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Using Profiles of Saccharin and Water Drinking to Detect and Discriminate Actions of Drugs and Toxicants

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YAMAMOTO, B. K. AND C. L. KUTSCHER. *Using profiles of saccharin and water drinking to detect and discriminate actions of drugs and toxicants.* PHARMAC. BIOCHEM. BEHAV. 13(4) 507–512, 1980.—Experiments were conducted to investigate the feasibility of using the pattern of saccharin and water drinking to detect acute and chronic administration of drugs and toxicants. Procedural variables were found to be crucial. When rats were naive for the saccharin drinking fluid, a single injection of LiCl or 2-deoxyglucose produced persistant saccharin aversion. Hypertonic saline produced only a transient saccharin aversion. If rats were pre-exposed to saccharin, the 2-deoxyglucose injection and hypertonic NaCl produced an increase in saccharin drinking, but LiCl was without effect. Several types of chronic treatment were given to saccharin-experienced rats. Chronic 2-deoxyglucose, LiCl, and Pb administration produced gradually developing saccharin aversion and qualitatively different patterns of saccharin and water drinking. Chronic administration of hypertonic NaCl or insulin or chronic food deprivation had no impact on saccharin preference. It was concluded that patterns of saccharin and water drinking can be used to detect the administration of a drug or toxicant and perhaps even the time course of action, but may not detect a substance given previous to saccharin, perhaps because the animal cannot associate these now familiar perturbations with the novel saccharin solution. This means that existing toxic states may not be detected by using saccharin preference as a probe.

2-Deoxyglucose Drinking LiCl NaCl Saccharin Taste aversion Toxicants

IN psychopharmacology and behavioral toxicology a relationship is sought between the administration of a chemical and behavioral changes produced by this chemical perturbation of the organism's internal environment. Maickel and co-workers [10,11] suggested that responsiveness to taste stimuli, which is relatively easy to assess, may be related to type of drug administered. Their findings from studies of drinking behavior demonstrate that the taste of the sapid fluid ingested by the animal and the internal drug state may interact in the determination of the fluid volume consumed. They injected various drugs into water-deprived rats and offered them either water or a saccharin solution in order to study the behavioral profile of drug action. For example, chlordiazepoxide increased saccharin drinking proportionately more than water drinking [10] and methapyrilene decreased saccharin intakes relative to water intakes [11] in one-bottle tests. In a study using a two-bottle preference test, thirsty rats were given both water and 0.5% saccharin to drink. We found that injections of 2-deoxyglucose (2-DG) lithium chloride (LiCl), and hypertonic sodium chloride (NaCl) all produced a water preference in a 30-min drinking test given 15 min after injections but rats injected with isotonic NaCl showed a distinct saccharin preference [9].

In the following experiments we administered substances expected to produce a spectrum of changes in the internal environment including some which occur in attenuated form in untreated animals—hypoglycemia, hyperglycemia, glucoprivation, hypernatremia, and cellular dehydration. Because of the ubiquitous occurrence of conditioned taste aversion [13] following injection of a wide variety of chemicals, we also tested the action of chemical administration under conditions which should attenuate conditioned taste preference shifts, i.e., using rats experienced with the saccharin drinking fluid. In order to extend the taste preference model of drug detection to conditions more analagous to the usual chronic administration of medication of cumulative exposure to toxicants, we also tested chronic administration of the substances and long-term measurements of saccharin preferences.

EXPERIMENT 1

METHOD

Naive, male Long-Evans hooded rats 100–160 days old were used in this experiment. Rats were bred in the Syracuse University Psychology Research Laboratory from stock obtained from Blue Spruce Farms. During the experiment, rats were housed in individual 22×30×25 cm cages of steel and wire mesh. Testing was done in these housing cages. Drinking fluids were given in 100 ml graduated cylinders fitted with stainless steel sipper tubes. Food was Purina Chow pellets. Lights were on for 12 hr/day. During the dark cycle, two 25-W red lights were used to facilitate reading of drinking tubes. Ambient temperature was maintained at 21 ± 1°C.

Rats were given three days to adapt to the living arrangement. During the next 7 days, rats were given continuous access to demineralized water in a graduated cylinder. Food was always available. For 7 hr each day a cylinder of 0.5%

saccharin was placed on the cage for rats in the Saccharin Experienced condition. Rats in the Saccharin Naive condition were given 0.5% NaCl solution. Since saccharin and 0.5% NaCl cylinders were not refilled during the 7 hr access period, intake was limited to approximately 120 ml.

Following this 7-day period, rats were weighed and injected with one of the following substances given subcutaneously in a 0.5% body weight injection volume: 0.15 M NaCl saline control; 0.5 M LiCl; 2.74 M NaCl; and 0.18 M 2-DG (150 mg/kg). Injections were made at the beginning of the dark cycle. Food was removed from cages. Water and 0.5% saccharin cylinders were placed on cages and drinking was recorded at hourly intervals for the next 23 hr. For the Saccharin Naive animals, 4 were injected with 0.15 M NaCl and 5 were injected with each of the other substances. For the Saccharin Experienced rats, 9 were injected with 0.15 M NaCl and 10 were injected with each of the other substances.

RESULTS

Cumulative water and saccharin intakes over the 23-hr observation period for Saccharin Naive rats are shown in Fig. 1. The 4-hr and 23-hr cumulative intakes were chosen for statistical analysis by a two-way analysis of variance to determine effect of drinking fluid (water or 0.5% saccharin) and drug (saline, NaCl, 2-DG and LiCl) and the interaction of these two variables. At 4 hr, no significant differences were seen; however, at 23 hr, fluid intakes differed as a function of drug, $F(3,32)=2.95$; $p<0.05$, but not as a function of drinking fluid. The interaction was significant, $F(3,32)=3.88$; $p<0.02$. Tukey Type A tests [5] were used here and elsewhere in the paper for post-hoc comparisons. Differences reported in this paper are significant at least at the 0.05 level.

Water intakes over 23 hr did not differ as a function of drug injected. At least two patterns emerged for saccharin drinking, however. Saline- and NaCl-injected rats showed initial water preference and saccharin rejection (neophobia) followed by a gradual shift over to strong saccharin preference. The shift to saccharin appears retarded in time following NaCl injection. The 2-DG and LiCl injection produced prolonged saccharin aversion after small initial intakes. For 3 days following the test day, water and food were available continuously and 0.5% saccharin was presented for 17 hr/day. The saline and NaCl rats showed strong saccharin preference, but the 2-DG and LiCl rats showed salient but slowly extinguishing saccharin aversion.

Fluid intakes for the Saccharin Experienced rats are shown in Table 1. For all groups saccharin intakes were high and water intakes were proportionately trivial. Saccharin intakes were analyzed by a one-way analysis of variance with Tukey post-hoc tests to determine effect of drug on consumption. Cumulative saccharin consumption did not differ at 4 hr, but did differ at 23 hr, $F(3,39)=3.05$, $p<0.05$. Both NaCl and 2-DG significantly increased saccharin intake over the saline condition. The apparent increase with LiCl was not significant.

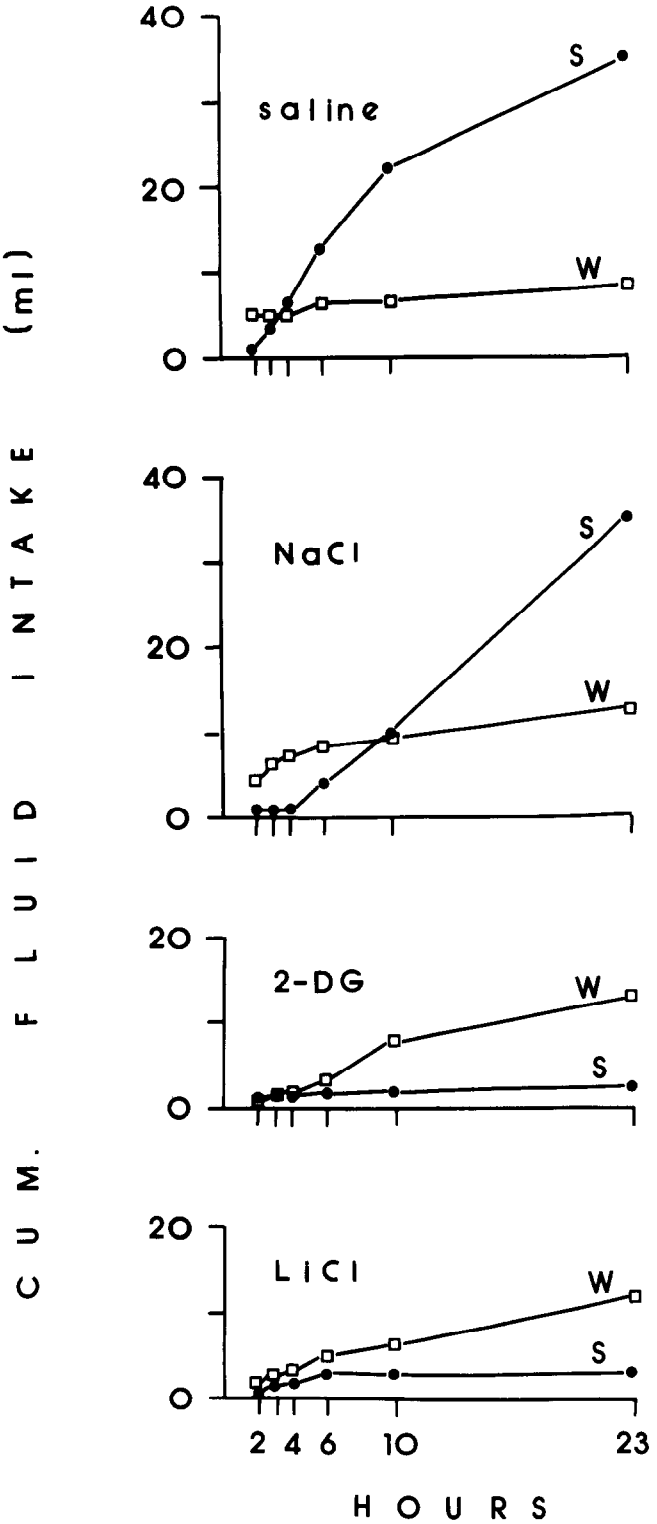

FIG. 1. Cumulative intake of 0.5% saccharin (S) and water (W) over the 23-hr drinking period for rats not initially water deprived and given subcutaneous injections at the beginning of the drinking period.

EXPERIMENT 2

This experiment examined the effect of the various injected substances on the intake of water offered as the only drinking fluid.

METHOD

Nine, naive, male hooded rats, 100–160 days old, were assigned to each of four groups: 0.15 M NaCl (saline control); 0.5 M LiCl; 2.74 NaCl; 0.18 M 2-DG (150 mg/kg). All injections were 0.5% body weight in volume and were made subcutaneously at the beginning of the dark cycle. Following injection, food was removed from the cage and water was

TABLE 1

CUMULATIVE INTAKE (MEAN ± SE) OF SACCHARIN AND WATER FOLLOWING DRUG INJECTION IN SACCHARIN EXPERIENCED RATS

		Saline	LiCl	NaCl	2-DG
Saccharin	4 hr	26.0 ± 5.0 ml	19.3 ± 4.2	35.0 ± 7.8	33.0 ± 4.6
	23	72.0 ± 11.6	96.7 ± 16.1	120.7 ± 17.1	125.6 ± 11.7
Water	4	0.2 ± 0.2	3.2 ± 1.4	3.8 ± 1.6	0.8 ± 0.8
	23	1.8 ± 1.5	4.4 ± 1.7	4.4 ± 1.8	1.0 ± 1.0

TABLE 2

CUMULATIVE WATER INTAKES (MEAN ± SE) FOLLOWING DRUG INJECTIONS

Injection	4 hr	23 hr
Saline	4.4 ± 0.8 ml	17.6 ± 2.5
LiCl	1.9 ± 0.4	10.0 ± 2.2
NaCl	15.1 ± 2.0	31.3 ± 1.0
2-DG	3.2 ± 0.7	14.7 ± 2.0

available continuously for the next 23 hr. Prior to injections rats were given water in the graduated cylinders and were given food ad lib for 7 days after being placed into individual steel mesh cages which served as both living and test cages. Rats were not deprived when injected. Water intakes were measured 4 and 23 hr following injection.

RESULTS

Cumulative water intakes are shown in Table 2. Intakes for 4 hr and for 23 hr were analyzed separately by a one-way analysis of variances. At 4 hr the effect of drug was significant, $F(3,32)=26.28$; $p<0.001$. NaCl produced polydipsia relative to the other groups which did not differ from each other. The drug effect was also significant at 23 hr, $F(3,32)=21.00$; $p<0.001$—NaCl produced polydipsia relative to the other groups which did not differ from each other.

The polydipsic action of NaCl is nonspecific since it is produced when either water or saccharin are presented as the drinking fluid. The 2-DG action is differentiated by these two drinking fluids producing polydipsia only for saccharin ingestion.

EXPERIMENT 3

Experiment 1 showed that 2-DG produced no saccharin aversion whatever during the course of a 24-hr observation period if rats were experienced in saccharin drinking. Here we examined the effect of chronic 2-DG injection on saccharin preference. For comparison we also used two other treatments which also produce glucoprivation and increased feeding—insulin injection and food deprivation.

METHOD

Twenty-eight naive, male rats, 100–160 days old were used in this experiment. They were placed into individual steel mesh cages at the beginning of the experiment and were given 3 days to adapt. Purina Chow was available at all times except during the specified food-deprivation intervals. For 12 consecutive days, two 550 ml plastic bottles were available on the cage. One contained 0.5% sodium saccharin and one contained demineralized water. Bottle positions were changed daily. Intakes, determined by weighing bottles, were recorded for 48-hr periods. Rats were weighed every 2–4 days.

At the end of this baseline period, 7 rats were given each of the following treatments: (a) 10 daily injections of 0.15 M saline; (b) 10 daily injections of 300 mg/kg 2-DG; (c) 10 daily injections of 3 U/kg protamine zinc (slow acting) insulin followed by 6 daily injections of 6 U/kg; (d) 8 days of total food deprivation with daily injections of 0.15 M NaCl. All injections were 0.5% body weight in volume and were made subcutaneously.

RESULTS

Water and saccharin intakes during food deprivation and under chronic injections of saline, 2-DG, and insulin are plotted in 48-hr intervals in Fig. 2. Mean 2-day saccharin intakes and water intakes were calculated for each animal over the last 8 days of the pretreatment period and the last 8 days of the treatment period and were analyzed by a 2×2 analysis of variance (treatment vs posttreatment and saccharin vs water) with a separate analysis for each drug. For the 2-DG group, saccharin intake exceeded water intake, $F(1,24)=21.21$; $p<0.001$, but total fluid intake was not changed by the 2-DG injection. The interaction was significant, $F(1,24)=8.55$; $p<0.01$. During the preinjection period, a strong preference for saccharin was found which disappeared with chronic injection because of increasing water intake and decreasing saccharin intake. No significant change in saccharin or water intake or in saccharin preference was produced by chronic saline injection or by glucoprivic manipulation with either insulin or prolonged food deprivation.

EXPERIMENT 4

In this experiment, we studied chronic administration of substances which were ingested with food to provide a safe, sustained level of administration at a relatively steady rate. We found previously that chronic daily bolus injection of hypertonic NaCl produced skin damage and chronic daily injection of LiCl produced high mortality.

METHOD

Thirty-six naive, male rats 100–160 days old were used in this experiment. Each test substance—NaCl, Pb, and LiCl were dissolved in water and mixed into Purina Chow mash so that the final mixture consisted of approximately 600 ml of water and precisely 500 g of combined mash and test substance. The percentages of adulteration given below refer to gram of toxicant per 100 g of the toxicant-mash combination.

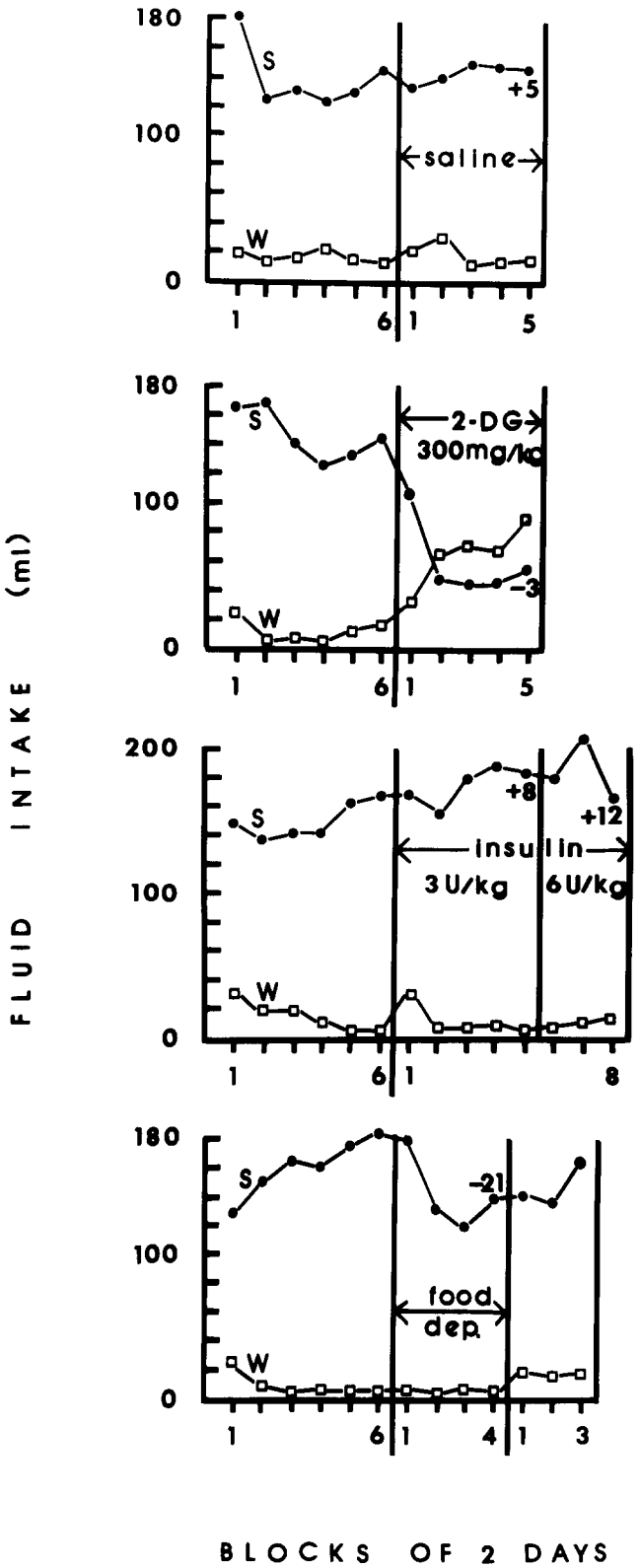

FIG. 2. Forty-eight hour intakes of 0.5% saccharin and water for rats given 12 days of exposure to saccharin before daily subcutaneous injections with saline, insulin, 2-DG or exposure to total food deprivation (with daily saline injection). Numbers on saccharin intake plot indicate percentage change in body weight from last pretreatment day.

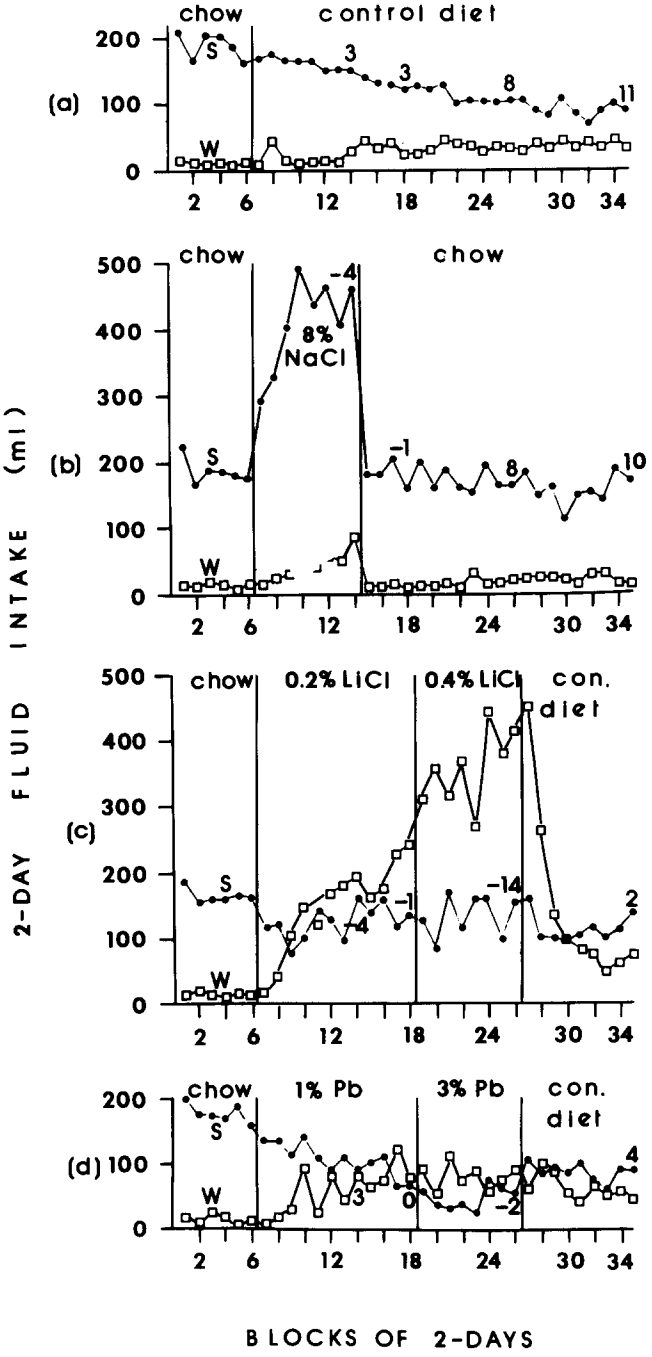

FIG. 3. Forty-eight hour intakes of 0.5% saccharin and water for rats given 12 days of saccharin exposure before special diets were introduced. Chow indicates Purina Chow pellets. Control diet indicates mash cakes made without toxicant. Numbers indicate percentage change in body weight from last pretoxicant day.

After mixing, the wet mash was placed into foil pans, sliced into blocks and dried at 55°C overnight.

Nine rats were assigned to each of 4 conditions: (1) Control—mash mixed with water only and dried; (2) 8% NaCl; (3) 0.2% and 0.4% LiCl; (4) 1% and 3% Pb acetate. The NaCl was given for 16 days (8, 2-day blocks) before Chow pellets were returned. The LiCl and Pb acetate were given for 24 days at the lower dosages and for 16 additional days at the higher dosages. Then these two groups were given the

same unadulterated, reconstituted diet given to the control group.

At the start of the experiment, Purina Chow pellets were provided continuously for 12 days before experimental diets were introduced. Intakes of 0.5% saccharin and water and body weights were measured over 2-day periods. Position of drinking bottles was alternated every 2 days.

RESULTS

Patterns of water and saccharin drinking are shown in Fig. 3. Mean 2-day intake volumes for the rats ingesting the 8% NaCl diet were calculated over the last 8 days of the pre-NaCl period, the NaCl period, and the post-NaCl recovery period. Mean intake volumes were also calculated for the Control group over these same time periods. These mean 2-day intakes were analyzed by a separate 2×3 analysis of variance for each group to determine effect of drinking fluid (saccharin vs water) and treatment effect. Tukey tests were used for comparisons of individual means. Differences were significant at least at the 0.05 level.

For the Control group saccharin intakes were higher than water intakes, $F(1,48)=121.06$; $p<0.001$. Total fluid intake did not differ as a function of measurement period. The interaction was significant, $F(2,48)=6.80$; $p<0.005$, due to a decrease in saccharin intake from the pre-NaCl to the post-NaCl period. The trend for increased water intake was not significant.

For the NaCl group, saccharin intake exceeded water intake, $F(1,48)=304.60$; $p<0.001$, and total fluid intake increased with the presence of NaCl in the diet, $F(2,48)=61.21$; $p<0.001$. The interaction was also significant, $F(2,48)=32.32$; $p<0.001$. The NaCl diet produced polydipsia with greatly increased saccharin drinking, but only a trend for increased water drinking. Termination of the diet produced a rapid return of saccharin intakes to control levels.

For the LiCl and Pb Groups means 48-hr intakes of saccharin and water were analyzed by analysis of variance for the last 8 days of the chow feeding, the last 8 days of the low level of LiCl and Pb, and the last 8 days of the high level, and the last 8 days of the control diets given during recovery. A similar analysis was made for the Control Group over these same time intervals.

As Fig. 3 shows, LiCl produced polydipsia, but the pattern of preference behavior was different from that seen for NaCl-induced polydipsia. Over the 4 test periods saccharin intake did not differ from water intake, but total fluid intake did change with test period, $F(3,64)=15.45$; $p<0.001$. The interaction was also significant, $F(3,64)=15.85$; $p<0.001$. The polydipsic response was produced by water intake increasing from control levels with the 0.2% LiCl diet and increased still further with the 0.4% LiCl diet which produced a clear water preference. With termination of the LiCl diet, water intakes returned to a level statistically indistinguishable from prediet levels.

Rats receiving the Pb diet showed saccharin intakes different from water intakes, $F(1,64)=17.15$; $p<0.01$; however, the interaction was also significant, $F(3,64)=18.18$; $p<0.001$. Although total fluid intake did not change with test period, saccharin preference shown in the pre-Pb period was abolished by the Pb administration, as water intakes increased and saccharin intakes decreased. Preference did not re-emerge during the recovery interval.

Over these test periods the Control Group had generally higher intake of saccharin than water, $F(1,64)=95.5$; $p<0.001$, but the interaction was significant, $F(3,64)=7.83$; $p<0.001$. Total fluid intake did not differ over these periods. Post hoc analysis showed that saccharin intakes declined significantly until there was no longer a statistically significant saccharin preference during the last test period. The trend for water intakes to increase was not significant.

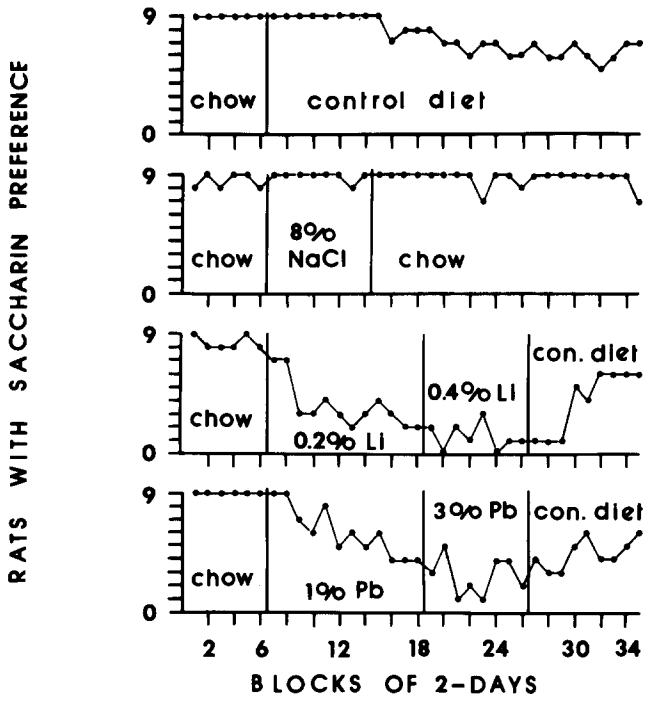

FIG. 4. Number of rats (out of 9) showing saccharin preference during each 48-hr observation period.

The change in saccharin preference over time for the Control Group is a major problem in using preference change to detect the action of a toxicant. Another is the individual variability shown by animals. For example, Fig. 4 shows that even when strong water preference is shown in group means during the 0.4% LiCl administration, some rats still showed a saccharin preference. Clearly, however, the low doses of Pb and LiCl did not produce rather quickly some preference shifts not seen in the Control Group. These shifts were intensified by the higher levels of dietary toxicant and tended to revert to saccharin preferences when toxicants were removed from the diet.

DISCUSSION

The above experiments using a variety of injected and ingested substances and several experimental procedures provide some support for the hypothesis that fluid intake resulting from an interaction of taste and internal state may be a means to detect and characterize action of drug or toxicant [10,11], but it is clear that procedural variables are crucial. Using acute administration of drug to nonfluid-deprived rats given 24-hr drinking periods (Experiment 1) and using water deprived rats and 30-min drinking periods [9], we found that saccharin experience precluded the development of saccharin aversion. This finding is expected if the aversion seen is a persisting conditioned taste aversion formed by a backward paradigm [4]. The aversion to 2-DG and LiCl seen in Experiment 1 is presumed to be learned since it persisted for at least 3 days following the injection. In saccharin-experienced rats where conditioned taste aversion is less

likely to result from a single drug administration, 2-DG strongly increased saccharin intake compared to the saline control group. In the Maickel experiments [10,11] it was not indicated if rats were saccharin-experienced, but the absence of strong saccharin aversion suggests that they were. The weak and transient aversion produced by the strong NaCl injection in the present experiment is consonant with our previous attempts to use NaCl to establish saccharin aversion under other paradigms [3, 7, 9]. Hypertonic NaCl was effective in establishing a taste aversion to quinine, a salient and aversive drinking fluid [2].

The acute-chronic dimension is also critical. Acute 2-DG increased saccharin intake in experienced rats, but chronic administration decreased saccharin intake. Although chronic 2-DG produced only a 3% weight loss over a 10-day treatment period, the dosage was substantial. Plasma glucose levels were determined by an enzymatic colorimetric assay (Sigma Kit No. 510) in naive saline-injected rats and in rats 1 and 2 hr following a single subcutaneous 2-DG injection (150 mg/kg). The 2-DG produced a 45% increase (over controls) in plasma glucose by 1 hr which subsided to a 21% excess by 2 hr.

Clearly, however, not every strong stimulus will produce taste aversion even if chronically administered supporting the contention that drugs may have differential action on taste preference profiles. Food deprivation presumably produced glucoprivation plus a variety of metabolic changes and endocrine changes including hypovolemia [6] and a 21% drop in weight yet produced no taste aversion. The 3 and 6 U/kg insulin dosages used in Experiment 3 were given as the slow release protamine zinc form. When given as regular fast-acting insulin, the 6 U/kg is lethal and the 3 U/kg produced a 51% reduction in blood glucose in 1 hr and a 73% reduction by 3 hr. The impact of the 8% NaCl diet is indicated by the immediate and strong polydipsia seen in Fig. 3, yet no saccharin aversion ensued.

It is tempting to speculate that chronic treatments which produce in the body stimulus changes which are normally experienced by the animal, although in greatly attenuated form, will not produce taste aversion in saccharin-experienced animals. Such perturbations might include hypoglycemia, hypernatremia and glucoprivation. Perhaps exogenous chemicals, which produce novel pharmacologic actions produce the aversion, but familiar perturbations do not. This speculation is supported by the finding that chronic dietary lead administration produces strong aversion when saccharin was introduced before or simultaneously with Pb [8]; however, when Pb was given 30 days before saccharin and Pb toxicosis was presumably well developed no taste aversion was seen.

Comparison of chronic Pb and LiCl administration shows the establishment of two different profiles of intake and the importance of the choice of behavioral measure. If preference is measured by a preference ratio, both toxicants show the development of saccharin aversion, but LiCl does not produce a decrease in volume of saccharin intake and Pb does. Rats, polydipsic from diabetes mellitus induced by alloxan [1] and hypothalamic lesions interfering with vasopressin function [12], also showed stronger water preference relative to a sapid fluid than did control rats.

The hypertonic NaCl diet experiment, however, shows that polydipsia and polyuria do not necessarily produce taste aversion.

In using shifts in taste aversion, or any other behavioral measure, to detect the presence of a drug or toxicant in the body, there are at least three questions which can be addressed. First, we can use taste preference shifts to indicate if a drug or toxicant can be detected. If we administer the drug in close temporal proximity to the presentation of a novel taste stimuli, conditional taste aversion may be produced if the drug dosage is sufficient. Since so many substances produce taste aversion [13] this test is probably nonspecific. Secondly, we can ask if taste preference shifts reflect the initiation and termination of the action of the toxicant given chronically to animals already experienced with the sapid fluid. For Pb and LiCl these expectations are fulfilled reasonably well (Figs. 3 and 4). Thirdly, it would be very useful if we can use taste aversion as a probe to detect a toxicosis which is already established. This question was not directly addressed here, but in a previous experiment [78], we found that animals with long exposure to a Pb diet showed no taste aversion whatever although non-ingestive behavioral measures such as gross activity have shown significant differences (Yamamoto, unpublished observations). As an indicator of drug or toxicant action, taste aversion may fail in detecting chronic exposure which probably is the most important function of a behavior toxicity measure, suggesting that alternate behaviors should be studied.

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