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Alcohol Drinking Induced in the Monkey by Tetrahydropapaveroline (THP) Infused into the Cerebral Ventricle

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MYERS, R. D., M. L. McCALEB AND W. D. RUWE. *Alcohol drinking induced in the monkey by tetrahydropapaveroline (THP) infused into the cerebral ventricle.* PHARMAC. BIOCHEM. BEHAV. 16(6) 995–1000, 1982.—In the female macaque monkey acclimated to a primate chair, Collison cannulae were stereotaxically implanted bilaterally in the lateral cerebral ventricle. The voluntary self-selection of ethyl alcohol versus water was determined repeatedly during a series of 12-day test sequences in which the concentration of the alcohol solution offered to the primate was increased systematically over 12 successive days from 3% to 30%. Following control preference sequences, the dopamine-dopaldehyde condensation product, tetrahydropapaveroline (THP), was infused daily in each monkey's cerebral ventricle (ICV) in a volume of 200–400 μl. THP was dissolved in an artificial CSF, with pH adjusted to 3.8 with 0.1 mg/ml ascorbate, and infused in one of ten doses varying from 0.125–400 μg. Each monkey was administered one low and one high dose of the condensation product throughout each of two successive alcohol preference tests. When THP was infused in doses of less than 2.0 μg, the monkeys' alcohol preference failed to change. However, a marked increase in alcohol intake, in terms of both g/kg/day as well as the proportion of alcohol to water selected, was produced by THP infused ICV in doses of 5.0 to 20.0 μg. Although average intakes in the latter animals were between 4.0 and 5.0 g/kg/day, the monkeys selected certain concentrations of alcohol in amounts of up to 7.0 g/kg/day. The two highest doses of THP, 40.0 and 400.0 μg, inhibited the self-selection of alcohol even when presented in low, non-aversive concentrations in the 3% to 6% range. Overall, these results with the primate corroborate earlier findings in the rat of abnormal alcohol intake produced by centrally infused THP. They further support the theory that amine-aldehyde metabolites, if present in certain concentrations in the brain, may constitute a causal neurochemical factor in the addictive or otherwise immoderate drinking of alcohol.

Alcohol drinking Alkaloid condensation product Tetrahydroisoquinoline (TIQ)
Tetrahydropapaveroline (THP) Cerebral ventricle infusion Dopamine-dopaldehyde product
Opiate-alcohol interaction Primate's alcohol preference Ethanol self-selection
Monkey cerebroventricular infusion

THE chronic infusion of acetaldehyde into the cerebral ventricle (ICV) of either the rat or monkey can markedly alter the animal's voluntary drinking of ethyl alcohol [25,29]. During acetaldehyde infusions, alcohol surprisingly is consumed in concentrations which ordinarily are gustatorily aversive. Following on from this observation, it was found that certain alkaloid metabolites which derive from a condensation reaction of an aldehyde with an endogenous amine also may influence the selection of alcohol [20].

Five years ago it was discovered that the chronic infusion of tetrahydropapaveroline (THP) or a beta-carboline into the cerebral ventricle of the rat causes the animal to consume alcohol in abnormally large amounts [22]. The central effect of the tetrahydroisoquinoline (TIQ) condensation product is uniquely characterized by its longevity, apparent irreversibility, and the consequent preference by the rat of alcohol in concentrations as high as 40% [13]. Moreover, signs of withdrawal, elevated levels of blood alcohol and other sequelae associated with physical dependence occur [13]. Although the phenomenon of THP-induced drinking of alcohol has been replicated in the rat [4, 7, 24], inconsistent findings have been reported which are presently inexplicable [27].

Evidence continues to accumulate toward the viewpoint that a "family" of amine-aldehyde metabolites is involved in the aberrant drinking of alcohol [19]. A most important finding is that identified amine aldehyde products are elevated in both the urine and cerebrospinal fluid of the human alcoholic patient even several days after alcohol clearance is complete [3,5]. In this context, the present study was undertaken to determine whether a TIQ would alter the pattern of alcohol

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intake in the infra-human primate. This animal was selected even though nearly all experimental manipulations fail to affect the primate's inherent aversion to the fluid [1, 16, 26, 28].

In the current experiment, each monkey was offered a choice of alcohol in concentrations ranging from 3% to 30% during successive 12-day test sequences. THP was selected as the condensation product to be infused repeatedly into the animal's cerebral ventricle because it is the most potent of all of the TIQ metabolites examined thus far in terms of the pharmacological induction of alcohol drinking [7,19].

METHOD

Adult female macaque monkeys of either the rhesus or nemestrina species were ovariectomized for ease of husbandry during the periods of restraint. Each of the monkeys, which weighed between 2.6 and 4.0 kg, was maintained during the course of the test sequences on an ad lib supply of water and 1.0 g banana-flavored pellets prepared from Purina Monkey diet. In addition, a portion of fresh orange or apple was provided to the animal every other day. The rooms containing the primates were kept at an ambient temperature of 22°C to 24°C and were illuminated on a 12-hr light-dark cycle.

Prior to the start of the experiments, each animal was acclimatized to a Foringer primate chair and, while seated, trained to pull a Plexiglas finger lever which electrically activated the rotary dispenser of the banana pellets. Following this training, the animals were kept on a fixed-ratio reward schedule of FR 5 to FR 25, which was in effect for a one-hr period both at 8:00 a.m. and 4:00 p.m. The amount of food and fluid consumed was recorded at the same time on every day or at more frequent intervals as required during the test sessions.

Alcohol Self-Selection Procedure

A three-spout holder was affixed to the neck plate of each chair and positioned within easy access of the monkey's tongue. The tip of each spout was comprised of a leak-proof "Mini-lixit" fluid valve, placed equidistantly 2.0 cm apart from the other valves. A set of three 1000 ml inverted Nalgene graduated cylinders was attached to the chair and connected to each of the respective fluid spouts via a short length of Tygon tubing. One cylinder contained a solution of alcohol, another water and the third was kept empty to serve as a "dummy." The daily rotation of the two fluids on a predetermined schedule prevented the monkey from developing a right- or left-sided position habit [28].

Each alcohol test solution was prepared volumetrically every day with 95% reagent grade ethyl alcohol and tap water. Each preference sequence consisted of a 12-day interval with the following ascending order of concentrations of alcohol offered on successive days: 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, 25 and 30 percent. Measures of fluid and food intake were recorded and the drinking tube re-filled with the new solution at the same time every day.

Neurosurgical Implantation of Ventricular Cannulae

After an individual monkey was anesthetized with a 25–30 mg/kg sodium pentobarbital given intravenously, the animal's head was positioned in a Kopf stereotaxic instrument. Following rigid aseptic precautions described previously [29], an incision was made on midline and the underlying aponeurosis and muscle retracted. Two holes were drilled equidistantly 6.0–7.0 mm off midline in the coronal plane of 12.0–14.0 mm anterior to stereotaxic zero. Once each craniotomy hole was threaded by a matching tap, a modified Collison cannula was screwed into the calvarium.

The indwelling portion of the cannula was cut from 18 gauge stainless steel thin-walled tubing to a length so that the tip rested just above the lateral ventricle at a depth 10.0–12.0 mm below the surface of the dura mater. Anchor screws were inserted in the calvarium and then cranioplastic cement was packed around each and bridged so as to secure the entire bilateral array. The portion of skin overlying the cap of the cannula was incised and then the midline incision was closed with continuous suture subcutaneously. Postoperatively, penicillin was administered intramuscularly for 10 days.

Intracerebroventricular (ICV) Infusions

Each solution was prepared with pyrogen-free glassware in sterilized artificial CSF which consisted of a 5-ion solution [17] adjusted to pH 3.8 with 0.1 mg/ml ascorbate. A stock solution of THP hydrobromide (Hoffmann-La Roche) of 1.0 mg/ml of the salt was diluted subsequently to one of ten concentrations which ranged from 0.125 to 400 μg per 200–400 μl. The respective aliquots were passed through a 0.22 micron Swinnex millipore filter and then kept frozen in pyrogen-free glass vials at −20°C until required for injection.

To make a unilateral infusion, a 20 gauge stainless steel injector needle having a side-opening at the tip [18] was attached to a pre-calibrated length of PE tubing filled with the THP or CSF control solution. Following aseptic procedures, the injector needle was lowered through the rubber diaphragm of the Collison cannula to the depth within the lateral ventricle at which the solution began to flow by gravity. Patency with the ventricle was always assured by the presence of pulsations of the solution in the PE tubing reflecting CSF pressure fluctuations [18].

Prior to a series of ICV infusions, a 12-day 3% to 30% alcohol control test was completed in order to determine the individual pattern of alcohol self-selection for each monkey. A series of control injections of the artificial CSF [17] was given also in selected monkeys once per day during another 3% to 30% alcohol preference test carried out again over a 12-day interval. Either the control CSF or the THP solution was injected ICV once daily at the same time, following the morning feeding session, usually between 9:00 a.m. and 10:30 a.m. Each of the infusions was given in a volume of 200 to 400 μl with the first made on the day prior to the start of the alcohol preference sequence and then given on every day for the next 12 days.

Because of the constraints imposed by the small number of animals, each monkey was given two different doses of THP during each of two 12-day experimental test sequences. In all but one case, the lower dose always preceded the higher. In three monkeys the lower dose was increased 10-fold during the second alcohol preference test; in the fourth animal the dose was increased 8-fold; and in the fifth monkey THP was increased 40-fold. Alcohol drinking data on a sixth monkey obtained during infusions could not be considered because of pathological edema to its hindlimb and repeated bouts of diarrhea. The interval which elapsed between each of the series of 12-day alcohol preference sequences ranged from 3 to 35 days.

RESULTS

Overall, the mean intake of absolute alcohol across all 12

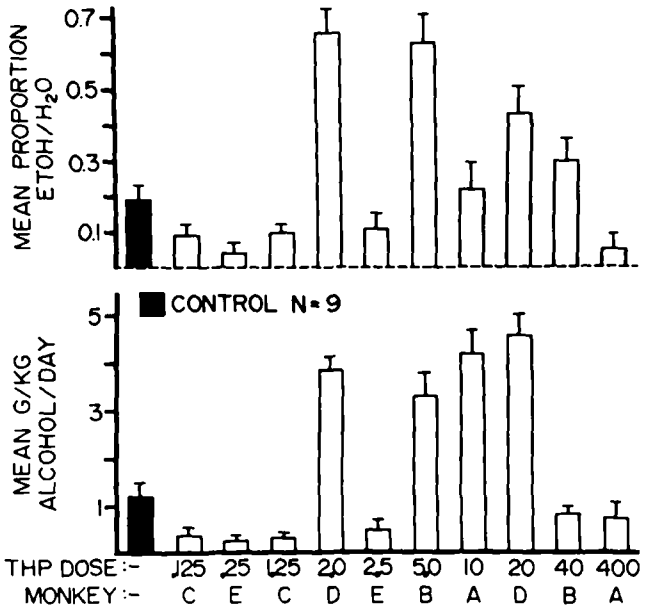

FIG. 1. Mean proportion of alcohol to water (top) and mean g/kg (bottom) per day for each of five monkeys. Designated on the abscissa is the THP dose for each respective monkey (A–E) infused daily during the 12 day alcohol preference sequence. Control values are the composite means of sequences during both CSF and non-infusion conditions.

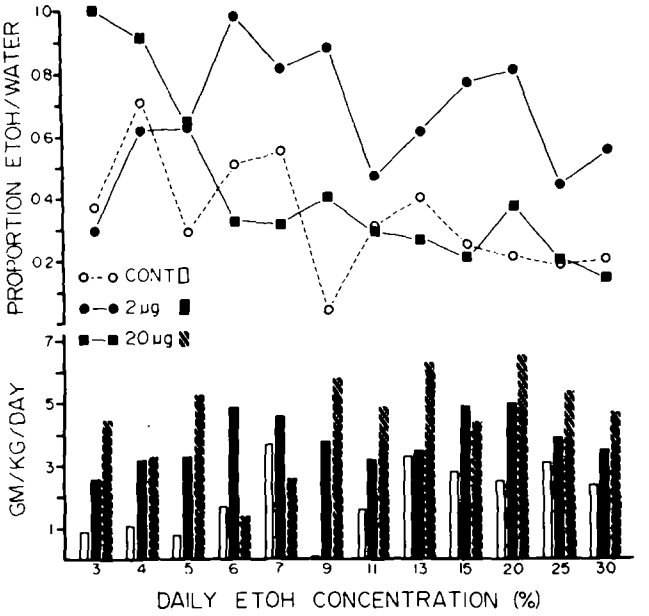

FIG. 2. Proportion of alcohol to water (top) and g/kg/day for one monkey during control and alcohol preference tests during which 2.0 µg (first sequence) and 20.0 µg (second sequence) of the THP was infused once daily. Concentration of alcohol solution offered on successive days is depicted on the abscissa.

concentrations of the fluid was 1.89±0.28 g/kg/day during ICV infusion of THP with all doses of the condensation product combined. The mean intake of absolute alcohol combined for all of the control preference test sequences was 1.21±0.26 g/kg/day. The mean proportional intake of alcohol of the monkeys during the test sequences of THP-infusions, again with all doses combined, was 0.26±0.05 and for the control sequences the overall proportion was 0.19±0.05.

Dose Response Analysis

The potent effect of ICV infusions of THP on the volitional ingestion of alcohol was clearly evident only when an analysis of the dose response for the respective monkeys was completed. Figure 1 presents the mean alcohol consumption over the 12-day test sequence in terms of both the ratio of alcohol (ETOH) to water (top), expressed as the proportion of alcohol to total fluid, and the absolute intake in g/kg/day (bottom). In comparison to the mean control values, the proportional and absolute intakes for Monkeys C and E given doses of 0.125, 0.25, 1.25 and 2.5 µg per infusion revealed virtually no alteration in alcohol drinking. However, the alcohol intake of Monkey D given the 2.0 µg THP dose averaged over 3.8 g/kg/day with the proportional intake reaching 0.66 for the 12-day test sequence. Thus, since the 2.5 µg dose given to Monkey E did not alter its alcohol drinking, this dose level was apparently at the compound's threshold of effect. Following ICV doses of 5.0, 10.0 and 20.0 µg of THP, the g/kg intakes of alcohol were greatly elevated in Monkeys B, A and D, respectively. Although the two highest doses of THP, 40 and 400 µg, suppressed alcohol g/kg intakes of Monkeys B and A, the proportional value of Monkey B was elevated above the control to a level of 0.30.

Patterns of Alcohol Drinking

The drinking pattern of each monkey differed in response to the presence of exogenously administered THP in the brain. In general, the amine-aldehyde condensation product exerted its effect within 24 to 48 hr after the initial injection, i.e., on the first self-selection day at 3% alcohol. Representative changes in alcohol preference in terms of the direction of shift, enhancement or suppression, as well as the magnitude of intake of specific concentrations of alcohol are illustrated for three monkeys in Figs. 2, 3 and 4.

Figure 2 presents the proportion of alcohol to total fluid consumed (top) and absolute intake in g/kg/day (bottom) for Monkey D which was given the 2.0 and 20.0 doses of THP. The proportional value of alcohol intake during the infusions of the 20.0 µg dose overlapped closely with that of the control test sequence. During the ICV infusions with the 2.0 µg dose, proportional intakes beyond 3% (Fig. 2, top) exceeded or equaled 0.50 at every test concentration offered to the primate, $t(22)=2.41$, $p<0.05$, with little or no overlap with control or 20.0 µg THP values.

Following the 2.0 µg dose of THP, the g/kg/day measure also increased significantly above the control measures, $t(22)=4.58$, $p<0.01$, from the 3% through 30% concentrations. At all but one concentration offered to Monkey D exceeding 7% alcohol, the 20.0 µg dose of THP produced even higher g/kg intakes. In fact, more than 5.0 g/kg/day of alcohol of the 5%, 9%, 11%, 20% and 25% solutions were consumed by the animal, with the highest intake of 6.6 g/kg reached at the 20% concentration.

In Monkey B, which exhibited a different drinking response, the 5.0 µg dose of THP shifted the proportional intake above the control (Fig. 3, top) at all concentrations of

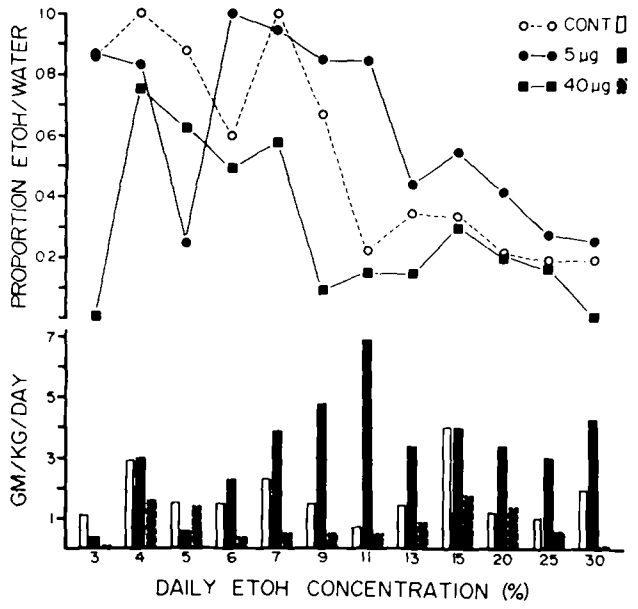

FIG. 3. Proportion of alcohol to water (top) and g/kg/day for one monkey during control and alcohol preference tests during which 5.0 μg (first sequence) and 40.0 μg (second sequence) of THP was infused once daily. Concentration of alcohol solution offered on successive days is depicted on the abscissa.

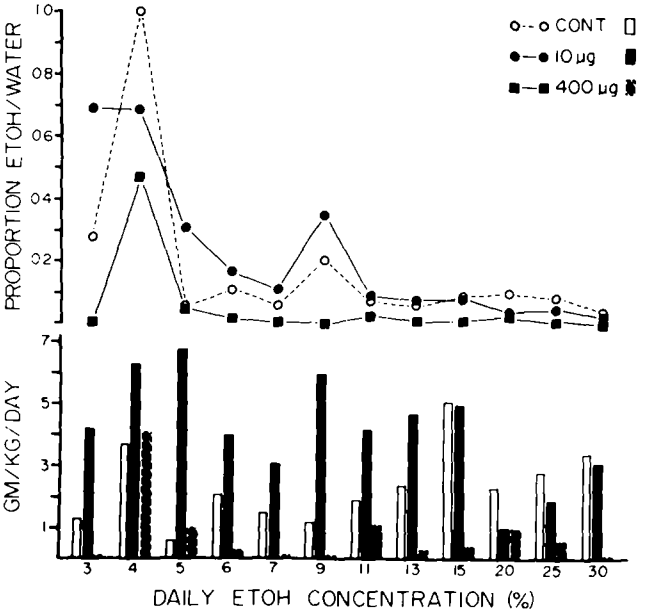

FIG. 4. Proportion of alcohol to water (top) and g/kg/day for one monkey during control and alcohol preference tests during which 10.0 μg (first sequence) and 400.0 μg (second sequence) of THP was infused once daily. Concentration of alcohol solution offered on successive days is depicted on the abscissa.

alcohol beyond 7%. The g/kg intake of alcohol during the 5.0 μg THP infusions was generally much higher, $t(22)=3.04$, $p<0.01$, than that of the control except at 3%, 5% and 15% solutions (Fig. 3, bottom). The monkey drank nearly 5.0 g/kg of the 9% concentration, 7.0 g/kg at the 11% concentration and over 4.0 g/kg was consumed of 30% on the last day of the sequence.

The preference test sequence during which the 40.0 μg dose of THP was infused ICV portrays the THP compound's clear-cut inhibition of alcohol drinking. Both the measures of proportion (Fig. 3, top) and g/kg/day (Fig. 3, bottom) reflect the marked decline in alcohol preference even of less aversive solutions of 6% to 11% as well as at noxious concentrations of 25% and 30% which were consumed during 5.0 μg ICV infusions.

THP infused ICV in Monkey A in a dose of 10.0 μg caused a significant enhancement of alcohol self-selection in g/kg intakes, $t(22)=3.05$, $p<0.01$, particularly of the lower concentrations offered to the animal. As depicted in Fig. 4 (bottom), this increase was entirely abolished, however, by the highest ICV dose of THP used in this study, 400 μg, $t(22)=5.83, p<0.01$. A slight increase in alcohol intake above control occurred only at the 4% alcohol concentration during infusions of this high dose.

The proportional measures for Monkey A during the control, 10 μg and 400 μg THP infusions were essentially indistinguishable from one another (Fig. 4, top) because of the considerable overlap throughout all test concentrations. Moreover, the proportion values were nearly always in the 0.1 to 0.2 range, or lower, at test concentrations of alcohol higher than 4%. The reason for this is that Monkey A exhibited a remarkable polydipsia described in the next section.

Comparison of Volumes of Fluid Consumed

Table 1 presents the average volume of fluid consumed per day for each monkey as well as the constituent alcohol and water intakes in ml±SE during control and THP infusion sequences. As reflected by the individual records of drinking, the change in the ml of alcohol ingested per day at the 2.0, 5.0, 10.0 and 20.0 μg doses of THP relates directly to the absolute intake in g/kg. However, the individual characteristics in proportional measures, i.e., as observed for Monkey A (Fig. 4, top) was determined essentially by the overall amount of water consumed. As portrayed in Table 1, the mean intake of water was so high, as much as 10 times greater than Monkeys B and C, that a proportional value would not reflect the animal's degree of alcohol preference.

The doses of THP which augmented the overall ingestion of fluid by more than 100 ml were two of the three highest doses infused, 20.0 and 400.0 μg. Thus, the central control of water-electrolyte balance may be affected by THP in such a way that a polydipsia is evoked.

DISCUSSION

Because of the phylogenetic proximity of the macaque monkey to man, the augmentation of alcohol drinking in this infra-human primate by an amine-aldehyde metabolite has considerable significance to the clinical issues surrounding the etiology of alcoholism. Our present pharmacological results relate directly to the recent biochemical findings that salsolinol or a related TIQ derivative is detectable in the urine, CSF or both fluids of the human alcohol patient [3,5]. Levels of the condensation products are still elevated even during the latter stages of detoxification when clearance of

TABLE 1

INTAKES OF ALCOHOL, WATER AND THE TOTAL OF BOTH EXPRESSED AS THE MEAN ml ± S.E. ON EACH DAY OF THE 12-DAY ALCOHOL-WATER PREFERENCE SEQUENCE

Monkey	THP Dose	Total Fluid	Alcohol	Water
	Control	1185 ± 166	141 ± 36	1044 ± 177
A	10.0	1222 ± 139	240 ± 60	982 ± 154
	400.0	1423 ± 183	49 ± 32	1374 ± 194
	Control	184 ± 22	83 ± 21	101 ± 21
B	5.0	218 ± 22	141 ± 27	77 ± 17
	40.0	134 ± 16	38 ± 12	96 ± 16
	Control	167 ± 18	42 ± 12	125 ± 10
C	0.125	109 ± 9	11 ± 3	98 ± 8
	1.25	129 ± 10	15 ± 3	114 ± 9
	Control	383 ± 34	131 ± 24	252 ± 26
D	2.0	414 ± 106	241 ± 41	173 ± 79
	20.0	653 ± 52	281 ± 60	372 ± 60
	Control	161 ± 17	12 ± 3	149 ± 16
E	0.25	119 ± 13	11 ± 4	108 ± 14
	2.5	104 ± 20	6 ± 3	98 ± 19

The dose of THP is expressed in terms of μg/infusion/day.

alcohol from the body is metabolically complete [3,5]. Taken together, it is apparent that in the primate species this class of amine-aldehyde condensation product satisfies two of the important neurochemical criteria required of an endogenous substance to be considered as a factor in the addictive process underlying alcoholism: (1) pharmacological initiation of aberrant alcohol consumption by the TIQ when introduced into the brain; and (2) the presence of the TIQ in the CNS of the alcohol-drinking individual.

A most interesting experimental aspect of the present results is the very narrow range of doses of THP which are effective in inducing a shift in an individual monkey's preference for alcohol. This dose delimitation reported previously for the upper range of doses tested in the rat [4, 7, 24] is particularly pertinent to the findings of other investigators for two reasons. First, one dose of a TIQ may not affect an individual animal, but in another represents a potent concentration when the exogenous alkaloid is applied to the brain. In our study, the 2.0 and 2.5 μg doses of THP illustrate this point. Second, the selection of a single dose or even two doses for usage with a given species or strain of animal is clearly inappropriate when a pharmacological study of condensation products is undertaken. In essence, the matter of dose could well explain an inconsistency in effect on alcohol preference of a given dose of a TIQ even when the paradigm of repeated ICV infusions is used [32]. Of course, other experimental factors including the patency of the ventricular cannula as well as genetic and strain differences undoubtedly account for other variations in observation [20,27].

Historically, the infra-human primate has not evolved as a useful model for investigations of alcohol drinking [12, 26, 29] although a monkey can be trained to self-administer alcohol intravenously [6,10]. For example, when physical dependence on alcohol is induced by prolonged treatment of the monkey with the fluid, the animal nevertheless fails to increase its preference for alcohol [15, 16, 29]. After extensive behavioral conditioning procedures are utilized to induce drinking of alcohol, the absolute intakes of 8%, 16% or 32% alcohol during a three-hour test session are only about 1.0 g/kg or less [8]. In contrast, ethyl alcohol or acetaldehyde infused chronically ICV can induce sporadic drinking of alcohol in concentrations of up to 20% [29]. In view of the present results with the TIQ, protracted behavioral training and acclimation to the aversive taste of alcohol are not now necessary prerequisites for the induction of the volitional intake of pharmacologically significant quantities of this fluid.

Since the maximal clearance rate of alcohol administered orally has been reported to range between 142 to 167 mg/kg/hr for the female macaque monkey [9,30], it would appear that alcohol consumed at a rate of greater than 3.5 to 5.0 g/kg/day would well exceed that which could readily be degraded metabolically [11]. Thus, the g/kg intakes above this level observed in the present study would conceivably be intoxicating and potentially addictive to the monkey. In future studies with the infra-human primate, signs of physical dependence, blood alcohol determinations in relation to drinking patterns and tests of the longevity of action of a TIQ [13] should be observed and quantitated.

In spite of the fact that both THP and salsolinol given ICV induce drinking in the rat, in all likelihood other alkaloid conjugates are equally involved neurochemically in the addictive process. Already it is known that a tetrahydro-β-carboline infused directly into the brain of the rat also evokes abnormal consumption of alcohol in unusually high concentrations [23, 24, 33]. These and complementary findings have led to the postulation that a "family" of alkaloid metabolites constitutes the missing metabolic link in the etiology of an individual's craving for or addiction to alcohol [19]. Although the precise cellular mechanism of action of an amine-aldehyde product is presently unknown [21], each can exert a myriad of effects on nerve cells including: the synthesis, release and uptake of neurotransmitters such as dopamine and serotonin [14]; binding and transport of Ca^{++} ions [31]; and the activity of opioid peptides [2]. New research toward the elucidation of each of these central mechanisms will provide a better understanding of the irreversible perturbation of one's normal pattern of alcohol drinking.

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