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Alcohol Drinking in the Rat: Increases Following Intracerebroventricular Treatment with Tetrahydro-β-Carbolines

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TUOMISTO, L., M. M. AIRAKSINEN, P. PEURA AND C. J. P. ERIKSSON. *Alcohol drinking in the rat: Increases following intracerebroventricular treatment with tetrahydro-β-carbolines*. PHARMAC. BIOCHEM. BEHAV. 17(4) 831–836, 1982.—Voluntary alcohol intake has been reported to increase in rats after the repeated intracerebroventricular (ICV) administration of 1,2,3,4-tetrahydro-β-carboline (THBC) and some tetrahydroisoquinolines, although negative results have also been reported. THBC is a normal constituent in human plasma and platelets; 1-methyl-1,2,3,4-tetrahydro-β-carboline (1-Me-THBC), however, occurs in the blood after a person drinks alcohol. We have evaluated the effects of two doses of THBC and 1-Me-THBC on voluntary alcohol consumption in rats. ICV infusions were given with Alzet® minipumps for 14 days rather than giving repeated ICV injections. Stability of the drugs in the pump was verified using mass spectrometry. On each day the rats chose between water, alcohol (increasing concentrations from 3 to 30%) and an empty bottle. Alcohol intake increased by about 100% ($p<0.05$) during the last six days when 47 nmoles/hr of either THBC or 1-Me-THBC was infused. At the end of the experiment elevated blood concentrations of alcohol (0.02–0.78 ‰) were found in rats belonging to the THBC or 1-Me-THBC groups and drinking 30% alcohol. The infusion of 0.47 nmoles/hr of either drug did not increase alcohol intake as compared to control.

Alcohol preference β-Carbolines Drinking Intracerebroventricular infusion Rat Alzet® minipump

RECENT studies (see [2]) have demonstrated that 1,2,3,4-tetrahydro-β-carbolines formed from formaldehyde and indoleamines are normal constituents of mammalian urine, blood and brain, and that after ethanol intake, acetaldehyde forms corresponding 1-methylated tetrahydro-β-carbolines. In our GLC-mass spectrometric studies, 1,2,3,4-tetrahydro-β-carboline (THBC, tetrahydronorharman, tryptoline, noreleagnine), formed from tryptamine and formaldehyde, has occurred in nanomolar quantities in human platelet-rich plasma; about 50% or more was in platelets [14,15]. After alcohol intake, 1-methyl-1,2,3,4-tetrahydro-β-carboline (1-Me-THBC, tetrahydroharman, methtryptoline), the condensation product of tryptamine and acetaldehyde, occurred in the platelets and plasma of all the nine volunteers studied, even 48 hr after alcohol intake. Before this experiment, the compound was found only in platelets and plasma of one person ([25], and Peura *et al.*, unpublished).

According to Myers and coworkers [20,21] and others [10] voluntary alcohol intake in rats increases when certain tetrahydroisoquinolines like salsolinol, the condensation product of dopamine and acetaldehyde, or THBC are injected intracerebroventricularly (ICV) every 30 min or once daily for 12 days. Others, however, have been able to repeat only partly [10,30] or not at all [31] the results of the once-daily experiments of Myers and Oblinger [22], although a full report of the most similar experiment [30] has not yet been published.

The purpose of this study was to (1) repeat the ICV experiments of Myers and Melchior [21] with THBC, and (2) study the effect of 1-Me-THBC. Continuous ICV infusions with Alzet® minipumps were used instead of repeated injections.

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METHOD

Animal Experiments

In preliminary experiments we tested three strains of male rats Kuo: WIST, F 344/Kuo and BD IX/Kuo and female Kuo: WIST rats. For the actual experiments, 40 naive male Kuo: WIST rats weighing 170–250 g (46–63 days) were used. During experiments, the rats were housed in individual cages at a room temperature of 20±1°C and relative humidity of 40–50% and fed standard pellets (Tuohilampi). The light/dark cycle was 14/10 hours with lights on from 0600 to 2000.

The rats were studied for their voluntary alcohol intake during a twelve day experiment using the methods of Myers and Melchior [21]. The rats had a free choice between water and increasing concentrations of alcohol. An empty bottle was also included, and the positions of the three bottles were changed daily in random order so that the rat did not develop a position habit. The alcohol solutions were prepared in deionized water and the concentrations (v/v of 100% ethanol) on successive days were: 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, 25, and 30%. Consumption of alcohol and water were measured daily by weighing each bottle. The drugs to be studied were infused (0.47 and 47 nmoles/hr) into the lateral cerebral ventricle by an Alzet™ 2002 osmotic minipump connected to a permanent ICV cannula by a polyvinyl tube. Tests of drinking behavior were begun two days after the cannula was implanted and lasted until the 14th day after the operation, i.e., the reliable pumping time for the pump used.

The drugs were dissolved in artificial cerebrospinal fluid (CSF) consisting of 7.46 g NaCl, 0.19 g KCl, 0.14 g $CaCl_2$ (anhydrous) and 0.19 g $MgCl_2 \cdot 6H_2O$ per liter of deionized water, including 0.1 mg/ml ascorbic acid to retard degradation of alkaloids [20,21]. Artificial CSF, also containing ascorbic acid, was used as a control vehicle. Solutions were always sterilized by passing them through a membrane filter (Gelman Acrodisc® 0.2 μm pore size). The nominal rate of infusion was 0.5 μl/hr.

To implant the permanent cannulae, the animals were anesthetized with chloral hydrate (300 mg/kg), and placed in a stereotaxic instrument. The tip of the cannula was positioned at the following coordinates [17]: Lat 0.16, a–p +0.58, d–v +0.20. To check the correct position of the cannula in the ventricular system the cannula and tubing connected to it were always first filled with artificial CSF to make sure that the liquid was freely flowing inwards. After this the cannula was lifted up and the system was filled with the drug to be studied and connected to the minipump. The tip of the cannula was then lowered back to exactly the same position. The cannula was fixed into the skull with screws and dental cement (Durelon®). The minipump was placed under the skin of the neck. The wound was closed with Mersilene® sutures and it healed within a week.

After the experiment was completed the rats were offered 30% alcohol and water for an additional night, and blood samples for alcohol determination were taken between 0000 and 0100 a.m. from the tail in heparinized 100 μl capillaries. After the experiment, the contents of the minipumps were analyzed for THBC and 1-Me-THBC to determine whether or not the drugs had deteriorated during the two-week experiment. The position of the cannula was verified post mortem by injecting methylene blue through the cannula. The results of two rats were discarded due to incorrect positioning of the cannula (one in THBC 47 nmoles/hr group and the other one in 1-Me-THBC 0.47 nmoles/hr group).

Analytical Methods

Analysis of THBC and 1-Me-THBC. The contents of the Alzet® minipumps were made alkaline with sodium carbonate and extracted into dichloromethane; the extracts were analyzed quantitatively by mass spectrometry (Jeol JMS D 300 mass spectrometer with JMA 2000 mass analysis system) via direct inlet probe at electron energy of 70 eV. The mass spectra m/z (rel.int%) of extracts containing 1,2,3,4-tetrahydro-β-carboline (THBC) were 172(51), 171(13), 169(10), 144(20), 143(100), 115(12) and those of extracts containing 1-methyl-1,2,3,4-tetrahydro-β-carboline (1-Me-THBC) were: 186(72), 185(25), 172(11), 171(100), 169(9), 157(35), 156(25), 154(10).

The quantity of THBC in the Alzet® minipumps after the animal experiments was measured by Perkin-Elmer fluorescence spectrophotometer MPF-3 using an exitation wavelength of 296 nm and an emission wavelength of 320 nm. For quantitative assay of 1-Me-THBC, the extracts were eluted in a RP-18 column (Varian MCH-10) isocratic with methanol-water-formic acid (166:34:1) with a Varian liquid chromatograph model 5000 [28]. The flow-rate was adjusted to 2.0 ml/min and the wavelength of detector to 280 nm. Under these conditions the retention time of 1-Me-THBC was 1.75 minutes.

Determination of blood alcohol. Alcohol in blood samples was determined with head-space gas chromatography, as described for acetaldehyde by Eriksson *et al.* [12].

Chemicals and standards. THBC hydrochloride and 1-Me-THBC hydrochloride were prepared by the Pictet-Spengler condensation reaction [26]. The doses of drugs refer to free base of the drug.

Calculations and statistics. Consumption of alcohol solutions was converted to intake of absolute alcohol in grams, taking the specific gravity of alcohol into account. The consumption of alcohol was also calculated per weight of the animal as well as cumulatively during a given period with the results expressed as means±S.E.M. Students' *t*-test was used to evaluate the significance of differences between means.

RESULTS

Preliminary Experiments

The daily consumption of alcohol in the preliminary experiments, shown in Fig. 1, slowly increased in male Kuo:WIST and in male BD IX/Kuo rats during the twelve-day period when increasing concentrations of alcohol were available. Initially, alcohol consumption was 0.87±0.07 g/kg (n=6) and 1.01±0.27 g/kg (n=6), respectively, and it increased up to 6.53±0.77 ($p<0.001$) and 4.83±0.34 g/kg ($p<0.001$), respectively. The alcohol intake of female Kuo:WIST (3.94±0.59 g/kg) and of F 344/Kuo rats (4.02±0.33 g/kg) was high from the very beginning and did not significantly increase during the experiment ($p>0.05$ in both groups). This was also evident when the ratio of intake of alcohol solution versus total fluid intake was calculated (Fig. 2).

No correlation (r=0.0002–0.001) was found between the weight of the animal and the total consumption of alcohol/kg. A group of BD IX/Kuo rats was subjected to a second test of alcohol consumption three weeks after beginning the first test. At the time of the second test they weighed ca. 100 g more, but the alcohol intake per kg body weight was almost

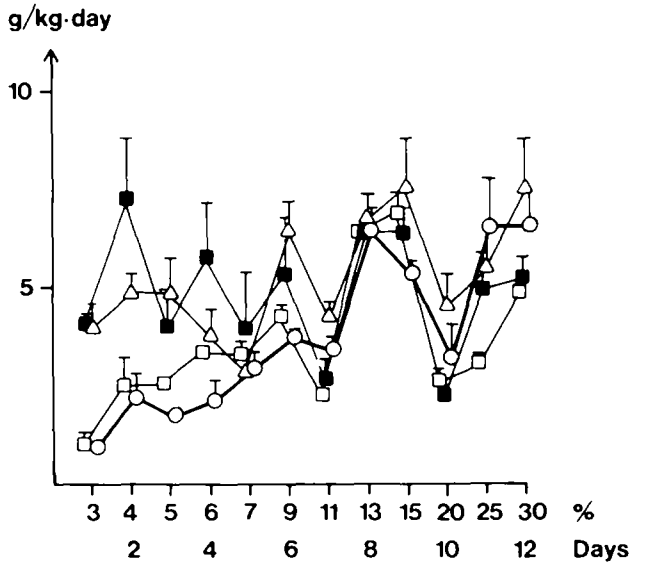

FIG. 1. The spontaneous daily consumption of alcohol in untreated rats of different strains. ■–■ F344/Kuo ♂, △–△ Kuo: WIST ♀, □–□ BD IX/Kuo ♂ and ○–○ Kuo:WIST ♂. Mean · S.E.M., n=6 in all groups. Alcohol was available on a free choice basis in increasing concentrations from 3 to 30%.

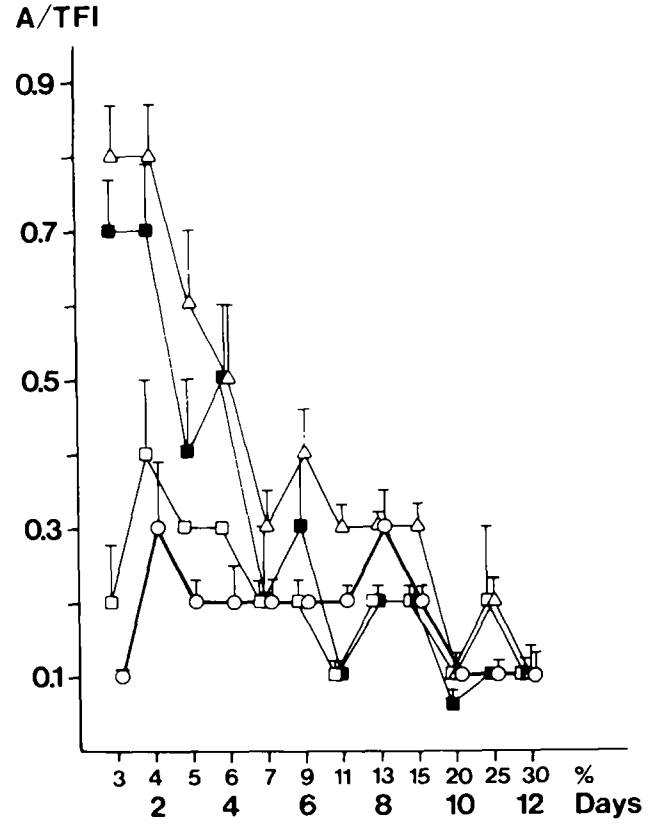

FIG. 2. The ratio, mean±S.E.M. of the intake of alcohol solution (A) versus total fluid intake (TFI) in untreated rats of different strains. ■–■ F 344/Kuo ♂, △–△ Kuo: WIST ♀, □–□ BD IX/Kuo ♂ and ○–○ Kuo: WIST ♂. Conditions as in Fig. 1.

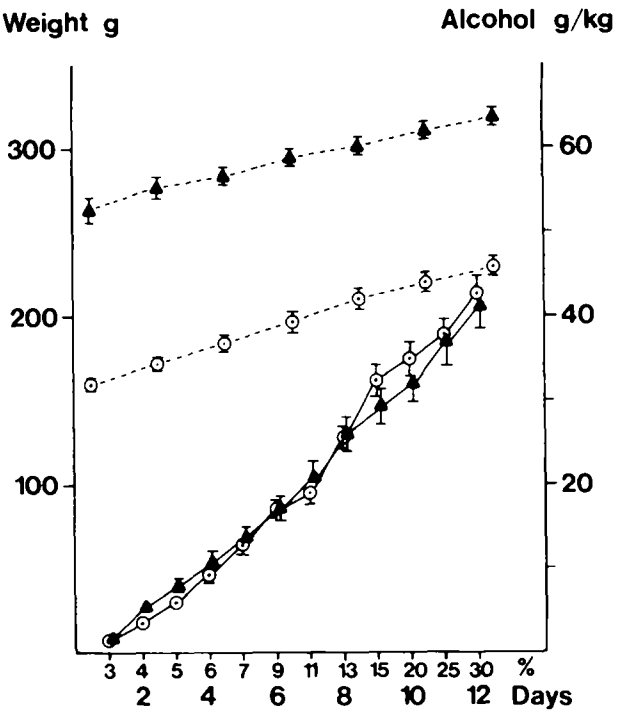

FIG. 3. Body weight and consumption of alcohol in a group of BD IX/Kuo rats subjected twice to a test of alcohol consumption with alcohol concentrations increasing daily from 3 to 30% in a free choice situation. Body weight (○---○ and ▲---▲) and alcohol consumption (○–○ and ▲–▲) in the first and second experiments, respectively. Mean+S.E.M. (n=6).

equal in both tests (Fig. 3). Thus, the tendency to consume more alcohol at the end of the first test period had also practically disappeared during the nine alcohol-free days between experiments. The next day after cessation of alcohol availability, piloerection and tremor were observed in most of the rats as probable signs of withdrawal.

Main Experiments: General

The weight of the animals decreased 10–20 g during the two first days after the operation. From the second day onwards, however, when the test for alcohol preference was begun, they seemed healthy and their weights increased steadily and similarly in all groups. There was no significant difference in food consumption between the groups. Regardless of drug treatment, the rats receiving alcohol tended to become hyperactive and more difficult to handle.

Effect of THBC and 1-Me-THBC

When 47 nmoles/hr of either THBC (0.8 μg/hr) or 1-Me-THBC (8.7 μg/hr) were infused (0.5 μl/hr) into the lateral cerebral ventricle, the intake of alcohol was similar in the control and treated rats during the first six days (Fig. 4). During the last six days, however, the animals given either β-carboline compound consumed significantly more ($p<0.05$) alcohol than did the respective controls (Figs. 4 and

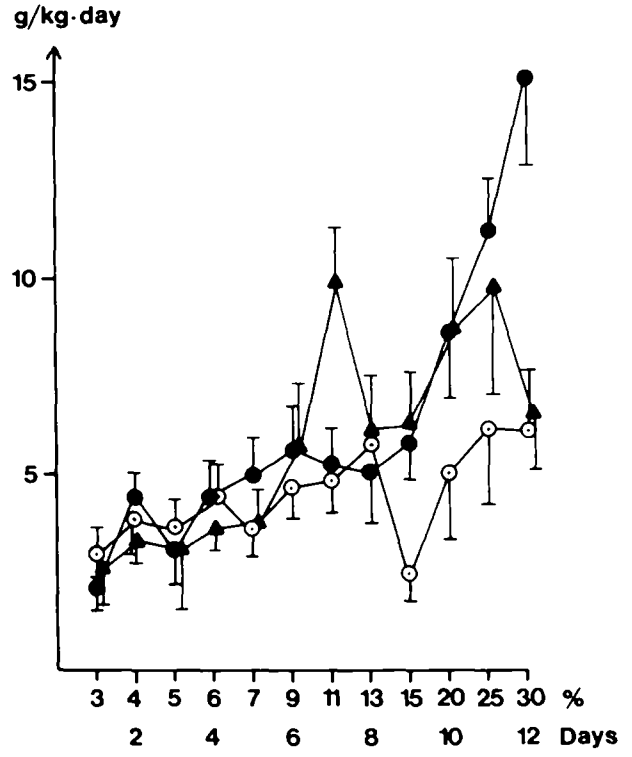

FIG. 4. Intake of alcohol in rats during ICV infusion of 47 nmoles/hr of tetrahydro-β-carboline (THBC) (▲–▲, n=5) and of 1-methyl-tetrahydro-β-carboline (1-Me-THBC) (●–●, n=7) and during the infusion of artificial CSF (⊙–⊙, n=9). Alcohol was available on a free choice basis in increasing concentrations from 3 to 30%.

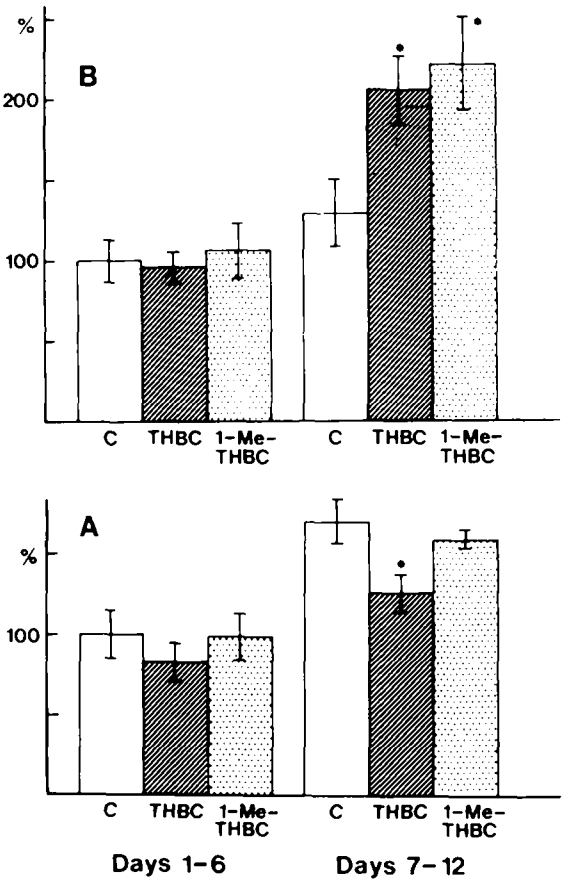

FIG. 5. The consumption of alcohol during the first and last six days in two sets of experiments with ICV infusion of (A) 0.47 nmoles/hr (B) 47 nmoles/hr either THBC or 1-Me-THBC or of artificial CSF (C). The mean amount of alcohol consumed by the control rats (C) during the first six days was taken as 100%. Panel A: n=6 (C and 1-Me-THBC) or 5 (THBC). Panel B: Data from Fig. 4. *$p < 0.05$.

5). The proportion of alcohol solution to total fluid intake decreased in all groups when more concentrated alcohol solutions were offered (Fig. 6), but not as much in the treated groups as in the controls.

ICV infusion of 0.47 nmoles/hr of either drug did not increase alcohol intake; but rather alcohol intake during the second week was significantly ($p<0.05$) less in the THBC treated group than in the controls (Fig. 5). During the alcohol consumption test, wet-dog shakes, tremor or convulsions were not seen in any of the groups when observed during the period of routine daily care, around noon.

Content of the Minipumps

The stability of THBC and 1-Me-THBC in the minipumps during the experiments was determined by thin layer chromatography and mass spectrometry. The compounds which were protected by an antioxidant, remained unchanged, although the degradation of hydroxyl or methoxyl substituted tetrahydro-β-carbolines with oxidative agents occurs readily [1]. Amounts remaining in the pumps were also close to the values calculated from the original amount and the theoretical release during the experiment, which was about 80% of total.

Blood Alcohol

Elevated concentrations of blood alcohol (0.02–0.78 ‰) were found in four rats. All belonged to the groups treated with 47 nmoles/hr of alkaloids (3 in THBC group and 1 in 1-Me-THBC group). The alcohol concentration in the blood of the controls was ≤0.001%. Although the correlation between blood alcohol level and the amount of alcohol ingested could not be assessed on the basis of so few data, the highest concentration of alcohol was in the rat that also had ingested by far the most (27.6 g/kg) alcohol during the previous day.

DISCUSSION

Voluntary alcohol intake increased in rats given 47 nmoles/hr of THBC or 1-Me-THBC ICV. This increase occurred during the latter part of the 12-day experiment, when high concentrations of 11–30% alcohol solutions were offered. The result with the high dose of 47 nmoles/hr (8 μg/hr) of THBC agrees with the report of Myers and Melchior [21] who found an increased voluntary intake of alcohol in rats with repeated injections of 4 μg of THBC every 30 minutes. Also in their study alcohol intake increased particularly when high alcohol concentrations were offered. The increasing effect of 1-Me-THBC on alcohol consumption is of special interest since 1-Me-THBC is a condensation product of

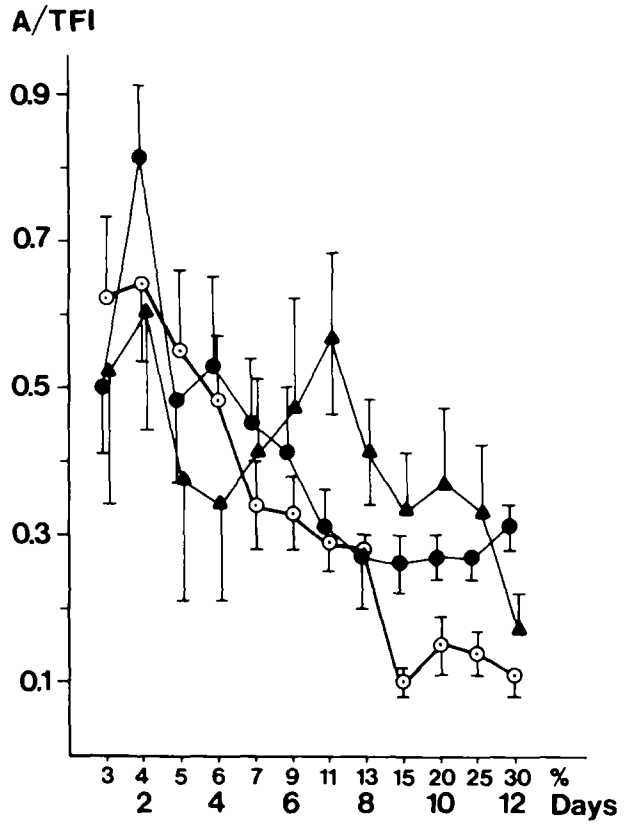

FIG. 6. The ratio, mean±S.E.M., of the intake of alcohol solution (A) versus total fluid intake (TFI) in rats during ICV infusion of 47 nmole/hr of either THBC (▲–▲, n=5) or 1-Me-THBC (●–●, n=7) and in controls (○–○, n=9). Conditions as in Fig. 4.

acetaldehyde, the main metabolite of ethanol. Although 1-Me-THBC has been found in human urine under normal conditions [6] its occurrence in plasma and urine has been associated with ethanol intake [25,27]. 1-Me-THBC is also present in some alcoholic beverages [7] but not in distilled ethanol which was used in the present experiments.

The lower dose of 0.47 nmoles/hr did not increase alcohol consumption, and there was more of an increase in the respective control. The individual variation among the rat species seems to be rather large as also noted by Myers *et al.* [23]. In part this could be due to small changes in the environment as suggested by variation from experiment to experiment. Therefore, the discrepancy to the positive result of Myers and Melchior [21] at this lower dose level is not surprising since the results, particularly the positive ones, are obtained with limited number of rats, and our preliminary studies also showed that the spontaneous consumption of alcohol differs between strains of rats.

The mechanism underlying the increased alcohol intake caused by THBC is not known, although several biochemical actions of β-carbolines might be related to it. β-Carbolines, including THBC and 1-Me-THBC, may increase the concentration of free amines in the brain, because they are inhibitors of MAO [13]—particularly of A type [8,18]. They also inhibit the uptake of 5-HT and catecholamines [5, 16, 32] and show an affinity to several membrane receptors in the brain. Although the binding of β-carbolines to the benzodiazepine and opiate receptors is interesting, the affinity of THBC and 1-Me-THBC used in the present study is very low [4,19]. On the other hand, 1-Me-THBC has a significant affinity for 5-HT receptors and spiroperidol-sensitive dopamine receptors [19].

The increased intake of alcohol may also be due to the possibility that the treated rats perceived the taste of the strong alcohol solutions to be less noxious than the controls. This is supported by the finding of Nance and Kilbey [24] that a related compound, 6-methoxy-THBC, abolished the increased sucrose preference induced by *p*-chlorophenylalanine in rats. A role of taste in alcohol preference in rats is suggested by the finding that genetically alcohol avoiding (ANA) rats [11] accepted more alcohol when it was given as wine or punch [33]. The few studies concerning direct taste changes during ICV treatment with THBC leave the question unanswered [21,22]. Since the present experimental design using increasing concentrations of alcohol also presents the problem of taste changes, studies with constant concentrations of alcohol would be of interest.

Symptoms very similar to hangover, delirium tremens, and other alcohol withdrawal symptoms have been described after many of the β-carbolines that are administered to man and animals [3]. Myers and Melchior [21] have also found some of these symptoms after giving THBC ICV to rats. Although our daily dose was the same as theirs, we did not see such prominent symptoms. Our rats received the drug evenly with no high peaks, and therefore the effect may be different. We cannot, however, exclude the possibility that the rats had some kind of dysphoria and were really drinking alcohol in order to relieve it. Although some high values of blood alcohol in the β-carboline groups support this suggestion, experiments of longer duration seem necessary.

As stated recently [9,29], a conclusion about human alcoholism based on alcohol selection studies in rats must be considered with great caution. However, together with earlier studies [21,25], our present results could be of heuristic value in an attempt to find a biological basis for alcoholism.

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