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Craving for alcohol in the rat
Adjunctive behavior and the lateral hypothalamus

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Abstract

A review of previous results and the new data in this report show clearly that the Falk model of adjunctive behavior is an adequate analogue of human alcoholism and can be applied to induce excessive ethanol consumption. New data on the consumption of sweet flavored ethanol solutions and, especially, sweet alone solutions during brief periods of ethanol withdrawal provide some significant insights concerning the possible physiological basis for cravings in humans. Because voluntary consumption of ethanol is the normal process by which alcoholism develops, a general set of environmental and other experimental conditions that produce behavioral excess; adjunctive behavior, electrical stimulation of the brain, and salt arousal of drinking are discussed in some detail. Neuronal circuits of the lateral hypothalamus are important because some of the cells are chemosensitive and monitor osmolality of the blood and initiate drinking in the normal regulation of body fluids. Alcohol in very small amounts has a direct effect on these cells that also project to lower spinal motor neurons and modulate the level of excitability in spinal reflexes and thereby reactivity to environmental stimulation. Taste and other sensory information from the mouth arrives in presynaptic endings on these same cells by a multitude of indirect multisynaptic pathways. A theoretical model is developed to explain how tactile and taste sensory information and what is initially a nonspecific general state of motor arousal interact together to produce an excessive consumption or craving for ethanol. © 2002 Published by Elsevier Science Inc.

Keywords: Alcohol craving; Lateral hypothalamic area; Adjunctive behavior; Schedule-induced drinking; Taste; Salt arousal of drinking; Brain electrical stimulation

1. Introduction

1.1. Animal models of alcoholism

Many animal models of alcoholism have evolved and there is a long history of these attempts to demonstrate the characteristics of human alcoholism in a single model. Most of the literature has been reviewed periodically in an effort to define the important variables and requirements necessary to provide an adequate analogue for human alcoholism (Mello, 1973; Eriksson et al., 1980; Falk, 1980; Falk and Tang, 1977; Meisch, 1982; Myers et al., 1998; Tabakoff and Hoffman, 2000). A major difficulty has been to discover a means by which animal aversions to ethanol solutions can be overcome and voluntary consumption increased (Myers and Ewing, 1980). Another critical requirement has been that sufficient ethanol intakes must be maintained, in the presence of equally palatable fluids, to sustain the necessary high blood alcohol levels required to produce physical dependence (Falk, 1980; Lankford and Myers, 1994). Models that administer ethanol by gavage, inhalation of ethanol vapor, and chronic intravenous and intraventricular techniques can produce addiction and physical dependence rapidly; but these methods have been criticized for bypassing the normal oral route of self administration in humans (Cicero, 1980). Water and food deprivation induced drinking of ethanol containing fluids and forced drinking of a single alcohol containing mixture has not been acceptable because they are not a voluntary self administering alcohol model (Cicero, 1980). Several models that add glucose and artificial sweeteners to the ethanol solution to increase its palatability can induce significant increases of ethanol consumption even in subhuman primates (Dalterio et al., 1988), but insufficient intakes occur and do not produce dependence over long periods of time. Consumption seems to be limited by the rate at which the ethanol is metabolized and eliminated.

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Humans find alcohol solutions aversive and many alcoholic beverages are initially rejected unless they are sweetened or made more palatable in some other way. Most, if not all, of the animal models have not been able to explain how some humans initially overcome the aversive sensory qualities of many alcoholic beverages and the unpleasant after effects and begin to drink excessively over time and become alcoholics (Myers and Ewing, 1980). Many social drinkers appear to display similar behavior patterns in drinking alcoholic beverages and never become addicted (Parsons and Nixon, 1998). It seems reasonable therefore to assume that a genetic basis will eventually explain the differences between these two human drinking populations and we will be able to discriminate between them experimentally (Froehlich, 1995; Froehlich and Li, 1991; Froehlich et al., 2000).

An important genetic factor seems to be a sensitivity to cognitive impairment by alcohol (Parsons and Nixon, 1998; Erblich and Earleywine, 1999). Although one of the cognitive effects of ethanol is well known, anterograde amnesia for short-term memory, it was not until 1997 that it was shown that angiotensin was the neuromediator involved. In rats, angiotensin containing cells in the lateral hypothalamic area (LHA) project directly to the dentate gyrus of the hippocampus (Wayner et al., 1997b). These angiotensin LHA neurons are imbedded in $GABA_A$ sensitive circuits that respond to low doses of alcohol and inhibit long-term potentiation in dentate granule cells (Wayner et al., 1997a), thereby impairing learning and memory (Lee et al., 1995; Tracy et al., 1997). These impairments were prevented by pretreating the animals with losartan, an angiotensin II receptor antagonist (Tracy et al., 1997). In a recently selectively bred strain of high ethanol preferring rats (Myers et al., 1998), it was found that they are less sensitive to ethanol inhibition of dentate granule cell long-term potentiation than normal control Spragae–Dawley animals (Wayner et al., 2000). Myers high alcohol preferring animals are also hyperexcitable (Jones and Mormede, 2000), and the females appear to be less taste reactive to both 3% and 30% ethanol than males (McMillen et al., 2000). These observations are important because taste reactivity correlates with palatability and has a high heredibility in rats (Kiefer, 1995). Similar strains of alcohol preferring and nonalcohol preferring animals have been used to study taste reactivity in determining alcohol sensitivity (Bice and Kiefer, 1990; Kiefer and Badia-Elder, 1997). High alcohol sensitive and low alcohol sensitive rats did not differ in taste reactivity responses nor did they differ in response reactivity to single concentrations of sucrose or quinine; however, rats bred for high and low ethanol consumption did show clear differences in reactivity changes following access to alcohol. These data and the results of other recent studies are emphasizing and calling attention again to the role of taste in the alcohol addictive process (Danilova and Hellekant, 2000). Detoxified males have a much higher sweet preference than normal subjects (Kampov-Polevoy et al., 1997) and these data led to the development of an hypothesis that sweet preference might be a marker for alcoholism. Subsequent results in support of a strong preference for sweet positively associated with a paternal history of alcoholism (Kampov-Polevoy et al., 2001) could not be confirmed (Kranzler et al., 2001). A partial conclusion to these studies was that high sweet preferences might be a consequence of chronic alcohol consumption. Results reported here support a role for increased taste preference for sweet during withdrawal and possibly during the early developmental stages of alcohol addiction.

It seems apparent that the alcoholic addictive process begins with oral self administration of the drug; and therefore taste discrimination and preference for alcohol, in comparison to other palatable fluids, has been emphasized in animal models for alcoholism. Alcohol taste sensitivity varies widely in terms of absolute sensitivity between different animal species, cat, dog and rat (Hellekant et al., 1967). The rat has a relatively high threshold for the direct effects of alcohol on the tongue. Therefore, in the rat model of alcoholism, the direct effect of alcohol on tongue taste receptors cannot be a critical variable; the first interaction of taste and alcohol must take place somewhere else in the brain, probably in the nucleus of the solitary tract. Actually, the tactile stimuli that are associated with a fluid only initiate the ingestive process by means of a brief increase in neural activity that the additional taste stimulation modulates in an ongoing stream of sensory neural activity (Travers and Norgren, 1986; Travers et al., 1986). Based upon conditioned taste aversion data, alcohol taste in the rat appears to be a combination of sweet and bitter qualities (Di Lorenzo et al., 1986). In the same study, an analysis of single unit neuronal activity in the nucleus of the solitary tract for the same tastants in combination with 6% or 9% ethanol revealed only a significant correlation between 6% alcohol and sucrose. In humans, the detection threshold for alcohol in water is 4% or 5% and it is perceived as a sweet tastant (Ewing, 1981), and when the percentage is increased to 20–25%, individuals begin to experience a slight burning sensation.

The converging taste sensory receptor information from the oral cavity is complex, arriving by afferents in three different nerves: the chorda tympani, glossopharyngeal and vagus. A multitude of other converging sensory information must be important in the development of the alcohol addictive process as the taste signals travel along multisynaptic pathways into other parts of the brain (Travers et al., 1986). What is unique about ethanol is the brain site where its enhancing effect on these converging pathways takes place (Wayner, 1970). Taste interactions with other sensory modalities in the development of alcoholism have not received much attention (Martin and Pangborn, 1970). An alcoholic's sensitivity to sweet (Kampov-Polevoy et al., 1997) might increase and be part of the physiological urge to drink and it can be associated with a craving for sweets; for example a variety of candies, especially choc-

olates and sweet drinks. The craving of alcoholics especially when alcohol is not available can have bizarre effects; for example, opening a jar of pickles, throwing the pickles away and drinking the pickle juice!

1.2. Adjunctive behavior: an animal model of craving

Craving can be a type of excessive behavior that displays a specificity for a particular fluid or food and results in an over indulgence in the substance. Schedule-induced behavior in animals and humans (Kachanoff et al., 1973; Falk, 1971; Wallace et al., 1975) has been an effective experimental model for inducing and studying similar types of excessive and bizarre behavior. B.F. Skinner was the first to comment on these human idiosyncrasies "...interesting examples are found in the field of psychotic behavior, where the patient engages in compulsive or other idiosyncratic ways only when he is not executing the behavior under the control of a given schedule" (Skinner and Morse, 1957). In 1961, Falk (1961) described schedule-induced drinking, and Lester (1961) was the first to report scheduled induced excessive ethanol drinking and alcohol intoxication. Within the next 10 years, several other investigators confirmed these results in rats (Holman and Myers, 1968; Freed and Lester, 1970) and in monkeys (Schuster and Woods, 1966; Mello and Mendelson, 1971). In both rat (Holman and Myers, 1968) and monkey models (Mello and Mendelson, 1971), sufficient quantities of ethanol were not consumed to produce the excessive intakes necessary to produce physical dependence. By 1972, Falk had solved most of these problems and also the criticisms of an adjunctive model of alcoholism (Falk et al., 1972), and a brief review of his findings appeared in 1980 (Falk, 1980). The only major remaining criticism had been that these animals develop the excessive alcohol drinking only if they are maintained at 80–85% of their normal body weight and on a schedule of food reinforcement (Cicero, 1980). However, even if schedule-induced ethanol drinking did not satisfy this specific requirement for a general model of alcoholism, it proved to be a valuable method for producing addiction and physical dependence. In 1981, Colotla (1981), after a more extensive review of the schedule-induced polydypsia literature, concluded that adjunctive polydypsia was the best available model of alcoholism. Falk in 1988 also produced a more comprehensive treatment of the schedule-induced drinking literature (Falk and Tang, 1988). Both reviews emphasize palatability as a significant factor in the modification of alcohol consumption and the importance of environmental stimulation in determining when an individual drinks. Also, suggestions were made for the possible development of human alcoholism intervention strategies in terms of altering situational parameters to completely changing the environment.

Weight restriction is not a factor in human adjunctive behavior and excessive fluid intakes have been observed on a variety of reinforcement schedules in normal and schizophrenic humans (Kachanoff et al., 1973; Wallace et al., 1975) and, in addition to excessive fluid intakes, episodes of bizarre behavior also occur (Kachanoff et al., 1973; Wallace et al., 1975). Doyle and Samson (1985) were the first to demonstrate in humans a schedule dependent schedule-induced increase in alcohol consumption. Monetary reinforcement was delivered by a computer controlled slot machine on two fixed interval schedules, F1-30-s and F1-90-s. Water, nonalcoholic beer and beer were freely available. Although the F1-90-s schedule was most effective and produced the largest intakes for water, more beer was also consumed on this schedule.

1.3. Alcohol craving in the rat

It is important when studying the addictive behavioral process in animal models to take the time and invest the effort to carefully observe the rat, for example, under similar conditions to those under which alcoholism develops in humans (Wayner and Barone, 1980). Alcoholism develops slowly in humans. Both humans and rats find their initial experiences in drinking alcoholic beverages to be distasteful and aversive and tend to avoid consuming these fluids. An important question that needs to be answered is: Why do humans overcome this initial aversion and begin to drink alcoholic beverages? It seems reasonable to assume that when excessive alcohol drinking occurs it depends upon current stimulation in the environment, what were the critical stimuli in the past in that environment and the consequences of that stimulation. In the adjunctive behavior model of the rat, the operants to be emitted in a standard test chamber are changed, for example, by the induction of schedule-induced drinking. Several months later when animals are returned to the test chamber the probability has been increased to drink and animals drink. If a sweetener is added to the water in the tube, animals drink more. When glucose and alcohol are added to the water in the tube, animals drink much more. The following experimental results demonstrate that schedule-inducing behavioral procedures can be used to produce excessive alcohol drinking in the rat and alcohol dependence. Schedule-induced drinking was induced at 80% body weight, in order to change the probabilities for drinking to be evoked by the stimuli in a standard test chamber, and then the animals were used several months later when the animals were at normal body weight.

Fig. 1 illustrates samples of records of two animals, rats 17 and 14, who were treated in the same way (Wayner and Rondeau, 1976). Both of them developed schedule-induced polydipsia on a fixed interval 1-min schedule, FI-1, at 80% body weight. These cumulative data recordings illustrate the frequencies of lever pressing, pellets and licking and tap water intakes for these two animals on the 21st 60-min test session at reduced body weight and on the 18th daily and 9th weekly 60-min test sessions at recovered body weight. The schedule-inducing sessions and test sessions following

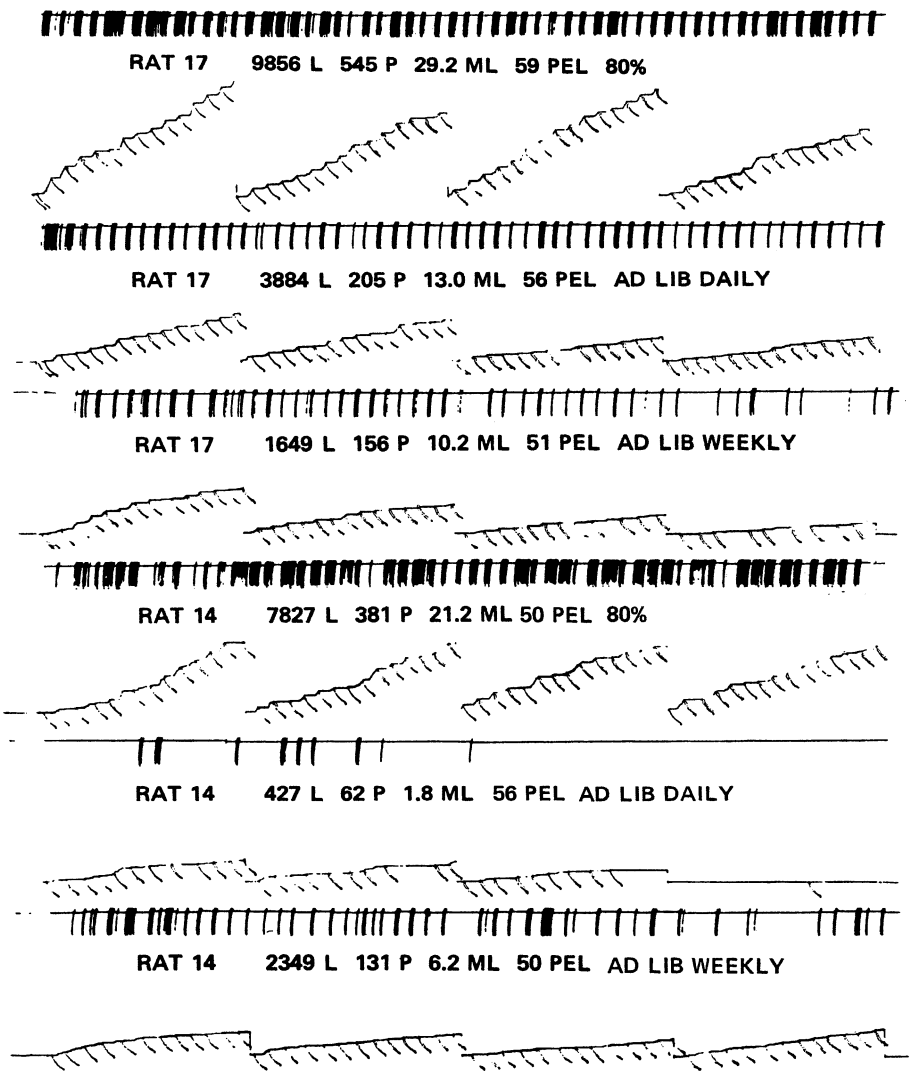

Fig. 1. Photographs of cumulative recordings obtained on two animals on the 21st 60-min test session at reduced body weight and on the 18th daily and 9th weekly 60-min test sessions at recovered body weight. In each session record, in the top tracing, one downward deflection represents five licks; number of presses and food pellet reinforcements are indicated in the bottom tracing. Total licks, number of pellets and fluid intakes (ml) for each session are also included on the recordings. Animals were drinking tap water. Reprinted from Wayner MS, Barone FC, A human model of animal alcoholism. In: Eriksson K, Sinclair JD, Kiianmaa K, editors. Animal Models in Alcohol Research. 1976. pp. 140–143. By permission of Academic Press, London.

recovered body weight were terminated after 60 min or when the animal received 60 45-mg pellets. Body weights recovered to their initial amounts over a 5-day period by gradually increasing the daily food rations in the home cages. Animals were not tested during this period. Animals were at their initial body weights and continued to increase during this period. Individual differences are readily observable. Rat 14 whose responses appeared to be extinguishing on the ad lib daily schedule displayed significant increased bar pressing, licking and water consumption when tested ad lib weekly. Animal 17 displayed more robust lever pressing, licks and water consumption at 80% body weight and when tested daily as compared to animal 14. Both animals displayed similar patterns when tested weekly. These individual differences in adjunctive behavior, when animals are tested in the same environment, can provide important insights about the environmental factors determining these effects. Observing these animals over long periods of time represents a very different experimental strategy than the more frequently used factorial design, when all the animals in a group are expected to produce similar results.

Fig. 2 illustrates typical data obtained from an animal that had been studied over an 18-month period (Wayner and Barone, 1980). It is a copy of the cumulative record of licks made by a rat for 5% ethanol + 3% glucose + 0.125% Na saccharin in distilled water and lever presses in a standard operant behavior test chamber during a 24-h period. The pellet activation mechanism was set to deliver on a FI-1-min schedule. The delivery of a pellet was preceded by a brief illumination of six standard test lights. A dim house light was on continuously. The top tracing in each part indicates five licks per downward deflection. The bottom tracing in-

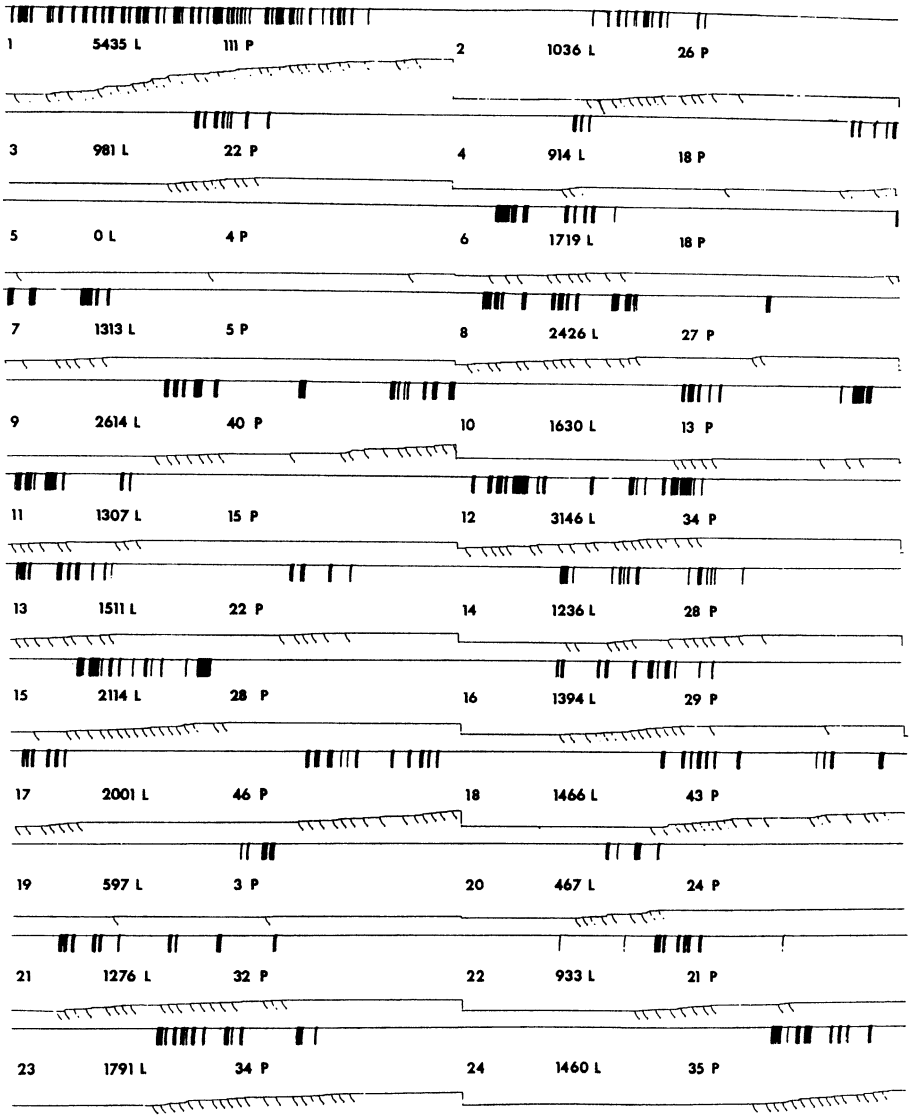

Fig. 2. Similar to Fig. 1. Photographs of an entire 24-h test session. The number of licks, five licks per downward deflection, are indicated in the top tracing; number of presses and food pellet reinforcements are indicated in the bottom tracing. Number of licks and presses per hour are also indicated on the records. Animals were drinking 5% ethanol + 3% glucose + 0.125% Na saccharine in distilled water. Reprinted from Wayner MS, Barone FC, A human model of animal alcoholism. In: Eriksson K, Sinclair JD, Kiianmaa K, editors. Animal Models in Alcohol Research. 1976. pp. 140–143. By permission of Academic Press, London.

dicates number of presses and food pellet delivery. Number of licks and presses per hour is also indicated on the record. During the 24-h test period, there were 38,767 licks, 678 bar presses for 346 pellets and the animal consumed 154 ml of fluid in the test chamber. The animal had not been deprived, lived in an individual cage, and had food and water available continuously in its home cage. During this part of the experiment, 5% and 20% ethanol were also available every other day in the home cage. Periodic withdrawal of the ethanol solutions from the home cage was undertaken to enhance the animal's home cage consumption of ethanol (Wayner and Fraley, 1972; Wayner et al., 1972b). By inducing additional ethanol consumption in the home cage in this manner, along with the excessive 24-h intakes on the test days, relatively high blood alcohol levels were likely to have been maintained and contributed to the dependence and withdrawal effects in these animals. In the adjunctive polydipsia model of alcoholism, making alcohol available in the home cage and introducing a schedule of daily intermittence in its availability, seems to be an important factor in producing dependence and withdrawal.

Some additional data concerning its previous history will be reported. Initially, the animal was one of several selected and set aside in an individual cage for another experiment. For approximately 1 month, the animal had been placed on a restricted daily food ration, reduced to 80% free feeding body weight and trained on a FI-1-min food reinforcement schedule in the same test chamber to produce schedule-induced polydipsia. The animal was then returned to free feeding and drinking and was provided with a continuous

choice of several fluids in its home cage by means of graduated plastic cylinders attached to stainless steel ball point spouts. One cylinder was always empty and the other three were filled with tap water, 5% and 20% ethanol. Cylinders were refilled daily and positions were changed in a nonsystematic way. After 30 days of ad lib feeding and drinking, the animal was returned to the test chamber for 60 min. The animal had been drinking approximately 50–75% of its daily fluid intake as 5% ethanol during this period. The Long–Evans strain of animals that were studied usually drink low concentrations of ethanol up to about 5% but tend to avoid concentrations of 6% or greater. Occasionally, the animal drank from 1 to 5 ml of 20% ethanol. The animal was free feeding and drinking, body weight was normal, and the animal was tested for the recovery of schedule-induced drinking (Wayner and Rondeau, 1976). Five months later, after a 3-week interval during which the animal was not tested at all and following a 24-h period of ethanol withdrawal from the home cage, the animal was placed in the test chamber for 24 h and the data illustrated in Fig. 2 were obtained. Home cage ethanol solutions were also removed every other day in an attempt to increase ethanol consumption. As expected, the animal pressed the bar for pellets regularly and consumed an intoxicating quantity of ethyl alcohol, slept for 30 min, pressed and licked again for 15 min, and continued a similar pattern for the remainder of the 24-h period. It was then returned to the home cage. During the successive 1-h periods, the ethanol consumption was never as much as it was during the first hour as indicated by the number of licks in Fig. 2.

Data obtained when the animal was tested six times under the same conditions on test Days 3, 10, 15, 20, 25 and 28 are summarized in Table 1. The amount of ethyl alcohol in grams per kilogram consumed during the first hour, the entire 24 h, and the home cage consumption of 5% and 20% for the next 24 h are presented. An examination of the first hour consumption of ethanol reveals some evidence of tolerance. The animal can tolerate a larger dose before becoming inebriated and drinking ceases. The increase in ethanol consumed during the first hour over the 25-day period can be seen in Table 1, an increase from 1.6 to 2.2 g/kg. Animals under these conditions usually drink copiously during the first hour and then become inebriated, as indicated by an impaired gait and eventually sleeping. This animal actually slept for 30 min at the end of the first hour and beginning of the second hour, then pressed and licked again, repeating this pattern interspersed with periods of sleeping. Similar data were obtained for the additional five 24-h test periods over this 25-day period. The home cage consumption occurred over the next 24 h following the test period. The home cage consumption also increased significantly over the 25-day period from 5.8 to 9.6 g/kg. The increase in home cage consumption of ethanol was enhanced by the periodic withdrawal technique (Wayner et al., 1972b). The pattern of oral self-administration indicated by the distribution of licks throughout the 24-h period in Fig. 2 is similar to that observed for intravenous self-administration in other species (Woods et al., 1971). The periodic withdrawal technique produced the expected increase in home cage consumption of 5% ethanol; however, the ingestion of 20% ethanol, which began following the fourth 24-h session, was unexpected and the total ethyl alcohol consumed in the home cage reached 9.6 g/kg. After several more sessions over a 2-week period, the excessive consumption of ethanol persisted. When ethanol was withdrawn the animal became hyperexcitable and, when tested for withdrawal symptoms, convulsed and died. A severe tonic–clonic seizure was induced in the animal by briefly shaking a bunch of keys. Consequently, in animals subjected to these conditions producing high ethanol consumption, key shaking initially to induce mild seizures as a sign of withdrawal was discontinued. Animals were hyperexcitable and displayed increased responsiveness to tactile stimulation when handled.

Table 1
Alcohol consumption, 5% ethanol + 3% glucose + 0.125% Na saccharin in distilled water (g/kg) for the first hour and for the entire 24-h of the test session and the home cage consumption of 5% and 20% ethanol for the next 24-h (modified after Wayner and Barone, 1980)

Day	1 h (g/kg)	24 h (g/kg)	Home cage consumption		
3	1.6	9.3	5%, 20%	79 ml	5.8 g/kg
10	1.6	11.6	5%, 20%	67 ml	5.2 g/kg
15	1.6	9.6	5%, 20%	100 ml	7.7 g/kg
20	2.0	11.5	5%, 20%	58 ml, 6 ml	6.3 g/kg
25	2.2	11.0	5%, 20%	68 ml, 4 ml	6.4 g/kg
28	2.1	11.7	5%, 20%	70 ml, 14 ml	9.6 g/kg

The animal was apparently consuming more ethanol than it was metabolizing and blood alcohol levels were undoubtedly being maintained at a relatively high level. Falk (Falk et al., 1972; Samson and Falk, 1974; Tang and Falk, 1986) had observed large schedule-induced quantities of 5% ethanol and found that the animals could physiologically tolerate these volumes quite well (Falk and Tang, 1977). After 5 months, animals were not suffering from a water electrolyte imbalance and plasma volume, extracellular volume and serum electrolyte concentrations were normal. Significant decreases in ethanol administration were also observed when animals were on this type of schedule-induced ethanol drinking for at least 3 months, decreases from a normal 50 mg/100 ml blood/h to approximately 35 ml/100 ml blood/h. A 450-mg liver powder food supplement mixed with two drops of water added to the food cup daily resulted in normal rates of ethanol elimination (Samson et al., 1976).

Results on another animal are illustrated for a 24-h test period in Fig. 3 (Wayner and Barone, 1980). This animal was treated similarly over the same period of time with 7% ethanol + 3% glucose + 0.125% Na saccharin in distilled water. During the test period, the animal licked 22,212 times and drank 9.1 g/kg of ethyl alcohol, and pressed the

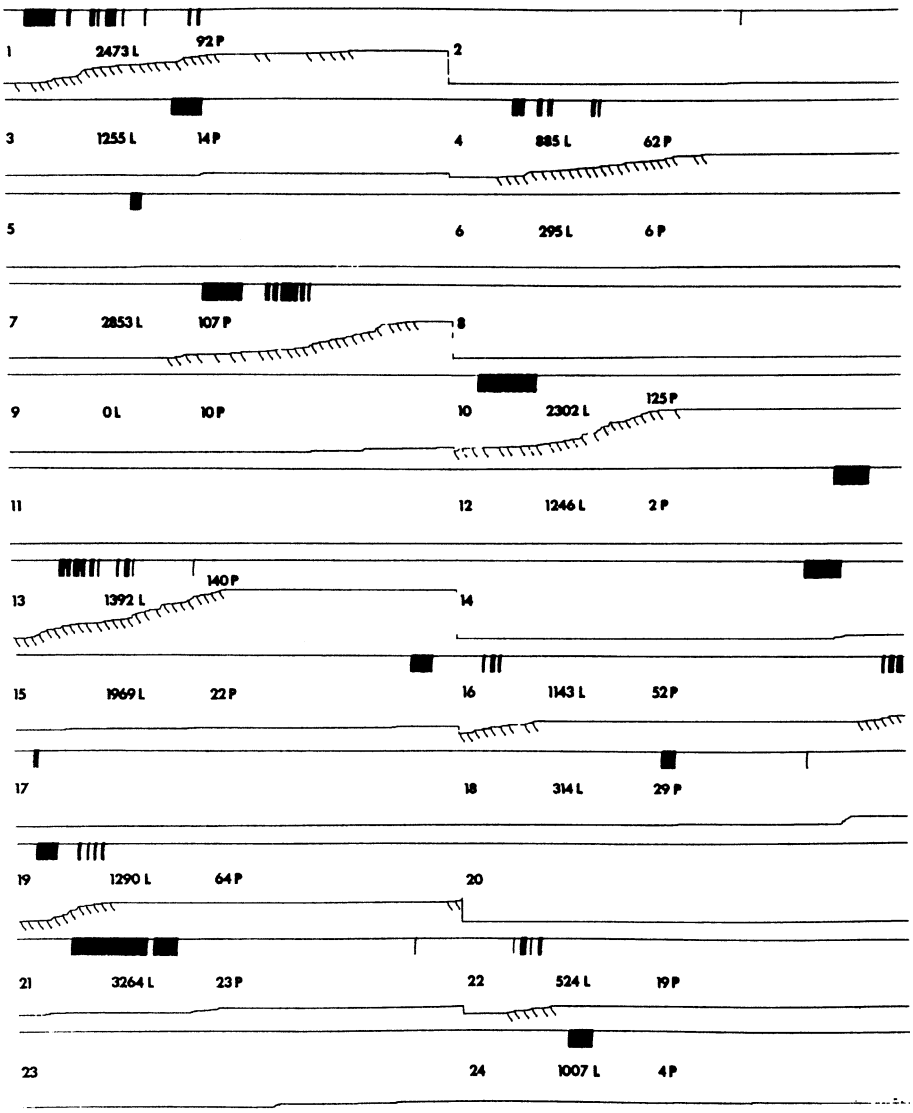

Fig. 3. Same as Fig. 2 except for a different animal. This animal had 7% ethanol + 3% glucose + 0.125% Na saccharine in distilled water to drink. Reprinted with permission from Wayner and Barone (1980).

lever 771 times for 164 pellets. Home cage consumption of 7% and 20% ethanol had been increased to combined intakes of 8–11 g/kg of ethyl alcohol daily. The data of Fig. 3 were obtained in the test chamber towards the end of this period of elevated home cage ethanol consumption. The data on this animal are particularly relevant and important in the present context. The lick pattern is very different than that of the animal in Fig. 2, and it is characterized by long bursts of sustained licking. Gulping of sweetened ethanol, periods of inebriation, increased sleeping time, decreased food and water consumption, and a general lack of responsiveness and inactivity are symptoms of human alcoholism and are displayed by excessive ethanol consuming rats under these experimental conditions. There are many human drinkers who are typified by an individual who is quiet, sits and sips for long periods of time, and another pattern can be observed in the individual who is active, then sits and stares at a half filled glass of whiskey, and then suddenly gulps it down. Some of these similarities between human alcoholic drinking patterns and those of adjunctive ethanol drinking rats are striking.

1.4. Major hypothesis and purpose of the present study

These results and the well-known similar data on humans show that it is possible to develop an adequate model of human alcoholism in the rat and induce sufficiently high amounts of ethanol consumption to produce physical dependence. However, it is not easy and a considerable amount of time must be invested in the careful control of the relevant interacting sensory modalities and environmental cues involved. It is also known that human alcoholism usually develops slowly over time and that alcoholics have a higher preference for sweet than normal subjects (Kam-

pov-Polevoy et al., 1997). The purpose of the present study was to control the consumption of various sapid solutions in the rat, including mixtures with ethanol, by means of a modified schedule-induced drinking paradigm. Animals lived in individual test chambers and were tested continuously from 6 to 8 months. The main emphasis was to determine the role of taste in the early development of high levels of ethanol consumption and eventual alcohol dependence. Because the craving for ethanol must be very intense during the early stages of withdrawal, the effects of brief periods of alcohol withdrawal were also determined on drinking of the following substances: water, alcohol, saccharin, quinine hydrochloride and citric acid, and several mixtures of these substances including glucose. The major hypothesis was that taste is an important variable in the early stages of the alcohol addictive process and also important in withdrawal when the craving for ethanol is becoming very intense. Results show that the sweet taste and glucose are most effective in the enhancement of ethanol consumption both in the initial addictive process and later during withdrawal. Exceptionally large amounts of fluids were consumed and provide a basis for future studies of the intense and idiosyncratic cravings for ethanol containing fluids and sweet substances in alcoholics. A physiological basis for the drinking of large quantities of sapid fluids incorporating the mutual enhancing interactions between environmental stimulation and the changes in the internal environment controlled by converging sensory inputs in the LHA is discussed.

2. Methods

Eight male Long–Evans rats, 350–430 g in weight, were used in this experiment. All the procedures utilized in this study are in compliance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals revised in 1996. Animals were housed and maintained in an individual room in the animal facility. The experimental procedure was developed and described by Falk (Tang and Falk, 1977). Each animal lived in a standard test chamber in which three graduated 250-ml glass tubes with stainless steel ballpoint drinking spouts were attached to one of the Plexiglas walls. The position of each tube was changed every day in a nonsystematic order. A 45-mg food pellet was delivered automatically every 2 min during 1-h feeding periods that were separated by 3-h intervals. Therefore, there were six feeding periods in each 24-h cycle delivering a total of 180 pellets or 8.1 g of food. All animals were placed in the test chambers at ad lib body weight. In order to prevent the animals from losing more than 15% of initial body weight, food supplements were administered periodically. Fluid consumption in ml and body weight data were collected daily and were used to calculate daily intakes in ml/100 g body weight. Daily amounts of alcohol consumed were expressed in g/kg body weight. These animals normally prefer to drink copious amount of 5% alcohol and cut off at 6–7%; therefore, the baseline data were obtained with 5% alcohol and the other two tubes were empty. Alcohol solutions were mixed v/v from 95% ethanol and distilled in water. Glucose solutions (GLU) were always 3.0% w/v in distilled water or in a 5% or 6% ethanol solution. Sodium saccharin (SACC) was used as an artificial sweetener, 0.125% w/v in distilled water or in a 5% or 6% ethanol solution. To obtain control baseline data for the glucose plus saccharin (GLU + SACC) solution and saccharin alone (SACC) solution, consumption under the same conditions without alcohol in an additional four animals were used, two in each control group. Data were collected on the four control animals for 40 consecutive days.

3. Results and discussion

The results for the two control animals for SACC alone as the only fluid available indicated that SACC consumption gradually increased a small amount and became stable after the first 10 days of the 40-day period. Fluid intakes were similar to those of the animal in Fig. 4 when the only fluid available was 6% ethanol + SACC. Results with GLU+ SACC, in the other two control animals, showed an initial high fluid intake over the first 15 days, of the 40-day period, which then leveled off and stabilized over the last 10 days. When the mixture of 6% ethanol+GLU+SACC was given to the animal in Fig. 5, a similar effect can be observed: an initial increase in fluid intake and then a gradual decrease to a stable level. The addition of 0.125% NaSACC or 3.0% glucose + 0.125% NaSACC to a 6% ethanol solution therefore did not appear to have any significant effects on daily fluid consumption under these experimental conditions over a long period of time.

Results are illustrated for the four experimental animals in Figs. 4–7. Each animal was treated differently during the course of the study. The basic design was essentially the same for each animal, the critical difference being the tastant combined with the alcohol during withdrawal. The alcohol intake for the animal in Fig. 4 stabilized at about 65 days and then, when the fluid was changed to 6% alcohol + 0.125% Na saccharin + distilled water, increased from 11.0 to 15.0 g/kg/day and stabilized for the next 50 days, when the animal was switched to a choice of 6% alcohol+ SACC, or SACC alone, or distilled water (HOH). This change produced a slight decrease in the amount of alcohol consumed and the animal began to drink a small amount of the SACC solution on Day 160. At Day 169, the 6% alcohol+SACC was removed and the animal had only a choice between plain SACC and water. The dramatic increase in SACC consumption is obvious over the next 11 days reaching a peak of 79 ml/100 g of body weight for a total of 194 ml/24 h. The mean and SEM for the last 10 days of the 40 days of the 6% ethanol+SACC, SACC alone or HOH was 31.3 ± 1.1 ml/100 g body

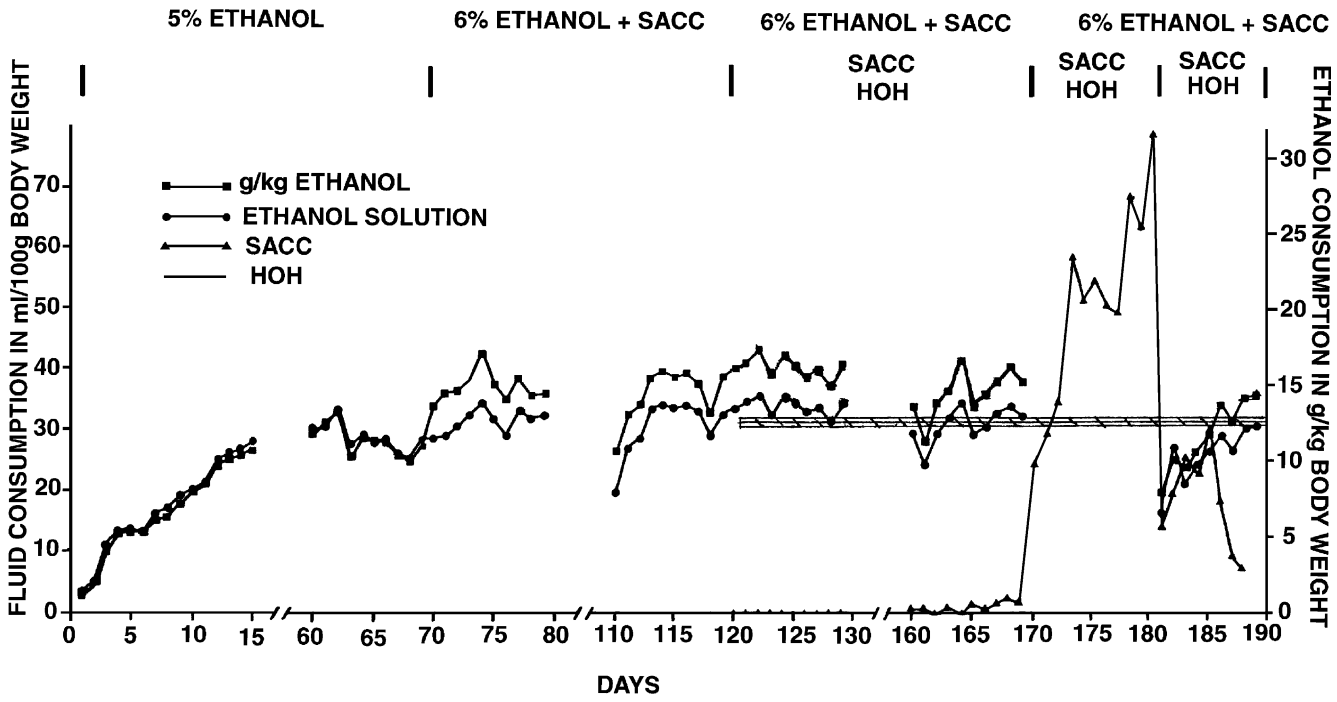

Fig. 4. An individual daily presentation of fluid consumption (ml/100g body weight) and ethanol consumption (g/kg body weight) for animal #4. The various solutions available over the 190 days are indicated at the top: 5% ethanol, 6% ethanol + 0.125% Na saccharin (SACC), 0.125% Na saccharin (SACC) and distilled water (HOH). All mixtures were in distilled water. The time breaks along the abscissa indicate that there was no significant change in the fluids consumed during those periods.

weight/24 h and is illustrated by the horizontal and diagonal lined hatched area parallel to the abscissa. When the alcohol solution was replaced, consumption of the 6% alcohol+SACC returned to previous levels including the intake of SACC alone which was still slightly elevated, this animal did not drink any water.

The only difference between the animal in Fig. 5 and the one in Fig. 4 is the fact that the animal in Fig. 5 was given a mixture of 6% alcohol+3% glucose (GLU) + 0.125% Na saccharin in distilled water (SACC). The other two choices were between glucose plus saccharin (GLU+SACC) and distilled water (HOH). GLU was added to determine if it had any special effects in addition to being sweet. This animal drank more alcohol and the increase in consumption when first exposed to the 6% alcohol + GLU + SACC occurred over the first 3 days. The animal became intoxicated, went to sleep and over indulged again periodically similarly to the animal in Fig. 2. Since SACC alone was not given to this animal, it is not known if the intake under these conditions would have been minimal. The response to the GLU+SACC during the period when the alcohol was removed from the fluid is notable on Day 223 and reaches its peak 140 ml/100 g body weight for a total of 455 ml in 24 h on the seventh day of ethanol withdrawal. When the 6% alcohol+GLU+SACC was replaced, GLU + SACC consumption was decreased to that observed prior to alcohol withdrawal. The 6% alcohol+GLU+SACC and alcohol consumption was also similar to that observed prior to alcohol withdrawal. The animal did not drink any water during the course of the experiment. Body weight did not change significantly during alcohol consumption. The mean and S.E.M. of 51.5 ± 3.1 ml/100 g body weight/24 h was calculated for the last 10 days of the 40 days of 6% ethanol + GLU + SACC and is illustrated by the horizontal and diagonal lined hatched area parallel to the abscissa.

In Fig. 6, results are presented on a sixth animal treated in a similar way to the animals in Figs. 4 and 5, except that this animal was tested with quinine hydrochloride (QHCl), 0.0003% w/v in distilled water, in place of the glucose. This animal was different than the other two and continued to drink a small amount of water whenever it was available. When quinine was first introduced as a choice with water the animal displayed a preference for the quinine solution and drank significant amounts. When the 6% alcohol and SACC were made available, it was clearly preferred and the animal drank insignificant amounts of quinine and water. On Day 138, the first day of alcohol withdrawal, intakes of quinine and water increased significantly and then declined to the usual minimal daily intakes. However, consumption of SACC was not only excessive on the second day but also continued to increase over the 10-day period reaching 63 ml/100 g body weight/day before alcohol was made available. Immediately the animal switched to drinking the alcohol+SACC solutions and the intakes of quinine and water returned to minimal values. After 15 days and the prewithdrawal pattern of drinking 6% alcohol+SACC in

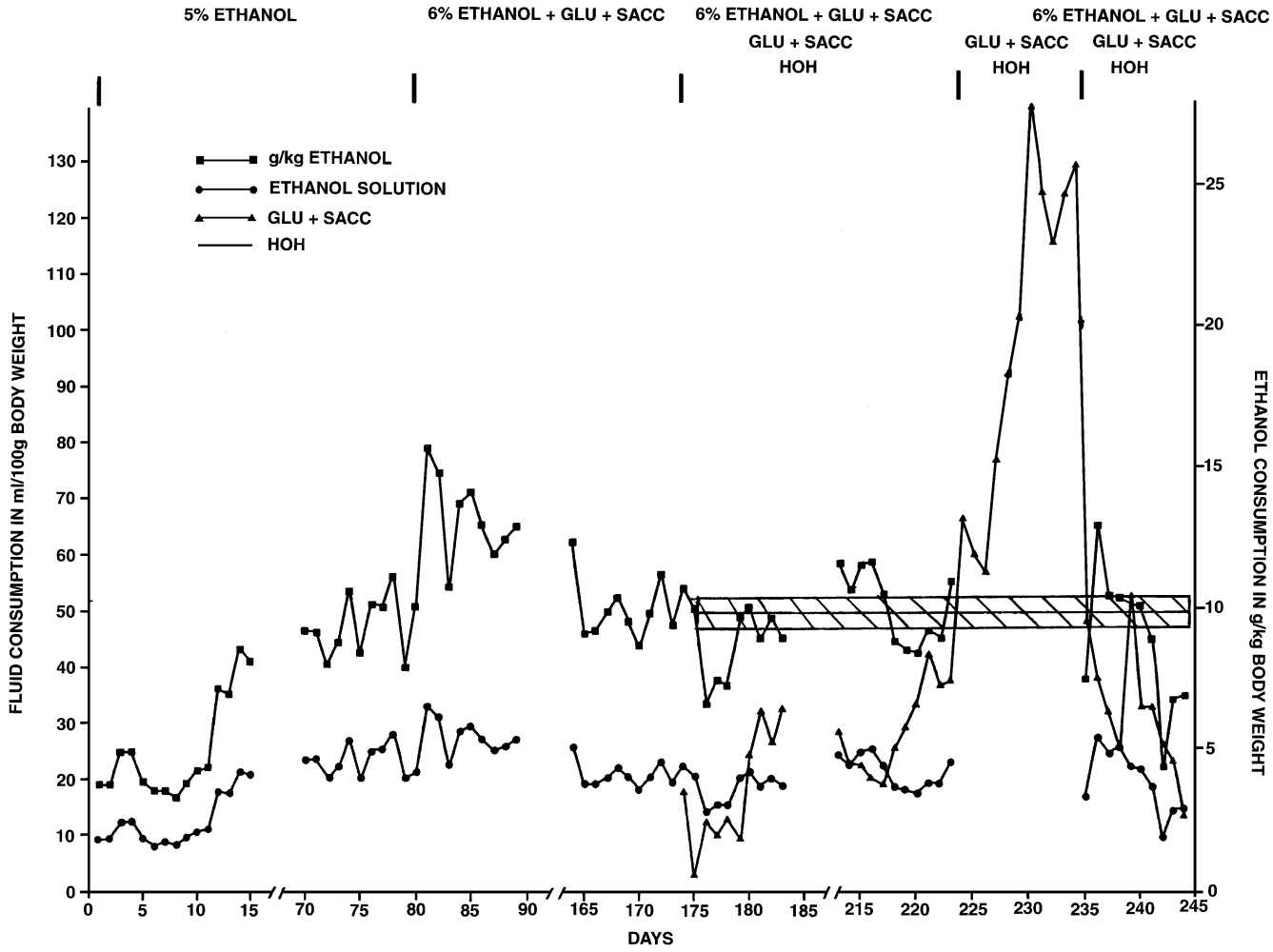

Fig. 5. Same as Fig. 4, except for a different animal and different solutions available over 245 days. The solutions were 5% ethanol, 6% ethanol + 3% glucose (GLU) + 0.125% Na saccharin (SACC), 3% glucose (GLU) + 0.125% Na saccharin (SACC) and distilled water (HOH). All mixtures were in distilled water.

preference to QHCl and HOH had returned, the ethanol and SACC solution was withdrawn again and the animal now had a choice between the QHCl and HOH. During the first 7 days, the animal preferred and drank the QHCl solution. During the next 3 days the animal alternated between both the QHCl and HOH. At the end of this 10-day withdrawal period, 6% ethanol and SACC were available along with QHCl and HOH and the animal immediately switched to drinking the ethanol solution and drank only minimal amounts of QHCl and HOH. These results show clearly that the animal prefers a sweet solution, as compared to QHCl or HOH immediately during withdrawal. However, the animal did drink increased quinine flavored distilled water during two withdrawal periods when the only other choice was water.

Results on animal #7 are presented in Fig. 7. This animal was treated similarly to the animal in Fig. 6, except that citric acid, 0.05%w/v in distilled water, was substituted for the QHCl. In the first day on 6% ethanol+SACC, the animal's consumption declined much more than animal #6 (see Fig. 6, Day 70). Other than this difference both animals were very similar; drinking small amounts of water when available and drinking significant amounts of citric acid in preference to water when the 6% ethanol and SACC solution was not available. Following the second period of ethanol withdrawal when SACC was also a choice with citric acid and water, the animal preferred SACC with an immediate increase in consumption. There was also a small increase in the citric acid and water intake on the first day of withdrawal similar to what occurred in animal #6 when QHCl was a choice with SACC and water. A peak intake of SACC, 63 ml/100 g body weight, was attained on the fourth day of withdrawal and then decreased significantly to below that observed prior to the period of ethanol withdrawal. When ethanol + SACC was restored as a choice, relatively small intakes occurred as the animal alternated between drinking the citric acid and water; then consumption of the 6% ethanol + SACC solution increased to the prewithdrawal level; then a second 10-day period of ethanol withdrawal was imposed with only citric acid and water available. Both

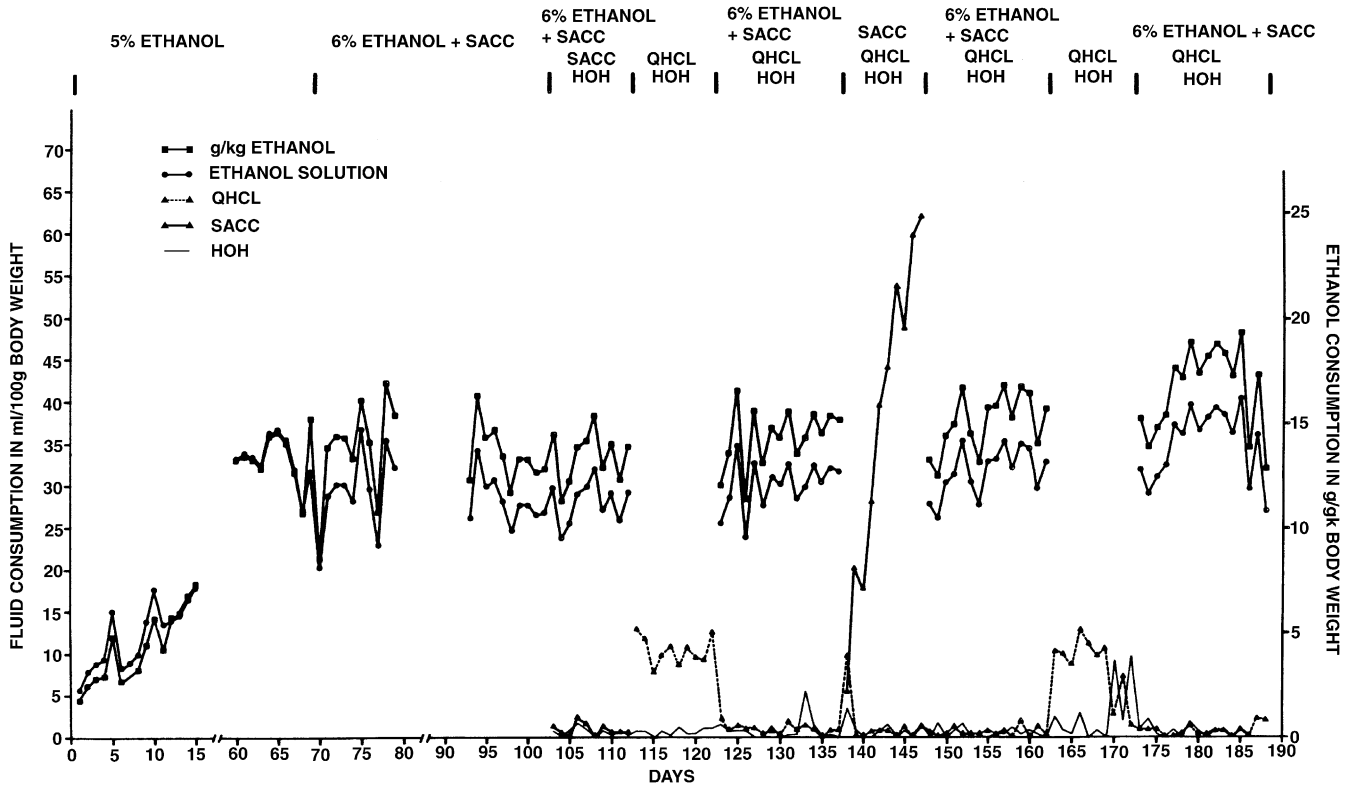

Fig. 6. Same as Fig. 4, except for a different animal and different available solutions over 190 days. The solutions were 5% ethanol, 6% ethanol + 0.125% Na saccharin (SACC), 0.125% Na saccharin (SACC), distilled water (HOH) and 0.0003% quinine hydrochloride (QHCL). All mixtures were in distilled water.

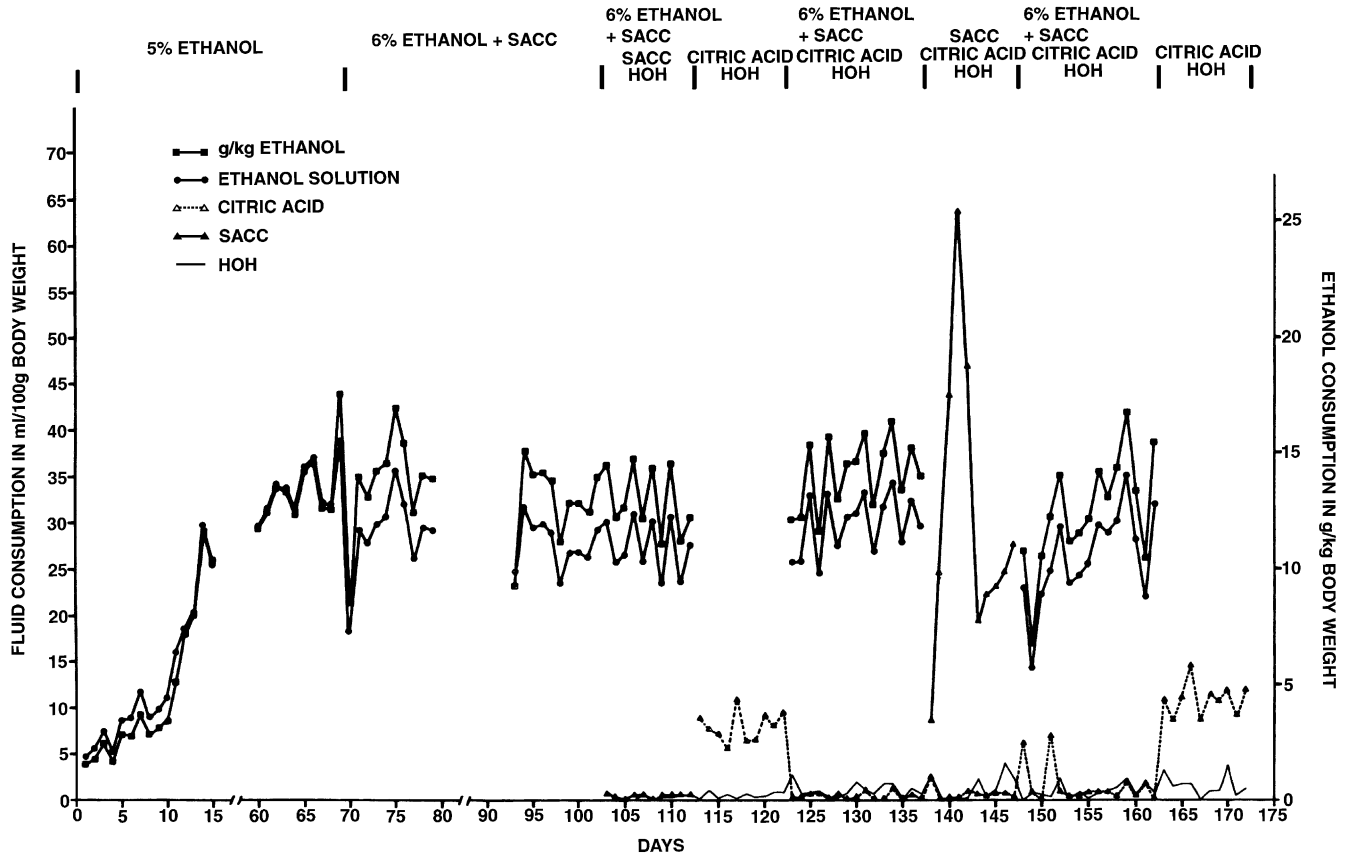

Fig. 7. Same as Fig. 4, except for a different animal and different available solutions over 175 days. The solutions were 5% ethanol, 6% ethanol + 0.125% Na saccharin (SACC), 0.125% Na saccharin (SACC), 0.05% citric acid and distilled water (HOH). All mixtures were in distilled water.

citric acid and water intakes increased significantly as before. These results confirm the observation with QHCl with one important difference. QHCl, the bitter tastant, appears to have an enhancing interaction with sweet SACC and the excessive consumption of SACC during withdrawal persisted longer than with citric acid. After 4 days, SACC intake diminished during withdrawal, whereas the SACC intake was continuing to increase in animal #6 in Fig. 6. The interaction between bitter and sweet as well as bitter alone with alcohol needs to be examined more thoroughly. Several bitter and bitter sweet alcoholic beverages are consumed in large quantities.

Excessive ethanol consumption can be induced in rats and maintained for a sufficient amount of time to result in physical dependence. Some of the animals in this report have never been food or water deprived or subjected to any stress in the presence of the ethanol solutions they eventually began to consume in large quantities. Only a brief period of food deprivation and body weight reduction was necessary to induce scheduled induce polydipsia in the test environment. Robust schedule-induced drinking occurs rapidly, becomes dependent upon the environmental cues in the test chamber, and is relatively resistant to extinction as shown in Fig. 1. The animals in Figs. 2 and 3 show clearly that animals with a prior history of schedule-induced drinking in a test chamber are at risk for becoming alcohol dependent when placed in the same familiar environment in the presence of a 5% or 7% solution of ethanol. These data on excessive intakes of ethanol and physical dependence confirmed the earlier results of Falk (Falk and Tang, 1977; Falk et al., 1972). Falk had observed similar ethanol intakes of 13.0 g/kg/day and blood concentrations of greater then 100 mg/dl for most of the 24-h periods and often values between 150 and 300 mg% were observed. When tested for physical dependence by a brief shaking of a bunch of keys, severe tonic–clonic seizures were observed and some animals died. As some of our animals convulsed and died when tested for physical dependence, we looked for mainly hyperactivity and increased taste reactivity responses associated with the drinking spout during withdrawal. Animals in Figs. 4–7 were not food or water deprived at any time prior to living in the test chambers. Food was delivered automatically and the polydipsia for 5% ethanol developed rapidly. As mentioned earlier, 5% is normally preferred when offered as a choice to water in this strain of rats, and would be comparable to beer being available as the only other fluid choice in comparison to water in the home. These data confirm the results of Falk (Falk, 1980).

3.1. Importance of intermittent sensory stimulation in adjunctive behavior

The intermittence of food delivery is crucial in the development of polydipsia, and if animals are given food all at once, following food deprivation, polydipsia does not develop, although some prandial drinking will occur associated with eating dry food. Also, if animals are offered saccharin or glucose or glucose plus saccharin solutions and water continuously in the home cage, their initial reaction is to drink more of the sweetened solution and, as they become accustomed or acclimated to the presence of the sweetened solutions, the amount decreases. Results with the control animals confirm this conclusion. In addition, comparing the animal in Fig. 4, 6% ethanol + 0.125% Na saccharin Days 169–180, with the animal in Fig. 5, 6% ethanol + 3% glucose + 0.125% Na saccharin Days 224–235, the excessive intake of glucose plus saccharin during withdrawal of the ethanol cannot be attributed to taste alone. The data in Fig. 5 show clearly that the animal adapted to the addition of glucose and the consumption of 6% ethanol+GLU+SACC leveled off, Days 165–174. The excessive consumption of glucose plus saccharin when the ethanol was no longer available, Days 224–235, seems to be due to the additional direct postsynaptic effects of the glucose on the glucose sensitive neurons in the LHA drinking circuits. Consumption in acclimated or taste-adapted animals can be increased significantly by removing the sweetened solution and returning it periodically (Wayner and Fraley, 1972; Wayner et al., 1972b). Similar effects can be observed with ethanol, quinine hydrochloride, sodium chloride, and citric acid. Periodic withdrawal of the ethanol solution from the home cage for the animal in Fig. 2 not only increased home cage ethanol consumption significantly (see Table 1), but must have produced a sufficiently high continuous blood level over the 25-day period to account for the observed withdrawal symptoms. These data on taste indicate that the sensory stimuli associated with the intermittence, or timing, of the delivery of the food pellet are the initial determining factors of adjunctive behavior. Sensory feedback from making the lever pressing responses are not a necessary condition because an easy way to induce polydipsia is with a fixed time schedule that does not require the animal to bar press for the food pellet (Wayner and Greenberg, 1973). Periodic withdrawal schedules of home cage availability of tastants can overcome the initial aversiveness of ethanol, as well as other tastants, and induce excessive consumption of alcoholic beverages. It seems reasonable to assume that withdrawal of certain sensory stimuli can be stimulating; in that the remaining environmental stimuli might evoke other similar types of responses and behavior to an excessive degree. Certain types of excessive behavior might be explained in this way particularly when the withdrawn stimulation is unknown to the observer.

Since schedule-induced drinking becomes stereotyped within a few days, what happens when the water or the drinking spout is removed? Stein (1964) was the first to show that when the water was removed animals quickly stopped licking at the empty tube. Later it was reported that if the drinking tube is made inaccessible then other types of activity occur more frequently (Wayner, 1974). In a more comprehensive study by Cook and Singer (1976), animals did not stop licking entirely when the drinking tube was

removed or replaced with a dry tube; the drinking behavior was displaced for the most part, to other activities that depended on the available environmental stimulation. The behavior of these animals is very similar to that observed in our ethanol dependent drinkers during withdrawal. Animals become hyperexcitable, increase motor activity, and climb all over the drinking tubes, bite around the edges of the hole in the wall, gape, and then emit other types of behavior; sniffing, rubbing the sides of their snouts, other types of grooming, and rearing. A naive observer might report that these animals were displaying excessive and bizarre drinking behavior since the animals were not water deprived or in a state of negative water balance.

Myers was the first to show that the odor of a specific concentration of alcohol enhanced the activity of rats, in this case of the high ethanol preferring P animals (Myers et al., 1997). Apparently, odor is an important factor in these results both in the development of excess ethanol consumption and increased sniffing during withdrawal. When potent taste and odor sensory inputs converge with sensory feedback from tactile and muscle receptors on the internally relevant LHA chemosensitive neurons, associated movements quickly become stereotyped. Intermittent presentation of germane sensory stimulation further enhances the level of excitability by reducing desensitization or habituation in the responding reflex pathways.

4. General discussion

The previous discussion focused on our results and those environmental conditions that produce excessive schedule-induced ethanol consumption. Since excessive fluid intakes can be produced in some other ways, we will describe them and the behavioral similarities that support a common underlying physiological process.

4.1. Brain electrical stimulation

Drinking and other behaviors that are emitted by rats during electrical stimulation of the LHA are similar to that of adjunctive behaviors (Wayner, 1970; Valenstein et al., 1969). The term stimulus-bound is used to describe behaviors that occur during electrical stimulation of the brain. These are physiological meaningful behaviors and the fluids and food during electrical stimulation are actually consumed. The drinking and eating can also be switched from eating to drinking and drinking to eating by removing either the water or the food and presenting only the other substance. Switching usually occurs readily but occasionally relatively long periods of overnight electrical stimulation is required. After switching, the second substance is dominant when both substances are tested simultaneously. These behavioral changes are similar to the displacement activities observed by Cook and Singer (1976) when the drinking tube is removed and the animals are still at 80% of initial body weight and displaying intense schedule-induced drinking. The hypothalamic physiological effects of 80% reduction in body weight are equivalent in several specific ways to electrical stimulation in the LHA. Both experimental treatments indirectly produce a general increase in motor excitability, in many spinal reflex pathways, that is reflected as an increase in motor response sensitivities to specific sensory stimuli (Wayner, 1970). Some of the early observations of Valenstein (Valenstein et al., 1969) are pertinent here. During LHA electrical stimulation when animals were tested with both glucose and water the motor components of the "...stimulus-bound behavior were dominant over the sensory input..." also animals when tested with "...a water tube...after water was removed from the bottle...demonstrated a remarkable resistance to extinction of the response pattern...one rat licking the tube on every one of the 175 stimulations presented..." (Valenstein et al., 1969, pp. 274 and 276). This resistance to extinction is similar to the resistance to extinction displayed by adjunctive drinking animals and was discussed earlier and illustrated in Fig. 1. The unusual dominance of the motor components observed with glucose was difficult to explain at that time because it was unknown that glucose is not only a sweet tastant but it also has a direct postsynaptic effect on some of the LHA neurons (Oomura et al., 1969, 1974). This is also true of salt.

The remarkable similarities between adjunctive behaviors and those emitted during electrical brain stimulation strongly suggest that these behaviors are being generated by the same underlying physiological process. Behaviors are complex compositions of specific motor responses that must blend with and still emerge from all of the ongoing muscular activity required to maintain postural and other physiological requirements. The physiological process, neural circuits involved, and initial probabilities of the responses evoked by the stimulation of the test environment are determined for the most part genetically and, to an extent, upon how these probabilities have been modified by prior experience. Electrical stimulation of the LHA results in a general increase in the neural activity of many specific LHA circuits. The axons of many of these cells project within the spinal cord and synapse with spinal motorneurons. In this way these LHA neurons can have a direct influence on the excitability of a multitude of spinal motorneurons involved in the final common motor pathways for many of these behaviors and produce an increase in the general level of excitability—a potential state of general arousal. In many situations, overt responses will not be observed and increased responding will occur only when elicited by the prepotent environmental stimuli: visual, auditory and olfactory, and the sensory feedback from muscles, and tactile and taste receptors.

Behaviorally, this means that the probability of the animal making any response involving these spinal motorneurons has increased; and specific responses will depend upon the available environmental stimuli. Taste sensory information travels over multiple synaptic pathways and

arrives in presynaptic endings of neurons in the LHA. Two blood born tastants glucose and salt also have powerful postsynaptic effects on some of these LHA neurons. These local LHA circuits regulate the activity of the neurons embedded within them and project directly to spinal motorneurons. An increase in the activity in some of these long neurons traveling down the spinal chord will potentiate the postsynaptic level of excitability in the motorneuron pools in the hypoglossal motor nucleus that control muscles in the tongue and thereby licking. Consequently, what the animal does initially in the test chamber during electrical stimulation of the LHA is conditional upon prior experience and evoked by immediate contacts with stimulus objects in the environment.

4.2. Salt arousal of drinking

In studies on the salt arousal of drinking, when hypertonic salt solutions are administered by chronic cannulation of the carotid artery, animals typically drink water in a familiar test environment. However, when animals were placed in a standard test chamber for the first time and then carefully observed, many of the animals did not drink for as long as 1 h, the length of the test period (Wayner et al., 1966). Animals were hyperexcitable and hyperactive, sniffing, grooming and tail chasing, rearing and shuffling the wood chips on the floor of the test chamber. When returned to the home cages, these animals drank copious amounts of water. In the test cage when an animal fortuitously licked at the drinking spout, it drank and left and quickly returned to the water spout and began to drink again and then copiously. Adjunctive behavior, behavior elicited during electrical stimulation of the LHA and behavior elicited during the salt aroused of drinking experiments, all display a similar pattern of behaviors that become focused on a particular type of environmental sensory stimulation. As the germane sensory stimulation continues, the stereotyped licking and other related motor movements develop more fully. Sensory feedback from the tactile and muscle receptors are an important part of this neural process. What appears to be most important is the sensory stimulation associated with the initial contact; and then subsequent sensory feedback to the hypothalamic neurons that sense the normal underlying physiological changes during water and food deprivation. Taste receptors are important both for taste discrimination in selecting edible food and potable water and rejecting possible poisonous bitter ones. They also play a critical role in the initiation and the maintenance of the ingestive process that might fail otherwise to provide sufficient intakes. A failure to sustain an adequate fluid intake has occurred in military troops marching in the desert, workers in a hot environment, and airline passengers on long flights. This condition was originally referred to by Adolph (1964) as voluntary dehydration. Under these conditions, usually making cooled artificially flavored fluids readily available can prevent dehydration by increasing drinking.

4.3. Path neurons of the LHA neuropil

The LHA is a vital and unique region of the rat brain. It is a vital part of the brain because if it is destroyed bilaterally by experimental lesions in the rat, not only is electrical stimulation not effective; but adjunctive behavior, salt arousal of drinking, as well as water deprivation induced drinking will not occur and animals die, if not force fed water (Wayner et al., 1966, 1977). The LHA is unique because it is a confluence of ascending and descending pathways within the brain and the bed nucleus of the medial forebrain bundle (Morgane, 1969). The cells that make up the bed or neuropil were first described by Millhouse (Millhouse, 1969) and referred to as path neurons. Further characterization of the path neurons was carried out by Palkovitz (Palkovits and Van Cuc, 1980). Several features of these path neurons of interest here are: (a) some of these cells are highly vascularized (Palkovits and Van Cuc, 1980) and make direct contact with blood vessels (Wayner et al., 1997b). We assume that these cells are the ones that are osmosensitive and respond to changes in the osmolality of the blood and participate in drinking circuits. (b) Some of these cells are osmosensitive and glucosensitive and respond to changes in blood sodium and glucose concentrations and participate in drinking and eating circuits (Oomura et al., 1969). (c) The dendrites of these path neurons are very extensive and invade many parts of the brain. (d) These neurons are densely covered with spines (Millhouse, 1969) and receive as many as 26,000 presynaptic endings per cell (Palkovits and Van Cuc, 1980). (e) Functionally, spontaneous activity of these cells can be modulated by stimulating every sense modality (Wayner, 1970). Because of the long latencies multisynaptic pathways must be involved in these modulatory effects of sensory stimulation. (f) The extensive connections between these cells and other parts of the brain include, for example, direct afferent and efferent connections to the cerebral cortex (Kita and Oomura, 1981) as well as direct projections to the lower lumbar region of the spinal chord (Emmers, 1959, 1961; Scharoun et al., 1980).

When the LHA is destroyed extensively many vital physiological functions are disrupted or lost including the ability to drink (adipsia) and eat (aphagia) and animals die, as mentioned earlier. More discrete lesions however can produce more selective deficits as adipsia and aphagia, without disrupting temperature, blood pressure, and other vital physiological functions, and animals will live if fed fluids and food by gavage. Discrete lesions can also eliminate adjunctive behavior (Wayner et al., 1977), salt arousal of drinking, water deprivation induced drinking, as well as the enhancement of lumbar spinal reflex pathway excitability during the course of salt arousal of drinking. The enhancement in lumbar spinal reflex pathway excitability, in the anesthetized rat preparation, during the intracarotid administration of various hypertonic solutions has been measured (Wayner et al., 1966). Alcohol applied directly

to osmosensitive cells in the LHA and indirectly by means of intravenous injection reveal changes in single neuronal activity that correlate very closely with the potentiation of spinal reflex excitability by activating the same osmosensitive cells of the LHA (Wayner et al., 1971, 1972a). These early observations have provided very useful information in the formulation of the present model for understanding some of the mechanisms involved in the craving for ethanol. Alcohol is a $GABA_A$ agonist and it has a specific low dose effect in the LHA drinking circuitry (Wayner et al., 1971, 1997a; Phelix et al., 1999). As mentioned earlier in this report similar LHA alcohol sensitive circuits project to the hippocampus where they produce anterograde amnesia for short-term memory (Wayner et al., 1997b).

The present model incorporates the following key features: (a) The low dose effects of alcohol on the LHA drinking circuit is to increase the rate at which the path neurons are firing. (b) Alcohol also increases the taste sensory input into the same neurons. (c) This combined effect increases the efferent output from these neurons into pools of spinal motorneurons and increases their level of excitability. (d) More muscle fibers will thereby be activated and drinking will be sustained for a longer period of time. (e) More alcohol will therefore be consumed. The timing of the intermittent reinforcement schedule and the availability of the environmental stimulation are crucial. In the test chamber, if the rat is distracted from the drinking tube or if the spout is relatively inaccessible or on one of the other walls, not close to the spout, schedule-induced drinking is limited and depends upon a time window of opportunity that is relatively small. The potentiating effect of the pellet endures for approximately 5 min (Wayner and Greenberg, 1973). Schedule-induced eating does not occur as readily as schedule-induced drinking. Schedule-induced eating will occur only if the food is almost in contact with the water; and shows that the physical accessibility of the stimulus objects is of the utmost importance before schedule-induced eating will occur. It is also an example of how certain behaviors can be incompatible within a given environment (Bellingham et al., 1979). A clever bartender is aware of these limitations and will place the beer nuts or paprika flavored potato chips immediately in front of or within easy reach of a customer before or soon after the drink is served.

Glucose and sodium chloride solutions are another effective means to augment schedule-induced drinking (Wayner et al., 1978). Both glucose and sodium chloride have complex effects in these LHA circuits because they also modulate activity of the postsynaptic cells directly. The osmosensitive cells of the drinking LHA circuitry are most sensitive to sodium changes (Oomura et al., 1969) in the extracellular fluid and respond initially due to an osmotic change in volume. These volume changes distort the sodium channel, sodium conductance varies, and thereby changes excitability and level of activity (Chakfe and Bourque, 2000). Some of these LHA neurons have glucoreceptors and respond to changes in blood glucose concentration and participate in the control of eating (Oomura et al., 1974). Both glucose and sodium therefore have a direct postsynaptic effect via the blood supply as well as an indirect presynaptic modulatory influence over multisynaptic afferent paths into the LHA. The dual effect of glucose explains the difficulty Valenstein encountered in trying to explain why a glucose solution in place of water during LHA electrical stimulation resulted in a stronger motor component in the stimulus-bound behavior.

In light of the results of the studies revisited and the new data presented, the Falk model of adjunctive behavior when applied to induce excessive ethanol consumption is an adequate analogue of human alcoholism, and also provides some insights into how the craving of any flavorful substance can be produced. The rat model is also important because we understand the physiologic basis; the neural circuits, critical environmental stimulation, as well as the role that taste and odor play in the induction of excessive alcohol consumption, physical dependence and withdrawal. Alcohol turns out to be a unique, dangerous and interesting drug because it has a direct low dose effect in the lateral hypothalamic neuronal circuits that control drinking. These neurons are also unique because they sense the changes in the internal physiological environment and normally monitor fluid balance and regulate drinking. When drinking alcohol it is important to never drink alone. If you are a social drinker, when you notice that you are becoming more sensitive and crave chocolate or other sweets at the end of a drinking party or shortly thereafter, you might be starting to show the early signs of dependence.

In conclusion, an adequate model of human alcoholism is available and a physiological basis for excessive alcohol consumption, in the rat, has been described. The initial contact with ethanol and the flavor, taste and odor, and the environmental setting are important in the development of excessive alcohol consumption. Taste also seems to play a critical role immediately in withdrawal and might serve as a useful indication of the early development of alcohol addiction.

Acknowledgments

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