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ETHANOL CONSUMPTION SUBSEQUENT TO PHYSICAL DEPENDENCE

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A number of elegant techniques have been developed to induce pharmacological dependence on alcohol in animals. However, our understanding of the behavioral aspects of alcohol ingestion or self-administration is still quite limited. It is only quite recently that the relationship between physical dependence and subsequent alcohol intake has been investigated. Unfortunately, the few findings obtained by different investigators appear to be quite contradictory. An early study by Freund (1969) concluded that mice do not change their preference for ethanol subsequent to physical dependence. A study by Myers, Stoltzman and Martin (1972) dealt with the effects of ethanol dependence induced artificially in the Rhesus monkey on the subsequent preference for alcohol. Their findings show that each monkey rejected the ethanol solution offered even at low concentrations, in spite of the fact that symptoms of physical dependence on alcohol were quite manifest. In a more recent experiment, Deutsch and Koopmans (1973) demonstrated a large and lasting enhancement of alcohol consumption over control levels after direct infusion of 10% alcohol into the stomach of rats for six days.

Because of the inconsistency in past findings, we undertook to study ethanol consumption subsequent to physical dependence on ethanol.

EXPERIMENT 1

The subjects were 40 male Long Evans hooded rats, 10 weeks old and weighing 250-300 gm. at the start of the experiment. The

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animals were housed individually in rat cages. The room temperature was kept at 76° F. and a 12-hour day and night cycle was maintained by an automatic timer. The animals were always given food and water ad lib.

Alcohol preference was measured with the use of a two-bottle method, which is a modification of a previously described procedure (Myers and Veale, 1972). The animals were simultaneously offered a choice between plain water and a solution of 95% ethanol prepared volumetrically with tap water. The fluids were contained in two 100 ml. inverted graduated bottles which were fitted with steel spouts that protruded into the cage. The bottles were placed randomly and their positions were interchanged daily to eliminate error due to position or bottle preference. Fresh solutions of alcohol and water were placed in the bottles daily.

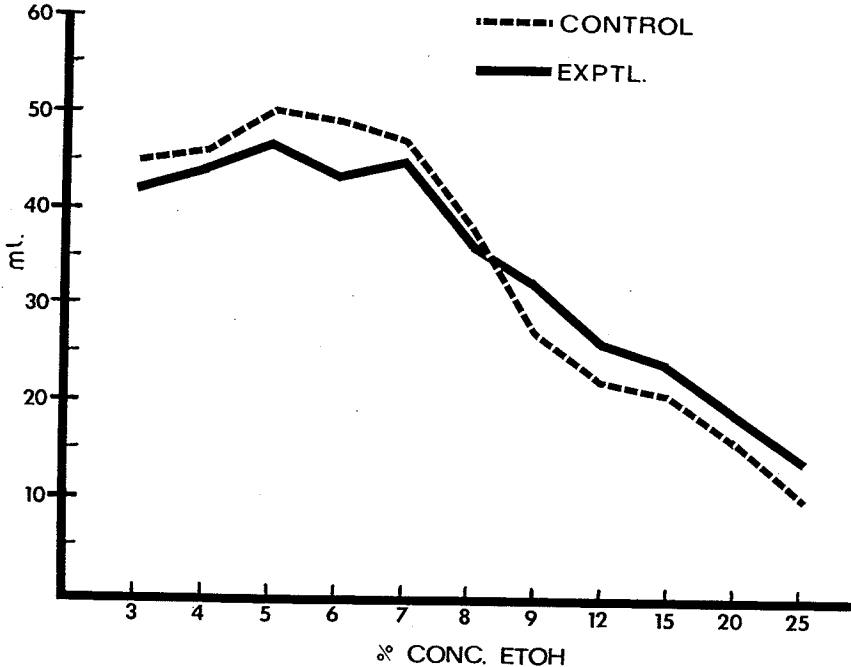


Figure 1

For the baseline period, measurement of alcohol preference and consumption was established by increasing the concentration of alcohol solution each day in a stepwise fashion as follows: 3, 4, 5, 6, 7, 9, 12, 15, 20 and 25%. Only one concentration of this ascending series was offered per day for the 10 days of baseline. The daily fluid consumption was recorded at 9 a.m., 11 a.m. and 2 p.m. Subsequent to the baseline period, half the animals (N = 20) were randomly assigned to the experimental group, the other half to the control group. In the experimental group, animals were intubated daily with 4 g/kg of alcohol for the first 10 days, 5 g/kg for the second 10 days, and with 6 g/kg for the final 10 days. The control animals were intubated with an equivalent amount of water.

After 30 days of intubation, withdrawal symptoms were precipitated by total removal of alcohol. We observed withdrawal signs, e.g., hyperactivity, body tremors, spasticity, hyperreflexia, piloerection, episodes of generalized convulsions with prominent clonic components in 87% of the experimental animals. After the last intubation alcohol preference was again established with the method described before, that is by increasing the concentration of alcohol solution each day in a stepwise fashion.

A statistical comparison of alcohol preference and consumption between the experimental and control animals did not yield a significant difference. (See Figure 1)

EXPERIMENT 2

It is possible that the negative results obtained in our previous experiment might be due to the fact that a long-term pattern of physical dependence had not been established. Consequently, we carried out an experiment in which 15 experimental animals were intubated with ethanol as described before and 15 control animals were intubated with water. All animals were subjected to three different periods of intubation. Each 20-day period of intubation was followed by withdrawal symptoms described before.

Subsequent to these three separate epochs of withdrawal symptoms, all animals were again tested for alcohol preference with the method described before.

A statistical comparison of alcohol preference and consumption between the experimental and control animals did not yield a significant difference. (See Figure 2)

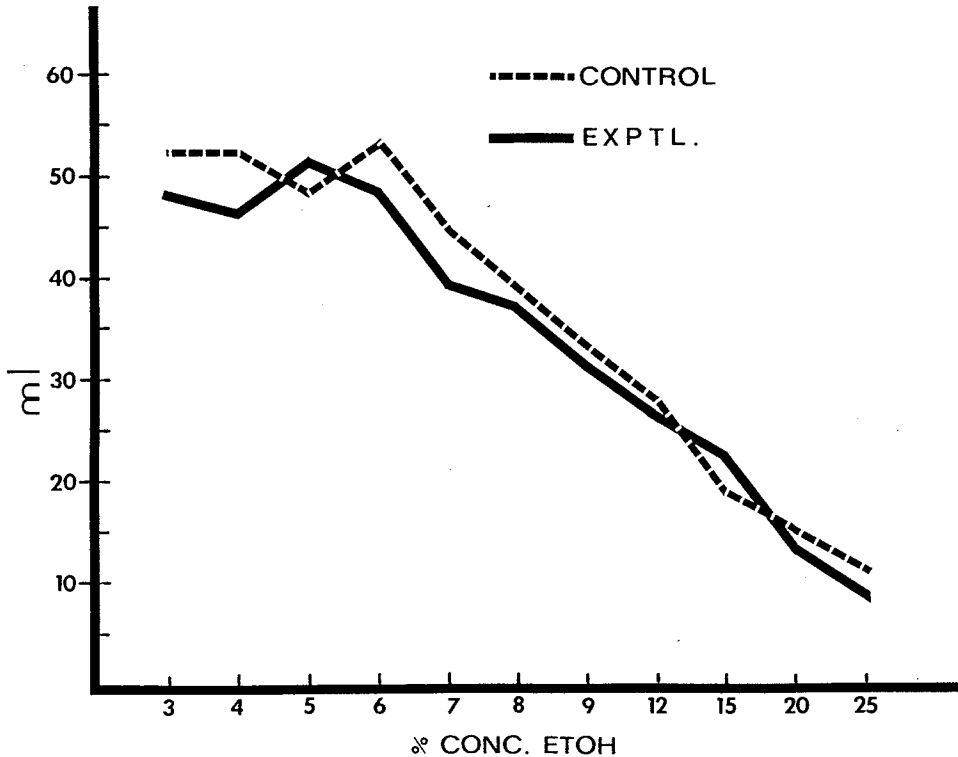


Figure 2

EXPERIMENT 3

It is quite conceivable that our failure to obtain greater alcohol preference subsequent to withdrawal was caused by the inability of the animals to associate the intake of ethanol with the attenuation of the stress of withdrawal. Consequently, we carried out an experiment in which the experimental animals were administered alcohol to relieve signs of withdrawal.

In this experiment, alcohol preference was again established for 12 experimental and 12 control animals. The experimental animals were intubated with 6 g/kg of ethanol for a period of 20 days, and withdrawal symptoms were induced by the removal of alcohol.

While the experimental animals were manifesting signs of withdrawal, they were again intubated with 1 g/kg of alcohol. The intake of alcohol was quite efficacious in relieving all observable

signs of withdrawal in all experimental animals. The animals were allowed a period of 5 days subsequent to withdrawal, during which time they were given just food and water ad libitum. Then, once again, the process to induce physical dependence was reinitiated. The same animals were intubated for a period of 20 days followed by total withdrawal from alcohol. During withdrawal all animals were again intubated with 1 g/kg of alcohol which brought about substantial relief from the withdrawal syndrome. Finally, after another 5-day period of rest, the same process was reinstated for a period of 20 days.

Subsequent to removal from alcohol, alcohol preference was established by the previously described method.

A statistical comparison of alcohol preference and consumption between the experimental and control animals did not yield a significant difference. (See Figure 3)

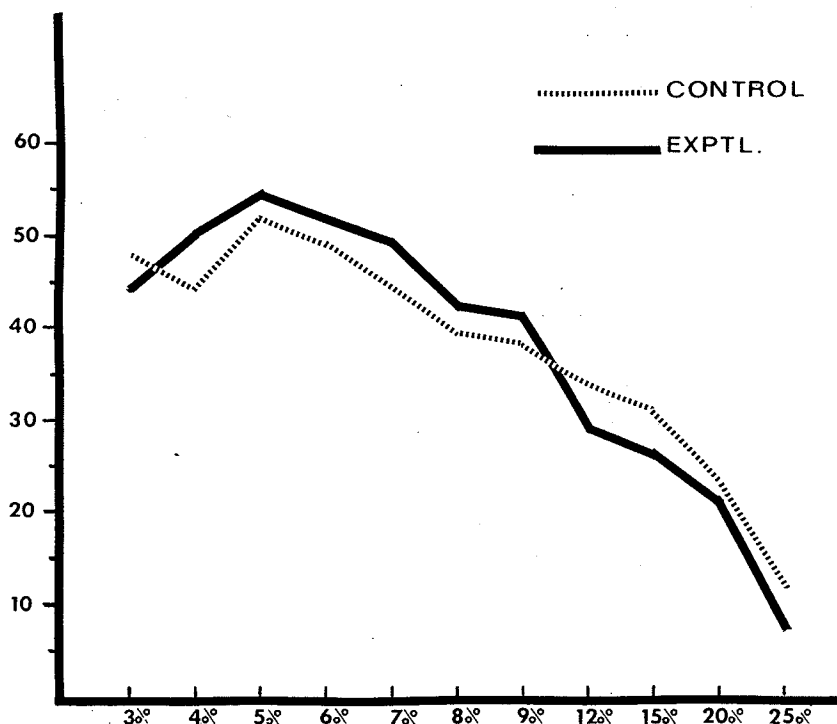


Figure 3

DISCUSSION

The most significant and consistent finding of our experiments is that rats did not show an increase in alcohol preference, in spite of the fact that some symptoms of physical dependence on this drug were strikingly obvious. In recent years a number of elegant methods have been developed to artificially induce physical dependence on ethanol. It has been shown that intravenous self-administration, intragastric intubation, forced feeding of a liquid diet and inhalation of ethanol vapor can be used rather successfully to induce symptoms of withdrawal. However, it is quite possible that while these methods appear quite efficacious in eliciting withdrawal symptoms, they are somewhat ineffective in producing a complete state of physical dependence. It is possible that withdrawal symptoms represent only a partial aspect of the physical dependence phenomena. While the experimental methods may be useful for investigating the biological symptoms of withdrawal, the results of our experiments imply that a theoretical basis for examining the development of an abnormal consumption of ethanol requires a more inclusive experimental procedure than the systematic administration of alcohol, though this appears to be quite sufficient in the case of morphine intake in animals.

It is probable that the development of physical dependence on ethanol can only take place with the use of a procedure which involves voluntary ingestion of a palatable solution.

While our results indicate that in rats ethanol consumption does not increase subsequent to signs of withdrawal, it is quite probable that the etiology of a long term high intake of alcohol is specific to man.

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