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Intravenous Self-Administration of Acetaldehyde in the Rat as a Function of Schedule, Food Deprivation and Photoperiod

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MYERS, W. D., K. T. NG AND G. SINGER. *Intravenous self-administration of acetaldehyde in the rat as a function of schedule, food deprivation and photoperiod.* PHARMAC. BIOCHEM. BEHAV. 17(4) 807–811, 1982.—The present series of experiments were conducted to discover whether rats would self-administer acetaldehyde (AcH) intravenously. The first study establishes the basic parameters for AcH self-injection in rats at 80% reduced body weight on a fixed-time 1 min (FT-1) food delivery schedule tested in the dark phase of a 12:12 light/dark cycle. The results show a dose-dependent effect with 1.3% AcH being the preferred dose as measured by the number of infusions. In the second experiment rats were on 100% free-feeding and at 80% reduced body weight, both conditions either with or without the influence of a FT-1 min schedule. The findings indicate that an interaction between dose, food deprivation and a FT-1 min schedule appears to initiate and maintain high levels of AcH self-injection in the dark. In a further experiment using 1.3% AcH the self-injection rates of animals at 80% body weight with a FT-1 min schedule reveal that the time of day of testing may be an important variable for inducing AcH intake. The results suggest that under altered environmental conditions AcH may have both an aversive and reinforcing effect.

Self-injection Body weight reduction Food delivery schedule Acetaldehyde Dark/light cycle

RECENT findings have suggested that the aversive effects of acetaldehyde (AcH), the proximate metabolite of ethanol, are mediated by peripheral toxicosis [2,12] rather than pharmacological actions of AcH in the brain [4, 8, 10]. Systemic administration of AcH has been shown to be capable of producing conditioned taste aversions in laboratory rats [8] whereas AcH is reported to be readily self-infused intraventricularly by rats during the dark but not light period of a 12:12 dark/light cycle [7]. In an attempt to explain these seemingly contradictory observations a biphasic model has been suggested whereby AcH could have both an aversive and a reinforcing effect [9].

In most of the above mentioned studies the interaction of environmental, pharmacological and nutritional factors has been neglected. The present series of experiments uses a method which permits the study of the interaction between elements in the stimulus situation in laboratory rats [27,31]. This method, which involves a combination of intravenous self-injection and scheduled food delivery has been successfully adapted to induce self-administration of ethanol in rats in our laboratory [20,29]. Testing in the light period of the dark/light cycle, an optimum response rate was obtained with rats at 80% body weight coupled with an FT-1 min food delivery schedule [20]. While at 100% body weight, the infusion rate of ethanol was found not to be significantly different from the infusion rate of saline controls. Further studies using an FT-1 min schedule showed that rats on 100% free feeding tested in the dark phase of a 12:12 light/dark cycle were also trained to self-administer ethanol intravenously [29], suggesting that the increased rate of infusion in the light with rats reduced to 80% normal body weight may be associated with arousal and increased general activity [34,35] in a period when the animals are normally inactive [5,25]. Since AcH is reported to cause behavioral effects similar to those during ethanol administration [13, 15, 22] the possibility arises that under similar conditions of intravenous self-injection rats may be induced to self-administer AcH.

Using the above method of schedule-induced self-injection (SISI) it has been possible to classify drugs into four groups [27]: some opiates like heroin [16] and ethanol [20] are self-injected without the presence of a food delivery schedule, but the role of self-injection is enhanced by the schedule. Nicotine [28] and Δ^9-Tetrahydrocannabinol (Δ^9-THC) [31] are only self-injected in the presence of a schedule. Self-injection of stimulants like amphetamine [30] and cocaine [23] is dependent on reduced body weight. Self-injection of haloperidol, a dopaminergic blocker, was not achieved with this paradigm [27]. It has also been shown that the presence of food delivery schedules leads to an increase in plasma corticosterone levels, indicative of mild stress [27]. In the present experiments the interactive effects of stress-producing schedules, body weight and light/dark cycles on AcH self-injection will be investigated and an attempt made to fit AcH into the above classification scheme for psychoactive drugs.

GENERAL METHOD

Animals

One hundred and twenty-eight experimentally naive,

male Long Evans hooded rats weighing between 380 and 400 g were used. All animals were housed individually in wire mesh cages (26×34×20 cm) under constant temperature 21±1° C and placed on a 12:12 light/dark cycle (lights on 0300 hr). Food and water were available ad lib. In experiments requiring rats at 80% of their body weight these were reduced prior to surgery and then maintained at that weight with water freely available.

Procedure

All animals were habituated to the 12:12 light/dark cycle for 14 days prior to surgery. Intravenous catheters (SP 28 Dural Plastic, o. d. 0.88 mm, i. d. 0.40 mm) were surgically implanted into the jugular vein of animals under anaesthesia (pentobarbitone sodium, 60 mg per ml; 1 ml/kg, IP) according to procedures described previously [27,29]. The rats were fitted with harnesses designed to support the implanted venous catheters, with a swivel system to allow relatively unrestricted movement. Two days following the insertion of the catheter animals were assigned to their treatment groups and tested individually in modified operant chambers for 1 hr/day over 10 consecutive days, at the same time each day. The modified operant chamber (35×32×32 cm) consisted of a bar and food pellet dispensing unit attached to one side wall. The bar operated a syringe infusion pump (Sage Instruments, model 341) which delivered 0.07 ml of AcH solution or saline when triggered. Each experiment commenced by priming the animal with an initial dose of drug or saline solution. When an animal pressed the operant bar, the pump was activated for 5 sec and an infusion of fluid (0.07 ml) was delivered into the jugular vein. During the 5 sec infusion interval, additional presses did not reactivate the pump and were not recorded. All infusions during each one hour test session were automatically monitored on cumulative recorders. In experiments when the fixed-time 1 min (FT-1) schedule was operating, Noyes food pellets (45 mg) were delivered non-contingently at the rate of one pellet per minute. The animals were not pretrained to press the bar.

Drugs

Acetaldehyde (99.5%) was supplied by B.D.H. Chemicals Australia Ltd. and was freshly prepared for intravenous administration prior to each test session by diluting it in 0.9 percent saline. The control solution consisted of 0.9 percent saline. Due to the tendency to polymerize mainly to the trimer paraldehyde [14], the AcH sample was periodically distilled before use and then diluted and stored at 4° C. The purity of the distilled AcH sample was analysed by NMR spectroscopy (Perkin-Elmer, R32A).

EXPERIMENT 1: DOSE RESPONSE PATTERNS OF ACETALDEHYDE SELF-INJECTION IN THE DARK

Since to our knowledge there have been no published studies of intravenous self-injection of AcH, an attempt was made in this experiment to establish the basic parameters. This study was carried out under optimum conditions for self-injection, i.e. in 80% body weight rats on a FT-1 min schedule in the dark [29,30].

Animals and Procedure

Six groups of eight rats were randomly assigned to the following treatments: five doses of AcH (0.375, 0.75, 1.3, 3 or 6% v/v; 0.835, 1.67, 2.89, 6.66 or 13.33 mg/kg/infusion, respectively) and a saline control. The selection of doses of AcH was based on previous experiments in which this substance was administered intraventricularly [3, 7, 8, 19] and intravenously [15,21]. For all conditions animals were at 80% reduced body weight with a FT-1 min schedule. All rats were tested 2 hours after onset of the dark period, and were weighed before each daily test session. During the entire period of experimentation all procedures were carried out under red light.

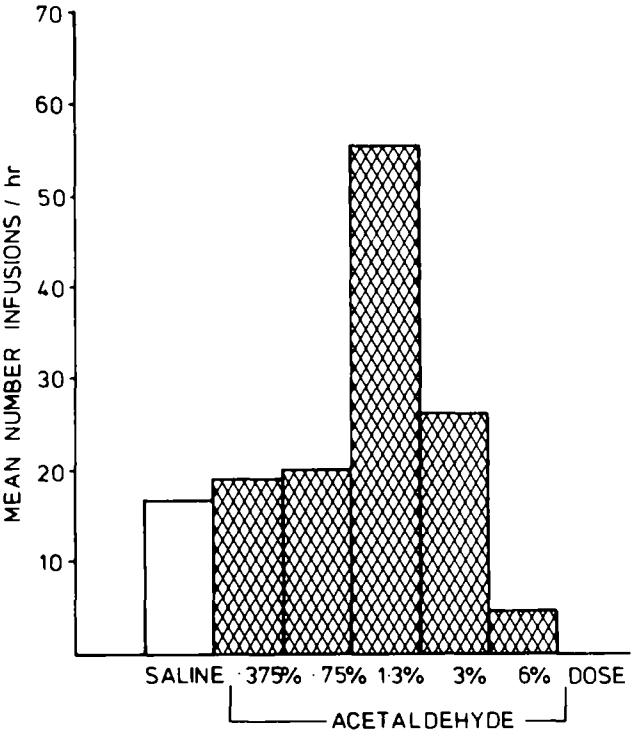

FIG. 1. The overall mean number of infusions for the control solution and Acetaldehyde at 0.375, 0.75, 1.3, 3 or 6% v/v; 0.835, 1.67, 2.89, 6.66 or 13.33 mg/kg/infusion, respectively, for animals at 80% reduced body weight and FT-1 min schedule.

RESULTS AND DISCUSSION

Figure 1 presents the mean number of infusions for all 5 dose levels of AcH and saline for the one hour daily session. The pattern of AcH self-injection over days in food deprived rats on a FT-1 min schedule is shown in Fig. 2. A two-way ANOVA with repeated measures over the days factor yielded significant main effects of drug treatments, $F(5,42)=13.213$, $p<0.001$, and days, $F(9,378)=4.156$, $p<0.001$. A significant drug × days interaction $F(45,378)=2.471$, $p<0.001$, indicates that the pattern of self-injection for animals in the 1.3% and 3% AcH groups showed an initial hyperactivity followed by a depression in the overall drug response, whereas for the 0.75% AcH group the inverse of this trend seemed to occur (see Fig. 2). Animals in the 0.375% AcH group, like animals in the saline group, gradually increased their intake over the first eight days of experimentation, but showed a depressant effect on days 9 and 10, unlike the saline group who maintained their stable

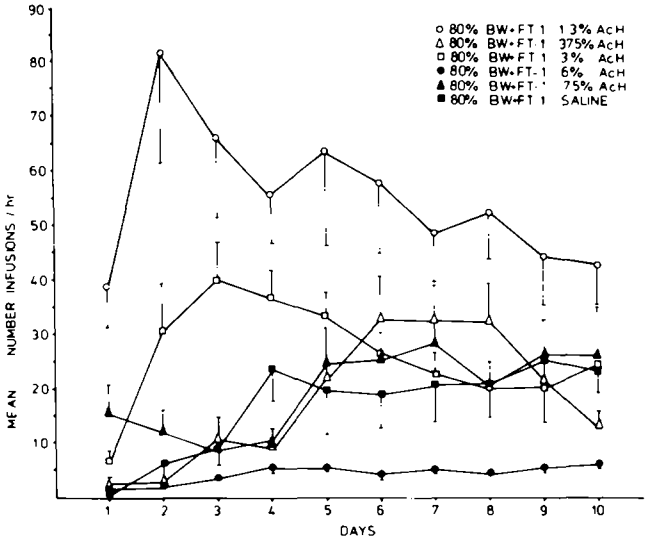

FIG. 2. Mean number of saline or Acetaldehyde infusions ±S.E.M., self-injected by rats for each daily one hour test session at 80% reduced body weight and FT-1 min schedule.

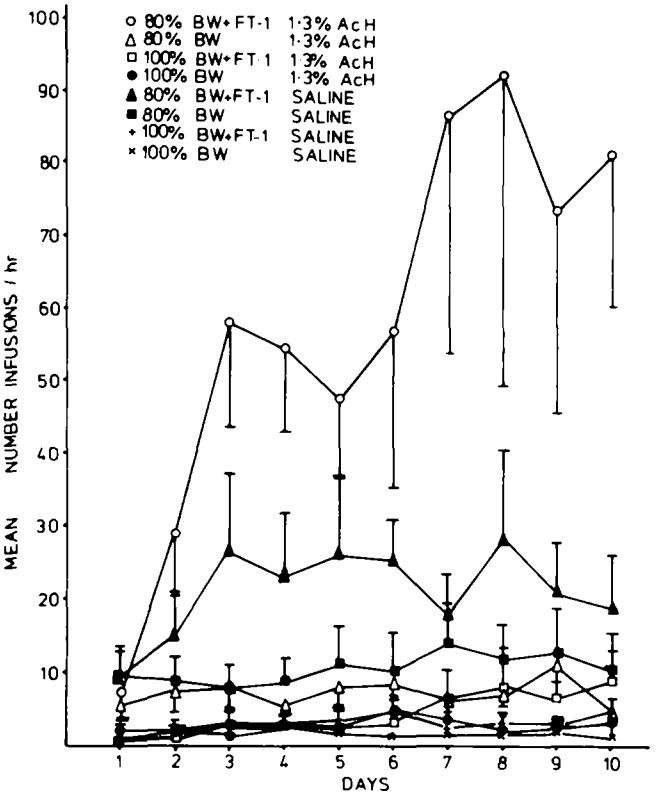

FIG. 3. The mean number of infusions for Acetaldehyde (1.3% v/v; 2.89 mg/kg) or saline ±S.E.M., for each session of the eight groups of animals.

pattern of self-injection (Fig. 2). Post hoc analyses with Newman-Keuls comparisons showed that animals at 80% body weight receiving a 1.3% AcH dose coupled with a schedule self-injected significantly more AcH ($p<0.01$) than animals on any other treatment dose. It was also found that at a dose of 3% AcH animals self-injected significantly greater amounts of AcH ($p<0.05$) than at the 6% dose. It is of interest to note that the difference in infusion rates between the 6% AcH group and the saline control group, although not statistically significant, suggests a toxic effect of AcH at the 6% dose. Analysis of the days effect showed significantly lower infusion rates on day 1 in comparison to all other experimental days (see Fig. 2), possibly indicating an effect due to "novelty" [24].

The findings thus indicate the 1.3% AcH is the optimum dose for self-injection under these conditions.

EXPERIMENT 2: EFFECTS OF ENVIRONMENTAL MANIPULATION ON ACETALDEHYDE SELF ADMINISTRATION

The aim here was to explore the interaction between elements in the stimulus situation by manipulation of internal (nutritional factor) and external (schedule) environmental conditions while making available AcH or saline for self administration.

Animals and Procedure

Eight groups of eight male Long Evans rats each were placed in the test chamber with saline or AcH (1.3% v/v; 2.89 mg/kg/infusion) available through bar pressing. For each drug or saline condition the animals were randomly allocated to the four schedule conditions: 100% body weight under FT-1 min schedule and without schedule; and 80% body weight under FT-1 min schedule and without schedule. The apparatus and procedure were identical to that described in General Method and used in Experiment 1. All rats were tested two hours after onset of the dark period under red light conditions.

RESULTS AND DISCUSSION

A four-way ANOVA with one repeated measure applied to the data yielded a significant difference in overall infusion rates of animals in the 80% and 100% body weight groups, $F(1,56)=21.556$, $p<0.001$; a significant schedule main effect, $F(1,56)=12.258$, $p<0.001$, and days main effect, $F(9,504)=4.452$, $p<0.001$. The differences in body weight and schedule conditions over days are seen in Fig. 3. No significant difference between the overall rate of AcH and saline infusion was found. However, there were significant interaction effects between drug × schedule, $F(1,56)=4.948$, $p<0.05$, and drug × body weight × schedule conditions, $F(1,56)=4.723$, $p<0.05$, suggesting that the high rate of AcH infusion in comparison to that of saline infusion as shown in Fig. 3 depends upon a food deprivation state plus food delivery schedule. A significant body weight × schedule interaction $F(1,56)=10.317$, $p<0.01$, also indicates that when the food deprivation factor was removed the pattern of AcH intake was not maintained, regardless of whether or not a FT-1 min schedule was in operation. It thus appears that rather than any intrinsic reinforcing effect of AcH, it is the interaction of external and internal environmental stimuli that is producing the high rate of AcH self-injection (drug × body weight × schedule × days interaction was significant, $F(9,504)=1.899$, $p<0.05$).

A feature of the pattern of AcH (1.3% v/v; 2.89 mg/kg/infusion) self-administration initiated and maintained

in the present experiment is the large individual variations in AcH intake within the same experimental animal together with the increase in voluntary AcH intake over days (Fig. 3). This trend may provide some evidence to suggest that AcH could have both an aversive and reinforcing effect in the same animal and supports the proposal of Eriksson and Deitrich [10] that there are animals capable of overcoming possible temporary aversive effects of AcH. Further experiments are needed to confirm this tendency and to determine whether this is an artifact or a biphasic effect of AcH.

EXPERIMENT 3: SELF-ADMINISTRATION OF ACETALDEHYDE IN THE LIGHT

The previous results show that a moderate dose of AcH (1.3% v/v; 2.89 mg/kg/infusion) and the interaction between food deprivation state and the environmental factor introduced by a FT-1 min schedule are critical variables in the acquisition and maintenance of a pattern of AcH self-injection in the dark period of a 12:12 light/dark cycle. This experiment was designed to determine whether there was a significant difference between the rates of AcH and saline infusion under light conditions.

Animals and Procedure

Two groups of eight male Long Evans rats were used in the present study. They were randomly allocated to one of two groups: AcH (1.3% v/v; 2.89 mg/kg/infusion) or saline. All animals were at 80% reduced body weight and under a FT-1 min schedule. All procedural details are the same as in Experiments 1 and 2, except that animals were tested two hours after the onset of the light period.

RESULTS AND DISCUSSION

A two-way ANOVA with repeated measures over days showed that animals at 80% reduced body weight on a FT-1 min schedule did not show a significantly higher rate of self-injection of 1.3% AcH than of saline in the light. Neither the main effect of days nor the interaction term was statistically significant at $\alpha=0.05$.

It is of interest to compare the data from this experiment with those from Experiment 2 for animals in the saline and AcH (1.3% v/v; 2.89 mg/kg/infusion) groups at 80% body weight and FT-1 min schedule tested in the dark (Fig. 4). Inspection of Fig. 4 indicates that while overall rates of infusion for saline were consistent across light/dark conditions, 80% reduced body weight animals under FT-1 min schedule self-injected more AcH (1.3% v/v; 2.89, mg/kg/infusion) under dark than light conditions. These findings suggest that the time of day of testing appears to be as important a variable as are food deprivation state and FT-1 min schedule for inducing the animal to self-administer a moderate dose of AcH intravenously. It is possible that increased self-administration in the light may occur with some other dose of AcH.

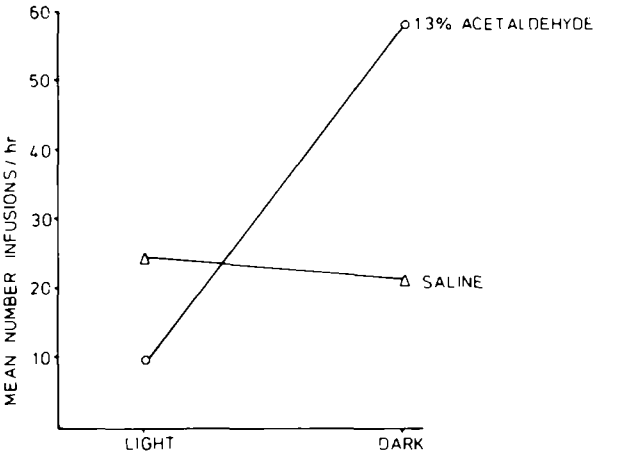

FIG. 4. The overall means of infusion for the saline and Acetaldehyde groups under light and dark conditions.

GENERAL DISCUSSION

The results of the present series of experiments have shown that to induce high levels of intravenous AcH self-injection, the interaction of pharmacological properties with a food deprivation state plus a FT-1 min schedule in the dark period of a 12:12 light/dark cycle is critical. The importance of light/dark variations in schedule-induced self-injection of AcH is consistent with findings obtained by other workers [7] who report that rats will only self-administer significantly more AcH than control solution intraventricularly under dark but not light conditions, when general activity is low. That circadian variation in activity may affect self-administration of drugs is also in agreement with reports that rats self-administer greater quantities of morphine and phenobarbital [36] and methadone [17] during the dark than during the light periods.

It is interesting to note that the rats used by Brown and associates [7] had free access to food, whereas in the present studies it was shown that animals under similar free feeding conditions did not self-administer more AcH than saline in the dark. While this may be a function of the duration of exposure of the animal to the test environment, i.e., 24 hr per day over 11 consecutive days [7] as compared to 1 hr daily over 10 consecutive days, it is also possible that this food deprivation state is a factor strong enough to overcome a temporary aversive effect of AcH self-injected intravenously, and supports the proposal that AcH may have differential effects depending on route of administration [8].

That internal variables (nutritional state) may interact with external environmental variables (schedule factors; possible effect of photoperiod on endogenous substrates) to alter the actions of intravenously self-administered AcH, suggests that the molecule alone is not sufficient for the acquisition of drug intake behavior and that the total stimulus complex needs to be considered in accounting for how this phenomenon might take place. Recent data pointing to the possibility of a change in endorphin levels in the brain and pituitary of food deprived and obese animals in response to stressing environmental manipulations [11, 18, 26] may provide important clues in a definition of the nature of the mechanisms involved in the interaction model proposed here.

Accurate assessment of the behavioral effects of AcH in animal studies has been difficult, since the actions of single doses of this substance are reportedly brief [15]. Circulating AcH is known to have a half-life of only a few minutes because it is rapidly destroyed by aldehyde dehydrogenase [33], the enzyme responsible for the oxidation of AcH to acetate [37]. Our method of schedule-induced self-injection

thus seems a promising technique in the attempt to overcome this problem since the animal can voluntarily self-inject multiple doses of AcH and is limited only by the 5 sec delay incorporated into the drug delivery system. However, further research is necessary to clarify the nature of the mechanisms involved in the mediation and regulation of intravenous AcH self-injection. In this regard we are at present involved in the determination of blood AcH and ethanol concentrations following voluntary intravenous self-administration of AcH.

From experiments reported here, it is apparent that the conditions of self-injection for AcH are similar to those found for group 2 in our classification of drugs according to acquisition patterns [27], i.e., nicotine [28] and Δ^9-THC [31] and are different from those found for ethanol [20], an FT-1 min schedule being a necessary condition for AcH, nicotine and Δ^9-THC but not ethanol self-injection.

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