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The Effects of Food Schedule Adaptation on the Ability of Naloxone to Suppress the Acquisition of Schedule-Induced Polydipsia

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GETER, B., M. A. KAUTZ, C. L. WETHERINGTON AND A. L. RILEY. *The effects of food schedule adaptation on the ability of naloxone to suppress the acquisition of schedule-induced polydipsia.* PHARMACOL BIOCHEM BEHAV **38**(1) 85–92, 1991.— Naloxone suppressed the acquisition of schedule-induced polydipsia (SIP) in rats given no previous exposure to the feeding schedule. Adaptation to the feeding schedule prior to SIP acquisition attenuated this suppression. Specifically, water consumption, bout probability, licks/bout and maximum lick rates during the interpellet interval (IPI) were significantly increased by adaptation. Although adaptation attenuated the suppressive effects of naloxone on SIP, this attenuation was not complete. Adapted, naloxone-treated subjects displayed both decreased water consumption and bout probability as compared to distilled water-treated controls. Unlike the effects of adaptation on naloxone's suppression of SIP, adaptation completely eliminated naloxone's suppression of feeding. That adapted subjects ate at control levels while still displaying a lower level of SIP suggests that the suppressive effect of naloxone on the acquisition of SIP is not an indirect effect of naloxone on feeding, but rather a direct effect of naloxone on developing SIP. Given that naloxone has a general suppressive effect on drinking (including SIP), what remains to be determined is why naloxone has no effect on established SIP. Possible explanations for this are discussed.

Schedule-induced polydipsia Naloxone Food adaptation Opiates and drinking Opiates and feeding

THE role of the opiates in ingestive behavior has been of interest to researchers since 1929 when Flowers and his colleagues reported that the exogenous opiate, morphine, increased water intake in rats (6). In 1963, Martin reported that morphine had the ability to increase food intake as well as water ingestion (17). Since the discovery of the endogenous opiate ligands (12,14), attempts have been made to identify the effects of these endogenous compounds on ingestive behavior. Grandison and Giudotti (9), for example, demonstrated that when the endogenous opioid, beta-endorphin, was injected into the ventromedial region of the hypothalamus, feeding was increased in rats. Thus it has been shown that both exogenous and endogenous opioid compounds

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influence ingestive behavior (18,19).

Consistent with these findings is the fact that the opiate antagonist, naloxone hydrochloride, suppresses food intake in the rat. Holtzman (11) demonstrated that rats deprived of food for 48 hours and subsequently injected with doses of naloxone ranging from 0.3 to 10 mg/kg decreased food consumption during a two-hour period in a dose-dependent manner. Since Holtzman's finding, it has been reported that naloxone and a variety of other opiate antagonists (e.g., naltrexone and diprenorphine) decrease both food and water intake under a range of experimental procedures. Naloxone, for example, suppresses food intake in hypothalamically obese rats (13), in rats subjected to tail-pinch stress (16) and in rats receiving electrical stimulation of the lateral hypothalamus (2). Additionally, naloxone suppresses drinking induced by hypertonic NaCl (4), angiotensin (27) and chlorodiazepoxide (3).

Despite naloxone's capacity to affect food and water consumption under a wide variety of experimental conditions, it has failed to suppress drinking induced by the spaced delivery of food, i.e., schedule-induced polydipsia or SIP (1, 15, 31). Brown and Holtzman (1), for example, demonstrated that naloxone at doses as low as 0.1 mg/kg suppressed drinking in water-deprived rats, while a 10 mg/kg dose failed to affect SIP. Recently, however, Riley and Wetherington (24) reported that developing SIP is suppressed by naloxone. Rats given a 10 mg/kg injection of naloxone during the acquisition of SIP exhibited retarded acquisition relative to vehicle-injected rats. Consistent with prior research (see above), when naloxone was given once SIP had been established, there was little effect.

A study by Sanger and McCarthy (28) suggests that adaptation to the feeding schedule may be the basis for the differential effects of naloxone on the acquisition and maintenance of SIP. In an attempt to determine the effects of adaptation to the feeding schedule on the suppressive effects of naloxone on food-deprived eating, they exposed rats to food for 6 hours each day until all animals were consuming similar quantities of food prior to injecting them with either 0.1, 1.0 or 10 mg/kg of naloxone. Similarly injected control animals were not food adapted. Whereas naloxone suppressed food consumption in nonadapted subjects by 26%, 40% and 53%, respectively, it had only a marginal effect in food-adapted subjects, suppressing consumption of food by 6%, 2% and 7%, respectively. These findings suggest that the differential effects of naloxone on developing and established SIP may result from differential effects of naloxone on feeding during the acquisition and maintenance of SIP. That is, given that animals receive no adaptation to the feeding schedule when naloxone is administered at the outset of SIP training and that animals receive adaptation to the feeding schedule when naloxone is given once SIP has been established, it is possible that naloxone is differentially affecting food consumption during acquisition and maintenance. The effects of naloxone on SIP acquisition thus may be a by-product of the effects of naloxone on feeding, i.e., animals do not drink because food consumption is suppressed. Indeed, this possibility is consistent with Riley and Wetherington's (24) observation that, while naloxone suppressed food consumption throughout the acquisition phase, it did not affect food consumption once SIP was established.

If the naloxone-produced suppression of SIP during acquisition is a by-product of naloxone's suppression of feeding and if naloxone's effect on feeding is attenuated by adaptation to the feeding schedule, then adaptation to the feeding schedule *prior* to the acquisition of SIP should attenuate naloxone's suppressive effects on feeding and, in turn, on SIP acquisition. This prediction was tested in the present study by examining the effects of naloxone on water and food intake during the acquisition of SIP in rats already adapted to the feeding schedule.

METHOD

Subjects

The subjects were 48 experimentally naive, female rats of Long-Evans descent (mean weight = 246.5 g), approximately 90 days of age at the beginning of the experiment. They were housed in individual wire-mesh cages and were maintained on a 12-h light/12-h dark cycle and at an ambient temperature of 23°C. Water was continuously available in the home cage.

Apparatus

The four identical chambers (26.5 × 19.2 × 16.0 cm) had sides and ceiling made of 0.6-cm clear Plexiglas and a grid floor constructed of 0.4-cm diameter stainless-steel rods spaced 2 cm apart. A 1 × 3 cm food hopper was centered on the front wall 3 cm above the grid floor. A graduated Nalgene drinking tube located outside the chamber was positioned such that the Girton metal drinking spout was flush with the outer wall 3 cm above the grid floor and 7 cm to the left of the hopper. Licks were detected by a drinkometer (Lafayette Model 55008). A continuously illuminated 28-V houselight was centered on the front wall of each chamber 13.5 cm above the grid floor. All schedule events were programmed on a TRS-80 Model III microcomputer interfaced to the chambers via an Alpha Interfacer 80 that also recorded all lick responses. For a detailed description of both the hardware and software used in the conduct of this research, see Riley, Schoening and Wetherington (23).

Procedure

Phase I: Food adaptation. Subjects were randomly divided into three groups (n = 16 per group) and given either 0, 10 or 20 days adaptation to a fixed-time 60-s (FT 60) schedule in which a single 45-mg Noyes pellet was delivered every 60 s for a total of 60 pellet deliveries. Food intake was recorded after each session. Water was not available in the chambers during these sessions.

Phase II: Acquisition. Subjects in each of the three groups were further randomly divided into two groups (n = 8 per group) and were given an intraperitoneal injection of either naloxone hydrochloride (10 mg/kg) or an equivolume of distilled water 15 min prior to each session, resulting in Groups 0W, 0N, 10W, 10N, 20W and 20N. For each group, 0, 10 and 20 refer to the number of days of food adaptation and W (water) and N (naloxone) refer to the solution injected prior to each session. All subjects received food according to the same FT 60 feeding schedule as in Phase I. Water was continuously available via the graduated Nalgene tubes. After each session, total water and food intake were recorded for each rat and lick data were stored to disk. This phase was in effect for 10 consecutive days. Throughout both phases, subjects received food supplements after sessions to maintain weights at 85%.

Drugs

Naloxone hydrochloride was prepared as 1 mg/ml in distilled water and injected in a volume of 1 ml/kg of body weight. Naloxone was generously supplied by DuPont Pharmaceuticals, Inc.

RESULTS

The comparison of interest is naloxone's effects on SIP acquisition in rats nonadapted and in rats adapted to the feeding schedule. An unexpected result, however, was that food adaptation itself had a suppressive effect on SIP acquisition, i.e., the control baselines of SIP varied with adaptation. Based on Kruskal-

Wallis One-Way Analysis of Variance ($p<0.05$) of group means averaged on Days 1–5 and 6–10 of the acquisition phase, subjects in the three distilled water-treated groups varied in mean water consumption, mean probability of postpellet licking and mean number of licks/bout. For example, on Days 6–10 the adapted, distilled water-treated groups (i.e., Group 10W and 20W) consumed less water than did the nonadapted, distilled water-treated group (i.e., Group 0W), H(1) = 5.83 and 4.86, respectively. On Days 6–10, Group 20W attempted significantly fewer bouts than Group 0W, H(1) = 3.57. In addition, Groups 10W and 20W made significantly fewer licks/bout than the nonadapted group on Days 1–5, H(1) = 5.77 and 5.77, respectively, and 6–10, H(1) = 6.82 and 6.82. Given that adaptation alone had a suppressive effect on SIP, the data for each naloxone-treated group are presented as the percent shift from its respective distilled water-treated control across the 10-day acquisition period, i.e., [(naloxone − distilled water)/(distilled water group)]*100. All statistical comparisons are made on these percent shifts and are based on Kruskal-Wallis One-Way Analysis of Variance with $p<0.05$. All between-group comparisons during the 10-day acquisition period are based on group means averaged on Days 1–5 and 6–10.

Water Consumption

Figure 1 presents mean absolute water consumption during the 10-day acquisition period for the distilled water (top panel) and naloxone (middle panel) groups. The bottom panel shows the percent shift in mean absolute water consumption between each naloxone group and its respective distilled water-treated control group. On Day 1 of SIP acquisition, the mean water consumption for subjects in Group 0N was 81% less than that for subjects in Group 0W; consumption for subjects in Group 10N was 55% less than that for subjects in Group 10W, and consumption for subjects in Group 20N was 44% less than that for subjects in Group 20W. For each group comparison, the percent shifts did not consistently vary over sessions.

The mean percent shift in water consumption for Group 0N was significantly greater than that for Groups 10N and 20N on Days 1–5, H(1) = 6.82 and 6.82, respectively, and Days 6–10, H(1) = 6.82 and 6.82, respectively. The percent shifts for Groups 10N and 20N did not differ for either of these comparisons.

Bout Probability

As presented in the bottom panel of Fig. 2, on Day 1 of SIP acquisition the mean bout probability of postpellet licking (i.e., the number of interpellet intervals containing at least one lick divided by 60, the total number of interpellet intervals within a session) for subjects in Group 0N was 52% less than that for subjects in Group 0W, for subjects in Group 10N it was 42% less than that for subjects in Group 10W, and for subjects in Group 20N it was 54% less than that for subjects in Group 20N. For each group comparison, the percent shifts did not consistently vary over sessions.

The mean percent shift in bout probability for Groups 0N and 20N was significantly greater than that for Group 10N on Days 1–5 H(1) = 6.82 and 6.82, respectively, and 6–10, H(1) = 6.82 and 5.77, respectively, of acquisition. Groups 0N and 20N did not differ in percent shifts for either of these comparisons.

Licks/Bout

As presented in the bottom panel of Fig. 3, on Day 1 of SIP acquisition the mean number of licks/bout (see above) for subjects in Group 0N was 37% less than that for subjects in Group 0W; Group 10N, 17% less than that for subjects in Group 10W; and Group 20N, 24% more than subjects in Group 20W. For each group comparison, the percent shifts did not consistently vary over sessions.

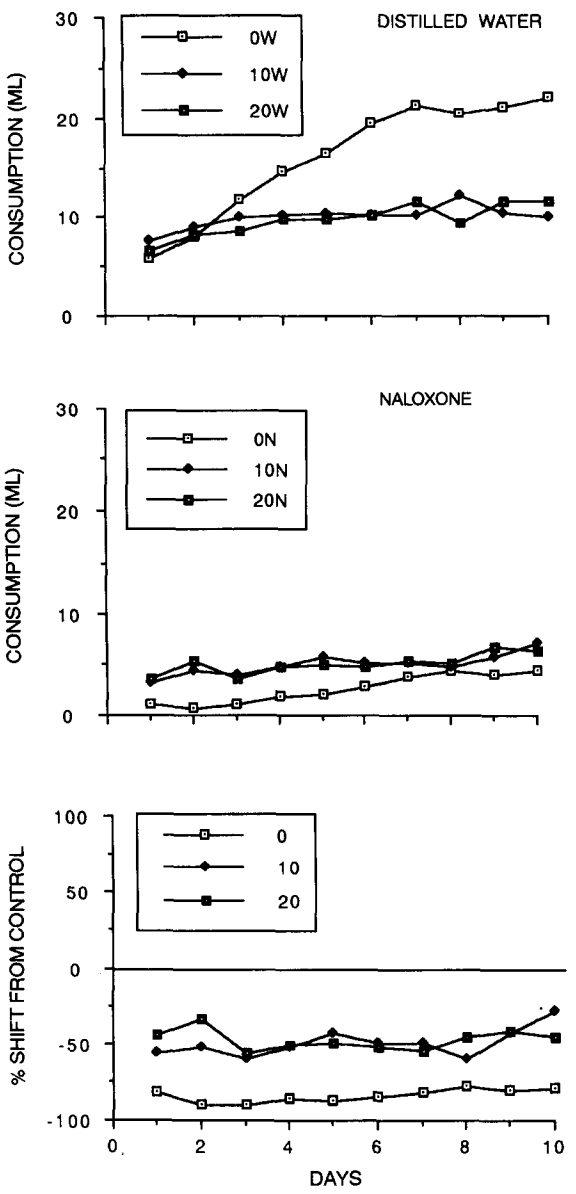

FIG. 1. Mean absolute water consumption for subjects in distilled water-treated (top panel) and naloxone-treated (middle panel) groups during acquisition. Bottom panel presents percent shift in mean absolute water consumption between naloxone-treated groups and their respective distilled water-treated control groups.

The mean percent shift in number of licks/bout was significantly greater for Group 0N than for Groups 10N and 20N on Days 1–5, H(1) = 6.82 and 6.82, respectively, and 6–10, H(1) = 6.82 and 6.82, respectively, of acquisition. The percent shift for Group 20N was greater than for Group 10N for each of these comparisons, H(1) = 3.94 and 4.82, respectively.

Temporal Distribution of Licking

Figure 4 illustrates the postpellet temporal distribution of lick-

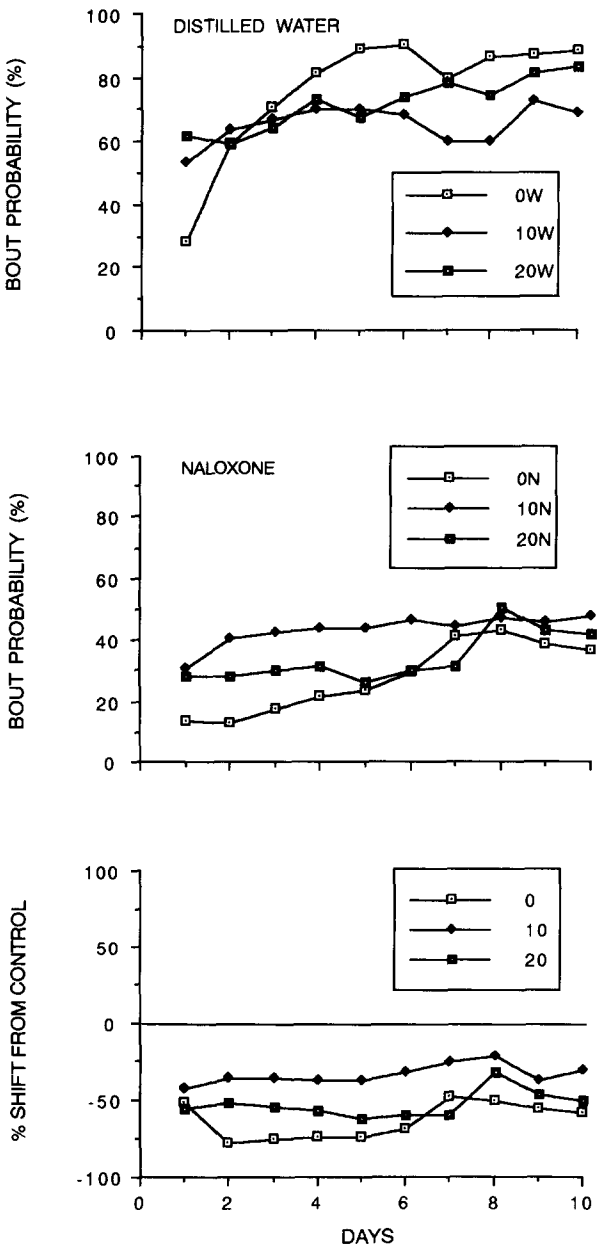

FIG. 2. Mean bout probability for subjects in distilled water-treated (top panel) and naloxone-treated (middle panel) groups during acquisition. Bottom panel presents percent shift in mean probability of postpellet licking between naloxone-treated groups and their respective distilled water-treated control groups.

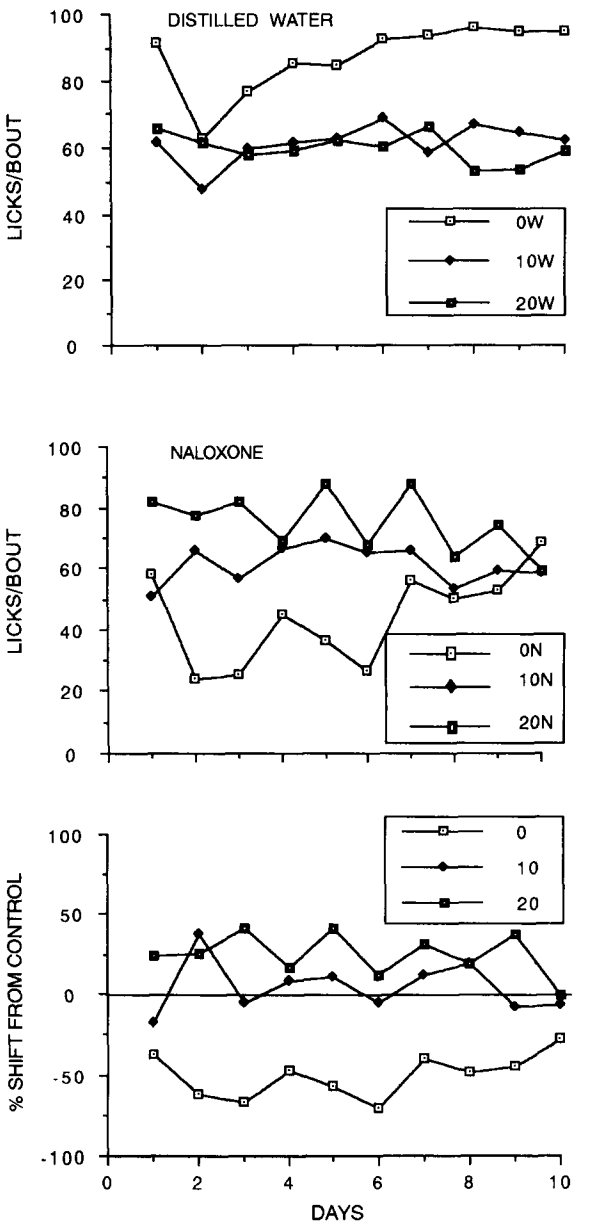

FIG. 3. Mean licks per bout for subjects in distilled water-treated (top panel) and naloxone-treated (middle panel) groups during acquisition. Bottom panel presents percent shift in mean number of licks per bout between naloxone-treated groups and their respective distilled water-treated control groups.

ing in consecutive 5-s bins of the 60-s IPI averaged for each attempted bout over the 60-min session. As illustrated in Panel A, on Day 1 subjects in Group 0W displayed evenly distributed mean lick rates across the IPI. By Day 3, a licking pattern emerged typical of SIP, i.e., an initial low rate of licking immediately postpellet followed by a sharp increase in Bin 2 or 3 with lick rates then decreasing for the remainder of the IPI. Over sessions, maximum lick rates increased and mean lick rates decreased in the latter third of the IPI. (Due to equipment failure, the lick rates for Day 10 are missing.) Similar to subjects in Group 0W, subjects in Group 0N (Panel B) displayed evenly distributed mean lick rates on Day 1 of SIP acquisition. These subjects, however, did not display a typical SIP temporal distribution until Day 8. In comparison to Group 0W, Group 0N displayed suppressed maximum lick rates that occurred late in the IPI and overall more late interval licking.

Panel C shows that subjects in Group 10W displayed a licking pattern typical of SIP on Day 1 of acquisition. Over sessions, maximum lick rates increased and mean lick rates decreased in the latter third of the IPI. Conversely, subjects in Group 10N (Panel D) displayed evenly distributed mean lick rates on Day 1

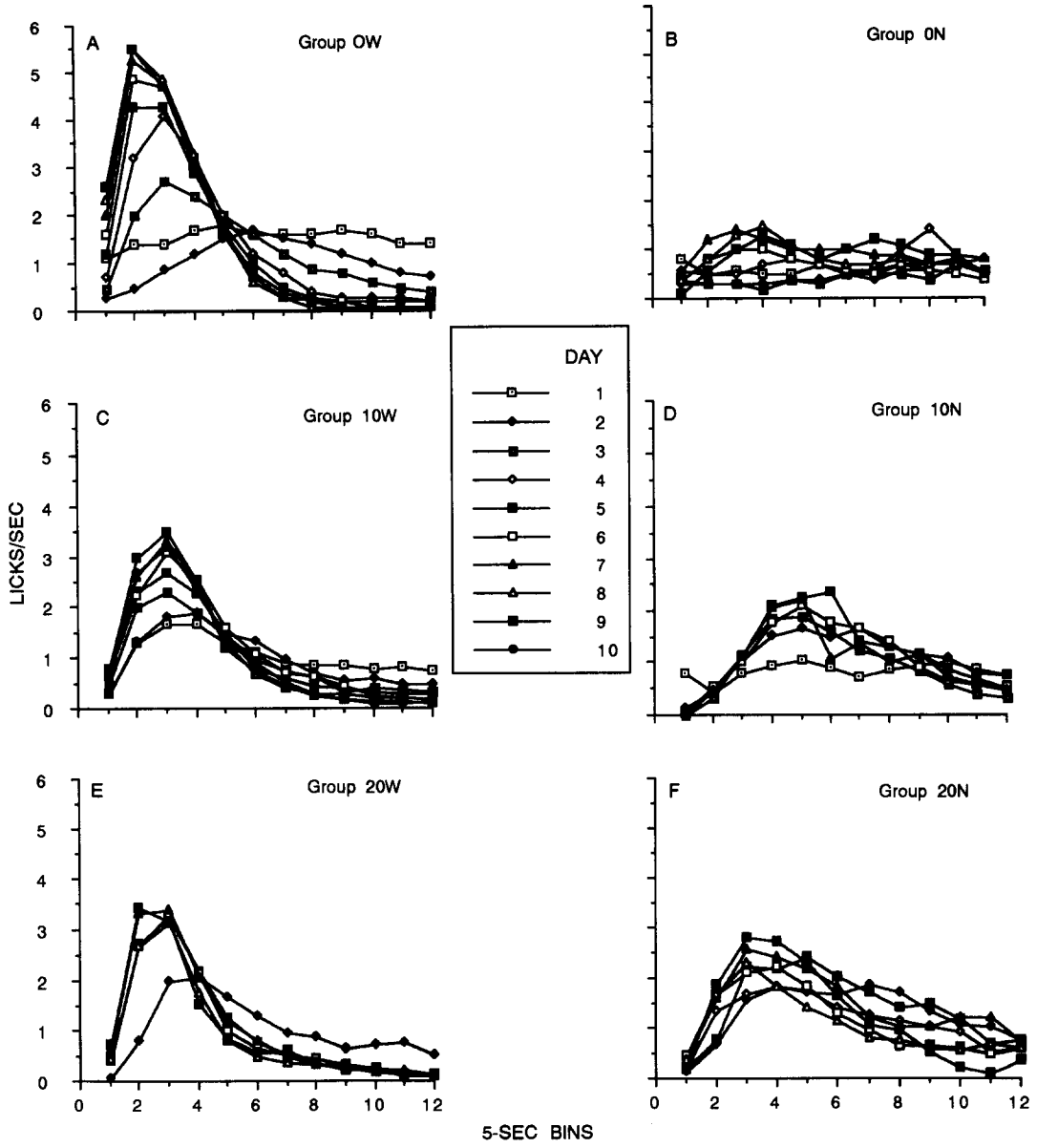

FIG. 4. Mean licks per second across consecutive 5-s bins within the interpellet interval during acquisition for subjects in each of the six groups. Due to equipment malfunction, the following days are missing for each group: Group 0W, Day 10; Group 0N Days 5 and 10; Group 10W, Days 4 and 7; Group 10N, Days 4, 8, 9 and 10; Group 20W, Days 1, 3, 4 and 10; and Group 20N, Days 1, 3 and 10.

of SIP acquisition. Over sessions, maximum lick rates increased. Subjects in Group 10N did not display a typical SIP temporal distribution until Day 7. As compared to subjects in Group 10W, the maximum lick rates for these subjects were reduced and shifted to the right in the interval. Furthermore, these subjects showed overall more late interval licking than subjects in Group 10W.

Subjects in Group 20W (Panel E) displayed a typical SIP licking pattern on Day 1 of acquisition. Over sessions, maximum lick rates increased. As depicted in Panel F, subjects in Group 20N displayed evenly distributed mean lick rates on Day 2 of acquisition. (Due to equipment failure, lick rates for Day 1 are incomplete.) By the fourth session, a licking pattern emerged typical of SIP. As compared to subjects in Group 20W, the maximum lick rates for these subjects were reduced and shifted to the right in the interval. Furthermore, these subjects showed overall more late interval licking than subjects in Group 20W.

Pellet Consumption

The mean pellet consumption for subjects in each of the adapted groups (i.e., Groups 10W, 10N, 20W and 20N) was approximately 59 pellets (from the 60 presented) by the end of the adaptation phase. At no point during adaptation was there any significant difference in mean pellet consumption between subjects in Groups 10W and 10N and between subjects in Groups 20W and 20N. On Day 1 of SIP acquisition, subjects in Group

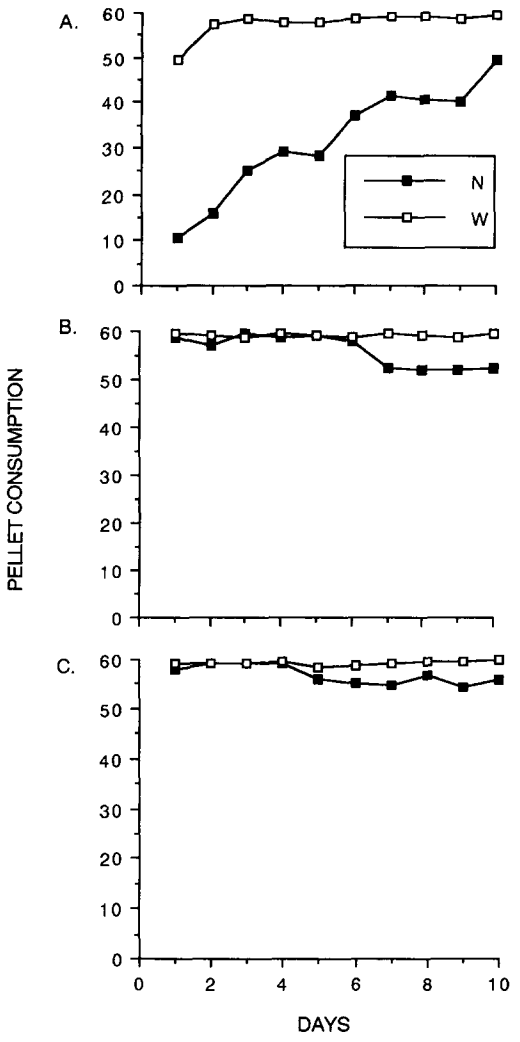

FIG. 5. Mean pellet consumption during acquisition for subjects in Groups 0N and 0W (A), Groups 10N and 10W (B) and Groups 20N and 20W (C).

0W consumed a mean of 49.5 pellets (see Fig. 5, Panel A). Mean pellet consumption reached 57.5 by Day 2 and remained at this level throughout acquisition. Subjects in Group 0N consumed a mean of 10.5 pellets on Day 1 and gradually increased consumption over sessions, reaching a mean of 49.63 pellets on Day 10. Mean pellet consumption on Days 1–5, $H(1) = 11.29$, and 6–10, $H(1) = 3.78$, for Group 0W was significantly greater than that for Group 0N.

Subjects in Group 10W consumed approximately 59 pellets/day throughout acquisition. Subjects in Group 10N also consumed pellets at this level for the first six days of acquisition. For the remainder of this phase, mean pellet consumption decreased to 52.34 pellets, reflecting a change in the pellet consumption of a single subject. Mean pellet consumption between Groups 10W and 10N did not differ on Days 1–5 and 6–10 of acquisition.

Mean pellet consumption for subjects in Group 20W was approximately 59 pellets/day throughout acquisition. Subjects in Group 20N also consumed pellets at this level for the first five days of acquisition. For the remainder of this phase, mean pellet consumption decreased to 55.32 pellets, reflecting a change in the pellet consumption of a single subject. Mean pellet consumption between Groups 20N and 20W did not differ on Days 1–5 and 6–10 of acquisition.

Among the three distilled-water-treated groups, the mean number of pellets consumed on Days 1–5 during acquisition was significantly less for the nonadapted group (i.e., Groups 0W) than for the two adapted groups [i.e., Groups 10W and 20W; $H(1) = 10.77$ and 10.68, respectively]. On Days 6–10, the mean number of pellets consumed did not differ between subjects in Group 0W and in Group 10W, although the mean number was significantly less for subjects in Group 0W than for subjects in Group 20W, $H(1) = 5.27$. There were no significant differences between Groups 10W and 20W for either of these comparisons (i.e., Days 1–5 and 6–10). Among the three naloxone-treated groups, the mean number of pellets consumed on Days 1–5 during acquisition was significantly less for the nonadapted group (i.e., Group 0N) than for the adapted groups [i.e., Groups 10N and 20N; $H(1) = 11.32$ and 11.31, respectively]. On Days 6–10, the mean number of pellets consumed was significantly less for subjects in Group 0N than for subjects in Group 10N, $H(1) = 5.61$, but was not different between subjects in Group 0N and 20N or between subjects in Groups 10N and 20N.

DISCUSSION

Similar to its effects on polydipsic consumption, naloxone dramatically suppressed food consumption in nonadapted animals. However, the effects of adaptation on naloxone's suppression of feeding and drinking were markedly different. Whereas adaptation only partially attenuated naloxone's suppressive effects on SIP, it completely eliminated naloxone's suppressive effects on feeding. Throughout acquisition, adapted naloxone-treated subjects ate at control levels. That adapted subjects displayed a lower level of SIP while still eating at control levels indicates that naloxone's effects on feeding and drinking can be dissociated by adaptation to the feeding schedule. These findings also indicate that the suppressive effect of naloxone on the acquisition of SIP [Group 0N; see also (24)] is not totally due to suppressed feeding.

That the suppression of the *acquisition* of SIP by naloxone is not totally due to the indirect effect of naloxone on feeding suggests that naloxone may be directly affecting polydipsia, an effect consistent with other reports demonstrating the suppression of drinking by naloxone in a variety of experimental conditions [see (3, 4, 27)]. Given the general effects of naloxone on drinking (including SIP), what remains to be determined is why naloxone has no effect on *established* SIP.

The relative insensitivity of established SIP to naloxone is consistent with other reports assessing the effects of various manipulations on established SIP. For example, Riley, Lotter and Kulkosky (22) demonstrated that established schedule-induced saccharin consumption was only marginally and temporarily affected by conditioned taste aversions (CTAs). Specifically, animals induced to drink saccharin by spaced food delivery were poisoned with lithium chloride (LiCl) following the schedule-induced saccharin consumption. Although schedule-induced drinking was reduced on the following exposure to saccharin, this aversion rapidly extinguished, an effect that is in marked contrast to the generally slow extinction of aversions tested under water deprivation or under ad lib feeding and drinking conditions [e.g., (10,21)]. Similar results on the resistance of established SIP to suppression have been reported with amphetamine (34) and with water and saline preloads (20). Interestingly, each of the aforementioned manipulations readily suppresses SIP acquisition. That CTAs and other manipulations have been unable to markedly suppress established SIP suggests that once the behavior is reliably elicited, it is difficult to suppress. This possibility is sup-

ported by Riley, Wetherington, Wachsman, Fishman and Kautz (26) who examined the effects of conditioned taste aversions on the specific components underlying schedule-induced consumption. They reported that the decrease in SIP by CTAs was effected primarily by a decrease in the number of licks/bout, particularly those licks occurring between 10 and 20 s after pellet delivery. Bout initiation and licking immediately postpellet (i.e., within the first 10 s following pellet delivery) were most resistant to suppression and appeared to be responsible for the relative insensitivity of established schedule-induced drinking to CTAs. Given that bout initiation is resistant to CTAs, these animals suppress fluid consumption by decreasing the number of licks/bout. This modifiability of the frequency of interpellet licking is consistent with the present data. In the present paper, during acquisition (before bout initiation was well established) naloxone suppressed SIP in adapted subjects by decreasing the number of bouts initiated. In turn, these subjects were able to compensate partially by increasing lick frequency when bouts were initiated [see also (5, 7, 8, 33)]. In the report of the effect of CTAs on SIP, once SIP was established and bout probability was high and resistant to suppression, animals modulated the amount of water consumed by varying the number of licks/bout. Thus modifying the number of licks/bout seems to be the mechanism in effecting changes in intake when manipulations disrupt SIP.

Given the differential effects of various manipulations on the acquisition and maintenance of SIP, it remains to be determined at which point SIP becomes insensitive to naloxone suppression. Preliminary data from this laboratory indicate that naloxone has no effect on SIP five days into acquisition. That bout probability is above 90% by day five of acquisition [present data; (24)] and that naloxone is unable to suppress SIP at this point (unpublished data) support the idea that once the behavior is reliably elicited, it becomes highly resistant to suppression.

Although the focus of this study was the examination of the effects of naloxone on the acquisition of SIP in animals given prior adaptation to the feeding schedule, an additional effect of adaptation on SIP was observed. Specifically, adapted, distilled water-treated subjects (i.e., Groups 10W and 20W) displayed suppressed SIP as compared to nonadapted, distilled water-treated animals (i.e., Group 0W). The disruption of the development of SIP in rats adapted to the polydipsic feeding schedule is consistent with a recent study by Tang, Williams and Falk (30) which demonstrated that food-deprived rats given approximately 128-days exposure (2 hours/day) to a food schedule similar to that used in the present study (i.e., FT 60-s) were subsequently retarded in the rate of acquisition and final level of SIP relative to animals maintained at 80% of their body weight for approximately 109 days in their living cages prior to SIP training. The present study further showed that these overall decreases in schedule-induced water consumption are associated with decreases in bout probability, licks/bout and maximum lick rates within the IPI. Although the basis for these effects of adaptation are unknown, it is possibly due to the development of "superstitious" behaviors between pellet deliveries during the adaptation period [see (29)] which later disrupted the development of SIP during acquisition.

Interestingly, in this study adapted subjects displayed more rapid development of the postpellet temporal distribution characteristic of SIP than did the nonadapted subjects. That drinking and its temporal distribution can be differentially affected by adaptation is consistent with other reports showing a dissociation of the induction of a behavior and how that behavior is temporally distributed. Riley, Wetherington, Delamater, Peele and Dacanay (25), for example, reported that although wheel running was not induced by the spaced delivery of food, when running did occur in the interfood interval its distribution was an inverted-U-shaped function similar to that found in SIP and was similarly affected by variations in the interpellet intervals. Similarly, Wetherington and Riley (32) noted that although the spaced delivery of water did not induce food consumption, when eating was evident in the interfood interval, it too displayed an inverted-U-shaped function. The fact that drinking induced by pellet delivery and its temporal distribution can be differentially affected by adaptation (the present data) and that the temporal distributions of some behaviors are present in the absence of induction suggest that the two can be dissociated [see (25,32)] and that the temporal modulating effect of the schedule is more fundamental than schedule induction [see (32)].

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