms).

Apparatus

The hot-plate consisted of a metal plate maintained at a temperature of 54°C±1° by a bath of distilled water which was constantly circulated and heated (Haake, model E2) below the plate. A clear Plexiglas cylinder (20 cm diameter, 23 cm height) was placed vertically on the hot-plate as a restrainer.

Procedure

Each rat received an injection followed by repeated hot-plate trials 5, 30, 80 and 180 min post-injection. After placing a rat on the hot plate, the latency (sec) to engage in the first hind paw lick was measured. A trial was terminated 30 sec after an animal was placed on the hot-plate if the animal engaged in at least one paw lick within that time interval. If a paw lick did not occur, then a rat was left on the hot plate for an additional 15 sec and if still no response resulted a further 15 sec time interval was added. A rat that did not paw lick therefore received a score of 60 sec. This protocol was instituted in order to avoid removing an animal immediately after a paw lick and possibly reinforcing the behavior. The injection groups were as follows: heroin 2 mg/kg, heroin 4 mg/kg, morphine 8 mg/kg, morphine 12 mg/kg and Ringer's 1 ml/kg. There were 6 rats in each group with the exception of the Ringer's group in which there were 12 animals.

RESULTS AND DISCUSSION

Table 1 presents the scores obtained for each injection

group. A two-way ANOVA yielded a significant groups effect, $F(4,31)=5.6$, $p<0.002$, a significant trials effect, $F(3,93)=11.01$, $p<0.0001$, and a significant groups $\times$ trials interaction, $F(12,93)=2.45$, $p<0.009$. The Newman-Keuls *post hoc* test ($\alpha=0.05$) was used to compare the group means on each trial [29].

At 5 min and 30 min post-injection the heroin 4 mg/kg group exhibited a significantly slower paw lick latency than the remaining groups thus demonstrating the greatest analgesic effect of the drug dosages tested. At 30 min post-injection the morphine 12 mg/kg group obtained a significantly higher latency score than either the Ringer's group or the heroin 2 mg/kg group. At 80 min post-injection the paw lick latency of the morphine 12 mg/kg group was greater than all groups except for the heroin 4 mg/kg group. No other significant differences emerged.

The paw lick latencies of the morphine groups were within the range of scores of the heroin groups. The fact that a lower dose of heroin than morphine produced analgesia is consistant with results obtained in other investigations [16,18] demonstrating that heroin is a more potent analgesic than morphine. Furthermore, heroin produced analgesia 5 min post-injection whereas morphine was effective only on the second trial (30 min post-injection). This observation parallels the finding that heroin penetrates the blood-brain barrier rapidly whereas morphine does not [15]. Thus, the present experiment demonstrates that heroin is a more effective analgesic than morphine at least on an acute basis whereas the combined results of Experiments 1 and 2 demonstrate that heroin is less effective than morphine as a CTA-inducing agent. It is possible that a fluid deprivation schedule identical to that used in Experiments 1 and 2 would have influenced analgesic responsiveness, however, there is no reason to suspect that fluid deprivation would interact differently with heroin analgesia than it would with morphine analgesia.

GENERAL DISCUSSION

It is suprising, indeed, that heroin did not induce a significant CTA whereas morphine did. Heroin is rapidly hydrolized to monoacetylmorphine and then to morphine [27]. Although heroin may conceivably be capable of inducing a stronger CTA given other conditions such as multiple flavor-drug pairings, the present study demonstrates that upon acute administration, heroin is not as effective as morphine in terms of CTA induction.

It is possible that the temporal nature of heroin may underlie its inefficiency as an aversive agent. Temporal factors have been shown to play a critical role in taste aversion conditioning by the psychoactive drugs cocaine and morphine [1, 9, 20]. Goudie *et al.* [9] specified two temporal properties that might facilitate the formation of CTAs: (1) a gradual rate of onset to peak behavioral activity and (2) a prolonged duration of action. Although there is evidence against duration of action as a main factor in the formation of CTAs [3,8], no such evidence exists regarding a drug's rate of onset to peak activity. In fact, this concept has received little experimental attention as concerns drug-reinforced behavior.

It has been demonstrated that at least for morphine to induce a CTA it must exert its peak behavioral effect with some delay after ingestion of a novel flavor [20]. A fundamental pharmacological difference between morphine and heroin is that heroin penetrates the blood-brain barrier more quickly than morphine [15] thus resulting in a more rapid rate of onset than morphine. The rapid onset of activity is demonstrated in Experiment 3 in which significant analgesia resulted with heroin on the first test trial 5 min after an IP injection. The results obtained in the present study are consistant with the proposal that a gradual onset of activity in the brain may be an important factor for the production of CTAs at least by opiate drugs. However, one must consider an alternative explanation that at least with regards to production of CTA, heroin and morphine operate via independent pharmacological mechanisms.

The assumption that heroin is but a more potent opiate than morphine is challenged by the results reported in this paper. Heroin seems to be more potent than morphine on certain measures ([12, 18, 23, 24], and Experiment 3), equipotent to morphine on other measures [11,13] and less potent than morphine at least in CTA induction (Experiments 1 and 2).

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