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Patterns of Drinking in the Rat following the Administration of Opiate Antagonists

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COOPER, S. J. AND S. G. HOLTZMAN. *Patterns of drinking in the rat following the administration of opiate antagonists*. PHARMACOL BIOCHEM BEHAV 19(3) 505–511, 1983.—Durations of drinking were recorded for water-deprived rats as they drank to satiety, following SC injections of naloxone (0.1–10.0 mg/kg), naltrexone (0.1–10.0 mg/kg) or saline vehicle. The results provided evidence for the effects of opiate antagonists on the temporal pattern of drinking exhibited by water-deprived animals. A separate, time-sampling procedure was used to supplement the drinking duration data, and showed that the opiate antagonists may suppress water consumption during a period 2.5–7.5 min after the start of the initial drinking bout. A second experiment confirmed that the pattern of drinking displayed during schedule-induced polydipsia in the rat is resistant to any suppressant effect of a moderate dose of an opiate antagonist. The similiarity between opiate receptor blockade and water preloading in their effect on drinking in response to water deprivation, and lack of effect on schedule-induced polydipsia is discussed. Opiate antagonists may affect drinking principally by imposing a thirst satiety signal.

Diprenorphine Drinking duration Naloxone Naltrexone Opiates Rat
Schedule-induced polydipsia Thirst

SUPPRESSION of drinking following the administration of pure opiate antagonists (naloxone, naltrexone, diprenorphine) has repeatedly been described in the rat made thirsty by water deprivation (e.g., [1, 2, 4, 5, 6, 7, 8, 10, 19, 20, 27, 28, 36, 37, 38]). This finding has contributed strongly to proposals that the blockade of opiate receptors attenuates the activity of endogenous opioid-related thirst mechanisms (e.g., [4, 6, 8, 23, 34]). In further support of this hypothesis, it has been shown that opiate antagonist administration can powerfully attenuate the drinking which is elicited by a variety of dipsogenic stimuli, including challenges with hypertonic saline [1, 3, 8, 12, 16, 34], polyethylene glycol [12, 29, 34], isoproterenol [6], intracerebroventricular injection of angiotensin II [6], intravenous infusion of angiotensin II [34], and sweet taste [13]. Furthermore, recent evidence indicates that naloxone and naltrexone abolish the enhancement of drinking which is produced by benzodiazepine treatment in the rat [10,12]. While opiate antagonists are effective in suppressing the drinking which follows as a response to thirst challenges, they are also effective in reducing water consumption in animals maintained on ad lib food and water [8, 22, 23]. Opiate antagonists have also been reported to suppress drinking in other species, mouse [2,3], squirrel monkey [4], and cat [18], for example, but not pigeon [15].

The behavioural and physiological substrates by which opiate receptor blockade reduces water consumption have not yet been clearly identified. There is evidence which tends to exclude pituitary factors [1,7], renal involvement [23] and post-absorption processes [32], as being essential to the opiate antagonist suppression of drinking. The relevant opiate receptors are likely to be located within the central nervous system, since experiments with quaternary derivatives of opiate antagonists indicate that peripheral opiate receptor blockade may be of no particular significance [5,29]. The effectiveness of central administration of opiate antagonists is consistent with a central location of the relevant receptors [5,36].

A promising approach to an increased understanding of the effects of opiate antagonists on drinking is to analyse their effects in relation to the pattern of drinking which is exhibited by the thirsty rat as it satisfies its water requirement [21]. Opiate antagonists, typically, do not affect the latency to begin drinking [6], indicating that they do not simply interfere with the initiation of drinking. They must, therefore, start to impose a suppressant effect after drinking has begun. But when? There are relatively few data which have a bearing on this point. Using 23 hr water deprived rats, Brown and Holtzman [6] reported that naloxone (0.2–10.0 mg/kg) had its greatest effect on drinking within the first 6 min. access to water. Relatively little drinking occurred in any group between 6 and 30 minutes. Using a finer-grain temporal analysis, Siviy *et al.* [37] recently observed that naloxone (0.01–10.0 mg/kg) had little if any effect on initial drinking in 23.8 hr water deprived rats. They showed that naloxone slowed sustained drinking after 2–6 min into the initial drinking bout.

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The first experiment of the present report attempts to supplement the available evidence concerned with patterns of drinking following opiate receptor blockade in several ways. First a comparison is drawn between the effects of naloxone and naltrexone in relation to the time course of drinking following a period of water deprivation. It is important to demonstrate a consistent relation between the effects of the two drugs administered at low doses, if the mechanism of opiate receptor blockade is to be invoked [35]. Secondly, the two published studies [6,37] relied upon records of licking activity to arrive at the patterns of drinking in the water deprived rat. The approaches adopted in the present work were to measure the time actually devoted to drinking throughout the drinking session and to adopt a time-sampling procedure to achieve a very fine-grain resolution of drinking patterns (cf [9,11]). There are interesting comparisons to be made between estimates of the effects of opiate antagonists as measured by licking activity, and those based on the measurement of the duration of drinking and on a time-sampling procedure. Lastly, small numbers of animals served as subjects in the earlier studies [6,37]; it is desirable to collect additional data based upon a larger series of subjects.

EXPERIMENT 1

METHOD

Animals

The subjects were naive, male, black hooded (General strain) rats bred in the Psychology Department, University of Birmingham. They were housed individually in stainless steel cages, normally with free access to food pellets (modified Diet 41B, Heygate and Sons, U.K.) and water. They were maintained under a 12 hr light–12 hr dark cycle (lights on at 7 a.m.), and the room temperature was kept constant at 21°C. Care was taken to familiarise the animals with relevant procedures before running the drug trials. They were handled and weighed regularly, and received experience of injections of isotonic saline. They weighed 350–450 g at testing.

Procedure

For the drinking duration tests, a calibrated cylinder containing water was clipped to the front of the cage, with the metal spout protruding into the interior. The volume of water consumed during the first 30 min access to water was determined to the nearest 0.5 ml by reading the level in the calibrated cylinder. Water was removed during a 24 hr period before the test, and food was removed during the drinking test. Each rat was run through the deprivation and test procedure twice before the drug trial was conducted. In addition to measuring water intake, the duration of drinking was also determined. An observer, who was blind to the injection conditions, pressed a key whenever the rat drank from the drinking tube (the criteria for drinking were licking at the spout, and ascending air bubbles in the tube). The duration of each key press was logged using a Commodore 2001 series microcomputer, which had been programmed to summate drinking durations (sec) within each 5 min interval of the 30 min test session. At the end of a test, a print-out of drinking durations (totals for consecutive 5 min intervals) was obtained. The drinking tests were run between 9.30 a.m. and 2.30 p.m.

To investigate the effect of naloxone in water deprived rats, 60 animals were allocated to 6 equal groups according to dose level: 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg naloxone respectively, and an isotonic vehicle condition. To investigate the effect of naltrexone, an additional group of 60 rats were allocated to the same dose conditions (10 rats per group). Injections were administered SC 15 min before the start of the drinking test, and doses are expressed in terms of hydrochloride salt, in both cases. The injection volume was 1 ml/kg. Drug effects were assessed by analysis of variance, followed by Dunnett's test to compare each drug-treated group against the corresponding control group.

For the time-sampling tests, 16 naive male rats were allocated to two groups to examine the effects of naloxone and naltrexone respectively. The animals were housed as described above, and were adapted over a period of 10 days to a 22 hr daily water-deprivation schedule. Each animal was tested twice, with a 48 hr interval between the two trials. One group were injected SC with saline on one occasion, and 10 mg/kg naloxone HCl on the other; the injection sequence was counterbalanced within the group. The second group were injected SC with saline on one occasion and 10 mg/kg naltrexone on the other, with a counter-balanced injection sequence. Injections were administered 15 min before the 30 min drinking test (food removed during the test). An observer then noted at 15 sec intervals throughout the test period whether or not the rat was engaged in drinking. The data provided, for a group of animals, a record of the frequency of drinking amongst the animals at 15 sec intervals. This method has been used previously in analyses of the time-course of drinking in drug-treated rats [9,11]. Drug effects were assessed using a *t*-test for correlated means.

RESULTS

Drinking Durations and Volumes

Naloxone produced a dose-related suppression of water intake, $F(5,54)=8.07$, $p<0.001$, (Table 1), but it did not have any observable effect on the latency to begin drinking. All animals began to drink within 1 or 2 sec access to water. A significant reduction in water consumption occurred with a dose as small as 0.1 mg/kg. The largest reduction in intake (59.2% less than the control intake) followed the administration of 10 mg/kg naloxone.

Vehicle-treated rats drank almost continuously throughout the first 5 min period of the test session. The time devoted to drinking began to decrease sharply within the second 5 min period. By the third period, drinking durations had reached low levels, and remained so for the rest of the test session (Table 1). Drinking durations showed some reduction during the first 5 min period after injection of naloxone, and significant effects occurred at the 1.0 and 10.0 mg/kg dose levels. Significant reductions in drinking duration were in evidence during the second 5 min period, for naloxone, 1.0–10.0 mg/kg (Table 1). At the larger naloxone doses, additional significant suppressions in drinking duration did occur later in the test session, although in absolute terms, these reductions were modest, and contributed little to the total drinking suppression.

Naltrexone also significantly attenuated water consumption at all doses tested, $F(5,54)=9.38$, $p<0.01$ (Table 2). There was relatively little increased effect with increasing dose level. At 0.1 mg/kg, naltrexone reduced water intake by 41.2%, whilst at 10.0 mg/kg it decreased intake by 49.6%. Vehicle-treated animals concentrated their drinking within

TABLE 1

EFFECTS OF NALOXONE ON WATER INTAKE (ml) AND THE DURATION OF DRINKING (sec) FOR CONSECUTIVE 5 MIN PERIODS OF A 30 MIN DRINKING TEST

	Naloxone (mg/kg)					
	0	0.1	0.3	1.0	3.0	10.0
Water intake* (ml)	15.7 ± 1.1	11.2† ± 1.1	9.4‡ ± 0.8	7.7‡ ± 0.9	8.6‡ ± 1.0	6.4‡ ± 0.9
% control	—	71.3	60.0	49.0	54.8	40.8
Drinking duration* (sec)						
Period 1	240.1 ± 24.2	252.9 ± 9.6	220.2 ± 9.6	175.4† ± 16.5	199.2 ± 22.7	179.1† ± 25.4
Period 2	162.2 ± 14.3	115.0 ± 34.8	111.5 ± 13.8	80.0‡ ± 21.1	96.8† ± 15.9	69.2‡ ± 15.9
Period 3	45.6 ± 21.4	35.8 ± 12.0	30.3 ± 13.2	12.4 ± 8.3	5.6† ± 3.0	1.3† ± 1.1
Period 4	16.6 ± 7.0	32.5 ± 24.7	5.8 ± 4.2	8.4 ± 5.1	0.0 —	5.1 ± 4.8
Period 5	9.7 ± 4.3	35.2 ± 28.3	22.9 ± 15.7	0.0 —	1.3 ± 1.3	1.4 ± 1.3
Period 6	17.0 ± 8.7	0.8 ± 0.8	21.9 ± 11.1	14.6 ± 7.1	15.0 ± 13.6	11.1 ± 7.0
Total duration	491.1	472.2	412.6	290.8	317.7	267.2
% control	—	96.2	84.0	59.2	64.7	54.4

Results are shown as mean (+S.E.M.). N = 10 per group. Water intake is shown as total intake over 30 min session.

*Statistical comparisons with corresponding control values (Dunnett's test): Levels of significance †$p < 0.05$; ‡$p < 0.01$.

the first 10 min of the test session, and for the remainder of the test, exhibited very low levels of drinking (Table 2). Naltrexone had no observable effect on drinking latency, since all rats began to drink almost as soon as water became available. It did, however, significantly reduce drinking durations within the first 5 min of the test session (Table 2). A significant reduction in drinking duration was present in the second 5 min period for the 1.0 mg/kg dose.

For both naloxone and naltrexone, the percentage reductions in the total drinking durations were too small to account fully for the reductions in water intake (Tables 1 and 2). Hence some additional factor other than a reduction in drinking duration may have to be invoked for naloxone and naltrexone, to explain completely the fall in water intake that occurred. Rate of water consumption (ml/100 sec drinking) may also have been reduced by the opiate antagonist treatments.

Time-Sampling of Drinking

The results of the time-sampling study are shown in Fig. 1, and provide a precise indication of the period when naloxone and naltrexone exert their main effect upon the occurrence of drinking in water-deprived rats. The figure shows the pattern of drinking for individual rats, and for convenience the 20 min period represented in the diagrams is divided into 2.5 min intervals. Since each animal was observed on 10 occasions within each interval, it is possible to compare drug treatments with the corresponding control conditions in terms of drinking scores per 2.5 min interval (maximum value being 10).

First, it should be noted that every animal was drinking within the first 15 sec of the test session. In the first 2.5 min interval, neither naloxone (10 mg/kg) nor naltrexone (10 mg/kg) had any effect on the pattern of drinking. In the second 2.5 min interval, however, naloxone significantly reduced the occurrence of drinking, $t(7)=3.05$, $p<0.01$, and naltrexone did likewise, $t(7)=2.20$, $p<0.05$. Similarly, in the third 2.5 min interval, naloxone and naltrexone significantly reduced the occurrence of drinking, $t=2.16$, $p<0.05$ and $t=3.18$, $p<0.01$, respectively. Thereafter, in later intervals of the test, neither drug produced any further significant effects. The timing of the effects of the opiate antagonists on drinking can therefore be accurately identified. The actions of the drugs took effect between 2.5 and 7.5 min into the test session.

DISCUSSION

The opiate antagonists, naloxone and naltrexone, produced a partial suppression of water ingestion in rats fol-

TABLE 2

EFFECTS OF NALTREXONE ON WATER INTAKE (ml) AND THE DURATION OF DRINKING (SEC) FOR CONSECUTIVE 5 MIN PERIODS OF A 30 MIN DRINKING TEST

	Naltrexone (mg/kg)					
	0	0.1	0.3	1.0	3.0	10.0
Water intake* (ml)	13.1 ±1.0	7.7‡ ±0.6	7.6‡ ±0.5	7.1‡ ±1.0	7.5‡ ±0.4	6.6‡ ±1.0
% control	—	58.8	58.0	54.2	57.3	50.4
Drinking duration* (sec)						
Period 1	237.7 ±12.6	199.6 ±8.3	158.0‡ ±20.7	184.0 ±23.4	149.8‡ ±18.4	165.2‡ ±20.6
Period 2	135.3 ±14.8	124.1 ±15.6	89.3 ±15.9	80.8† ±22.0	99.3 ±12.7	88.9 ±22.9
Period 3	26.4 ±6.2	25.3 ±6.5	40.5 ±16.1	10.5 ±7.3	39.4 ±12.5	13.1 ±8.2
Period 4	19.8 ±7.3	14.8 ±4.5	16.3 ±8.5	8.6 ±8.1	5.1 ±4.5	9.0 ±6.3
Period 5	18.2 ±8.2	12.1 ±6.0	23.1 ±10.2	5.7 ±5.4	1.8 ±1.7	0.0 —
Period 6	14.5 ±5.4	6.3 ±4.3	13.8 ±9.3	2.4† ±2.2	0.0 —	2.2 2.0
Total duration (sec)	451.9	382.2	341.0	292.0	295.4	278.4
% control		84.6	75.5	64.6	65.4	61.6

Results are shown as mean (±S.E.M.). N=10 per group. Water intake is shown as total intake over 30 min sessions.

*Statistical comparisons with corresponding control values (Dunnett's test): Levels of significance †$p<0.05$; ‡$p<0.01$.

lowing water deprivation. Neither drug affected the latency to begin drinking, confirming an earlier report [6]. Initiation of drinking in the water-deprived rat was not, therefore, in any way impeded by opiate receptor blockade.

The data of the present report are the first to represent the pattern of drinking following either naloxone and naltrexone administration in terms of either drinking durations or occurrence of drinking measured using a time-sampling procedure. Both opiate antagonists reduced drinking durations by a relatively modest extent within the first 5 min (by no more than 27% and 37% for naloxone and naltrexone, respectively). During the second 5 min period, both naloxone and naltrexone attenuated the drinking durations (the greatest reductions being 57% and 40% for naloxone and naltrexone, respectively). The finer-grained resolution offered by the 15 sec sampling procedure suggested that both drugs were most effective in reducing drinking behavior between 2.5 and 7.5 min after the start of drinking.

These results are in close agreement with the data of Siviy *et al.* [37], which were derived from numbers of licks detected by a drinkometer circuit. Their results for naloxone showed that there was little effect on initial drinking, but did attenuate drinking after 2 to 6 min into the drinking bout. Figure 1 provides a graphic confirmation of the time at which naloxone (and naltrexone) exert a brake upon drinking.

Previous work has shown that preloading water-deprived rats with 10 ml. water (administered by oral, intragastric or intravenous routes) reduces subsequent water intake over one hr period by 64–69% [31]. A similar preload of water (administered by oral route) has been shown to affect the pattern of drinking in much the same way as naloxone or naltrexone [11]. Drinking was relatively unaffected during the first 2 min of the initial drinking bout by the water preload, but afterwards, the pattern of drinking was noticeably suppressed [11].

Available data are suggestive, therefore, that naloxone and naltrexone treatments may be equivalent to a water preload in terms of their satiating effects upon drinking. One intriguing prediction of this hypothesis indicates a possible situation where opiate antagonists should fail to affect drinking. It has been reported that intragastric preloads of 5 ml water or intraperitoneal administration of 10 ml water or isotonic saline failed to modify the pattern of schedule-induced polydipsia in the rat [30]. It follows that the opiate antagonist may fail to affect schedule-induced polydipsia in the rat, and indeed there is evidence that naloxone and nal-

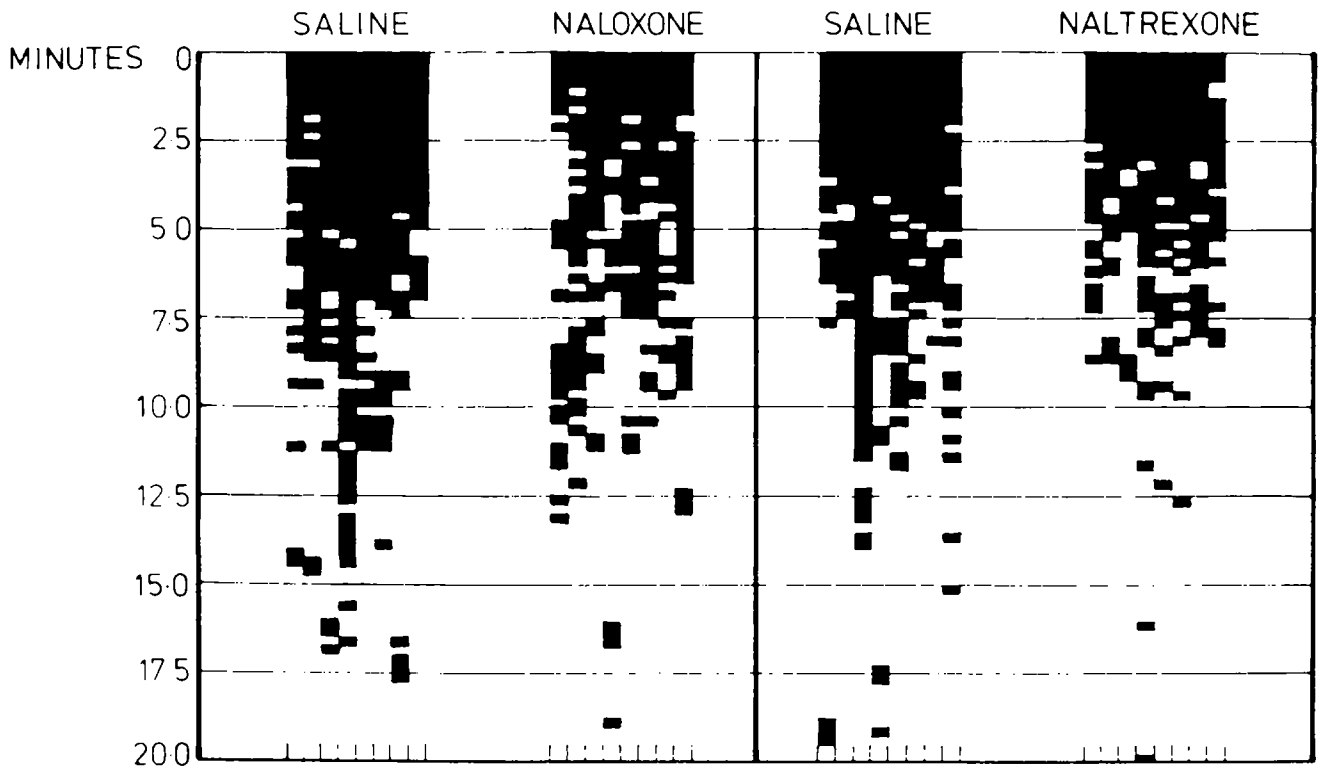

FIG. 1. A time-sampling technique applied to the pattern of drinking in the water-deprived rat. Black areas indicate drinking; white areas indicate no drinking. In the naloxone group (left hand panel), a group of 8 animals were observed in a drinking test following either isotonic saline or naloxone (10.0 mg/kg) injection (each rat was run under both injection conditions). The short vertical lines at the bottom of the figure indicate 8 columns corresponding to the 8 animals. Individual rats are shown in the same position for the saline and naloxone data. The animals were observed at 15 sec intervals, and the presence of drinking at each interval is indicated in the figure with a small black rectangle. A continuous black column indicates drinking was observed on a number of consecutive sampling intervals. The columns (representing individual patterns) are transected horizontally by lines indicating blocks of 2.5 min duration. Data for the first 20 min of the session are shown; little or no drinking occurred afterwards. Comparable data for the naltrexone (10.0 mg/kg) group are shown in the right hand panel.

trexone, at low to moderate doses, do not suppress schedule-induced polydipsia [6,24]. The lack of effect is particularly striking, given the wealth of evidence for suppression of drinking by opiate antagonists in many other circumstances (see the Introduction). The second experiment simply sought some confirmation that schedule-induced polydipsia is indeed refractory to the suppressant effects of two antagonists, naltrexone and diprenorphine.

EXPERIMENT 2

METHOD

Animals

The subjects were 5 male Sprague-Dawley derived rats (Holtzman Co, Madison, WI) weighing between 335 and 375 g at the start of the experiment. The rats were housed individually in a large colony room. The colony room was maintained at 22°C, which was illuminated between 7.00 a.m. and 7.00 p.m. The animals were reduced to 85% free-feeding weight by restricted feeding, but were allowed continuous access to water. The food was Rodent Laboratory Chow No. 5008, (Ralston Purina Co., St. Louis, MO).

Procedure

The schedule-induced polydipsia tests were conducted in two rat chambers (Model 1110, Grason-Stradler, Co., West Concord, MA), each housed in a light-proof, sound attenuating, and ventilated cubicle. Water intake was measured from a 50 ml graduated cylinder fitted with a metal drinking spout that was insulated except at the tip. The spout was positioned 3.5 cm above the grid floor, and was connected to a contact relay drinkometer (Model DR-901), BRS/LVE, Beltsville, MD), and licks were recorded on a counter and a cumulative recorder.

At the start of each 75 min session, animals were placed in the chamber and 45 mg food pellets (P.J. Noyes, Lancaster, NH) were delivered every 75 sec. A total of 60 pellets were delivered each session. Animals had continuous access to water, from the graduated cylinder. After daily training sessions to attain stable baselines in total licking activity, each rat was pretreated with naltrexone HCl (3.0 mg/kg), diprenorphine HCl (3.0 mg/kg) or isotonic saline, on three test occasions. Drugs were administered SC, 30 min before each test session, and doses are expressed as the free base. At least 48 hr intervened between each drug trial, and each rat received a different order of injection.

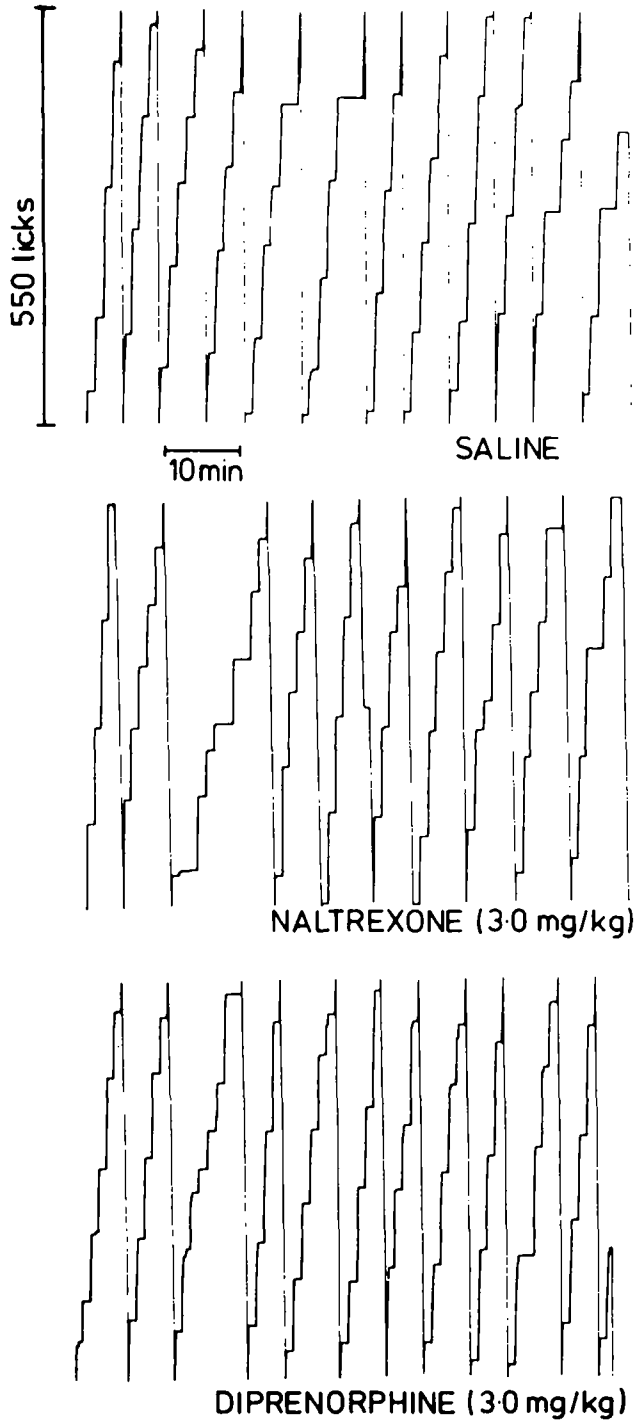

FIG. 2. Cumulative records of licking activity for a single representative rat which exhibited schedule-induced polydipsia in response to the delivery of a single food pellet every 75 sec. The records show schedule-induced polydipsia after injection of isotonic saline, naltrexone 3.0 mg/kg and diprenorphine 3.0 mg/kg respectively (top to bottom). The vertical scale indicates the number of licks, with automatic reset after 550 licks. The horizontal scale indicates the time. Each session lasted 75 min. For the group of 5 rats tested, there was no evidence of drug-induced suppression of water intake or licking activity, confirming an earlier report [6].

Water intake data were converted to ml of water intake per kg body weight, and licking activity is expressed as licks per min for comparability with the results of a previous study [6]. A correlated t-test was used to access the significance of any drug treatment effect.

RESULTS AND DISCUSSION

The naltrexone (3.0 mg/kg) and diprenorphine (3.0 mg/kg) treatments had no effect on the schedule-induced polydipisa. Mean intakes of water for saline, naltrexone and diprenorphine conditions were 58.1, 58.7 and 60.3 ml/kg respectively. The mean corresponding lick rates were 83.1, 85.0 and 86.1 licks/min respectively. Cumulative records for a single representative rat are shown in Fig. 2.

It has previously been reported that neither naloxone (0.1–10 mg/kg) nor naltrexone (0.1–10 mg/kg) had any effect on schedule-induced polydipsia in the rat, using procedures very similar to those used in the present study [6]. The results obtained here confirm that schedule-induced polydipsia is completely resistant to doses of opiate antagonists greater than those which reliably suppress drinking in water-deprived rats (e.g., [4, 6, 10]). Clearly, opiate antagonists do not simply inhibit or interfere with the motor responses required in the act of drinking. Furthermore, whatever factors maintain the constant high levels of drinking which are characteristic of schedule-induced polydipsia (Fig. 2), they appear to be unaffected either by opiate antagonists or by substantial water preloads [30].

GENERAL DISCUSSION

Analysis of patterns of drinking in the rat following water deprivation, indicate that opiate antagonists do not delay the onset of drinking and may have only the slightest of effects within the first 2 min, or so, of the initial bout of drinking. On the basis of Experiment 1 and other evidence [6,37], opiate antagonists suppress drinking from about 2 or 2.5 min onwards, during the time when drinking in control animals begins to be reduced [21]. Figure 1 suggests that naloxone and naltrexone simply advance the time-course of satiation, as opposed to producing any abnormal disruption of water ingestion. Rats typically indicate thirst satiation with intermittent breaks from drinking, and a shortening of the drinking episodes themselves (Fig. 1). Naloxone and naltrexone-treated rats did not depart from this temporal sequence but showed the signs of satiation earlier. The equivalence between water preloads and opiate antagonists, discussed above, is strongly suggestive that opiate antagonist treatment introduces a satiety signal which leads to a premature retardation of drinking activity.

Recently, increasing attention has been devoted to the effects of opiate antagonists on fluid consumption in relation to taste or palatability factors. Opiate antagonists suppress saccharin and sucrose intake [13, 14, 22, 25, 26, 28, 38, 39]. A palatable taste is a powerful incentive to drink excessively [17,33], and opiate antagonists may act to reduce the reward of a sweet taste [14,25]. What is not known, at present, is whether or not the putative satiety signal introduced by opiate antagonist treatment is sufficient to account for their reported effects on the consumption of flavored liquids. It is possible that a decrease in the reward of palatable fluids is closely associated with the induction of thirst satiety.

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