Pharmacology Biochemistry & Behavior, Vol. 17, pp. 563–567, 1982. Printed in the U.S.A.

Increased Intravenous Drug Self-Administration During Deprivation of Other Reinforcers

MARILYN E. CARROLL[1] AND IRWIN N. BOE

University of Minnesota, Minneapolis, MN 55455

Received 21 December 1981

CARROLL, M. E. AND I. N. BOE. *Increased intravenous drug self-administration during deprivation of other reinforcers*. PHARMAC. BIOCHEM. BEHAV. 17(3) 563–567, 1982.—Previous research has shown that food deprivation markedly increases self-administration of a variety of drugs. The present study concerns an extension of the food deprivation effect to a range of doses and other forms of deprivation. In each experiment, etonitazene infusions were continuously available to rats under the following sequence of satiation (S) or deprivation (D) sessions: S, S, D, S, S, D, S, S, D, S, S, S. Each infusion was contingent upon a lever-press response, and session length was 24 hr. In the first experiment, five groups of rats, each receiving a different etonitazene dose: 0 (saline), 5, 10, 20 or 40 μg/kg, were tested under conditions of food satiation (free access) and deprivation (8 g food/session). Food deprivation produced no increases in responding maintained by saline, but it produced nearly parallel increases in responding across all drug doses. In the second experiment, effects of water satiation (free access) and deprivation (no water) were tested at the 10 μg/kg etonitazene unit dose. Etonitazene-maintained responding was more than twice as high during water deprivation sessions as during satiation sessions. In the third experiment, rats receiving saline infusions (after brief exposure to 10 μg/kg etonitazene infusions to elevate response rates) did not show any systematic changes in saline-maintained behavior as a result of water deprivation or satiation. In the fourth experiment, rats were allowed continuous access to food, water and etonitazene infusions (10 μg/kg). In addition, they were given a drinking solution containing 3% glucose and 0.125% saccharin (G+S). When the rats were deprived of the G+S solution, they showed small but reliable increases in etonitazene self-administration. The present results extend previous findings with food deprivation to a range of doses and other deprivation conditions, suggesting that drug-maintained behavior can be controlled by alterations in a variety of other reinforcing events in the environment.

Dose response Etonitazene Food deprivation Glucose Intravenous drug self-administration
Rats Reward deprivation Saccharin Water deprivation

RECENT research has shown that food deprivation markedly increases intravenous self-administration of amphetamine [26], cocaine [5, 12, 23], ethanol [20], etonitazene [4,5], heroin [21] and phencyclidine [5]. Food deprivation has also been shown to increase oral self-administration of etonitazene in rats [6, 7, 9, 17], and phencyclidine in rhesus monkeys [8]. The present study concerns an extension of the food deprivation effect to a range of doses and other forms of deprivation. In most previous investigations, a single drug dose or concentration was used. While a range of feeding conditions has been studied [6, 9, 12], the effect of food deprivation on dose-effect relationships has not yet been determined. It is necessary to study a range of doses to determine whether there is a parallel shift in the dose-response curve or whether the food deprivation effect occurs under limited conditions.

While the food deprivation effect has now been reported by several laboratories [4, 12, 26], the effect of other deprivation conditions on drug intake has not yet been investigated. In the present study the effect of water deprivation on intravenous etonitazene self-administration by rats was tested. Water deprivation does not produce increases in general activity [1,2] or intracranial self-stimulation [18] as food deprivation does [3, 15, 18, 22]. However, in a choice test, water-deprived rats preferred lateral hypothalamic self-stimulation (at higher intensities) to water [19]. Water deprivation has also been reported to increase hippocampal self-stimulation [18]. Another type of deprivation used in the present study did not require withholding essential liquids and nutrients, and it presumably did not result in hunger or thirst. A palatable, sweetened solution of glucose plus saccharin (G+S) was presented along with free food and water, and it was then removed every third day. It has previously been reported that this solution functions as an effective reinforcer, as rats consume quantities far in excess of water [27].

METHOD

Animals

Forty-five naive male Wistar rats (Bio-Lab, Inc., St. Paul, MN) weighing between 375–445 g were used in these experi-

[1]Send reprint requests to Marilyn E. Carroll, Psychiatry Department, Mayo Box 392, University of Minnesota, Minneapolis, MN 55455.

iments. Separate groups of naive rats (ranging from 4 to 8 per group) were used for each experimental and control condition. Prior to the beginning of the experiments, the rats were housed in individual cages in a constantly illuminated room with the temperature maintained at 24°C. After each rat was implanted with a chronic jugular catheter, he was transferred to an experimental chamber for the duration of the experiment.

Drugs

Etonitazene hydrochloride (NIDA, Research Triangle Institute) solutions were prepared weekly in sterile saline. Etonitazene doses refer to the salt. The infusion volume for both etonitazene and saline was 0.125 ml/kg, and the infusion duration ranged from 8 to 11 sec depending upon the animal's body weights. The dose was varied by changing the concentration of the etonitazene solution. The glucose (3%) plus saccharin (0.125%) solution was mixed every three days in tap water and kept refrigerated. The G+S solution was presented to the rats at room temperature.

Apparatus

The experimental chambers and details of the infusion system were identical to those previously described [5]. Responses on a left lever (infusion-lever responses) resulted in activation of an infusion pump (Milton-Roy, Model 196-3) and illumination of a white light (4.76 W) located above the lever. Responses on a right lever were counted as an index of general activity. Responses during infusions were counted, but they had no programmed consequences. Both levers were placed 10 cm from the floor of the cage to minimize lever presses resulting from nonspecific activity.

Programming and data recording were automatically controlled by standard electromechanical equipment located in an adjacent room. Lever presses and infusions were recorded at 1-hr intervals by print counters and continuously by an event recorder. Means for infusion-lever responses, infusions, activity-lever responses and food intake (in Experiments 2–4) were obtained for each rat for the three deprivation sessions and the three satiation sessions immediately preceding them. Paired *t*-tests were used to compare the satiation and deprivation data within groups.

Procedure

All rats were surgically implanted with chronic jugular catheters according to methods previously described [5] that were modified from those of Weeks [28]. After at least 4 hr of recovery in the operant chamber, the rats were allowed to receive etonitazene infusions (10 μg/kg unit dose), or saline infusions in Experiment 1, under a fixed-ratio 1 (FR 1) schedule (i.e., each response on the infusion-lever produced an infusion of etonitazene or saline). Session length was 24 hr, beginning at 11:00 a.m. During the first session, the rats' food (Purina Laboratory Chow) was placed in a wire basket approximately 10 cm above the lever in order to increase the probability of a lever press. Most rats acquired a steady rate of lever pressing on the infusion lever, and they made several responses on the activity lever during this first session; however, the procedure was repeated for those that did not. Once the rats demonstrated a substantial rate of etonitazene self-administration (more than 25 responses per session), the daily food allotment was placed in the center of the chamber floor. The saline group was also required to make contact with both levers before the daily food allotment was placed on the floor of the cage and sessions were counted. After responding stabilized at the beginning of each experiment, the rats were either food, water or G+S satiated (S) or deprived (D) according to the following sequence over 12 successive 24-hr sessions: S, S, D, S, S, D, S, S, D, S, S, S. Stability of responding was defined as no steadily increasing or decreasing trend in the number of infusions over at least three sessions. Preliminary work with IV etonitazene self-administration in rats indicated that there were no cyclic patterns in 24-hr intake, as others have reported with oral etonitazene intake over several weeks [7,11]. The 24-hr sessions were originally selected to allow for the measurement of changes in the time course of different feeding conditions [4]. Preliminary studies indicated that chronic phases of deprivation, as used in previous studies [6–9], were not compatible with 24-hr drug access in terms of the health of the animals. Furthermore, it was found that two satiation sessions after each deprivation session were sufficient to allow the animals to return to baseline response rates and to maintain their health. The three satiation sessions at the end of each 12-session sequence were used to demonstrate the absence of nonspecific cycles of activity. At the end of each experiment, the rats were each given one infusion of sodium methohexital (1.25 mg/kg) to demonstrate the patency of the cannula systems. It was inferred that the cannula was delivering the solutions intravenously if the rat was immediately anesthetized.

Experiment 1: The Effects of Food Deprivation on Etonitazene Self-Administration as a Function of Dose

Twenty-six naive rats were used in this experiment. They were divided into groups of 4, 7, 5, 5 and 5, receiving etonitazene doses of 0 (saline), 5, 10, 20 and 40 μg/kg, respectively. After a steady rate of lever-pressing behavior was demonstrated with food and water freely available, the rats were either food satiated or deprived according to the 12-session sequence already described. During satiation sessions food was freely available; during deprivation sessions, 8 g of food was provided at the start of the session.

Experiment 2: The Effects of Water Deprivation on Etonitazene Self-Administration

A group of eight naive rats was trained to self-administer etonitazene (10 μg/kg unit dose). After a steady rate of lever-pressing behavior was demonstrated with food and water freely available, the rats were either water satiated or deprived according to the 12-session sequence. During satiation sessions, water was freely available; during deprivation sessions, no water was available.

Experiment 3: The Effects of Water Deprivation on Saline Self-Administration

In Experiment 1 responding by a drug-naive saline group (0) was low or negligible, even after initial lever contact had been induced by placement of the food over the lever. However, it is questionable whether or not this control group had lever-press experience that was comparable to the drug-exposed groups at the onset of deprivation conditions. In the present experiment, a group of five naive rats was first given exposure to etonitazene (10 μg/kg/infusion) self-administration with food and water freely available in order to generate an elevated rate of saline-maintained behavior.

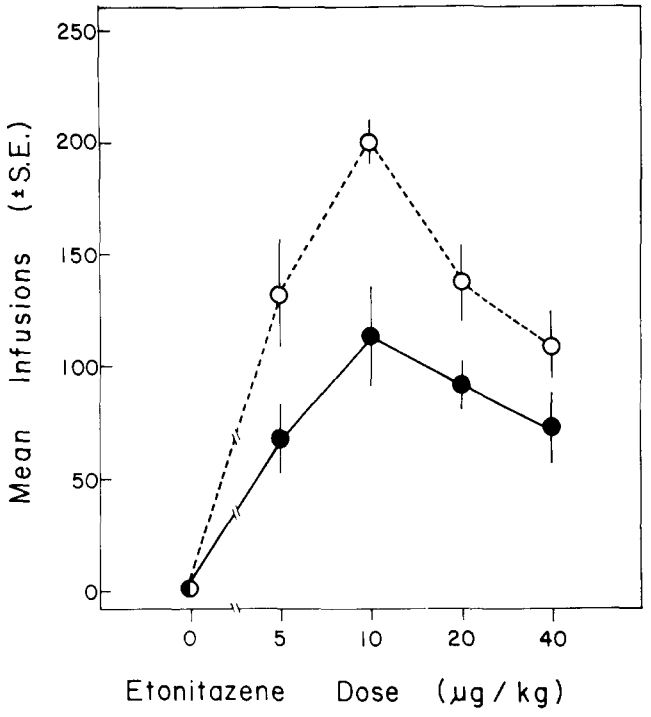

FIG. 1. Mean infusions (±S.E.) per 24-hr interval are presented for saline and four etonitazene doses. Filled circles: food satiation sessions; open circles: food deprivation sessions. Each point is a mean of three sessions × the number of rats in each group. The number of rats per group were 4, 7, 5, 5 and 5 for the 0 (saline), 5, 10, 20 and 40 µg/kg doses, respectively.

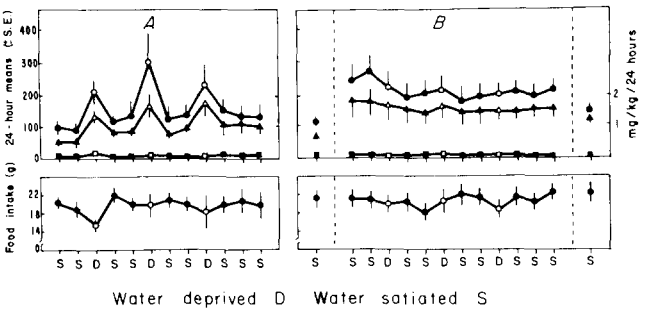

FIG. 2. Effects of water satiation (S) and deprivation (D) on etonitazene (Panel A)- and saline (Panel B)- (Connected points on Panel B)-reinforced lever responses (circles, upper frames), infusions (triangles), activity-lever responses (squares), etonitazene intake (triangles; scale on right ordinate), and food intake (circles; lower frames). Unconnected points on panel B refer to one session of etonitazene access before and after saline substitution. Filled symbols: water satiation sessions; open symbols: water deprivation sessions. Points on Panel A represent means (±S.E.) for eight rats, and points on Panel B represent means (±S.E.) for five rats.

The rats received access to etonitazene infusions for a minimum of one 24-hr session, and a criterion of 25 etonitazene infusions was required within a 24-hr period. The mean (±S.E.) number of etonitazene sessions to reach the criterion was 1.6 (±0.4). Subsequently, saline was substituted for etonitazene, and food and water remained freely available until the number of infusions were stable for at least 5 sessions. The mean (±S.E.) number of sessions required to meet the stability criterion was 8.6 (±0.9). The rats subsequently received the 12-session water satiation and deprivation sequence as previously described. At the end of this 12-session sequence, etonitazene availability was reinstated for one session. Previous research using a similar procedure with cocaine [5] and preliminary work with etonitazene showed that when saline was substituted for the drug under an FR 1 schedule, responding remained constant and resistant to extinction for several weeks. Holz and Gill [15] also reported that monkeys who previously self-injected d-methylamphetamine failed to extinguish saline-maintained responding under an FR 10 schedule after 2.5 months.

Experiment 4: The Effects of Deprivation of a Glucose and Saccharin (G+S) Solution on Etonitazene Self-Administration

A group of six naive rats was trained to self-administer etonitazene (10 µg/kg unit dose). Subsequently, the rats were given a solution of 3% glucose plus 0.125% saccharin (G+S). Food and water were always freely available. After G+S intake had stabilized, the 12-session G+S satiation-deprivation sequence was implemented. During the satiation sessions, G+S was freely available; during the deprivation sessions no G+S was available.

RESULTS

General findings throughout the four experiments were that all deprivation conditions produced increases in etonitazene-maintained responding; however, saline-maintained responding and activity-lever responding did not increase due to deprivation conditions. There were also no increases in infusion-lever responses or infusions during the last three satiation sessions in each experiment. In all experiments the number of responses were higher than the number of infusions (especially during deprivation conditions), since responding often occurred during infusions. When methohexital was injected upon completion of the experimental protocols, the rats were immediately anesthetized, indicating that the cannulae had been delivering the solutions intravenously.

Experiment 1: The Effects of Food Deprivation on Etonitazene Self-Administration as a Function of Dose

Figure 1 shows the dose-effect function during food satiation and deprivation conditions. Paired t-test comparisons of infusions during food satiation and deprivation at the four drug doses (5, 10, 20, and 40 mg/kg) revealed significant differences (t's=3.8, 6.9, 3.5, and 3.5, respectively, p's<0.05); however, there were not significant differences at the 0 (saline) dose (t=0.02, p>0.05). The patterns of responding during satiation and deprivation (at all doses except 0) were similar to those that have been previously reported [5]. During satiation sessions, there was a steady rate of infusions throughout the 24-hr session; however, during deprivation sessions, response rates increased after 8 hr.

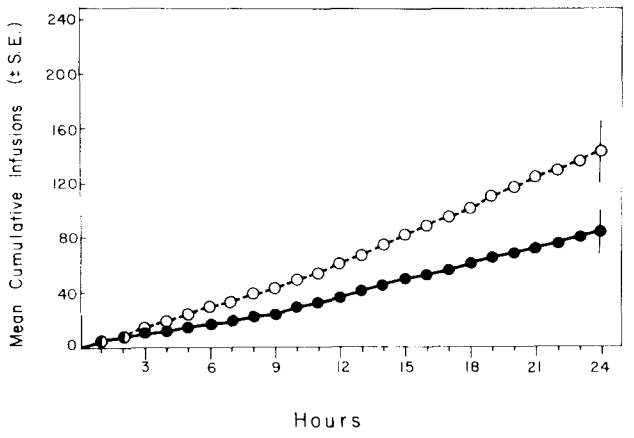

FIG. 3. Mean (±S.E.) cumulative drug infusions are presented for 24 successive 1-hr intervals. Filled circles: water satiation sessions; open circles: water deprivation sessions. Each point represents a mean of individual means for the eight rats in each group (N=24, 8 rats × 3 sessions). Each individual rat's mean was based on the cumulative infusions during the three water-deprivation sessions and the three water-satiation sessions immediately preceding them.

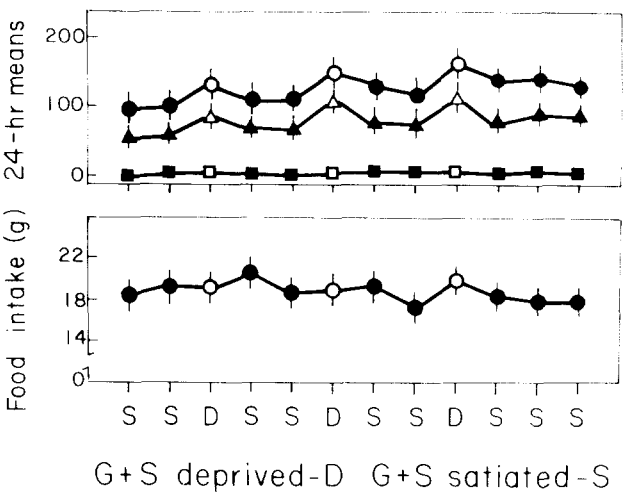

FIG. 4. Effects of satiation (S) or deprivation (D) of a glucose plus saccharin (G+S) solution on etonitazene-reinforced lever responses (circles, upper frame), infusions (triangles), activity-lever responses (squares) and food intake (circles, lower frame). Filled symbols: G+S satiation sessions; open symbols: G+S deprivation sessions. Each point represents a mean (±S.E.) for six rats, except the last four points refer to means for five rats, as one rat died before completion of the experiment.

Experiment 2: The Effects of Water Deprivation on Etonitazene Self-Administration

Figure 2A shows increases in infusion-lever responses and etonitazene infusions during water deprivation sessions (paired t's=2.82 and 3.43, respectively, p's<0.05). Activity-lever responses and food intake did not change systematically (paired t's=2.21 and 1.47, respectively, p's>0.05) with deprivation conditions.

The pattern of etonitazene self-administration is compared during water satiation and deprivation in Fig. 3. Increased responding due to water deprivation was shown after 2 hr of the 24-hr sessions.

Experiment 3: The Effects of Water Deprivation on Saline Self-Administration

Figure 2B shows that water deprivation had no effect on saline self-administration (paired t's=0.3, 2.27, 0.72 and 2.46, for infusion-lever responses, infusions, activity-lever responses, and food intake, respectively, p's>0.05). Saline-maintained responding initially showed a typical extinction burst, but responding was allowed to stabilize before the satiation-deprivation sequence began. Saline-maintained responding remained higher than the etonitazene-maintained responding that occurred before and after the saline sequence, and substantially higher than in the drug-naive saline group in Experiment 1.

Experiment 4: The Effects of Deprivation of a Glucose and Saccharin (G+S) Solution on Etonitazene Self-Administration

In Figure 4 a comparison of G+S satiation and deprivation conditions revealed small but significant differences in infusion-lever responses and etonitazene infusions (paired t's=2.93, and 3.9, respectively, p's<0.05) but not in activity-lever responses or food intake (t's=0.69, and 2.18, respectively, p's<0.05). Mean food intake during G+S satiation and deprivation sessions was 18.1 and 19.5 g, respectively, and food provided approximately 181.4 and 195.4 kcal/kg under G+S satiation and deprivation conditions, respectively. The overall mean session G+S intake for the six rats was 121.6 ml, and the G+S solution provided an additional 32.8 kcal/kg. The volume intake of G+S was 3 to 4 times higher than the mean daily water intake for rats of comparable weight, sex and strain in this laboratory [7].

DISCUSSION

Experiment 1 showed that etonitazene clearly functioned as a reinforcer at all doses tested. Food deprivation resulted in a nearly parallel increase (almost two-fold) in the etonitazene dose response function. Takahashi and coworkers [26] compared intravenous self-administration of three doses of d-amphetamine in rats maintained at free-feeding body weights and 80% of the free-feeding weights, and a similar parallel increase was found under food deprivation conditions with three doses on the ascending portion of a dose-response function. The second experiment showed that water deprivation increased etonitazene self-administration in magnitude similar to the results reported with food deprivation [4,5]. This result was apparently not indirectly due to lowered food intakes, which often accompany water deprivation [25], as there were no significant decreases in food intake during water deprivation. The increased drug intake occurred more rapidly (2 hr) with water than it did with food (8 hr) deprivation [5], suggesting the importance of physiological determinants of the deprivation effect. Earlier work indicated that weight loss vs absence of food [9] and the degree of weight loss [6] were important factors in deprivation-induced increases in oral drug intake. It appears that more subtle changes in physiological homeostasis may be responsible for increased intravenous drug intake. In the third experiment, saline-maintained behavior showed no significant changes during water satiation or deprivation, indicating that deprivation effects are specific to drug intake and not general liquid intake. Saline-maintained responding after brief exposure to etonitazene remained

stable and much higher than saline-maintained responding in drug-naive rats (Experiment 1). These results are similar to those previously reported concerning extinction responding after brief cocaine access [5]; however, extinction responding was almost four times higher after etonitazene than after cocaine. These differences may be due to the dose of etonitazene or to different reinforcing properties of the drugs. In the fourth experiment, substantial amounts of the glucose and saccharin solution were consumed although food and water were freely available. In fact, G+S intakes were several times higher than normal water intake, indicating that the G+S was functioning as a reinforcer. Withdrawal of the G+S solution resulted in small but reliable increases in etonitazene self-administration. The contrast in magnitude between food and water deprivation vs G+S deprivation also suggests that an altered physiological state may be an important component of the deprivation effect.

The results of these experiments extend the generality of previous findings with food deprivation to a range of drug doses, and to deprivation of substances other than food. A general explanation that has been suggested to account for the food deprivation effect [5] may also apply to the present findings. Water deprivation may produce novel interoceptive events that become associated with the reinforcing effects of etonitazene and come to serve as conditioned-reinforcing stimuli. However, the G+S deprivation data are not as easily explained by such a mechanism, as the rats were not deprived of essential liquids or nutrients. Another general explanation that would also account for the G+S data might be one of reward interaction or contrast; whereby, the absence of one reinforcing substance may be accompanied by increased responding maintained by another reinforcer. There are examples of reinforcement interaction with concurrent food schedules (e.g., [10, 14, 24]), and Driscoll and Lockard [13] reported increased water intake, beyond replacement values, in rats deprived of a saccharin solution. Furthermore, using intracranial self-stimulation (ICS), Katz and others [16] showed that ICS increased during food deprivation, and conversely feeding increased when ICS availability was decreased. Many specific explanations of this deprivation effect have been ruled out by the increased generality of the phenomenon across species, routes of drug administration, type of drug, drug dose and type of deprivation.

ACKNOWLEDGEMENTS

The authors are grateful to Rodney Rasmussen, Kevin Ryan and Dana Stotz for technical assistance in conducting the experiments and to Dr. James P. Goldberg for his helpful comments on the manuscript. This research was supported by NIDA grants DA00944 to Richard A. Meisch and DA02486 to Marilyn E. Carroll.

REFERENCES

1. Bolles, R. C. Effects of deprivation conditions on the rat's home cage behavior. *J. comp. physiol. Psychol.* **60:** 244–248, 1965.
2. Campbell, B. S. Theory and research on the effects of water deprivation on random activity in the rat. In: *Thirst*, edited by M. J. Wayner. New York: Pergamon, 1964.
3. Carey, R. J., E. Goodall and S. A. Lorens. Differential effects of amphetamine and food deprivation on self-stimulation of the lateral hypothalamus and medial frontal cortex. *J. comp. physiol. Psychol.* **88:** 224–230, 1975.
4. Carroll, M. E., C. P. France and R. A. Meisch. Food deprivation increases oral and intravenous drug intake in rats. *Science* **205:** 319–321, 1979.
5. Carroll, M. E., C. P. France and R. A. Meisch. Intravenous self-administration of etonitazene, cocaine and phencyclidine in rats during food deprivation and satiation. *J. Pharmac. exp. Ther.* **217:** 241–247, 1981.
6. Carroll, M. E. and R. A. Meisch. Determinants of increased drug self-administration due to food deprivation. *Psychopharmacology* **74:** 197–200, 1981.
7. Carroll, M. E. and R. A. Meisch. Effects of food deprivation on etonitazene consumption in rats. *Pharmac. Biochem. Behav.* **10:** 155–159, 1979.
8. Carroll, M. E. and R. A. Meisch. Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. *J. Pharmac. exp. Ther.* **214:** 339–346, 1980.
9. Carroll, M. E. and R. A. Meisch. The effects of feeding conditions on drug-reinforced behavior: Maintenance at reduced body weight versus availability of food. *Psychopharmacology* **68:** 121–124, 1980.
10. Catania, A. C. Concurrent performances: Inhibition of one response by reinforcement of another. *J. exp. Analysis Behav.* **12:** 731–744, 1969.
11. Chernov, H. I., F. G. Ambrose and A. J. Plummer. Pattern of consumption of etonitazene solutions by naive rats. *Archs int. Pharmacodyn. Thér.* **175:** 309–318, 1968.
12. de la Garza, R., J. Bergman and C. R. Hartel. Food deprivation and cocaine self-administration. *Pharmac. Biochem. Behav.* **15:** 141–144, 1981.
13. Driscoll, J. W. and R. B. Lockard. Replacement behavior following deprivation of a saccharin solution or water. *Psychon. Sci.* **7:** 21–22, 1967.
14. Herrnstein, R. J. On the law of effect. *J. exp. Analysis Behav.* **13:** 243–266, 1970.
15. Holz, W. C. and C. A. Gill. Drug injections as negative reinforcers. *Pharmac. Rev.* **27:** 437–446, 1976.
16. Katz, R. J., G. Baldrighi and K. Roth. Appetitive determinants of self stimulation. *Behav. Biol.* **23:** 500–508, 1978.
17. Meisch, R. A. and D. J. Kliner. Etonitazene as a reinforcer for rats: Increased etonitazene-reinforced behavior due to food deprivation. *Psychopharmacology* **63:** 97–98, 1979.
18. Milgram, N. W., A. C. Server and K. A. Campbell. Effect of food and water deprivation on hippocampal self-stimulation and poststimulation feeding. *Physiol. Psychol.* **5:** 43–48, 1977.
19. Morgan, C. W. and G. J. Mogenson. Preferences of water-deprived rats for stimulation. *Psychon. Sci.* **6:** 337–338, 1966.
20. Oei, T. P. S. and G. Singer. Effects of a fixed time schedule and body weight on ethanol self-administration. *Pharmac. Biochem. Behav.* **10:** 767–770, 1979.
21. Oei, T. P. S., G. Singer, D. Jeffreys, W. Lang and A. Latiff. Schedule-induced self-injection of nicotine, heroin and methadone by naive animals. In: *Stimulus Properties of Drugs: Ten Years of Progress*, edited by F. C. Colpaert and J. A. Rosecrans. Amsterdam: North Holland, 1978, pp. 503–516.
22. Olds, J. Effects of hunger and male sex hormones on self-stimulation of the brain. *J. comp. physiol. Psychol.* **51:** 320–324, 1958.
23. Papasava, M., T. P. S. Oei and G. Singer. Low dose cocaine self-administration by naive rats: Effects of body weights and a fixed-time one minute food delivery schedule. *Pharmac. Biochem. Behav.* **15:** 485–488, 1981.
24. Rachlin, H. Contrast and Matching. *Psychol. Rev.* **80:** 217–234, 1978.
25. Strouthes, A., A. M. Volo and T. Unger. Hunger, thirst and their interactive effects on the rat's drinking in a saccharin-water choice. *Physiol. Behav.* **13:** 153–157, 1974.
26. Takahashi, R. N., G. Singer and T. P. Oei. Schedule-induced self-injection of d-amphetamine by naive animals. *Pharmac. Biochem. Behav.* **9:** 857–861, 1978.
27. Valenstein, E. S., V. C. Cox and J. W. Kakolewski. Polydipsia elicited by the synergistic action of a saccharin and glucose solution. *Science* **157:** 522–554, 1967.
28. Weeks, J. R. Long-term intravenous infusion. In: *Methods in Psychobiology*, vol. 2, edited by R. D. Myers. London: Academic Press, 1972, pp. 155–168.