EXPERIMENTAL STUDIES ON THE CRAVING FOR ALCOHOL

I. ALCOHOLIC DRIVE IN MICE FOLLOWING ADMINISTRATION OF SALINE

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INTRODUCTION

It is recognized that there are various reasons, psychological and otherwise, why people drink alcoholic beverage. Similarly, the causes of alcoholism are numerous indeed, and its etiology comprises many factors.

In the majority of cases, it is probable that the emotional factors or some emotional disorders are the most prominent causes. However, there is not sufficient evidence to substantiate the claim that specific personality types predispose to alcoholism.

If "craving" is studied as an indication of bodily changes, there are two main alternatives. The first method is applicable only to human subjects. The second method is the only one applicable in experiments with animals.

In 1949, Williams *et al.* (1) indicated that alcoholism could be produced or accentuated by deficiencies in the nutritional state of the animal and that the vitamins or other suitable nutritional supplements could destroy the appetite for alcohol. This led to the concept that alcoholism was a genetotropic disease arising from a nutritional deficiency which is basically genetic.

In 1953, Stirnes (2) in his experiment with rats that had received subcutaneous injections of carbon tetrachloride, found that rats with definite cirrhotic changes of liver voluntarily consumed alcohol, as determined in autoselection experiments, that was approximately four times as great as in a control group of rats with normal livers.

Recently a number of reports based on clinical investigations have appeared indicating a possible hormonal derangement in alcoholism. In animal experimentation, Zarrow and Rosenberg (3) have shown that propyl thiouracil induced a definite alcoholism in the rat.

There is basis for the view that increased voluntary intake of alcohol among experimental animals which seems to indicate a craving for alcohol may have a physical basis.

In view of the fact that alcoholism may be due to a metabolic disturbance and also in view of the possible involvement of the endocrine system, the present investigation was undertaken to find whether it is possible to produce a state of alcoholism in mice by disturbances of electrolyte metabolism,

METHODS AND RESULTS

A. Alcoholic drive in mice treated with salts

In the present studies, male adult mice of the S-360-M strain weighing from 15 to 25 grams were used. They were housed five to a cage and were fed oats and drinking water *ad libitum* from three days before use. The general plan of the experiments was identical with the "self selection two choice type."

The mice were divided into two groups: to mice of one group, the control animals, was given a choice of water or 15% alcohol, and to mice of the other group a choice of one per cent NaCl solution or 15% alcohol in NaCl solution. Then the quantity of alcohol consumed by the two groups was measured daily (see Fig. 1).

FIG. 1. A cage provided with two drinking bottles containing 1% NaCl solution (A) and 15% alcohol in NaCl solution (B).

The control group preferred water to alcohol and did not tend to consume alcohol. On the other hand, the NaCl group acquired an appetite for alcohol within 3 days, and began to drink very moderately—just enough to show with certainty that they were drinking. But upon the replacement of NaCl solution by water all mice lost their alcoholic drive within a few days. The saline consumption increased for several days, following the development of alcoholic drive. This is well illustrated in Figure 2.

[Later, it was also found that daily intraperitoneal injections of saline (0.1 c.c./10g) produced an appetite for alcohol in mice.]

In an attempt to determine whether this "alcoholic drive effect" was chiefly due to Na ion or Cl ion, tests were made using sodium chloride, sodium acetate, potassium acetate, potassium chloride and potassium citrate,

FIG. 2. Alcohol (A) and saline (B) uptake in mice treated with saline.

It was found that sodium chloride and sodium acetate had the most powerful effect in respect to the creation of a craving. On the other hand, the mice treated with potassium chloride or potassium citrate drank very little alcohol.

This "alcohol drive" was increased by the daily subcutaneous administration of desoxycorticosterone acetate* (Schering) in doses of 0.3 mg or cortisone (Merck) in doses of 10 mg. But when the doses of DOCA were increased, the alcoholic drive was almost completely inhibited.

Vitamin treatment (vitamin A 1,000 I.U., thiamine 0.4 mg, nicotinamide 4 mg, sodium pantothenate 0.2 mg, vitamin C 15 mg, vitamin D₂ 80 I.U., vitamin B₂ 0.6 mg, vitamin B₆ 0.04 mg and vitamin B₁₂ 0.4 μ respectively *pro die*) was not effective in abolishing the appetite for alcohol.

Also that appetite was not affected by methionine (10 mg/mouse/day) or sodium glutamate (20 mg/mouse/day) (4). However, it was prevented to some extent by the addition of 5% glucose (glucose was added to the saline solution) (see Fig. 3).

* Abbreviated DOCA

FIG. 3. Effects of glucose on the alcoholic drive.

These findings may indicate that this "alcoholic drive effect" has an immediate connection with some disorder of the salt metabolism.

B. Alcoholic drive and tissue electrolyte contents

An elevation in brain excitability may be produced by an increase in brain intracellular sodium concentration (5).

The next investigation was undertaken in order to observe the relation between alcoholic drive and tissue electrolyte contents and to ascertain the mechanism involved in producing an appetite for alcohol.

For this study, mice were placed in a cage and provided with only the one drinking bottle containing one per cent NaCl solution. After 1, 2 and 4 weeks, they were sacrificed and brain and liver taken.

Total sodium and potassium contents of the tissues were measured flame-photometrically after digestion with nitric acid and hydrogen peroxide. The results of experiments are summarized in Table I.

It can be seen that there is practically no difference in Na and K contents between the mice treated with NaCl and the normal mice at least during two weeks. In the 4 weeks

TABLE 1. Tissue sodium and potassium contents of brain and liver tissue of mice treated with NaCl solution.

Sodium (mEq/kg)				
	Normal	1 week after	2 weeks after	4 weeks after
Brain	57.78 ± 7.71	56.46 (65.2—52.1)	56.42 (69.5—43.4)	59.10 (78.2—47.8)
Liver	52.09 ± 6.61	53.86 (60.8—47.8)	51.22 (60.8—39.1)	53.82 (65.2—43.4)
Potassium (mEq/kg)				
Brain	96.87 ± 13.27	96.77 (100.0—89.7)	93.86 (100.0—87.4)	89.26 (100.0—76.9)
Liver	86.87 ± 11.79	86.55 (94.8—79.4)	84.16 (89.7—76.9)	83.52 (94.8—74.3)

material, there was some indication of a slight increase in liver sodium content associated with a reduction in brain potassium content, but it was not statistically significant.

These data do not support the hypothesis that mice are driven to drink by the accumulation of sodium or by the disturbance in electrolyte balance in tissues.

C. Endocrine factors in alcoholic drive

Smith (6) reported that patients with symptoms of low adrenocortical activity were highly susceptible to alcoholism and concluded that in some instances alcoholism was the result of disturbed adrenal activity.

In the following experiments, the effects of hormones in connection with electrolyte metabolism on alcoholic drive were investigated.

An appetite for alcohol did not develop as a result of daily subcutaneous injections of ACTH (Armour), posterior pituitary hormones (Sankyo), in doses of one unit respectively, or DOCA in doses of 0.5mg for 10 days.

Similarly, no alcoholic drive was induced by antithyroid drug treatment, daily intraperitoneal injections of 6-methyl thiouracil (Chugai) in doses of 5 mg/10g body weight or oral administrations of 1-methyl-2-mercaptoimidazole (Chugai) in doses of 5 mg/10g body weight.

Total and unilateral adrenalectomy of mice were performed by modification of the original Firor and Grollman method (7). The adrenalectomized mice were put on the experimental regimen with one per cent saline to drink. No adrenalectomized mouse showed any appetite for alcohol.

DISCUSSION

The experiments demonstrated that:

1) the mice of the S-360-M strain which had one per cent NaCl solution to drink developed an appetite for alcohol within 3 days.

2) DOCA and cortisone treatments were effective in increasing the appetite for alcohol, while the addition of glucose tended to prevent the appetite for alcohol to some extent,

It is apparent from these results that the ingestion of saline can induce an alcoholic drive in mice, and adrenocorticoid hormones play a part in the production of alcohol appetite.

However, present results do not offer any possible explanation for this alcoholic drive action of saline.

Williams indicated that alcoholism could be produced or accentuated by deficiencies in the nutritional state of the animal and that the vitamins could abolish the appetite for alcohol.

Stirnes found that rats that had received injections of carbon tetrachloride had a voluntary intake of alcohol. (The results of his study were confirmed by author in mice.)

Sinaiko and Necheles (8) found that all dogs treated with DOCA and saline showed pathological changes in the livers. The changes in the livers consisted of focal and diffuse necrosis, fatty degeneration, hyperemia, hemorrhage and accumulation of pigment.

On the other hand, Fleetwood (9) reported that tension in alcoholics is associated with an unknown substance of cholinergic character in the blood which is much reduced in amount after intake of alcohol.

The nature of the alcoholic drive which is produced by a saline has not been clearly elucidated, but it may be a matter having to do with a secondary response due to dysfunction of liver (*see* Fig. 4).

In order to further clarify the response of liver damage, experiments are in progress.

FIG. 4. Mechanism of alcoholic drive.

CONCLUSIONS

1. An attempt was made to produce a state of alcoholism in mice by disturbances of salt metabolism.
2. Mice of the S-360-M strain which were kept on NaCl solution and alcohol developed an appetite for alcohol within 3 days.
3. This alcoholic drive was increased by the daily administration of desoxycorticosterone acetate or cortisone.
4. This alcoholic drive was prevented to some extent by the addition of glucose, but was not affected by vitamins.
5. The results of experiment led to the concept that alcoholism is the result of disturbed liver activity.

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