THE REINFORCING PROPERTY OF ETHANOL IN THE RHESUS MONKEY: I. INITIATION, MAINTENANCE AND TERMINATION OF INTRAVENOUS ETHANOL-REINFORCED RESPONDING*†

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Monkeys self-administer pharmacologically significant amounts of alcohol only under certain circumstances.[8] For example, Deneau and colleagues[1] used a method that permitted a rhesus monkey to voluntarily self-administer ethanol solution through an indwelling venous catheter. They found that three of five monkeys initiated and maintained response-contingent deliveries of ethanol at a dose of 200 mg/kg/inj; a fourth monkey initiated self-administration but discontinued spontaneously after one month; and the fifth monkey failed to initiate this behavior even after four weeks of programmed injections of 200 mg/kg/hr of ethanol. Periodic voluntary abstinence was characteristic of the three animals that maintained self-administration. The periods of cessation decreased in length from two to four days to seldom more than 24 hours with the passage of time. During self-administration, monkeys showed severe motor incoordination and stupor. In these alcohol-dependent animals, withdrawal signs appeared within six hours of the last dose of ethanol and consisted of tremors, vomiting, apparent hallucinatory behavior, and convulsions. Food intake throughout the course of the experiment was minimal, and all monkeys showed a marked loss of weight and cachexia. Two of the monkeys died because of suffocation from respiratory obstruction during ethanol-induced anesthesia.

The fact that monkeys will self-administer alcohol under these conditions might be viewed as (1) some direct or indirect consequence of physiological dependence (e.g. animals continue to administer alcohol to prevent the appearance of abstinence signs) and/or as (2) evidence that alcohol is behaving as a primary reinforcer (i.e., an effect of alcohol serves to increase or maintain the strength of responding that delivers the drug). A rigorous interpretation is clouded by the reluctance of some animals to self-administer ethanol and by the occurrence of periodic termination of responding, despite withdrawal signs. In an attempt to relate these facts to the reinforcing property of ethanol, we suggest that there is a threshold for alcohol reinforcement and that chronic excessive doses of ethanol produce conditions that override the reinforcing property of the drug. As will be clear from our observations, there is a set of circumstances in chronic ethanol self-administration whereby voluntary abstinence occurs with ensuing withdrawal; otherwise the toxicity of ethanol is sufficient to produce gross illness and even death.

In a previous publication[7] the authors reviewed various techniques of animal self-administration of alcohol and described their own experiments with rhesus

* Research supported by USPHS Grant MH 12084. G. W. was a predoctoral trainee supported by USPHS Grant NB 01311.

† This paper is based on a portion of a dissertation submitted to Rackham School of Graduate Study, The University of Michigan, by G. W. in partial fulfillment of the requirements for the Ph.D. degree in Psychology.

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monkeys. The present paper will give a more complete presentation of portions of these findings as well as report subsequent experimental results. It will examine various aspects of the initiation, maintenance, and termination of ethanol-reinforced responding in order to better understand the reinforcing property of ethanol.

Methods

Subjects

Fourteen juvenile rhesus monkeys of both sexes, weighing between 3 and 5 kg, were selected. Following a five-to-seven day period in which the animals adapted to restraint, each monkey was anesthetized with 30 mg/kg sodium pentobarbital, and under aseptic conditions a silicone catheter was inserted into the jugular vein. The distal end of the catheter was passed subcutaneously over the animal's shoulder to exit through the skin near the center of its back.

Apparatus

Each monkey was fitted with a stainless steel harness that circled the shoulders and waist, protecting the catheter at its site of exit. The harness connected to a jointed restraining arm made of stainless steel tubing and fastened at the rear of the cubicle. An extension of the animal's catheter passed through the restraining arm to an infusion pump located at the outside rear of the cage. The harness and arm restrained the animal in a $90 \times 75 \times 65$-cm open-faced cubicle, while allowing relatively free movement within the area.

A 4-w stimulus light, located on the inside rear wall of each cubicle was illuminated during periods of drug availability. Mounted below the light was a lever; a lever press of 100 g or more produced an injection when the drug was accessible. Details of the surgical procedure and apparatus are given by Deneau and coworkers.[1] Monkeys were fed twice daily with Purina® monkey chow that had 183 g/ton isoniazid added for control of tuberculosis and 6.8 g/ton of pyridoxine HCl added to prevent deficiency. Water was freely available.

Drugs

Ethanol (95%, U. S. P. grade) was diluted in distilled water to a concentration of either 15% w/v or 30% w/v. These concentrations were used to deliver 0.1 g/kg/inj and 0.2 g/kg/inj, respectively. Cocaine-HCl was dissolved in 0.9% NaCl solution while the sodium methohexital was dissolved in distilled water. These solutions were used to provide 0.5 mg/kg/inj of cocaine and methohexital. The methohexital solution also contained 6% sodium carbonate.

General Procedure

Initiation of Ethanol-Reinforced Responding

For a period of one to three weeks after surgery, all fourteen animals were given access to 15% w/v ethanol. In the beginning of the experiment, ethanol was available 24 hours per day. Later, when response rates increased markedly, ethanol access was limited to three hours per day in order to produce stable responding, as will be explained subsequently in this report. During periods of drug availability, each lever response resulted in an infusion; and if no responses

were made, an automatic infusion was delivered every six hours to prevent the catheter from clotting.

If an animal's response did not increase during initial exposure to ethanol, one of three options was selected:

a. The dose of ethanol was increased to 0.2 g/kg/inj.
b. Cocaine at a dose of 0.5 mg/kg/inj was substituted for ethanol.
c. Ethanol was replaced by sodium methohexital also at a dose of 0.5 mg/kg/inj.

If response rates increased under the conditions of the larger dose of ethanol, the dose was returned to 0.1 g/kg/inj, and subsequently the access period was limited to 3-hr/day. When cocaine or methohexital was used as an initiating agent, access time for either of these drugs was reduced to 3-hr/day after response rates increased. Following several days of access to one of these alternative drugs, ethanol at 0.1 g/kg/inj was reinstated under 3-hr/day access conditions.

Maintenance of Ethanol-Reinforced Responding.

One monkey from each of the ethanol-, cocaine-, and methohexital-initiated groups was studied in the maintenance phase of the experiment. Under 3-hr/day access conditions, approximately five days of response-contingent saline were alternated with approximately five days of response-contingent ethanol (0.1 g/kg/inj) for 80 or more days.

Termination of Ethanol-Reinforced Responding.

Seven monkeys, four of which were experimentally naive prior to this portion of the experiment and three of which had histories of ethanol self-administration (described in the previous sections), were placed on 24-hr access to 0.1 g/kg/inj of ethanol. They were allowed to take alcohol under these conditions until they voluntarily abstained from self-administration or until 15 days of intoxication had passed without voluntary abstinence. The animals were then placed on 3-hr/day access conditions for ten days before being returned to 24-hr access. Alternations of 3- and 24-hr access was continued until the animal no longer abstained under 24-hr conditions, until it died of ethanol toxicity, or until it was taken off the experiment.

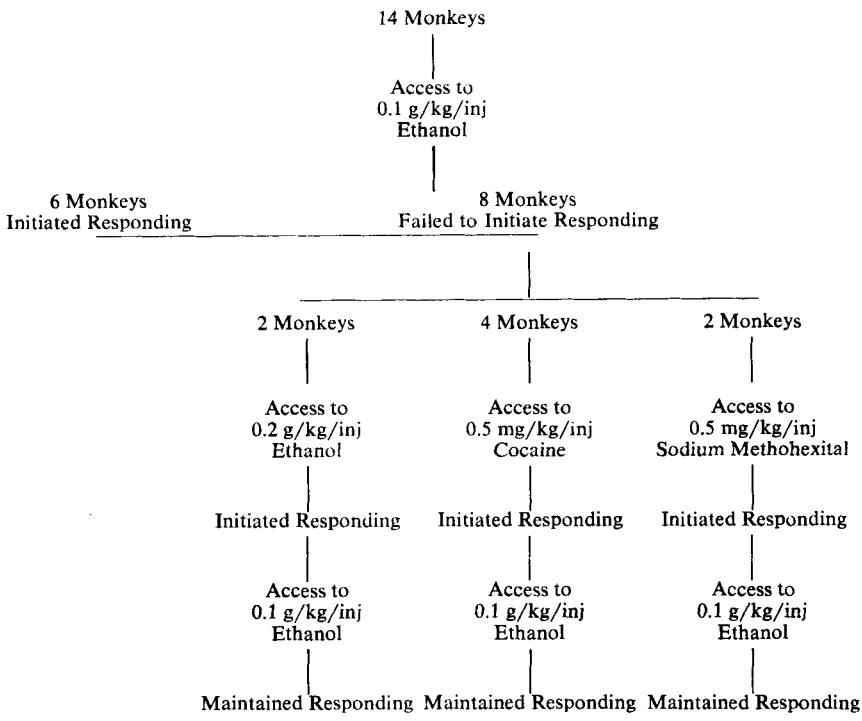
RESULTS

Initiation of Ethanol-Reinforced Responding

As shown in TABLE 1, six of the fourteen monkeys initiated responding during the introductory period of 24-hr access to 0.1 g/kg/inj of ethanol. Of the eight monkeys that did not initiate responding, two were given 24-hr access to 0.2 g/kg/inj of ethanol; four were given access to cocaine at 0.5 mg/kg/inj; and the last two were allowed to inject sodium methohexital, also at 0.5 mg/kg/inj. For the six monkeys that did initiate responding at 0.1 g/kg/inj of ethanol, the typical pattern was several days of low responses followed by an abrupt increase in the number of injections taken. This pattern was demonstrated by animals 384 and 327; it is represented by the graphs on the top half of FIGURE 1. Abruptly decreasing the access time, from 24 to 3 hours per day, resulted in temporary cessation of responding for animal 384 and the onset of mild withdrawal signs. In animal 327, reduction of access time was gradual, and no withdrawal signs were observed.

TABLE 1

INITIATION OF ETHANOL-REINFORCED RESPONDING



Animals 225 and 350 (bottom half of FIGURE 1) did not initiate responding within 10 days of 24-hr access to 0.1 g/kg/inj of ethanol; but when the dose was increased to 0.2 g/kg/inj, the monkeys increased responding, reaching an ethanol intake of over 8 g/kg/day. When the dose was subsequently returned to 0.1 g/kg/inj of ethanol, animal 350 maintained responding while animal 225 further increased the number of infusions until it eventually terminated responding; and following termination of ethanol-reinforced responding, abstinence signs were observed.

The effects of prior access to cocaine on ethanol-reinforced responding are shown in FIGURE 2. Each of the four monkeys was making fewer than 10 responses per day when a response resulted in the infusion of 0.1 g/kg/inj of ethanol. After the alcohol was replaced by cocaine, response rates increased dramatically within two days and stabilized under 3-hr access conditions of 30–50 injections per session. The monkeys were given four to ten days of access to cocaine, and then ethanol was made available again at a dose of 0.1 g/kg/inj under 3-hr/day access conditions. One animal (335) decreased responding for a period of ten days when ethanol was returned. Eventually the rates of all four monkeys became relatively stable at 35–45 injections per 3-hr session, and the animals appeared grossly intoxicated during the three hours of access.

Methohexital at 0.5 mg/kg/inj was used in a manner similar to cocaine for

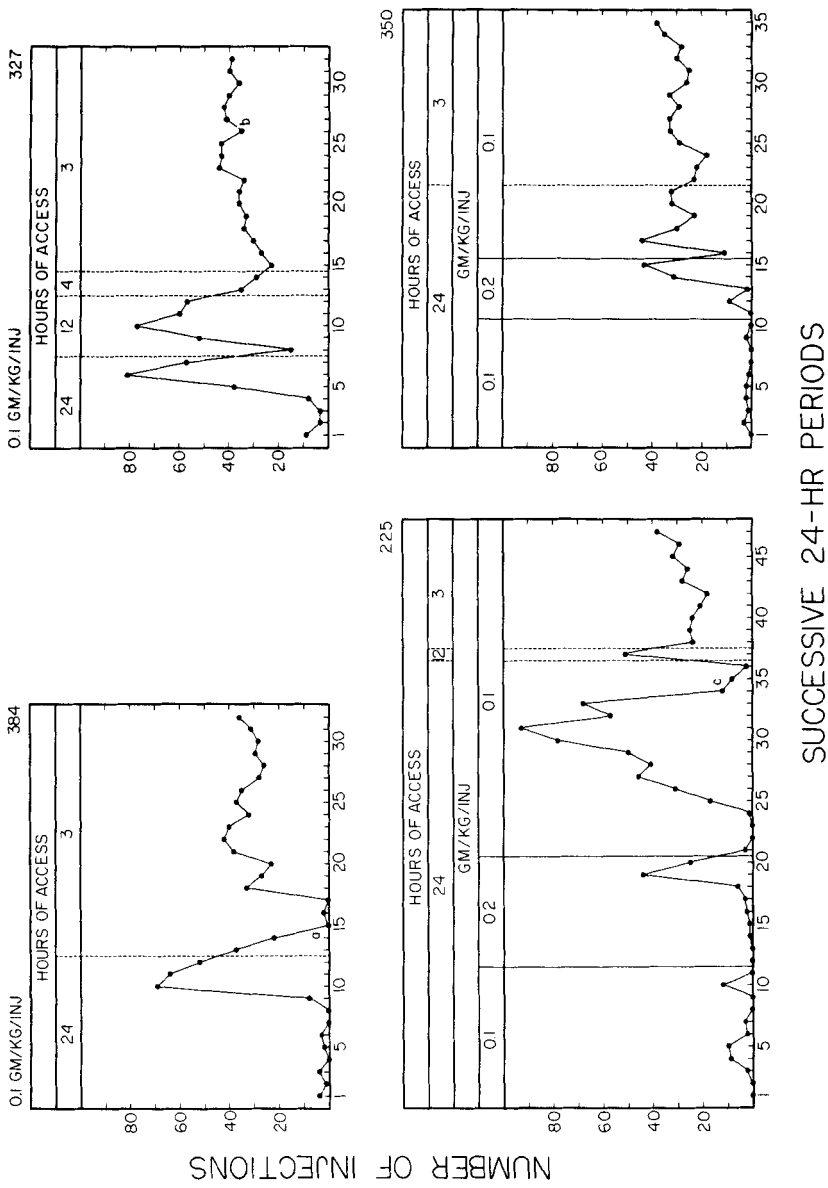


FIGURE 1. Initiation of ethanol-reinforced responding. Each graph represents the responses of an individual monkey with the number of injections/access period shown for each successive 24-hr period. The top two panels show animals (monkeys 384 and 327) that initiated responding when given 24-hr access to 0.1 g/kg/inj of ethanol. Monkeys 225 and 350 (shown in the lower panels) did not initiate responding when offered 0.1 g/kg/inj for a period of ten days but responded when the unit dose was increased to 0.2 g/kg/inj. Once initiated, responding remained stable for all four animals under 3-hr/day access. Note that mild withdrawal was observed at point (a) with 384 and at point (c) with 225. A catheter dislodged and was replaced in 327 at point b.

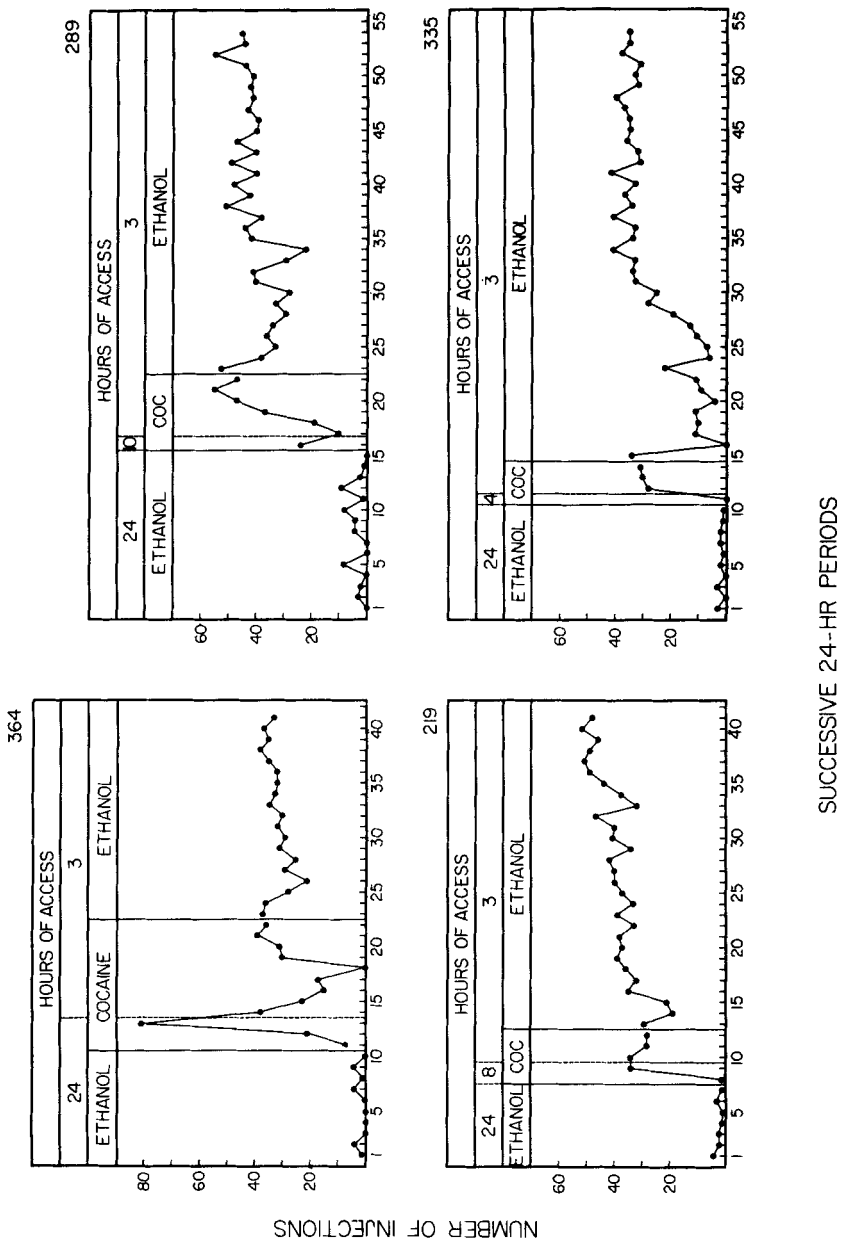


FIGURE 2. Initiation of ethanol-reinforced responding by using cocaine as a reinforcing agent. Each of these four monkeys failed to initiate responding when given 24-hr access to 0.1 g/kg/inj of ethanol. Cocaine (0.5 mg/kg/inj) was substituted for ethanol and the monkeys' responding increased; access to cocaine was then decreased to 3 hr/24 hr either abruptly (monkey 364) or gradually (289, 219, and 335). When response to cocaine was established at 30–50 injections/3-hr session, ethanol at 0.1 g/kg/inj was substituted for cocaine. For all four animals, the responding remained stable under 3 hr/day access conditions.

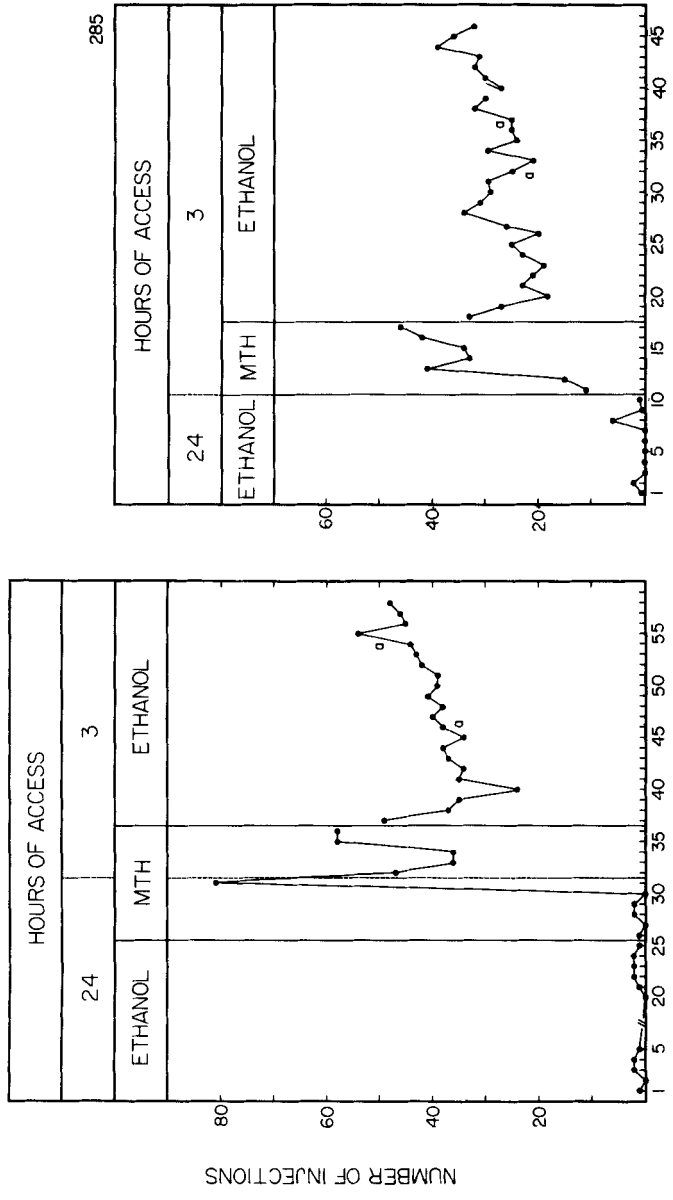


FIGURE 3. Initiation of ethanol-reinforced responding by using sodium methohexital as a reinforcing agent. Both monkeys failed to initiate responding when given 24-hr access to 0.1 g/kg/inj of ethanol for a period of 10–25 days. Sodium methohexital was substituted for ethanol under either 24-hr access (monkey 367, left panel) or 3-hr access (285, right panel), and the monkeys increased responding. Access to methohexital was then abruptly decreased to 3 hr/day for animal 367. When ethanol was substituted for methohexital, both monkeys maintained stable responding under 3 hr/day access conditions. Note that dislodged catheters were replaced at points indicated a.

initiating ethanol-reinforced responding and proved to be a reinforcing stimulus as demonstrated in FIGURE 3. Rates of responding, which were less than ten responses per day when ethanol at 0.1 g/kg/inj was available, increased to over 15 responses per hour when methohexital was injected. After five to seven days of 3-hr access to methohexital, ethanol at 0.1 g/kg/inj was returned, and rates were maintained between 30 and 35 responses per 3-hr session.

Thus, regardless of the method used to initiate ethanol-reinforced responding, the final rate of responding became stable under 3-hr/day access conditions, and the ethanol intake was much the same for all animals.

Maintenance of Ethanol-Reinforced Responding

In the maintenance phase of this experiment, animals 384 (ethanol-initiated), 364 (cocaine-initiated), and 367 (methohexital-initiated) were tested, and the results are represented in FIGURE 4. Under 3-hr/day access, periods of saline availability were alternated with periods of access to ethanol. The initial range of ethanol-reinforced responding was 28–55 responses/3-hr session. When saline was first substituted for ethanol, response rates for animals 364 and 367 decreased slightly on the first day and continued to decrease on the subsequent four days of availability. Animal 384, on the other hand, increased responding for the first four days of saline availability and only slightly decreased responding on the fifth day. In later periods of access to saline, response rates of all three animals dropped immediately on the first saline day and remained low throughout the five days. When ethanol was made available on alternate five-day periods, there was a rapid and often complete return to baseline of ethanol-reinforced response rates. There was no tendency for these ethanol-reinforced rates to change over the 80-day period of observation.

Termination of Ethanol-Reinforced Responding

Alternation of 24-hr and 3-hr access to 0.1 g/kg/inj of ethanol was given to seven monkeys (289, 337, 350, 225, 393, 328, and 250). Six animals showed one or more periods of high intake followed by voluntary abstinence under 24- hr access; one monkey (289) did not voluntarily terminate responding (FIGURE 5). Three of the monkeys showed only one episode of termination, and this was followed by high intake (FIGURE 5). On their second exposure to 24-hr/day access, these monkeys did not abstain from alcohol, although they became dangerously intoxicated and either were quite ill or died of causes related to ethanol toxicity. The last three monkeys (393, 328, and 250) showed more than a single episode of high ethanol intake followed by termination of responding under 24-hr access conditions (FIGURE 6). Monkeys 393 and 328 demonstrated a tendency toward shorted periods of intoxication prior to withdrawal after the first relatively long period of intoxication. The opposite tendency, that of longer periods of intoxication prior to withdrawal, was shown by animal 250. No termination occurred for animal 393 on the fifth exposure of 24-hr access conditions.

All of the monkeys that terminated responding showed signs of withdrawal, with the exception of animal 225 on its first termination. These withdrawal signs consisted primarily of hyperexcitability and generalized tremors.

DISCUSSION

Although self-induced intoxication by animals has been demonstrated only rarely,[2] the present study confirms the fact that rhesus monkeys will self-admin-

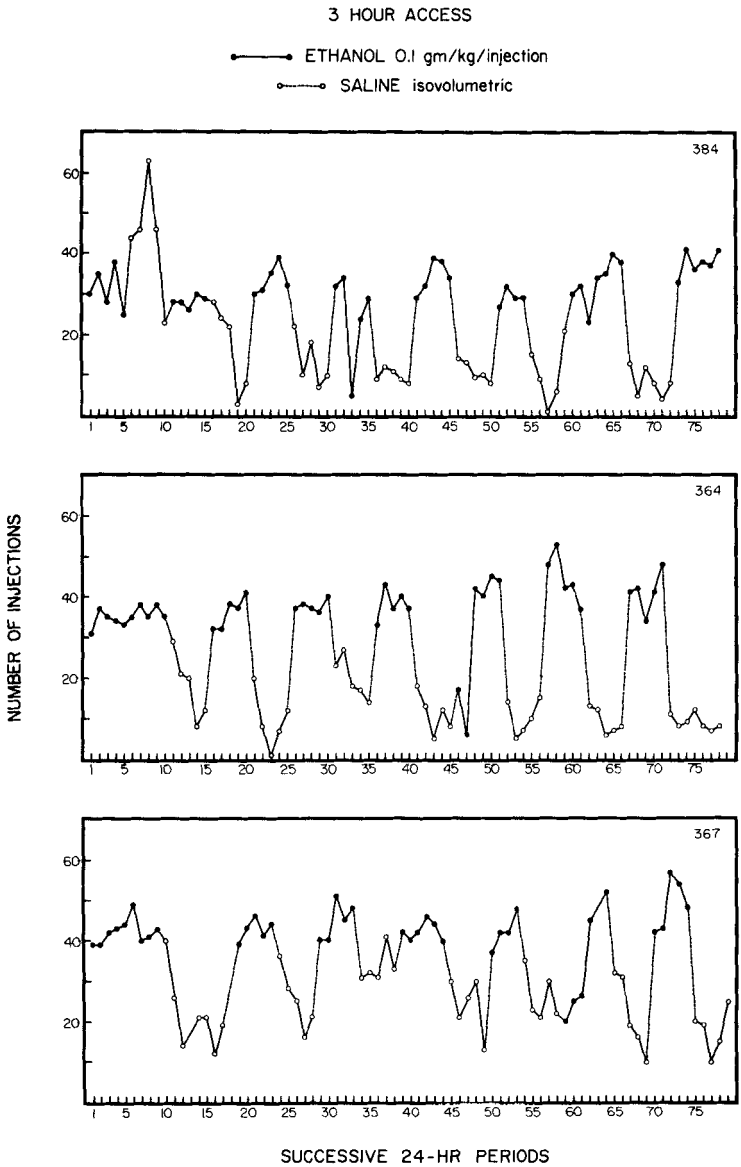


FIGURE 4. Alternation of ethanol access with saline access. Prior to these observations, each of the three monkeys (384, ethanol-initiated; 364, cocaine-initiated; and 367, methohexital-initiated) had maintained ethanol-reinforced responding for at least 20 days. After ethanol at 0.1 g/kg/inj was initially available for a series of testing sessions, saline was substituted for ethanol in equal volumes for five or more periods. Ethanol access and saline access then alternated every fifth period until the test was completed. Except for animal 384 (top panel) in its first exposure to saline, the monkeys did not maintain responding when given access to saline. Each time ethanol was available, responding returned to baseline and remained stable. Note that solid circles indicate ethanol was injected, open circles indicate access to saline, and dashed lines show a change in the response consequence.

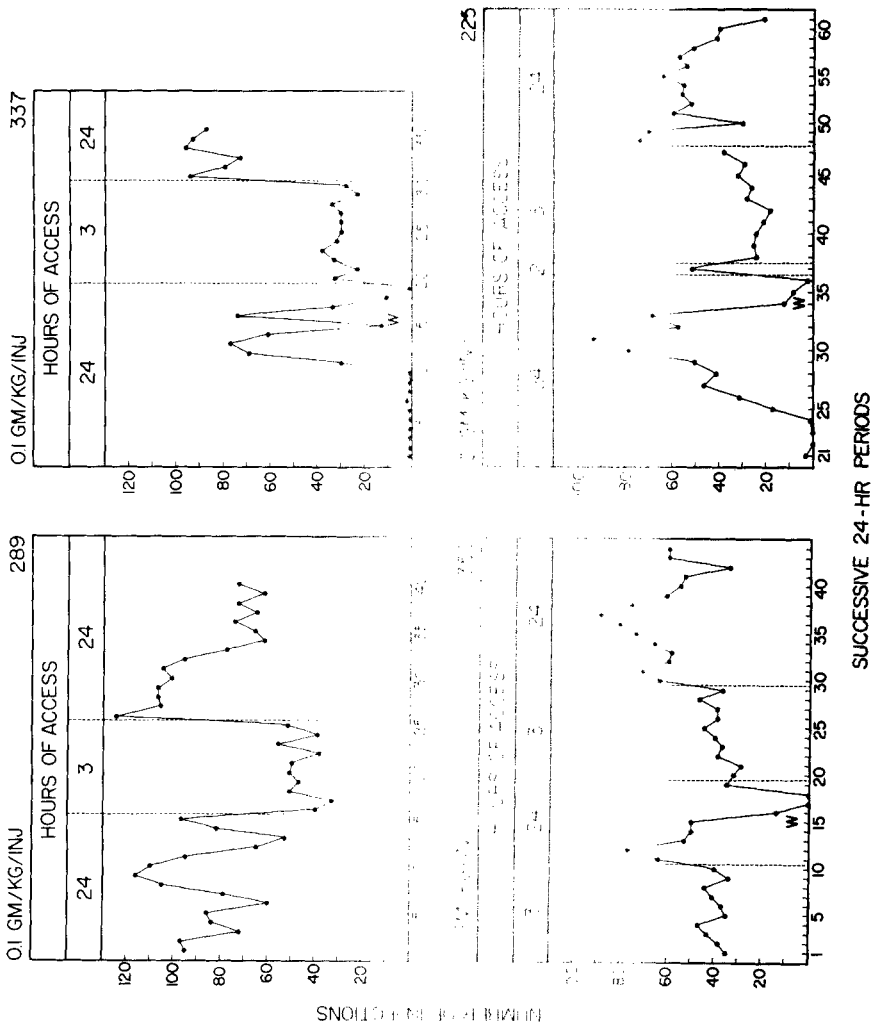


FIGURE 5. Alternation of 24-hr and 3-hr access to ethanol. As shown in the top left panel, monkey 289 did not voluntarily terminate responding after 15 days of 24-hr access to ethanol and was placed on 3-hr access for the next ten days. Each of the other three monkeys (337, 350, and 225; all ethanol-initiated) showed one episode of termination during 24-hr access to ethanol. Note that 289, 350, and 225 were exposed to ethanol previously; some of their history is indicated in FIGURE 1 and FIGURE 2. When voluntary abstinence occurred, 24-hr access was continued until responding increased, and then 3-hr access was instated for ten successive 24-hr periods. Note that occurrences of abstinence and withdrawal are indicated w.

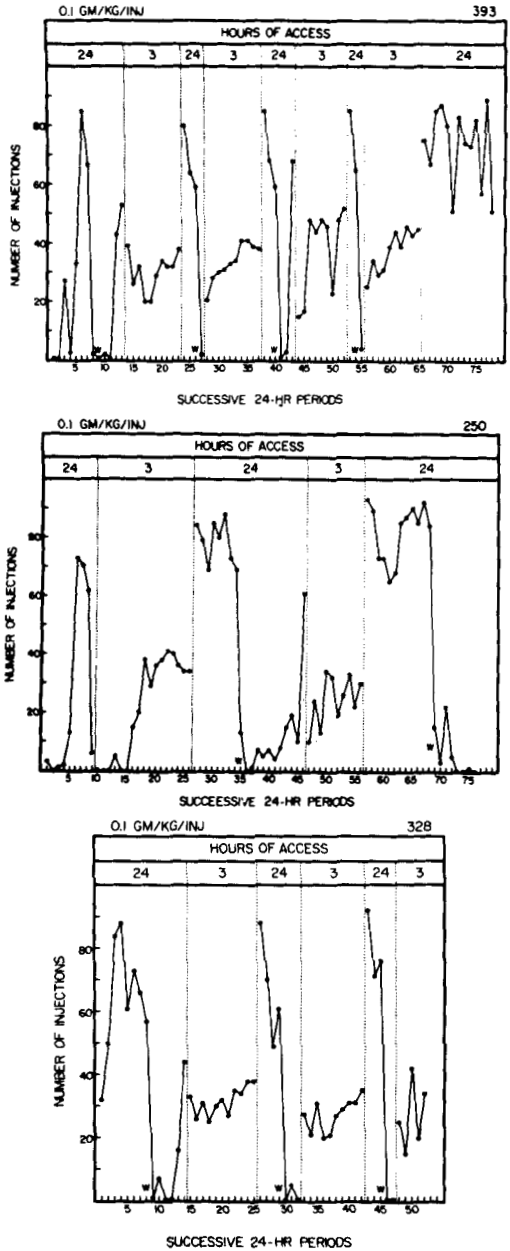


FIGURE 6. Alternation of 24-hr and 3-hr access to ethanol. Each of the three monkeys (393, 328, and 250) were given 24-hr access to 0.1 g/kg/inj of ethanol until responding terminated and withdrawal ensued (with the exception of animal 250 in the first exposure to ethanol). When responding increased again, the access was limited to 3-hr/day for approximately ten days, and then 24-hr access was returned. During 24-hr access, animals 393, 328, and 250 voluntarily terminated responding four, three, and two times, respectively. Monkeys 393 and 328 demonstrated a tendency toward shorter periods of high intake prior to withdrawal, while monkey 250 showed an opposite tendency, toward longer periods of high intake before withdrawal. Note that occurrences of withdrawal are indicated w on the graphs.

ister alcohol in grossly intoxicating amounts. Most of the findings of Deneau and colleagues have been replicated and extended in these experiments.

The observation that many monkeys did not respond at high rates when 0.1 g/kg/inj of ethanol was initially available has interesting implications concerning the reinforcing efficacy of intravenous ethanol. It suggests to the authors that there is a threshold for alcohol reinforcement. According to this hypothesis, a single response-produced injection is not a reinforcing stimulus; rather, a certain minimum amount of alcohol must be infused over a minimum length of time in order for the reinforcing property of the drug to be established. Thus, the animals that did develop high rates of responding may have been those making a sufficient number of spontaneous or accidental contacts with the lever to meet this "minimum amount/minimum time" requirement. Once this requirement was met, the rate of responding increased, such that ethanol under these conditions satisfied the definition of a reinforcing stimulus. Following this threshold notion, increasing the amount of ethanol delivered with each response should increase the probability that the "minimum amount/minimum time" requirement would be met. Accordingly, the two monkeys that did not respond to 0.1 g/kg/inj of ethanol but began responding when the dose was increased to 0.2 g/kg/inj were able to maintain responding when the dose was returned to 0.1 g/kg/inj (FIGURE 1).

Similarly, by first establishing high response rates with cocaine or methohexital as reinforcing stimuli, it was possible to insure a higher rate of responding when ethanol was substituted for the previous drug. When the animals were transferred back to response-contingent ethanol, they maintained elevated response rates indefinitely under 3-hr/day access conditions (FIGURES 2 and 3).

Since all fourteen monkeys in this study initiated (and maintained) ethanol-reinforced responding, the proportion of monkeys that will self-administer ethanol no longer appears to be an important datum. The earlier observation by Deneau and colleagues[1] that only some of the monkeys in their experiments self-administered ethanol may reflect the environmental circumstances used to assess the reinforcing efficacy of ethanol rather than individual differences in monkeys with respect to "addiction proneness." This notion might be further strengthened by explicitly training monkeys to respond with ethanol just as responses are trained with other reinforcers. In addition one might arrange, through conditioning, that a response with nondrug reinforcers, e.g. food or electric shock, have rates sufficient to induce ethanol-reinforced responding. We wish to stress that the amount and pattern of responding during the maintenance phase of this experiment appeared to be related more to the conditions of ethanol delivery (e.g. dose and access time) than to the kind of reinforcement used to initiate responding.

A striking characteristic of ethanol-reinforced responding is its ability to become stable under 3-hr access conditions. When ethanol-reinforced responding is alternated with periods in which saline is delivered rather than ethanol, the monkeys maintained much lower response rates when saline was available and resumed higher response rates only when ethanol was again response-contingent (FIGURE 4). With successive exposures to saline, each of the three monkeys tended to show a more rapid decrease in responding. This latter effect has been observed with nondrug reinforcers and has been called discriminated extinction.[5,6]

Comparison of FIGURES 5 and 6 with previous figures under 3-hr access conditions shows that ethanol-reinforced responding remained stable and the level of ethanol intake was much the same whether 3-hr access was held constant,

alternated with 24-hr access, or alternated with 3-hr/day access to saline. Self-imposed termination of ethanol-reinforced responding during 24-hr access schedules were confirmed in this study. However, the variability of the cyclic patterns was large, both among and within the animals (FIGURES 5 and 6). One animal (289) showed no termination (FIGURE 5); this could have been related to its long history of ethanol-reinforced responding under 3-hr/day conditions (FIGURE 2). The same monkey showed no abstinence signs when abruptly taken off 24-hr access. The other six animals demonstrated from one to four instances of self-imposed abstinence during 24-hr access. Although two of these monkeys were stopped after the third abstinence period, data from the remaining four animals suggested that when conditions of 24-hr access are alternated with 3-hr access, monkeys eventually cease their episodic intake pattern and maintain such high levels of ethanol intake that they may become quite ill and die.

Since self-termination of ethanol-reinforced responding was not observed under 3-hr access conditions, we have assumed that a necessary condition for its occurrence is high (i.e., > 6 g/kg), sustained intake of ethanol around the clock. One of the objectives of the alternation of 3-hr and 24-hr access was to examine the reliability of these periods of self-termination. The episodic nature was confirmed, but it is not clear what determines the length of the episodes or why they are less frequent as the monkey is exposed to ethanol over a longer period of time. The pattern of episodic high ethanol intake and the concomitant development of physical dependence, followed by voluntary cessation of responding and the onset of mild withdrawal signs observed in six of the seven monkeys tested, is important for two reasons: In the first place, this pattern of drug-reinforced responding is not seen with any other drug that produces physiological dependence. In contrast to ethanol, in morphine[9] and barbiturate[10] reinforced responding, response rates gradually increase with time, and responding does not cease, as in the case of ethanol-reinforced responding. Secondly, a commonality exists between human cases of alcoholism and these observations in rhesus monkeys. A pattern of responding resulting in "self-imposed abstinence" similar to the one exhibited by rhesus monkeys in this study has been demonstrated in humans under experimental conditions.[3,4] Should further investigation strengthen this notion, the value of the monkey as an experimental model of some of the characteristics of human alcoholism is greatly increased.

The temporal aspect of ethanol's effect on the rhesus monkey is considerably compressed relative to the human case. Monkeys may develop rapid alcohol-contingent responding within a single day, demonstrate one or more episodes of high intake and withdrawal, and die of alcohol-related causes within two or three months. The human counterpart, on the other hand, may take several years to develop an alcoholic syndrome with ethanol dependence, and he may survive for decades in varying degrees of this condition. This contrast between man and the rhesus monkey may depend more on the differences in patterns of self-administration than on differences in pharmacological processes between species.

CONCLUSIONS

Intravenous ethanol-reinforced responding in rhesus monkeys involves three behavioral processes: initiation, maintenance, and termination. It appears that a threshold must be met in order for the reinforcing property to be established. If monkeys do not spontaneously initiate responding, it can be facilitated by increasing the dose of ethanol or by increasing the rate of the lever-press response with cocaine or methohexital as reinforcing agents. Regardless of the method of

initiation, responding is stable when ethanol access is limited to 3 hr per day. Periodic, voluntary termination of ethanol-reinforced responding can be observed under an unlimited ethanol-access condition. The voluntary periods of abstinence may be caused by conditions that override the reinforcing properties of ethanol. Since there are similarities between the monkey's behavior on unlimited access to ethanol and the behavior of the human "binge" drinker, the rhesus monkey may be a valuable experimental tool.

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