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Alleviation of the Drunken Frenzy/Hangover-like Symptoms by SJS, a Japanese Herbal Medicine, in Mice

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Abstract: A Japanese herbal medicine SJS is made of hot water extract of Chishimazasa leaves (*Sasa kurilensis (Ruprecht)* Makino et Shibata: SS), and ethanol extracts of Japanese red pine leaves (*Pinus densiflora* Siebold & Zucc.: RP) and Ginseng roots (*Panax ginseng* C.A. Meyer: PG). The aim of this study was to assess the modification by SJS of the intoxication and drunken frenzy models in terms of discrete shuttle avoidance behavior in mice. The response rate (number of shuttles) was increased by ethanol (2 g/kg p.o.), but decreased by the combined administration of ethanol + Ca-cyanamide (10 mg/kg p.o.), an anti-alcoholic drug. Although SJS, freely given 10% solution for 4 weeks and longer, or acutely administered at doses of 10 and 20 ml/kg p.o., did not change the ethanol effect, it significantly recovered the decreased response rate by ethanol + Ca-cyanamide. A similar significant recovery of response rate was demonstrated by PR and SS, but not by PG. These results suggest that SJS alleviates the ethanol-induced drunken frenzy and/or hangover without significant effect on the ethanol intoxication (disinhibition).
(Reprint request should be sent to Hisashi Kuribara)

Key words: SJS, A Japanese herbal medicine, Ethanol, Drunken frenzy model, Discrete shuttle avoidance, Mice

Introduction

Ethanol is mainly metabolized to acetaldehyde through mainly two routes in the liver, alcohol dehydrogenase (ADH) and microsone ethanol oxidation system (MEOS), and somatic catalase in the whole body. 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, and finally to water and carbon dioxide.

The alcohol intoxication (YOI or MEITEI) is characterized by psychological, behavioral and somatic symptoms such as increase in the sensory threshold, prolongation of the response latency to external signal, muscle relaxation, motor impairment and ataxia, decrease in the cognitive function, disturbance of the memory (amnesia, blackout) etc. caused by a partial inhibition of the neocortex of brain (Rall, 1990). However, the drinkers sometimes misregard the central and peripheral symptoms of drunken frenzy (WARUYOI) such as 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) are similar to those of drunken frenzy, and acetaldehyde is considered to be intimately related to these aversive symptoms (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).

Ca-cyanamide is applied as an anti-alcoholic drug for treatment of the patient of alcohol dependence, because this drug inhibits 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 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 rats that these anti-alcoholic drugs could inhibit the stimulant effect of ethanol on the mesolimbic reward system in brain (Schulteis and Liu, 2006).

Furthermore, Kuribara (2011a) suggested from the changes in discrete shuttle avoidance response in mice that the increase in response rate following single administration of ethanol can be used as an alcohol intoxication (disinhibition) model, and that the significant decrease in response rate following administration of ethanol + Ca-cyanamanide and ethanol + disulfiram, anti-alcoholic drugs, can be applied as drunken frenzy and/or hangover model.

SJS (WMI, Tokyo), a Japanese herbal liquid medicine for oral intake, is composed of a water extract of Chishimazasa leaves (*Sasa kurilensis (Ruprecht)* Makino et Shibata: SS), and ethanol extracts of Japanese red pine leaves (*Pinus densiflora* Siebold & Zucc.: RP) and Ginseng roots (*Panax ginseng* C.A. Meyer: PG) in the ratio of 8:1:1.

The clinical case reports showed that the long-term consumption of SJS was effective for amelioration of various symptoms including fatigue, vegetative dystonia, depression, anxiety and sleeping disturbance (WMI, 1996a, 1996b; Ichikawa et al., 1998). In addition, some clinical experiences suggested that SJS intake prior to ethanol drinking lessened the symptoms of alcohol intoxication (Personal report from WMI). Although Murohashi et al. (2000) reported a protective effect of SS-containing solution on the liver function, there has been no report of SJS related to the ethanol-induced symptoms which can be classified into two types, i.e., ethanol intoxication caused by ethanol itself, and drunken frenzy and/or hangover caused by acetaldehyde, an intermediate metabolite of ethanol.

The aim of this experiment was to observe the effects of SJS and its constituents, SS, RP and PG, on the discrete shuttle avoidance behavior of mice following the single administrations of ethanol, and the combined administration of ethanol + Ca-cyanamide, an anti-alcoholic drug.

Materials and Methods

Experimental animals

Six groups (10 each) of male mice of ddY strain (SLC Japan, Hamamatsu) were used at 8 weeks of age and weighing 30-35 g at the beginning of discrete shuttle avoidance test.

Each group of ten mice was kept in a Polycarbonate cage of 25 cm (L) × 15 cm (W) × 10 cm (H) with paper bedding (SLC Japan), and these 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 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.

Avoidance test

The apparatus and procedures of the discrete shuttle avoidance test were almost the same as those used in the previous study (Kuribara, 2011a).

Briefly, the discrete avoidance test was carried out using a set of shuttle-boxes of 30(W) × 9(D) × 15(H) cm (GT-8450), avoidance controlling unit (De CARES GT-M5) and data-recording/printing apparatus (TIDP-10) (O'Hara & Co., Tokyo). In this study, two sets of the apparatus for 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.

In each avoidance session for 1 hr, 120 avoidance trials were held at intervals of 30 sec. The temporal parameters of discrete shuttle avoidance schedule were an intertribal interval of 25 sec and a 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, 50Hz AC) could be avoided. In contrast, when the mouse failed to make an avoidance response, an electric foot shock was delivered for 0.3 sec to the floor grid of shuttle-box.

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 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 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 values (baseline value ± 10%), the drug administration was

postponed to the next schedule day of 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 avoidance behavior.

The indices of avoidance response 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 according to the standard procedure (Kuribara and Tadokoro, 1986a, 1986b) was carried out daily, and the mice attained to show stable response rate and avoidance rate of higher than 90% were used for the following drug tests.

Drugs and administration schedules

In 100 ml of SJS, 80 ml of water extract of Chishimasasa leaves 317 g (SS), 0.3 g of ethanol extract of Japanese red pine leaves 3.9 g (RP), and 0.18 g of ethanol extract of dry roots of Panax ginseng 0.97 g (PG) are contained. SJS and its constituents SS, RP and PG were obtained from WMI (Tokyo).

Ethanol (Kanto Chemical, Tokyo) and Ca-cyanamide (Cyanamide Solution; Dojin-Mitsubishi Pharma, Osaka) were purchased. Ethanol and Ca-cyanamide were dissolved or diluted, respectively, by distilled water, and the concentration of each drug solution was adjusted so that the total volume administered (p.o.) was always constant at 0.1 ml/10 g body weight of the mouse regardless of the drug treatment and the dose.

Experiment 1. Ethanol administration to the mice freely consumed SJS

Two groups of 10 mice each were used in the Exp-1. The one group of mice were freely given tap water, and another group of mice SJS (10% solution) for the substitution of tap water. During the period of consumption of tap water and SJS, the avoidance responses of individual mice were observed once a day for 4 weeks.

Four weeks after the start of SJS consumption, the mice were administered ethanol (1 and 2 g/kg) at intervals of 3-4 days immediately before start of the avoidance test, and the observation of avoidance response was carried out for 1 hr. The response and avoidance rates on the days before drug administration were used for calculation of the baseline avoidance behavior. Before and after the ethanol treatments, tap water was administered as the control, and the mean values of response and avoidance rates were used as the control values.

Experiment 2. Combined administration of ethanol + SJS

Group of 10 mice (freely intake tap water) was administered ethanol (2 g/kg), and combined administration of ethanol + SJS (5, 10 and 20 ml/kg) in this order at intervals of 3-4 days. SJS and ethanol was given to the mice 1 hr and immediately, respectively, before the avoidance test for 1 hr. Before and after the drug tests, tap water was administered as the control.

Experiment 3. Combined administrations of ethanol + Ca-cyanamide + SJS or its constituents

Group of 10 mice (freely intake tap water) were administered Ca-cyanamide (10 mg/kg), SJS (10 and 20 ml/kg) and its constituents (SS: 16 ml/kg; RP: 0.06 g/kg; PG: 0.036 g/kg), combinations of two drugs; ethanol + Ca-cyanamide, ethanol + SJS and its constituents, and combinations of three drugs; ethanol + Ca-cyanamide + SJS and its constituents in this order at intervals of 3-4 days.

Ca-cyanamide and SJS were given 1 hr before, and ethanol was given immediately before the avoidance test for 1 hr. Before and after the drug tests of single administrations, combined administrations of two drugs and combined administration of three drugs, tap water was administered as the control.

Statistical analyses

The mean response rate (shuttles/min) and avoidance rate (number of avoidance response/number of avoidance trials were calculated, and the values were analyzed by ANOVA, and compared using Bonfferone correction. When p value was less than 0.05, it was considered to be significantly different.

Results

Experiment 1. Ethanol administration to the mice freely consumed SJS

Table 1 shows the avoidance behaviors following administration of ethanol to the mice freely consumed SJS for longer than 4 weeks.

The baseline response rate was slightly higher in the SJS group than that of the water group, though the difference was not significant.

Ethanol significantly increased the response rate at 1 g/kg in the SJS group, and 2 g/kg in both the water and SJS groups. There was no significant change in the response rate following ethanol administration in either water or SJS group.

Experiment 2. Combined administration of ethanol + SJS

As shown in Table 2, ethanol (2 g/kg) significantly increased the response rate. The treatment with SJS did not modify the ethanol-induced increase in the response rate. There was no significant change in the avoidance rate following any treatments.

Experiment 3. Combined administrations of ethanol + Ca-cyanamide + SJS or its constituents

As shown in Table 3, not only the single administration of SJS, its constituents (SS, RP or PG) or Ca-cyanamaide but also the combined treatment with Ca-cyanamide + SJS, SS, RP or PG did not change the avoidance behavior.

The single administration of ethanol significantly increased the response rate. However, the combined administration of ethanol + Ca-cyanamide caused a significant decrease in the response rate, and the effect was blocked by SJS (20 ml/kg), SS (16 ml/kg) and RP (0.06 g/kg). The effect of PG (0.036 g/kg) did not attain to the significant level. The response rate did not change significantly following any treatments.

Table 1. Effects of ethanol on the discrete shuttle avoidance response in the mice which have consumed SJS solution for longer than 4 weeks.

	Response rate (N/min)	Avoidance rate (%)
Intake of tap water		
Baseline (No treatment)	2.88 ± 0.24	97.7 ± 0.6
Control (Tap water)	2.78 ± 0.21	98.1 ± 0.4
Ethanol 1 g/kg	2.66 ± 0.13	97.4 ± 0.4
2 g/kg	3.28 ± 0.17*	98.7 ± 0.3
SJS (10%solution)		
Baseline (No treatment)	2.62 ± 0.09	97.0 ± 1.4
Control (Tap water)	2.58 ± 0.08	96.7 ± 1.1
Ethanol 1 g/kg	3.10 ± 0.20*	96.8 ± 0.5
2 g/kg	3.38 ± 0.16*	96.3 ± 1.3

Intake of SJS solution (10%) was longer than 4 weeks

*: $p<0.05$ vs. the control value (administration of tap water).

Table 2. Effects of the ethanol + SJS on the discrete shuttle avoidance response in mice.

	Response rate (N/min)	Avoidance rate (%)
Baseline (No treatment)	2.63 ± 0.13	99.0 ± 0.2
Control (Tap water)	2.57 ± 0.11	97.5 ± 0.6
Ethanol 2 g/kg	3.19 ± 0.15*	97.7 ± 0.3
SJS 5 ml/kg + ethanol 2 g/kg	3.03 ± 0.24	98.1 ± 0.5
10 ml/kg + 2 g/kg	3.34 ± 0.20*	97.6 ± 0.6
20 ml/kg + 2 g/kg	3.41 ± 0.26*	97.2 ± 0.8

*: $p<0.05$ vs. the control value.

Results of gross observation

The mice given ethanol exhibited mild ataxia, and this symptom did not modified by Ca-cyanamide, SJS or its constituents. The single treatment with Ca-cyanamide, SJS, SS, RP or PG did not induce any significant change in the behavioral or somatic condition. The combined treatment with ethanol + Ca-cyanamaide produced slight redness of nose, and this symptom was tended to reduce by the treatment with SJS, SS and RP.

Discussion

Ethanol is classified into general central depressant, and it inhibits the functions of central nervous system in an order of neocortex, limbic system, mesolimbic system, spiral cord, and brain stem dependent on the dose (Rall, 1990). The inhibition of the neocortex function results in the decrease in cognition, thoughts, learning and memory, sensory and motor functions. A partial inhibition of neocortex function, particularly prefrontal cortex, sometimes

Table 3. Effects of SJS and its constituents (SS, RP and PG) on the decreased response rate caused by the combined administration of ethanol + Ca-cyanamide.

	Response rate (N/min)	Avoidance rate (%)
Baseline (No treatment)	2.87 ± 0.21	98.3 ± 0.4
Control (Tap water)	2.69 ± 0.20	97.9 ± 0.5
SJS 10 ml/kg	2.55 ± 0.14	98.8 ± 0.3
20 ml/kg	2.52 ± 0.14	97.4 ± 1.0
SS 16 ml/kg	2.75 ± 0.18	98.1 ± 0.4
RP 0.06 g/kg	2.83 ± 0.19	98.4 ± 0.5
PG 0.036 g/kg	2.88 ± 0.24	98.5 ± 0.4
Ca-cyanamide 10 mg/kg	2.84 ± 0.18	98.8 ± 0.6
SJS 10 ml/kg + Ca-cyanamide	2.95 ± 0.32	97.9 ± 0.7
20 ml/kg + Ca-cyanamide	2.74 ± 0.23	98.3 ± 0.4
SS 16 ml/kg + Ca-cyanamide	2.51 ± 0.16	98.2 ± 0.4
RP 0.06 g/kg + Ca-cyanamide	2.60 ± 0.13	97.7 ± 0.4
PG 0.036 g/kg+ Ca-cyanamide	2.63 ± 0.11	98.0 ± 0.4
Ethanol 2 g/kg	3.28 ± 0.17*	98.7 ± 0.3
Ethanol + Ca-cyanamide 10 mg/kg	2.36 ± 0.07*,$	95.4 ± 1.1
SJS 10 ml/kg + ethanol + Ca-cyanamide	2.50 ± 0.10	97.3 ± 1.0
20 ml/kg + ethanol + Ca-cyanamide	2.77 ± 0.15#	97.6 ± 0.7
SS 16 ml/kg + ethanol + Ca-cyanamide	2.62 ± 0.09#	97.7 ± 0.5
RP 0.06 g/kg + ethanol + Ca-cyanamide	2.78 ± 0.18#	98.1 ± 0.4
PG 0.036g/kg + ethanol + Ca-cyanamide	2.44 ± 0.21	97.6 ± 0.7

*: $p<0.05$ vs. the control.
$: $p<0.05$ vs. the single administration of ethanol.
#: $p<0.05$ vs. the combined administration of ethanol + Ca-cyanamide.

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.

Acetaldehyde, an intermediate metabolite of ethanol with a central stimulant effect is considered to be a main causable compound of drunken frenzy and hangover characterized by the symptoms such as headache, nausea, vomiting, depression (Ritchie, 1970; Rall, 1990). Such aversive symptoms of drunken frenzy and hangover may frequently induce a decrease in willing of activity or motivation (Wiese et al., 2000; Sladek, 2003; Schulteis and Liu, 2006; Howland et al., 2008) as well as desire for alcohol drinking (Sinclair and Lindros, 1981; Kuribara et al., 1984).

Although the drunken frenzy and hangover are considered to be physiologically symptoms which can protect the alcohol dependence, these symptoms are uncomfortable for the drinker. Therefore, many treatments have been tried to ameliorate and/or protect the symptoms related to drunken frenzy and/or hangover (Paulsen, 1961; Sproonce et al., 1974; Ylikahri et al., 1976; Kaivola et al., 1983; Bogin et al., 1986; Pittler et al., 2003; Pittler et al., 2005; Hung et al., 2006; McGregor et al., 2007). The toxicity of acetaldehyde as well as the adverse effect of induction of aldehyde dehydrogenase have been reported in relation to the increase in risk of cancer and damage of liver function (Xiao et al., 1996; Kim et al., 2003). Under these circumstances, appropriate medical treatment has been looked for alleviation of symptoms of the drunken frenzy and hangover.

Ca-cyanamide and disulfuram, anti-alcoholic drugs, have inhibitory action on aldehyde dehydrogenase, and aversive symptoms such as headache, nausea vomiting etc. are produced by the accumulation of acetaldehyde when these drugs are pretreated prior to the alcohol drinking (Ritchie, 1970). Kuribara (2011b) reported in terms of the discrete avoidance response in mice that the increased response rate following administration of ethanol, indicating the disinhibitory action of ethanol, was reduced by the pretreatment with Ca-cyanamide or disulfiram, and suggested that such behavioral change was one of the behavioral models of drunken frenzy and/or hangover. According to these basic results, in this study, the author assessed the modification by SJS and its constituents, SS, RP and PG, of the avoidance response following the single administration of ethanol alone and the combined administration of ethanol (2 g/kg) and Ca-cyanamide (10 mg/kg).

The decrease in response rate caused by the combined administration of Ca-cyanamide + ethanol was inhibited by the free consumption of SJS solution (10%) for longer than 4 weeks, suggesting that SJS is effective for improvement or protection of symptoms related to drunken frenzy/hangover. Although the mechanism of effectiveness was not investigated in this study, long-term consumption of SJS is reported to improve the liver function (Murohashi et al., 2000), which may result in an increase in the metabolism of acetaldehyde. It is also possible to consider as a mechanism that some constituents of SJS pharmacologically antagonize the effect of acetaldehyde.

On the other hand, the single treatment with SJS or the constituents of SJS, (SS, RP or PG) did not change the avoidance response, or modified the increased response rate caused by ethanol. These results indicate that the central effect of SJS is very weak, and that SJS may not affect the central depressive effect of ethanol. It is therefore emphasized that the amelioration by SJS of decreased response rate following the combined administration of Ca-cyanamide + ethanol reflects the SJS-induced acceleration of metabolism of acetaldehyde. However, further studies including the measurements of blood ethanol and acetaldehyde concentrations, activities of ADH, MEOS and ALDH are required to elucidate the mechanisms of action of SJS.

The effects similar to SJS were observed in the constituents of SJS. The effect was comparatively stronger in RP. Although the effectiveness was weaker than that of RP, SS, but not PG, also showed a significant protective effect. These results suggest that the protection of decreased response rate caused by the combined administration of Ca-cyanamide + ethanol is mainly caused by RP, and that SS and probably PG act to enhance the effectiveness of RP.

The analysis of amino acids of SJS and its constituents showed that ornitine, glucuronic acid, pantotenic acid and cystein, which have been considered to have protective action on liver, are contained in SJS (Kuribara, 2011b). The determination of the active compound(s) and the assessment of the role of active compound will be shown near future. However, the present results indicate that SJS may has a protective action on the drunken frenzy/and hangover without significant modification of ethanol intoxication.

Conclusion

The effects of Japanese herbal medicine SJS on alcohol intoxication and drunken frenzy/hangover were behaviorally assessed in terms of the discrete shuttle avoidance response in mice. Although ethanol increased the response rate, the combined treatment with Ca-cyanamide (10 mg/kg p.o.) + ethanol (2 g/kg p.o.) caused significant decrease in the response rate. Ca-cyanamide + ethanol induced decrease in the response rate was protected by SJS (free intake of 10% solution for longer than 4 weeks, and acute treatment at 10 and 20 ml/kg p.o.). Among the constituents of SJS, RP (2 ml/kg p.o.) strongly and SS (16 ml/kg p.o.) weakly but significantly protected the effect of Ca-cyanamade + ethanol. The single treatment with SJS, SS, RP or PG did not change the avoidance response, or the ethanol-induced increase in the response rate.

These results suggests that SJS may reduce the symptoms of drunken frenzy/hangover (WARUYOI or FUTSUKAYOI) without modify the symptoms ethanol intoxication (YOI or MEITEI).

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マウスの悪酔い／二日酔い様症状に及ぼす生薬製剤SJSの改善効果

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抄録： 生薬製剤 SJS は、チシマザサ葉の温水抽出エキス（SS）、アカマツ葉の ethanol 抽出エキス（RP）およびニンジン根の ethanol 抽出エキス（PG）からなる内服用液剤である。本研究では、飲酒による酩酊および悪酔い状態に及ぼす SJS の効果を評価する目的で、マウスのシャトル型非連続回避反応を指標に検討した。Ethanol（2 g/kg p.o.）を単独投与すると反応率は増加したが、ethanol と抗酒薬 Ca-cyanamide（10 mg/kg p.o.）を併用投与すると、ベースラインレベルより有意に低下した。この反応率低下は、SJS（10％液）の 4 週間自由摂取、あるいは SJS（10, 20 ml/kg p.o.）の併用投与によって有意に軽減された。また、SJS の構成生薬では、SS（16 ml/kg p.o.）および RP（2 ml/kg p.o.）が有効性を示したが、PG（2 ml/kg p.o.）の効果は軽微であった。一方、SJS の 4 週間自由摂取、および SJS、SS、RP、PG の単独投与はいずれも回避反応に有意の変化を引き起こさず、ethanol による反応率増加にも影響を及ぼさなかった。これらの結果は、SJS は、ethanol によって引き起こされる「酔い＝脱抑制」に対してほとんど影響しないが、ethanol の中間代謝物である acetaldehyde の蓄積に起因する「悪酔い」や「二日酔い」を軽減する可能性を示唆している。
（別刷請求先：栗原　久）

キーワード： 生薬製剤 SJS、Ethanol、抗酒薬 Ca-cyanamide、悪酔いモデル、シャトル型非連続回避反応、マウス