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Alcohol Intoxication and Drunken Frenzy and/or Hangover Models in Terms of Discrete Shuttle Avoidance Behavior in Mice

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Abstract: The aim of this study was to assess the modification of the behavioral effect of ethanol by anti-alcoholic drugs, Ca-cyanamide and disulfiram, in terms of discrete shuttle avoidance behavior in mice. Ethanol (2g/kg p.o.) significantly increased the response rate due to its central depressant action, i.e., induction of a disinhibition (alcohol intoxication: MEITEI or YOI in Japanese). Although the single administration of Ca-cyanamide (1-10 mg/kg p.o.) or disulfiram (3-30 mg/kg p.o.) did not change the response rate, the response rate following the combined administration of ethanol + Ca-cyanamide or disulfiram was significantly lower than the control level. A similar reduction of the response rate was produced by the combined administration of ethanol (2 g/kg) + acetaldehyde (1-10 mg/kg). These results suggest that the combined administration of ethanol and anti-alcoholic drugs caused an accumulation of acetaldehyde through inhibition of aldehyde dehydrogenase activity, and that the aversive feeling (WARUYOI and FUTSUKAYOI in Japanese, respectively) induced by accumulation of acetaldehyde resulted in the decreased response rate. It is therefore expected that the discrete shuttle avoidance behavior in mice can be applied for the behavioral investigation of both the disinhibition (alcohol intoxication) and the drunken frenzy (sickness) and/or hangover induced by large amount of ethanol drinking.
(Reprint request should be sent to Hisashi Kuribara)

Key words: Ethanol, Acetaldehyde, Anti-alcoholic drugs, Alcohol intoxication model, Drunken frenzy and/or hangover models, Discrete shuttle avoidance, Mice.

Introduction

The alcohol intoxication (MEITEI or YOI in Japanese) is characterized by the psychological, behavioral and somatic symptoms such as increase in the sensory threshold, prolongation of the response latency to external signal, muscle relaxation, motor impairment, decrease in the cognitive function, disturbance of the memory (amnesia, blackout) etc. caused by the partial inhibition of the neocortex of brain (Rall, 1990). However, the drinkers sometimes have misunderstood the central and peripheral symptoms of drunken frenzy (WARUYOI in Japanese) such as red flush, tachycardia, nausea, vomiting and headache produced by the accumulation of acetaldehyde, an intermediate metabolite of ethanol, as the alcohol intoxication (Wiese et al., 2000; Howland et al., 2008). In addition, the symptoms of hangover (FUTSUKAYOI in Japanese) are similar to those of drunken frenzy, and acetaldehyde is considered to be intimately related to these aversive symptoms of hangover (Sladek, 2003). Acetaldehyde has a central stimulant effect in contrast to the central depressant effect of ethanol (Swift and Davidson, 1998; Wiese et al., 2000).

Ethanol is oxidized to acetaldehyde by the actions of alcohol dehydrogenase (ADH), microsome ethanol oxygenation system (MEOS) and catalase. Acetaldehyde is then oxidized to acetic acid and/or acetyl-CoA by the action of aldehyde dehydrogenase (ALDH), particularly ALDH-E2 type with high activity.

Ca-cyanamide and disulfiram are used as the anti-alcoholic drug for the treatment of the patient of alcohol dependence, because these drugs inhibit the activity of ALDH, and ethanol drinking is followed by the aversive symptoms of drunken frenzy (Ritchie 1970; Rall, 1990).

The mice and/or rats pretreated with Ca-cyanamide or disulfiram show significant decrease in the consumption of ethanol solution of 5-10% (Sinclair and Lindros, 1981; Kuribara et al., 1984). It has also been demonstrated in the rats that these anti-alcoholic drugs could inhibit the stimulant effect of ethanol on the mesolimbic reward system in the brain (Schulteis and Liu, 2006). However, there has been no report of the study which behaviorally assessed the alcohol intoxication and the drunken frenzy and/or hangover at the same time in terms of the operant behavior in mice.

The aim of this experiment was to observe the discrete shuttle avoidance behavior of mice following the single administrations of ethanol and acetaldehyde, and the combined administrations of ethanol + acetaldehyde, ethanol + Ca-cyanamide and ethanol + disulfiram. Following the comparisons of the avoidance behaviors after these drug treatments, the validity of the combined administrations of ethanol + Ca-cyanamide and ethanol + disulfiram was discussed as the drunken frenzy and/or hangover models.

Materials and Methods

Experimental animals

Three groups (10 each) of male mice of ddY strain (SLC Japan, Hamamatsu) were used at 10 weeks of old and weighing 30-35 g at the beginning of the discrete shuttle avoidance test.

Each group of ten mice was kept in Polycarbonate cage of 25 cm (L) X 15 cm (W) X 10 cm (H) with paper bedding (SLC Japan), and the mice were allowed free access to a commercial solid diet (MF: Oriental Yeast, Tokyo) and tap water except during the avoidance test. The conditions of the animal room were controlled (a 12-hr light: 12-hr dark cycle, light on 07:00-19:00 hr, temperature: 24 ± 1˚C, and humidity: 55 ± 5%).

All experimental treatments of animals were carried out in accordance with "*The Guideline for the Animal Experiment*" of the Japanese Pharmacological Society.

Apparatus

The discrete avoidance test was carried out using the shuttle-box (GT-8450), avoidance controlling unit (De CARES GT-M5) and data-recording/printing apparatus (TIDP-10) (O'Hara & Co., Tokyo).

The shuttle-box was made of Acrylic resin and aluminum boards with dimensions of 30(W) X 9(D) X 15(H) cm. Two pairs of infrared beam generator and sensor were horizontally set at an interval of 18 cm in the shuttle box to detect horizontal movement of the mouse. The floor consisted of a stainless steel grid, which was wired to pass an electric current (US: unconditioned stimulus). A speaker for presenting the warning signal of 800 Hz tone (CS: conditioned stimulus) was installed in the center of the ceiling of the chamber.

In this study, two sets of the apparatus for the avoidance test were used, and each set of apparatus could control and record the avoidance behaviors of 5 mice at the same time. The shuttle-boxes were individually kept in sound proof boxes.

Avoidance schedule

In each avoidance session of 1 hr, 120 avoidance trials were held at intervals of 30 sec. The temporal parameters of discrete shuttle avoidance schedule were an intertrial interval of 25 sec and the maximum warning duration of 5 sec. During the warning period, a tone signal of 800 Hz was presented to the mouse as the conditioned stimulus (CS). When the mouse made an avoidance response (movement from one side to the opposite side in the shuttle-box, and cut the two infrared beams) during the warning period for 5 sec, the tone signal stop immediately, and the unconditioned stimulus (US) of electric foot shock (100 V, 0.3 mA, 50 Hz AC) could be avoided. In contrast, the mouse failed to make an avoidance response within 5 sec of the maximum warning period, the electric foot shock was delivered for 0.3 sec to the floor grid of shuttle-box.

The indices of the avoidance behavior were the response rate (frequency of shuttles) and the percent avoidance (avoidance rate: number of avoidance responses/number of avoidance trials). The training of the mice was carried out daily, and the mice attained to show stable response rate and the avoidance rate of higher than 90 % were used for the following drug tests.

Drugs and administration schedules

The drugs used in this experiment were ethanol (Kanto Chemical, Tokyo), acetaldehyde (Kanto Chemical), disulfiram (Nocbin; Mitsubishi Pharma, Osaka) and Ca-cyanamide (Cyanamide Solution; Dojin-Mitsubishi Pharma, Osaka).

These drugs were dissolved or diluted by distilled water, and the concentration of each drug solution was adjusted so that the total volume administered was always constant at 0.1 ml/10 g body weight of the mouse regardless of the drug treatment and the dose. All the drugs were administered per orally.

The avoidance tests were carried out 5 days in a week between 9:00 hr – 16:00 hr, and the avoidance test in each mouse was held at almost the same clock time of day. The stability of the response rate and avoidance rate was checked during the sessions of no-drug administration, and the drug administrations were carried out at intervals of 3 days, generally on Tuesday and Friday. If the baseline response rate or avoidance rate on the day before the drug administration was greater and/or smaller than the limited regions (baseline value ± 10 %), the drug administration was postponed to the next schedule day of the drug administration. Before and after the end of the drug test, distilled water was administered as the control administration. The average values of response rate and avoidance rate at the days before the drug administrations were considered as the baseline levels of the avoidance behavior.

Experiment 1. Administrations of single doses of ethanol and acetaldehyde, and combined doses of ethanol + acetaldehyde

The first group of 10 mice were given ethanol (0.5, 1 and 2 g/kg), acetaldehyde (1, 3 and 10 mg/kg), and ethanol (2 g/kg) + acetaldehyde (1, 3 and 10 mg/kg) in this order immediately before the avoidance test for 1 hr.

Experiment 2. Administrations of combined doses of ethanol + Ca-cyanamide

The second group of 10 mice were administered ethanol (2 g/kg), Ca-cyanamide (1, 3 and 10 mg/kg), and ethanol (2 g/kg) + Ca-cyanamide (1, 3 and 10 mg/kg) in this order. Ethanol and Ca-cyanamide were administered immediately before and 1 hr before, respectively, the avoidance test.

Experiment 3. Administrations of combined doses of ethanol + disulfiram

The third group of 10 mice were administered ethanol (2 g/kg), disulfiram (3, 10 and 30 mg/kg), and ethanol (2 g/kg) + disulfiram (3, 10 and 30 mg/kg) in this order. Ethanol and disulfiram were administered immediately before and 1 hr before, respectively, the avoidance test.

Statistical analysis

The mean values of 1-hr overall response rates and avoidance rates in each group of mice were compared using Student' s t-test. When p value was less than 0.05, it was considered to be significantly different.

Results

Experiment 1. Administrations of single doses of ethanol and acetaldehyde, and combined doses of ethanol + acetaldehyde

As shown in Table 1, the administration of distilled water (control) did not change the avoidance behavior, though ethanol increased the response rate in a dose-dependent manner without marked change in the avoidance rate. The response rate following 2 g/kg ethanol was significantly higher than the control value.

On the other hand, acetaldehyde dose-dependently decreased the response rate, and the rate following 10 mg/kg acetaldehyde was significantly lower than the control value. The response rate tended to be slightly decreased by the administration of acetaldehyde, though the change did not attain to the significant level.

The combined administrations of ethanol + acetaldehyde decreased the response rate in a dose-dependent manner of acetaldehyde. The response rate following administration of ethanol + acetaldehyde (10 mg/kg) was significantly lower than not only the control value but also the value following the single dose of ethanol, showing a complete blockade of the ethanol-induced increase in the response rate. There was no significant change in the avoidance rate after the combined administrations of ethanol + acetaldehyde.

The acetaldehyde-induced decrease in the response rate tended to be alleviated by ethanol, though the change did not attain to the significant level.

Experiment 2. Administrations of combined doses of ethanol + Ca-cyanamide

As shown in Table 2, the single administration of Ca-cyanamide (1-10 mg/kg) did not change the response rate or avoidance rate at any doses. Similar to the results of Exp-1, ethanol increased the response rate.

Table 1. Effects of the single administration of ethanol and acetaldehyde, and the combined administration of ethanol + acetaldehyde on the discrete shuttle avoidance behavior in mice.

		Response rate (N/min)	Avoidance rate (%)
Baseline (No treatment)		2.88 ± 0.24	97.7 ± 0.6
Control (Tap water)		2.83 ± 0.21	97.5 ± 0.5
Ethanol	0.5 g/kg	2.79 ± 0.22	98.3 ± 0.3
	1	3.09 ± 0.13	97.4 ± 0.4
	2	3.28 ± 0.17*	98.7 ± 0.3
Acetaldehyde	1 mg/kg	2.91 ± 0.19	97.6 ± 0.5
	3	2.54 ± 0.26	95.9 ± 0.9
	10	2.01 ± 0.25*	95.2 ± 1.3
Ethanol 2 g/kg + Acetaldehyde	1 mg/kg	3.30 ± 0.29	98.0 ± 0.4
	3 mg/kg	2.66 ± 0.24	96.9 ± 0.7
	10 mg/kg	2.31 ± 0.29*,$	96.6 ± 0.9

All drug administrations were carried out per orally immediately before the avoidance test for 1 hr.
*: $p<0.05$ vs. the control value following the administration of tap water.
$: $p<0.05$ vs. the value following the administration of the single dose of ethanol (2 g/kg).

Table 2. Effects of the combined administration of ethanol + Ca-cyanamide on the discrete shuttle avoidance behavior in mice.

		Response rate (N/min)	Avoidance rate (%)
Baseline (No treatment)		2.87 ± 0.21	98.3 ± 0.4
Control (Tap water)		2.79 ± 0.26	97.1 ± 0.5
Ca-cyanamide	1 mg/kg	2.90 ± 0.24	98.4 ± 0.3
	3	2.87 ± 0.22	97.9 ± 0.5
	10	2.84 ± 0.18	98.8 ± 0.6
Ethanol 2 g/kg		3.38 ± 0.17*	98.7 ± 0.3
Ethanol + Ca-cyanamide	1 mg/kg	2.72 ± 0.31	97.9 ± 0.5
	3	2.55 ± 0.42$	97.3 ± 0.4
	10	2.36 ± 0.07*,$	95.4 ± 1.1

All the drug administrations were carried out per orally. Ethanol and Ca-cyanamide were administered immediately and 1 hr, respectively, before the avoidance test for 1 hr.
*: $p<0.05$ vs. the control value following the administration of tap water.
$: $p<0.05$ vs. the value following the administration of the single dose of ethanol (2 g/kg).

The combined administration of ethanol + Ca-cyanamide resulted in a significant decrease in the response rate. The response rates following ethanol + Ca-cyanamide (3 and 10 mg/kg) were significantly lower than that following ethanol alone, and the value following ethanol + Ca-cyanamide (10 mg/kg) was significantly lower than the control value following distilled water.

There was no significant change in the avoidance rate after the any drug treatments.

Experiment 3. Administrations of combined doses of ethanol + disulfiram

As shown in Table 3, the single administration of disulfiram did not produce any significant change in both the

Table 3. Effects of the combined administration of ethanol + disulfiram on the discrete shuttle avoidance behavior in mice.

		Response rate (N/min)	Avoidance rate (%)
Basdeline (No treatmnet)		2.99 ± 0.23	98.1 ± 0.5
Control (Tap water)		2.93 ± 0.22	98.7 ± 0.3
Disulfiram	3 mg/kg	2.90 ± 0.23	98.5 ± 0.2
	10	2.91 ± 0.20	97.8 ± 0.4
	30	2.94 ± 0.19	98.5 ± 0.3
Ethanol 2 g/kg		3.45 ± 0.19*	99.0 ± 0.2
Ethanol + Disulfiram	3 mg/kg	2.96 ± 0.35	97.2 ± 0.8
	10	2.52 ± 0.34$	97.5 ± 0.6
	30	2.18 ± 0.16*,$	97.1 ± 1.0

All the drug administrations were carried out per orally. Ethanol and disulfiram were administered immediately and 1 hr, respectively, before the avoidance test for 1 hr.
*: $p<0.05$ vs. the control value following the administration of tap water.
$: $p<0.05$ vs. the value following the administration of the single dose of ethanol (2 g/kg).

response and avoidance rates. However, the ethanol-induced increase in the response rate was significantly inhibited by disulfiram (10 and 30 mg/kg). Moreover, the response rate following the combied administration of ethanol + disulfiram (30 mg/kg) was significantly lower than the control value.

There was no significant change in the response rate following any drug treatments.

Gross observation

Following the single administration of ethanol, the mice showed mild ataxia. The single administration of acetaldehyde, and the combined administration of ethanol + acetaldehyde, ethanol + Ca-cyanamide and ethanol + disulfiram caused slight redness of the nose of mouse.

Discussion

Ethanol is classified into general central depressant, and it inhibits the functions of the central nervous system in the order of neocortex, limbic system, mesolimbic system, spinal cord, and brain stem dependent on the dose (Rall, 1990). The inhibition of the neocortex function results in the decrease in the cognition, thoughts, learning and memory, sensory and motor functions. A partial inhibition of neocortex function, particularly prefrontal cortex function, sometimes blocks the inhibitory action of prefrontal cortex to the limbic system, and results in the disinhibition which is characterized by the behavioral and psychic symptoms of exciting with decreased cognitive, thoughts, sensory and motor functions.

In this study, 2 g/kg ethanol significantly increased the response rate, i.e., increase in the motor activity and decrease in the accuracy of response to the warning signal. However, ethanol did not change the avoidance rate at any doses. A gross observation revealed that the mice given ethanol showed muscle relaxation and mild ataxia in a dose-dependent manner. These behavioral changes may reflect the disinhibitory symptoms which are caused by the ethanol-caused inhibition of neocortex function. It is also considered that ethanol, at 2 g/kg, may not significantly disturb the cognitive, sensory, or learning and memory function.

Throughout Exp-1 to Exp-3, the baseline levels of response and avoidance rates as well the control levels of these indices following administration of tap water were almost the same among three groups of mice. Furthermore, the avoidance and response rates following administration of 2 g/kg ethanol were almost identical among groups of mice. These results indicate that baseline level of the discrete shuttle avoidance in the mice was stable for a long period, and that the increased response rate caused by etha-

nol is reproducible. It is there considered that the ethanol-induced behavioral change can be used as a model of disinhibition, one of the symptoms of alcohol intoxication.

Acetaldehyde is an intermediate metabolite of ethanol. Acetaldehyde has a central stimulant effect, and this compound is considered to be a main causable compound of drunken frenzy and/or hangover characterized by the symptoms such as headache, nausea, vomiting, depression (Ritchie, 1970; Rall, 1990). These aversive symptoms of drunken frenzy and/or hangover may frequently induce a decrease in willing of activity or motivation (Wiese et al., 2000; Howland et al., 2008). Because acetaldehyde is produced by the oxidation (dehydrogenation) of ethanol after the drinking, it is important to assess the combined effects of ethanol and acetaldehyde when the drunken frenzy and/or hangover are investigated behaviorally.

Experiment 1 of this study demonstrated inhibition of the avoidance response following both the single administration of acetaldehyde and the combined administration of ethanol and acetaldehyde. Although there was no significant difference, the decrease in the response rate following the administration of acetaldehyde alone was tended to be greater than that following the combined administration of ethanol + acetaldehyde. These results indicate that acetaldehyde is the main causable compound of drunken frenzy and/or hangover. It is also suggested that ethanol acts to partially alleviate the aversive effect of acetaldehyde, indicating a partial effectiveness of MUKAEZAKE (taking a hair of the dog) for hangover.

Both Ca-cyanamide and disulfiram, anti-alcoholic drugs, block the activity of ALDH, particularly ALDH-E2 with high activity. Ethanol drinking is followed by aversive symptoms of drunken frenzy and/or hangover caused by accumulation of acetaldehyde when drinker is pretreated with one of Ca-cyanamide and disulfiram (Ritchie, 1970; Rall, 1990).

Based on these preclinical and clinical results, the combined effects of ethanol + Ca-cyanamide and ethanol + disulfiram were assessed in Experiment 2 and Experiment 3, respectively. The doses of Ca-cyanamide and disulfiram were determined according to the guides for clinical use of these drugs.

The single treatment with neither Ca-cyanamide nor disulfiram induced significant change in the avoidance behavior in mice. However, the combined treatments with ethanol + Ca-cyanamide and ethanol + disulfiram produced significant decrease in the response rate without marked change in the avoidance rate. Such changes in the avoidance behavior were similar to those following the single administration of acetaldehyde, and combined administration of ethanol + acetaldehyde. In this study, the measurement of the blood concentrations of ethanol and acetaldehyde was not carried out. However, according to the similarity of these changes in the discrete shuttle avoidance behavior in mice, it is considered that the mice fell into unpleasantness and showed decrease in the response rate under the discrete shuttle avoidance situation which was induced by the accumulation of acetaldehyde following the combined administration of ethanol + Ca-cyanamide and ethanol + disulfiram. Schulteis and Liu (2006) observed significant decreases in the acute behavioral activity and brain reward potential of ethanol dependent on the increase in blood acetaldehyde concentration in rats.

The discrete shuttle avoidance behavior in mice is easy to conduct, and a stable behavioral baseline level can be maintained for a long period of 6 months (Kuribara and Tadokoro, 1986a,b). In addition, the drug effects observed in this study were highly reproducible. It is therefore considered that the present experimental procedure of the discrete shuttle avoidance in mice can be applied for investigation of the drunken frenzy and/or hangover caused as well as the disinhibition (intoxication) by ethanol.

Conclusion

In terms of the discrete shuttle avoidance in mice, the single treatment with ethanol increased the response rate. Although the single treatment with Ca-cyanamide or disulfiram, anti-alcoholic drugs, did not change the avoidance behavior, the combined administration of ethanol + Ca-cyanamide and ethanol + disulfiram produced a significant decrease in the response rate. Such behavioral changes were similar to those of treatment with the single administrations of acetaldehyde and ethanol + acetaldehyde.

These results indicate that the discrete shuttle avoidance may be applied for the behavioral investigation of the disinhibition (alcohol intoxication) as well as the drunken frenzy and/or hangover.

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マウスのシャトル型非連続回避反応からみたアルコール酩酊と悪酔い・二日酔いモデル

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抄録： マウスのシャトル型非連続回避反応を指標にして、ethanolおよびacetaldehydeの単独投与、ethanolとacetaldehydeの併用投与、さらにethanolと抗酒薬Ca-cyanamideまたはdisulfiramの併用投与後の回避反応の変化を観察した。反応率は、ethanol（2 g/kg p.o.）の単独投与によって増加し（脱抑制）、acetaldehyde（1-10 mg/kg p.o.）によって低下した。一方、Ca-cyanamide（1-10 mg/kg p.o.）およびdisulfiram（3-30 mg/kg p.o.）はaldehyde dehydrogenase活性を阻害するが、それぞれの単独投与は回避反応に影響を及ぼさなかった。しかし、ethanolとCa-cyanamide（3-10 mg/kg）あるいはdisulfiram（10-30 mg/kg）を併用すると、反応率は水道水投与の対照値より有意に低下した。これら回避反応の変化は、ethanolと抗酒薬の併用投与時に、ethanolの中間代謝産物であるacetaldehydeの蓄積が起こって嫌悪感が発現し、反応率の低下が引き起こされたことを示唆しており、悪酔や二日酔いの症状と共通点がみられる。本実験結果は、今回用いたマウスのシャトル型非連続回避反応における実験条件は、飲酒による脱抑制状態（酩酊）のみならず、悪酔いや二日酔いに関する行動科学的検討に利用できる可能性を示唆している。
（別刷請求先：栗原　久）

キーワード： Ethanol、Acetaldehyde、抗酒薬、アルコール酩酊、悪酔い・二日酔い、シャトル型非連続回避反応、マウス