THE EFFECT OF SCHEDULES OF ALCOHOL ADMINISTRATION ON VOLUNTARY ALCOHOL INTAKE IN ELECTRICALLY STIMULATED RATS

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ABSTRACT

The Effect of Schedules of Alcohol Administration on Voluntary Alcohol Intake in Electrically Stimulated Rats.

Electrical stimulation of the lateral hypothalamus has been shown to increase the consumption of alcohol in the laboratory rat. The present study was aimed at assessing whether different schedules of alcohol administration would alter the intake induced by the electrical stimulation, or whether electrical stimulation per se is the only condition affecting the intake levels. Four randomly selected groups of rats were each exposed to one of four different schedules during the period of stimulation; continuous forced alcohol, discontinuous forced alcohol, discontinuous free choice and adaptation.. It was found that the method of presentation markedly influences the development of alcohol preference. Animals exposed to the continuous forced alcohol schedule failed to develop a preference for alcohol, in spite of adequate stimulation. The adaptation and discontinuous free choice schedules were most efficient in producing high alcohol intakes suggesting that discontinuity of exposure to alcohol enhances the establishment of alcohol preference by electrical stimulation.

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OVERVIEW

Rats usually refuse to drink alcohol solutions in concentrations greater than 7% and normally only consume small amounts of solutions of lower strength. Several techniques including electric shock, cerebral ventricular infusion and chemical stimulation, have been successful in increasing alcohol intake. However the effect has only been temporary.

Recently several investigators have claimed success in enhancing the alcohol intake of rats by means of electrical stimulation of the lateral hypothalamus. A range of alcohol solutions of high concentration was used. The "preference" for alcohol (the consumption of more than 50% of the total fluid intake in alcohol solution) persisted for at least 3 months after cessation of the electrical stimulation. Other workers, on the other hand, failed to confirm these results. However, methods of presentation of alcohol differed in the different experiments.

It is the aim of this thesis to initially examine the role of alcohol presentation schedule in the development of a stable alcohol preference in rats

treated by electrical stimulation of the lateral hypothalamus. If schedule is important then this work would show that it is not permissible to compare results when different schedules have been used. In fact it will be shown that the type of alcohol presentation schedule is vital in determining the drinking pattern of animals following electrical stimulation.

INTRODUCTION

Genetic Predisposition

Genetic factors may be important determinants of alcohol selection (Rodgers & McClearn, 1962a). Preference for a 10% alcohol solution over water has varied with different species. On an adequate diet, deer mice and hamsters showed a marked preference for alcohol whereas Sprague-Dawley and cotton rats showed relatively low preference (Emerson, Brown, Nash & Moore, 1952). Wistar rats which differed in their alcohol consumption have been bred and two genetically distinct lines have been developed. Eriksson (1968) reports that by the eighth generation females consumed markedly more alcohol than males.

Stable strain differences in alcohol preference have also been established in the mouse (McClearn,1960; McClearn& Rodgers, 1961; Rodgers & McClearn,1962b) The C57BL/Crgl strain shows a high mean preference for 10% alcohol over water and the A, A/2, BALB/C and DBA/2N strains show a low mean preference. Differences in genetic constitution may account for the high variability in alcohol consumption between individuals.

Several studies have been concerned with breeding two strains of rats differing mainly in the degree of emotionality determined by the open field test. A low emotional strain of Wistar rats which displayed patterns of high physical activity and low defecation on the open field shows a lower mean preference for alcohol over water than the high emotional strain (Brewster, 1969) which demonstrates low physical activity and high defecation. This finding was not confirmed in two other investigations (Brewster, 1968, 1969) where it was reported that the low emotional strain shows a higher mean preference than the high emotional strain. In mice, the high preference C57BL/Crgl exhibits the characteristics of low

emotionality and the low preference BALB/C shows patterns of high emotionality (McClearn, 1960; McClearn & Rodgers, 1960, 1961; Rodgers & McClearn, 1962, 1964). It has also been concluded from a series of behavioral tests that the more timid animals consume less alcohol than those that are less timid (Tobach, 1957). Since 62 from a possible 66 behavioral measures do not yield significant correlations this conclusion needs to be treated with caution. While it seems that some data support the notion that high emotional animals ingest less alcohol than low emotional ones, the evidence is not at all clear-cut or conclusive.

Experimental Influence on Intake

Methods of alcohol presentation

Some investigations have been concerned with assessing the effects of a method or a combination of methods of alcohol presentation on alcohol intake. There are two basic methods: forced alcohol - in which alcohol solution is the only fluid offered to the animal; and free choice - in which both alcohol and water are made available. In the forced alcohol approach there may be no choice - only one solution may be offered; or there may be choice - more than one alcohol solution is

offered. Manipulations of the above techniques are: continuity - daily use of any one of the basic techniques; discontinuity - intermittent replacement of alcohol by water; adaptation - systematic change in alcohol concentrations in any of the above.

Forced alcohol - continuous. Richter (1926) reported that following a period in which alcohol was the only liquid offered the alcohol intake increased more rapidly. More recently, the same author (1957) stated that domesticated rats do not increase alcohol consumption after a period of forced administration of alcohol. Prieto, Varela and Mardones (1958) examined the effects of the forced alcohol no-choice situation using an alcohol concentration of 10%, 20% or 30% during periods ranging from one to five weeks. The results indicated that a period of forced ingestion of alcohol does not increase the preference of alcohol. Employing the same basic technique on Wistar rats, Rick and Wilson (1966) used a 2%, 4%, 8% or 16% alcohol solution over a period of six months. During the actual period of treatment rats slowly increased their alcohol intake. When subsequently presented with a choice of water and alcohol the groups given 2%, 4%

or 8% alcohol solutions drank similar quantities of alcohol (in terms of absolute content) to those consumed during the period of treatment. There was a decrease in alcohol consumption when 16% alcohol was offered.

In contrast with the findings of previous studies, Cicero, Snider and Swanson (1971) reported that a forced alcohol regimen was effective in producing a preference for alcohol over water. The no-choice presentation of alcohol was used with very young rats (days 21-60) of the Holtzman strain. Cicero et al. (1971) suggested that the age at which alcohol is introduced may be the crucial factor responsible for the increase in alcohol intake. The available evidence does not indicate a clear-cut relationship between age and alcohol. Parisella and Pritham (1964) found that rats aged 3-4 months showed a higher preference for 8% alcohol over water than did rats of other age groups (1-2, 10-15 and 20-24 months). However, Wallgreen and Forsander (1963) observed that rats aged 30 months developed alcohol preference to a greater degree than those aged 3 months. The explanation for the difference between the results

of Cicero et al. (1971) and those of the previous studies remains unclear.

Although the experiments on forced-alcohol, no-choice presentation vary in the length of exposure to alcohol, and also in the concentration of alcohol used, the overall findings (with the exception of Cicero et al., (1971) indicate that the forced-alcohol, no-choice method of alcohol presentation does not increase alcohol intake during a subsequent period when both water and alcohol are made available.

Forced alcohol - choice. Mendelson and Mello (1964) examined the combined effects of both continuous free and forced choice presentations of alcohol. All animals were treated with fourteen weeks of the free choice regimen followed by the forced choice situation. When rats were offered a choice between two alcohol solutions of the same concentration, the preference for alcohol over water was increased. This finding is unexpected in view of the results obtained from the no-choice alcohol studies. The Mendelson and Mello (1964) study suffers from the disadvantage that a continuous free choice period was inserted before the forced choice regimen so that the effects of forced

choice alone cannot be evaluated. No other studies bearing on this point could be found in the literature.

Free choice - continuous. Mendelson and Mello (1964) found that after a seventeen week continuous free choice period using 5% or 10% alcohol, hooded rats consumed more than 50% of the total fluid intake as alcohol. Sinclair and Senter (1967) also maintained a group of rats on a schedule of continuous free choice between 7% alcohol and water for twelve weeks. Approximately 58% of the total fluid intake consisted of alcohol. In a later study, (1968) the same authors found that when the free choice treatment was extended to six months, using 6% solutions, alcohol constituted 75% of the total fluid intake. When a 20% solution was used the volume of alcohol consumed as a percentage of the toal fluid intake was less but the amount of absolute alcohol ingested remained essentially unchanged. It would therefore seem that the continuous free choice method is an effective means of establishing stable alcohol preference in rats and is capable of producing an increase in alcohol intake over the duration of treatment.

Free choice - discontinuous. In the above studies alcohol was offered on a daily basis or continuously. Intermittent presentations have been used in several studies. Sinclair and Senter (1967) and Senter and Sinclair (1967) claimed that when alcohol is withheld for six days following a free choice schedule with 7% solutions, a higher alcohol preference is achieved than after continuous treatment. This enhancement of intake is maximal during the first two days of reintroduction of alcohol. Subsequently the intake falls until the post-deprivation alcohol consumption is approximately equal to that before deprivation. When a control study was done using sucaryl instead of alcohol, there was no significant increase in consumption after a period of deprivation. The increase in alcohol intake following a period of abstinence cannot therefore be accounted for solely by the novelty of the situation.

Senter and Richman (1969) reported that following six weeks of a free choice treatment, using 6% alcohol, a one-week period in which no alcohol was presented produced a subsequent preference for 20% alcohol over water. In fact the amount of absolute

alcohol consumed doubled. Animals deprived of alcohol and then presented again with a 6% solution did not show any significant increase in alcohol preference. Amit, Stern and Wise (1970) showed that in electrically stimulated rats a stable alcohol preference was developed in animals given alcohol on a discontinuous schedule. During a phase in which no alcohol was provided, lasting seventeen days, the subjects lost weight and showed abnormal behavior in the open field test. Similarly to the results of Senter and Richman (1969) the above authors found that the absolute alcohol consumption after the withdrawal period was approximately equal to that prior to deprivation.

It is possible that the failure of an abstinence period to increase alcohol intake may have been due to the already high consumption (90% of total fluid intake) achieved prior to the phase in which no alcohol was provided. Alternatively animals exposed to a given alcohol concentration for an extended period of time may develop such a stable response pattern that a deprivation period cannot alter it. Also, the period in which no alcohol was presented may

have been too long to produce an effect. Another possibility is that abstinence may still produce a need for alcohol which may not be reflected in the consummatory behavior but in some other type of behavior such as bar pressing or greater physical activity. It is concluded that abstinence from alcohol does not necessarily produce an increase in alcohol intake.

Adaptation. Alcohol intake changes as a result of repeated exposure to either increasing or decreasing alcohol concentrations. Richter and Campbell (1940) reported that rats preferred alcohol to water in concentrations ranging from 1.4% to 4.8% when the alcohol concentration was systematically increased. Kahn and Stellar (1960) confirmed that alcohol preference is established following a continuous ascending schedule of alcohol concentrations up to the 5% and 6% level. However, when the strength of alcohol solutions was progressively reduced, alcohol preference was not established. The subjects that were presented with the ascending schedule were also treated for a longer period of time than those on the descending schedule and this may account for the increase in alcohol intake with the ascending order of

alcohol concentration. Myers (1961) increased percentage concentrations from 5% and decreased concentrations from 15% in 1% steps on successive daily sessions after a no-choice period. Preference was established at the 4% concentration with the decreasing schedule and at 6% with the increasing one.

Veale and Myers (1969) investigated the effects of alcohol concentrations increased every third day (only water was presented on intervening days) in the following sequence: 3%, 5%, 7%, 9%, 12%, 15%, 20%, 25% and 30%. Sprague-Dawley rats which were initially presented with a 12% alcohol solution as the only source of fluid and then given the sequence of concentrations drank little alcohol regardless of concentration. Subjects that were not forced to consume alcohol before the ascending alcohol sequence selected a high 12% concentration in preference to water. In another study, Veale and Myers (1969) presented the above adaptation sequence continuously for a period of 9 days before and after either a 9-day, forced-alcohol, no-choice period (15% concentration), a 9 day abstinence period, or another, similar, 9 day adaptation sequence. They found that the mean daily alcohol intake of the group given the additional

adaptation sequence increased significantly by 0.45 gms of absolute alcohol between the first and third sequences. The abstinence group increased its alcohol intake by 0.38 gms per day, i.e., by a smaller but significant increase, and the no-choice group increased its mean daily alcohol consumption by only 0.11 gms per day (which was insignificant). The investigators concluded that when animals are given a choice between water and alcohol solutions of increasing concentration the preference for alcohol rises. It also appears from the available evidence that the ascending adaptation schedule is more effective in increasing alcohol intake than the descending one.

Permanency of intake

Many experiments have reported success in inducing increases in alcohol intake but the increases have declined rapidly following the termination of the experimental treatment. Few studies have incorporated a long exposure period to alcohol and consequently the permanence of the alcohol preference cannot be evaluated. A permanent preference for 5%, 10%, 15%, 20%, and 25% alcohol solutions over water in rats has been established by Mendelson and Mello (1964) in which the

treatment consisted of free and forced periods for a period of five months. In terms of absolute alcohol content the greatest amount was consumed in 20% and 25% concentrations. The same subjects were used in an investigation in which rats were trained to bar press for alcohol without any other motivating stressor (Mello & Mendelson, 1964). Veale and Myers (1969) also reported a permanent alcohol preference after the presentation of a series of alcohol solutions with different alcohol concentrations over a period of ten months. Amit, Stern and Wise (1970) and Amit and Stern (1971) showed that after electrical stimulation of the lateral hypothalamus in rats, the same high level of alcohol intake persisted for over seven months. All the studies showing a permanent preference for alcohol have used a free choice condition as well as a long alcohol exposure period.

The preference for alcohol over other solutions

Alcohol preference has usually been established when only alcohol and water are made available. A third solution has been incorporated in some investigations. Rats with an already established preference for alcohol over water decreased their alcohol consumption when a fat

solution was added as a third choice (Lester & Greenberg, 1952). Alcohol consumption did not change when a solution of B vitamins was offered (Mardones, Segovia-Riqueleime, Hedera & Aleaino, 1955). During the period when a saccharin solution was presented there was a considerable reduction in alcohol intake and high consumption of the saccharin solution (Lester & Greenberg, 1952; Mardones et al., 1955).

No alcohol is ingested in a situation where an 11.5% sucrose solution, 7.6% alcohol and water are made available (Lester & Greenberg, 1952). Using a similar sucrose solution Mardones et al. (1955) report a significant decrease in alcohol intake but not a complete suppression with vitamin deficient rats.

In mice, a greater preference for a 15% sucrose solution is exhibited than for either 10% alcohol or water (Rodgers & McClearn, 1964). In addition, nine mice strains show greater preference for sweetened alcohol solutions than for nonsweetened alcohol. This preference is augmented when the sucrose concentration is progressively increased.

It would seem that the presence of a third substance does influence alcohol preference to a marked

degree in both rats and mice. Whereas saccharin results in a reduced intake of alcohol, sucrose may completely inhibit alcohol consumption.

Stress

The role of psychological stress on alcohol intake has been examined. Masserman (1957) produced deviant behavior patterns such as aversion reactions, regression and catalepsy in cats by administering an electric shock or air blast as the animal approached a food box. These behavior patterns disappeared when alcohol was offered, leaving intact simple manipulation behavior patterns. Many animals preferred milk with 5 or 10% alcohol to plain milk. Clark and Polish (1960) indicate that monkeys may select a normally nonpreferred alcohol solution following a chronic period of responding on a continuous 24 hr shock avoidance schedule.

Other evidence (Myers & Holman, 1967) has indicated that rats do not increase their intake of alcohol when unavoidable shock is delivered intermittently. Similarly, Mello and Mendelson (1966) report that monkeys do not increase alcohol intake if unavoidable shock is given on a 24 hr schedule. Cicero, Myers and Black (1968) find that rats performing a discriminated shock

avoidance task increased their alcohol intake significantly when unavoidable random shock, signalled by a warning light, was administered simultaneously. When non-cued unavoidable shock was delivered the animals did not increase alcohol consumption.

There are some data which support the notion that stressed animals increase alcohol intake in comparison with those which are not stressed. Stressed animals appear to behave similarly to highly emotional ones in the open field in that frigid or cataleptic reactions occur. The conclusion from studies concerned with genetically determined emotionality contradicts that made from stress-induced emotionality in that the highly emotional animals ingest less alcohol than the less emotional ones in the latter studies.

Physiological factors

Alcohol can be used by rats as a calorie source to maintain body weight when it is partially substituted for food in the animal's diet (Richter, 1941, 1953; Gillespie & Lucas, 1958; Morgan, Brinner, Plaa & Stone, 1957). Westerfield and Lawrow (1953) reported that severe food deprivation increases alcohol preference although moderate food deprivation does not.

With restricted food intake, there is an increase of alcohol preference in rats (Zarrow & Rosenberg, 1953). It has therefore been suggested that alcohol may be consumed as a source of calories when animals are under severe food deprivation.

Several investigators found that some vitamin deficiencies will increase alcohol preference. Mardones (1951), Beersteecher, Reed, Brown and Berry (1951) and Mirone (1957) demonstrated that thiamine deficiency increased alcohol preference of rats and mice. Other vitamins, the deficiencies of which have been found to increase alcohol preference, are riboflavin, pantothenic acid, and pyridoxine (Beersteecher et al., 1951), vitamin B_{12} (Williams, Berry & Beersteecher, 1949a), vitamin A (Williams, Berry & Beersteecher, 1949b) and factor N_1 from the B complex family (Mardones, Segovia & Hederra, 1953). The increase in alcohol preference is not reversed by increased intake of any single vitamin if other vitamin deficiencies continue to exist.

The involvement of the thyroid in alcohol preference has been examined by Zarrow and Rosenberg (1953) who found that propyl thiouracil, an anti-thyroid drug increased alcohol preference of Sprague-Dawley

rats. Thyroidectomy had no effect on preference. They concluded that propyl thiouracil acts independently of the thyroid and that the gland itself is not directly involved in increasing alcohol preference. Richter (1957) found that thyroid hormone, thyroxine and tri-iodo-thyronine decreased alcohol preference of Norway rats whereas thyroidectomy tended to increase preference. The site or mechanism of propyl thiouracil or the thyroid derivatives is not yet clear.

The direct effect of alcohol on the pituitary and the indirect effect through the pituitary on either organ systems may account for the symptoms of alcohol intoxication and chronic alcoholism (Gross, 1945). Iida (1957) found a small increase in alcohol preference of saline-fed mice when they were injected with desoxycorticosterone acetate or cortisone in small doses. Large doses decreased the preference. Administration of ACTH, posterior pituitary hormone and desoxycorticosterone had no effect on preference. The implication is that pituitary-adrenal manipulation has only a small effect on preference.

There is the possibility that the pancreas may be involved in alcohol preference. Forsander, Kohonen

and Suomalainen (1958) report an increase in alcohol preference in rats fed N-sulfaminyl-N-n-butyl-carbamide ('Nadisan') and in rats injected with insulin. Liver damage and alcoholism have also been closely linked. Sirnes (1953) reported that experimentally induced cirrhosis of the liver markedly increased alcohol preference in rats.

Several investigators (Rodgers, Pelton & Williams, 1955, 1956) have explored the effects of various amino acids on alcohol preference and conclude that preference of alcohol in rats is decreased by ingestion of glutamine. No effect was obtained from ingestion of glutamic acid, sodium glutamate and glycine.

Alcohol infusion

Myers (1963, 1964) found that alcohol concentration in the cerebrospinal fluid of the rat was related to the preference for a particular alcohol concentration. A ten day infusion of 1 ml/min into the cerebral ventricles resulted in the selection of an 8% alcohol solution whereas the infusion of 3 ul 10% solution into the ventricles resulted in a preference for 30% alcohol. Animals that had been previously

exposed to alcohol did not show as great an alcohol preference as those who had not been previously exposed. Myers concluded that alcohol infused chronically into the cerebral ventricles produced a marked increase in the intake of alcohol. However, Koz and Mendelson (1967) failed to obtain an increase in alcohol intake with monkeys using a similar intraventricular infusion technique. Jones, Essig and Creager (1970) were also unsuccessful in obtaining a change in the drinking of alcohol in dogs when alcohol was infused via cannulae implanted in the left lateral cerebral ventricle. In addition, Myers and Veale (1969) have found that the oral intake of alcohol was increased not only by intraventricular infusion of alcohol but also when acetaldehyde (0.5%), paraldehyde (0.5%) or methanol (0.2%) were used. Paraldehyde produced a greater increase in alcohol preference than acetaldehyde or methanol. The reason for the effectiveness of intraventricular alcohol infusion in rats but not in other species is not obvious.

Withdrawal symptoms may be induced by depriving animals of alcohol after a period of gastric infusion of alcohol. Essig and Lam (1968) reported the occurrence

of convulsions in dogs upon the withdrawal of alcohol after two months of continuous administration through surgically implanted gastric cannulae. During the infusion period water was withheld to encourage oral intake of 10% alcohol for sixteen hours per day. Ellis and Pick (1970) found that termination of gastric infusion of alcohol after 10 to 18 days in rhesus monkeys resulted in signs of hyperexcitability which could be classified into tremulous, spastic and convulsive stages. The progressive severity of these stages was correlated with the declining blood alcohol concentration. Withdrawal symptoms have not been reported in rats after a period of gastric infusion (Amit & Stern, 1969). It appears that after a period of gastric infusion of alcohol, withdrawal symptoms may occur upon termination of the infusion in some species.

Neural manipulation

Lesion: Marfaiing-Jallat, Larue and LeMagnen (1970) found that after ventromedial hypothalamic lesions the majority of rats increased their intake of alcohol solutions. The authors attributed this increase to a freely available supply of calories in the form

of alcohol.

Chemical stimulation. The notion that chemical stimulation of the brain may cause a significant change in an animal's selection of alcohol has been examined by very few investigators. Cicero and Myers (1969) produced polydipsia in rats by injecting carbachol into the nucleus reuniens, preoptic region, septum or hypothalamus. When offered a forced alcohol choice of 4, 8 and 12% alcohol, the alcohol solutions were acceptable by animals deprived of all fluid for 23 hours but were rejected following a microinjection of carbachol in all regions. Cicero and Myers (1969) and Veale and Myers (1970) found that when levels of brain serotonin are lowered over a long period of time by p-chlorophenylalanine, a potent inhibitor of tryptophan hydroxylase, the animal's intake of alcohol is markedly reduced. Although intake of alcohol increased when rats were stressed by random intermittent unavoidable shock, intake again decreased during the period of random punishment when levels of brain serotonin were lowered. Reduced levels of serotonin can effect alcohol intake whereas carbachol does not.

Electrical stimulation. Segal, Nerobkova and Rybalkina (1969) reported that electrical stimulation

of the ventromedial hypothalamic nucleus resulted in short term increases in alcohol intake while stimulation of the lateral hypothalamus resulted in decreased alcohol intake. Amit, Stern and Wise (1970) and Amit and Stern (1971) found that electrical stimulation of the thirst areas of the lateral hypothalamus was effective in inducing a permanent preference for alcohol over water. The availability of alcohol in the stimulation boxes during the 30 minutes daily stimulation sessions was not a necessary condition for inducing a preference. In addition the preference was not correlated with stimulation-bound drinking since both stimulation-bound drinkers and non-stimulation-bound drinkers reversed their preference for alcohol. Neither was the development of a preference for alcohol correlated with the initial alcohol drinking pattern. The range of individual test solutions for subjects that reversed their preference was identical to that of those who did not. Amit and Stern (1971) concluded that it is the direct effect of the stimulation on hypothalamic tissue which constitutes the necessary and sufficient condition for the induction of alcohol preference. Neither alcohol drinking during stimulation nor any other consummatory responses appear necessary

(Amit & Stern, 1971). However electrical stimulation was not the only experimental manipulation in the studies of Amit, Stern and Wise (1970) and Amit and Stern (1971). Other features included an adaptation period where water was freely available and the alcohol concentration was gradually increased by 1% per day until the solution was rejected. There was a discontinuous free choice procedure during stimulation and post-stimulation periods.

The Present Investigation

The present investigation was concerned with the interaction of schedule of alcohol availability with hypothalamic stimulation. Brain stimulation increases alcohol intake when used in conjunction with adaptation and a discontinuous free choice schedule (Amit, Stern & Wise, 1970; Amit & Stern, 1971). The purpose of the present study was to determine the importance of adaptation, free choice and discontinuous presentations on this phenomenon.

METHOD

Subjects

The subjects were 36 adult male rats of the Wistar strain weighing 300-350 gms at the time of surgery.

Each animal was individually housed in a steel wire mesh cage and was maintained on a diet of Purina lab chow pellets and a fluid intake of water and/or alcohol. The rats were exposed to light for 16 hours a day, a constant temperature of 74° F and 40-55% humidity.

Apparatus

Intracranial electrical stimulation was delivered by a 60 Hz sine wave stimulator. Current was monitored with a microammeter and adjusted with a calibrated potentiometer. The schedule used was a twenty second-on-twenty second-off pattern of stimulation.

The experimental chamber in which subjects received stimulation measured 10 x 14 in. and was constructed from wood except for a sheet of clear plexiglass on the front wall. For the stimulus-bound drinking period, water bottles were mounted on the front walls with drinking spouts extending ½ inch into the box at a height of 2 inches from the floor. Room lights were on continuously. Consummatory responses could be observed through the plexiglass.

In the home cage alcohol solutions were presented in one of two 100 cc. graduated Richter-type

drinking tubes. Alcohol solutions were mixed volume by volume (vv) by adding tap water to 95% alcohol. For example, 1000 ml of a 10% alcohol solution contained 105.6 ml of 95% alcohol and 894.4 ml of water. For two days the alcohol was adulterated with quinine in a 0.05% solution.

Surgery

One monopolar stimulating electrode and one indifferent electrode were used in all subjects. A stereotaxic instrument (Scientific Prototype) with the incision bar located 3.2 mm above the interaural line was utilized to implant the stimulating electrode. The target coordinates were 1.5 mm left of the sagittal suture, 0.8 mm posterior to bregma and 7.5 mm below the superior surface of the skull. The stimulating electrode was a straight piece of stainless steel wire 0.01 inches in diameter. The wire was soldered to a miniature male connector and the electrode was dipped in lacquer and tested for insulation leaks. Three stainless steel screws were mounted in the skull to anchor the electrode assembly; one lateral, one anterior and one posterior to the stimulating electrode. The anterior screw served as the indifferent electrode,

which was connected by a stainless steel wire to a minature brass connector. A crown of dental cement was used to anchor the electrode assembly to the skull screws. A stainless steel bar was attached to the assembly to protect the electrode pins from damage.

Surgery was performed under barbiturate anesthesia (Equithesan) at a dose of 3 ml/kg intraperitoneally. Phenergan at 3 ml/kg was used initially to potentiate the effects of anesthesia and 60,000 I.U. Benzathine penicillin G was injected intramuscularly to reduce the chance of infection.

Procedure

During a two day training session signs of stimulus bound drinking and eating were noted. Each subject was given free access to water and food pellets which were spread on the floor of the experimental chamber. Sine wave stimulation was administered on a 20 second on 20 second off schedule. Current intensity began at a level of 5 uA and was raised by increments of 2 uA in successive 20 sec stimulation periods. If 100 uA was reached without any observed consummatory response, or if forced circling or jumping occurred the animal was returned to its home cage and

testing was discontinued. Animals which ate and drank during the entire session in which stimulation was received were retested on the following day.

Subjects were randomly assigned to one of four treatment groups, each treatment consisting of a specific method of presentation of alcohol (See Table 1).

The group design (Table 2) was aimed at assessing the influence of each of the methods of presentation on alcohol preference in rats all of which were treated with electrical stimulation for thirty days. Only Group 1 was adapted to alcohol during a prestimulation phase and this group received a free choice, discontinuous schedule during the stimulation phase.

Group 2 also received a free choice discontinuous schedule during electrical stimulation and served as a control for Group 1. Groups 3 and 4 received the discontinuous forced alcohol and the continuous forced alcohol schedules respectively during the stimulation phase of the experiment. Twenty per cent alcohol was presented only in the home cage and not in the stimulation box.

TABLE 1

Schedules of Alcohol Presentation

(1) Adaptation	Alcohol concentrations increased in 1% steps until a solution was rejected.
(2) Discontinuous Free Choice	20% alcohol every other day water available every day
(3) Discontinuous Forced Alcohol	20% alcohol every other day water only on the in-between days
(4) Continuous Forced Alcohol	20% alcohol every day no water

TABLE 2

DESIGN

Treatment Period		Post - Stimulation Phase			
Pre-Stimulation	Stimulation Phase	Alcohol Presentation	No Alcohol	Alcohol Presentation	Quinine Test
GP	(Days 1-30)	(Days 31-72)	(Days 73-90)	(Days 91-96)	(Days 97-100)
1. Adaptation	discontinuous free choice schedule	discontinuous free choice schedule	water only	discontinuous free choice schedule	discontinuous free choice schedule
2.	discontinuous free choice schedule	discontinuous free choice schedule	water only	discontinuous free choice schedule	discontinuous free choice schedule
3.	discontinuous forced alcohol schedule	discontinuous free choice schedule	water only	discontinuous free choice schedule	discontinuous free choice schedule
4.	continuous forced alcohol schedule	discontinuous free choice schedule	water only	discontinuous free choice schedule	discontinuous free choice schedule

The effect of the treatment was determined in a post-stimulation phase during which subjects were given access to 20% alcohol solutions on a 42-day, free choice, discontinuous presentation, then a 17-day period in which alcohol was temporarily withdrawn, and finally a six day period in which alcohol was presented again on a free choice discontinuous schedule (See Table 2). In order to assess the degree of motivation for alcohol, 0.05% quinine, a usually avoided substance, was combined with alcohol on days 98 and 100. Thus the procedure was similar to the Amit and Stern (1971) paradigm, except that (i) only 20% solutions were used (after adaptation in Group 1); and (ii) the importance of schedules of alcohol availability was assessed by examining the effects of the different schedules during either the prestimulation or stimulation period on the voluntary intake in the subsequent post-stimulation phase.

RESULTS

Stimulation phase

Both the adaptation and continuous forced alcohol groups drank overall means of 3.0 mls of absolute alcohol per day, the maximum mean daily intake reaching

4.2 and 4.0 mls respectively (See Fig. 1). On an average, the discontinuous forced alcohol group ingested 2.7 mls per day whereas the discontinuous free choice group consumed the least amount at 1.9 mls. The alcohol intakes of the four groups were in the same sequence relative to each other over the first six day period (See Fig. 1) as during days 24-30 of the stimulation phase.

Post-stimulation phase

Early period. The absolute alcohol intake of the continuous forced alcohol group dropped markedly to as little as 0.6 mls per day in the first twelve days after stimulation treatment (See Fig. 1). This constituted 9% of the total fluid intake in alcohol (See Fig. 2). Less alcohol was ingested by the continuous forced alcohol subjects than animals on the discontinuous forced alcohol schedule both in terms of absolute alcohol and percentage of total fluid intake. This was the reverse of the relative alcohol intakes of these two groups throughout the stimulation phase. The discontinuous forced alcohol group consumed 47% of the total fluid intake as alcohol solution which comprised approximately 2.1 mls absolute alcohol per day.

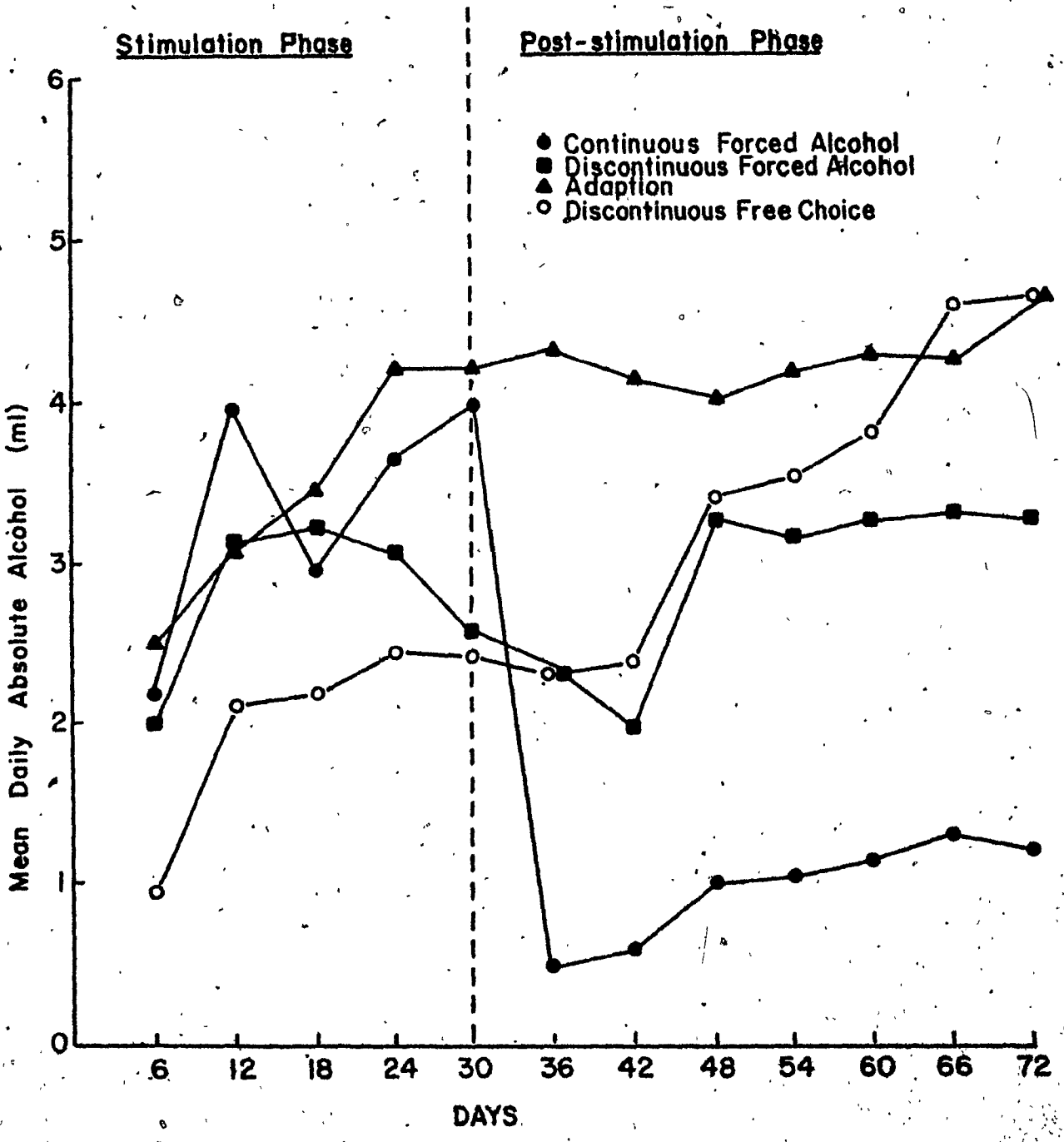

FIGURE 1: Mean daily alcohol consumption in absolute alcohol.

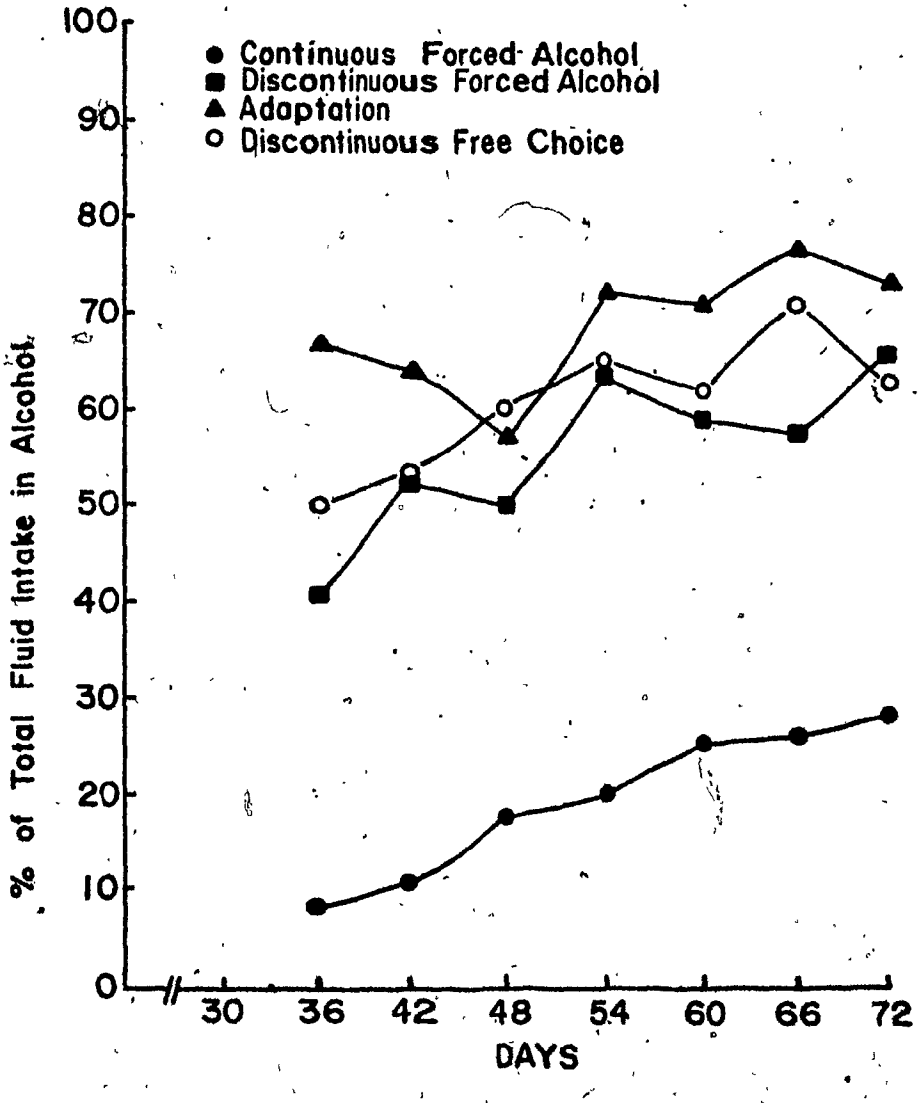

FIGURE 2: % of total fluid intake in alcohol in in the post-stimulation phase.

Similarly subjects on the discontinuous free choice schedule drank 51% of the total fluid intake in alcohol which makes up approximately 2.3 mls absolute alcohol daily. The consumption of the discontinuous free choice group was considerably less than that of the adaptation group with respect to both absolute alcohol and percentage of total fluid intake. In fact, the greatest alcohol intake was by the adaptation group which consumed 4.2 mls absolute alcohol per day and 65% of the total fluid intake in alcohol.

Later period. At the end of the test phase the subjects initially exposed to the continuous forced alcohol schedule continued to ingest very much less alcohol than the discontinuous forced alcohol group, both in terms of absolute alcohol ($U = 0$; $p < .002$) and percentage fluid intake ($U = 0$, $p < .002$: See Table 3). The animals in the former group consumed 27% of total fluid intake as alcohol solution which made up 1.2 ml of absolute alcohol daily. The discontinuous forced alcohol group drank 61% of total fluid intake in alcohol thus ingesting 3.3 ml absolute alcohol daily. If a preference for alcohol is defined

as an alcohol consumption greater than 50% of the total fluid intake, it is apparent that the continuous forced alcohol group did not develop such a preference.

Less alcohol was consumed by the discontinuous forced alcohol group than the adaptation group in terms of absolute alcohol ($U = 0$, $p < .002$) and percentage of total fluid intake ($U = 1$, $p < .004$). The adaptation group ingested 4.6 mls of absolute alcohol daily and 73% of the total fluid intake in alcohol whereas the discontinuous free choice group drank 4.4 mls absolute alcohol and 67% of the total fluid intake in alcohol. There was no significant difference between either the percentage of total fluid intake in alcohol ($U = 10$, $p > .240$) or the amount of absolute alcohol ($U = 23$, $p > .531$) drunk by subjects in the discontinuous free choice and adaptation groups.

Animals in each of the four groups increased their alcohol intake during the post stimulation phase. Mild alcohol preference was established within the first twelve days of this phase by subjects in the adaptation and discontinuous free choice groups. The discontinuous forced alcohol group did not manifest alcohol preference in the early period but developed it later. Subjects

TABLE 3

Mann Whitney U Test on averages for a 6 alcohol day period at the end of the test period - Two tailed (Days 61-41)

A. Absolute Alcohol

1. Continuous forced alcohol vs. discontinuous forced alcohol - U = 0 n = 6 p < .002*
2. Adaptation vs. discontinuous forced alcohol - U = 0 n = 6 p < .002*
3. Adaptation vs. discontinuous free choice - U = 23 n = 6 p > 0.531 NS

B. Percentage Alcohol Consumed

1. Continuous forced alcohol vs. discontinuous forced alcohol - U = 0 n = 6 p < .002*
2. Adaptation vs. discontinuous forced alcohol - U = 1 n = 6 p < .004*
3. Adaptation vs. discontinuous free choice - U = 10 n = 6 p > .240 NS

NS Non significant

* significant

exposed to a continuous forced alcohol schedule failed to develop an alcohol preference, the maximum percentage fluid intake in alcohol reached at the end of the post stimulation phase being 27%.

DISCUSSION

There was a clear influence of the different conditions of adaptation, choice and continuity on the alcohol intake of brain stimulated animals. The three discontinuous schedules (discontinuous free choice, discontinuous forced alcohol and adaptation presentations) were more efficient in producing an increase in alcohol consumption than was the continuous presentation. Preference for a 20% alcohol solution relative to water was clearly not established for the continuous forced alcohol schedule but did occur with the discontinuous schedules. Discontinuity therefore appears to be significant in increasing alcohol intake in stimulated animals. Investigations in which no stimulation is provided also show that discontinuous schedules produce a higher alcohol intake than continuous ones (Wise, 1973a, Wayner et al., 1972). The alcohol schedules used by Wise (1973a) were the same as those used in the present study. Wayner et al. (1972) used a free-choice,

discontinuous schedule with a periodic withdrawal of two days and reinstatement of the alcohol solution for two days. Thus discontinuity is important in producing high alcohol intakes in both stimulated and unstimulated animals.

Adaptation to alcohol in increasing concentrations had the initial effect of elevating absolute alcohol intake as reported earlier by Myers (1961), Veale and Myers (1969) and Wise (1973a). However a difference between the adapted and non-adapted was no longer evident by the end of the post-stimulation phase of the present study. Animals on the adaptation schedule did not differ in the later stages of the experiment from those on the discontinuous free choice presentation. The discontinuous free choice and the adaptation schedules were identical in procedure except that the adaptation group was exposed to alcohol prior to the stimulation period. Thus, it appears that adaptation does not have a persistent effect on alcohol intake. Since adaptation involves a longer exposure period to alcohol, the discontinuous free choice schedule without adaptation seems to be the quickest method to increase alcohol intake.

The discontinuous free choice group drank much more absolute alcohol than the discontinuous forced alcohol group. This suggests that free choice also may be a relevant factor in producing an increase in alcohol intake. However, in unstimulated animals Wise (1973a) found that less alcohol was consumed by the free choice discontinuous schedule than the forced alcohol discontinuous schedule. Moreover, the continuous free choice presentation does not produce high alcohol intakes (Wise, 1973a). Wayner et al. (1971) studied the continuous free choice schedules on electrically stimulated rats and found a low preference for alcohol. On the basis of this evidence it would appear that free choice is not sufficient for establishing alcohol preference. In order to decisively test the importance of free choice in stimulated animals, an experiment comparing the continuous free choice and continuous forced alcohol schedule in stimulated animals seems to be required.

Quantitatively the present results are consistent with the reports of others (Amit & Stern, 1971). Using an adaptation schedule Amit, Stern and Wise (1970) found that animals developed a strong alcohol preference

taking a mean of 98% of their total fluid as alcohol solution and drinking a mean of 5.11 mls absolute alcohol. These intakes were higher than those from adapted subjects in the present study. However the experimental design of these investigations was not identical. Amit et al. (1970) used only stimulus-bound drinkers with an alcohol solution provided in the stimulation box. In the present study stimulus-bound drinking was not a prerequisite and the animals were stimulated with no available alcohol. Using stimulation conditions more similar to those in the present study, Amit and Stern (1971) stimulated in an empty box and found that animals drank a mean of 4.0 mls absolute alcohol and 63% of the total fluid intake in alcohol solution. This is similar to the 4.5 mls absolute alcohol and 73% of the total fluid intake of the present study.

Despite this similarity of intakes, Amit and Stern (1971) found that when alcohol was adulterated with quinine it constituted 40-45% of the animals' total fluid intake. In the present study only 7.34% of the total fluid was drunk in quinine-adulterated solution. To the degree that the quinine test reflects

motivation for alcohol it would appear that animals in the present investigation were less motivated to drink alcohol than those in the study of Amit and Stern.

Also in contrast to the present findings, Amit (1970) found that on the first day of stimulation, animals on the adaptation schedule did not consume alcohol. Presumably this was due to Amit's use of a concentration of alcohol previously rejected by each animal. In the present study, twenty per cent alcohol solutions were given as the standard concentration, regardless of whether animals had consumed more concentrated solutions previously. Nine subjects in the adapted group of this study consumed at least a 20% solution prior to stimulation. Consequently, it is not surprising that on the first day of stimulation, a mean of 4.3 mls absolute alcohol was ingested by the adapted group in the present investigation.

In a control study of unimplanted, unstimulated subjects Wise (1937b) found high levels of intake which were surprisingly similar to those of the stimulated animals of the present study. However,

Wise's results cannot be compared directly with those in the present study because his animals were not implanted with electrodes. Implanted, unstimulated animals drink much less alcohol than do unimplanted ones (Wise, 1973b). This agrees with the results of Amit (1970) whose implanted control animals also drank less than the unimplanted ones. However, quantitatively there appears to be a discrepancy between the relatively high intake of Wise's unimplanted control animals and those in Amit's investigation. Further study is needed to determine the causes and parameters of surgery-induced suppression of intake. However it would appear that had Wise's (1973) animals been implanted they would not have consumed as much as was consumed by the animals in the present study.

Martin and Myers (1972) and Wayner et al. (1971) have recently challenged the conclusion that lateral hypothalamic stimulation increases alcohol intake. However comparisons between their investigations and those of Amit et al. (1970) are made difficult by genetic and strain differences in the rat population sampled, the type of schedule used, and also different stimulation methods. Wise (1973b) has

pointed out that firstly, neither Myers and Martin (1972) nor Wayner et al. followed the Amit, Stern and Wise (1970) or Amit and Stern (1971) procedures exactly, and secondly, that only the approach of Amit and Stern (in which there is a control group receiving identical treatment except for brain stimulation) can be used to determine the contribution of electrical stimulation. Amit et al. (1970) and Amit and Stern (1971) clearly show that brain stimulated animals voluntarily consume more alcohol than appropriate control animals. Thus for the Amit paradigm, brain stimulation increases alcohol intake significantly.

Several investigators have examined the possible mechanism underlying the enhancement of alcohol intake by electrical stimulation. Malmo (1967) developed a theory in which acquired homeostasis regulates alcohol intake. Alcohol dependence, he maintained, is similar to morphine dependence in that large quantities of ingested alcohol cause a deprivation in the metabolism of norepinephrine. This results in the formation of catecholamine catabolites that resemble morphine. Malmo suggested

that the catabolite levels are regulated by the acquired homeostatic mechanism.

Amit (1970) proposes that the tetrahydroisoquinoline alkaloids formed from the condensation of acetaldehyde with catecholamines (Cohen & Collins, 1970) are the substances with addiction liability. The role of electrical stimulation in producing a preference for alcohol over water depends on two facts. Firstly, acetaldehyde depletes levels of norepinephrine (Duritz & Truitt, 1966). Secondly, rewarding brain stimulation has the opposite effect, it leads to a significant increase in turnover and level of norepinephrine (Stein & Wise, 1969). Amit (1970) suggested that in investigations of alcohol preference, electrical stimulation has the role of either offsetting the depleting effect of acetaldehyde on norepinephrine, or even increasing the level of norepinephrine. The acetaldehyde can then combine with norepinephrine to produce TIQ alkaloids and thus start the alcohol intake process. Once the system has adapted to the alkaloid as a neural transmitter, the drinking of alcohol continues independently of electrical stimulation. However, the implication of Amit's argument is that for a given level of acetaldehyde,

a compensating amount of brain stimulation is required to create the necessary circumstances for elevated intake.

In the present study, the continuous forced alcohol schedule did not produce a preference for alcohol although electrical stimulation was used. The method of presentation may in effect offset the presumed effects of electrical stimulation. It is assumed in Amit's theory that the motivation to consume large amounts of alcohol regularly is a function of the synthesis of acetaldehyde and norepinephrine. With the continuous forced alcohol schedule, large amounts of acetaldehyde may be formed because of the continuous presentation of alcohol. This may have the adverse effect of depleting norepinephrine too strongly which would limit the production of TIQ alkaloids. Thus the schedule of alcohol presentation may alter the critical balance between the stimulation-induced levels of norepinephrine and the ingested alcohol and consequent acetaldehyde. The forced alcohol may lead to too much acetaldehyde for the amount of norepinephrine released by stimulation.

Whatever the underlying physiological or biochemical mechanisms may be, it is clear that

presentation schedules influence the oral intake of alcohol in rats. Discontinuous patterns of presentation appear to be superior to a continuous exposure both in association with or in the absence of electrical stimulation of the lateral hypothalamus.

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