ALCOHOL

Brief communication

Effects of alcohol hangover on cytokine production in healthy subjects

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Abstract

A hangover is the syndrome of physical and mental symptoms that occurs 8 to 16 h after alcohol consumption with a zero level of alcohol. The aim of the current study was to investigate the effects of the alcohol hangover on cytokine production in healthy subjects. The hangover state was defined as 13 h after drinking 1.5 g/kg of alcohol (blood alcohol level = 0). A venous blood sample was taken from 20 healthy adult men before consumption of alcohol and during the hangover state. Peripheral blood mononuclear cells were separated and stimulated with phytohemagglutinin. An enzyme-linked immunosorbent assay was used to measure the production of the following cytokines: interleukin (IL)-1β, IL-4, IL-6, IL-10, IL-12, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). We found that the concentrations of IL-10, IL-12, and IFN-γ were significantly increased during the hangover state compared with the concentrations in normal conditions. These results support the suggestion that the dysregulated cytokine pathway (IL-10, IL-12, and IFN-γ) is associated with the symptoms of hangovers. © 2003 Elsevier Inc. All rights reserved.

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1. Introduction

Hangovers rarely occur when the blood alcohol level is close to zero, as well as rarely occur until several hours after drinking of alcohol (Swift & Davidson, 1998; Wiese et al., 2000). Social drinkers complain of various discomforting conditions related to a hangover on the day after drinking alcohol. Harburg et al. (1993) reported that 75% of people who drank alcohol experienced a hangover once or more. The socioeconomic impact of a hangover is also prominent, because a hangover results in a decrease in work productivity and an increase in accident rates (Stockwell, 1998).

A hangover is defined as the presence of at least two symptoms, including headache, poor sense of overall well-being, diarrhea, anorexia, tremulousness, fatigue, and nausea, after

complete metabolism of alcohol after its consumption, with sufficient severity to disrupt the performance of daily tasks and responsibilities (Wiese et al., 2000). In an attempt to explain these physiologic changes during the hangover state, an imbalance in the immune system has been proposed. In particular, nausea, headache, diarrhea, and fatigue during a hangover are thought to be related to changes in the immune system. Thromboxane B_2 levels have been shown to increase during an experimentally induced hangover (Kangasaho et al., 1982). In addition, the prostaglandin inhibitor tolfenamic acid is effective for preventing these hangover symptoms (Kaivola et al., 1983).

To determine the association between hangovers and immune function, we experimentally induced hangovers for healthy subjects and compared the production of cytokines by peripheral blood mononuclear cells (PBMCs) during the hangover state with that in normal (control) conditions.

2. Methods

2.1. Subjects

Twenty, healthy, nonsmoking men with a history of drinking of alcohol and hangover after drinking and a Short

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Michigan Alcoholism Screening Test (SMAST) (Selzer et al., 1975) score of less than 2 were enrolled in the study. The subjects were not receiving any medications; specifically, aspirin, nonsteroidal anti-inflammatory agents, vitamin B_6 supplements, herbal medications, beta-blockers, steroids, and thyroid replacement therapy. They were not allowed intake of caffeine or drinks containing alcohol at least 1 week before the start of the study.

The average age, height, and weight of the subjects were, respectively, 24 years (range, 20–29 years), 175 cm (range, 170–181 cm), and 67.0 kg (range, 57–75 kg). Written informed consent was obtained from all subjects after they were provided a complete description of the study. The study was approved by the hospital ethics committee (Holy Family Hospital, The Catholic University of Korea, Seoul, South Korea), and the procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

2.2. Methods

2.2.1. Induction and evaluation of hangovers

All subjects were asked to abstain from food, coffee, and physical exercise from 4:00 p.m. on the day of the study and given a mixture of 23% alcohol (Soju) and orange juice at 7:00 p.m., so that the amount of alcohol would be 1.5 g/kg for each subject. The subjects drank this mixture within 60 min (10-min intervals). The subjects were instructed to read books or to have conversations, but they were forbidden to exercise (dancing or running) during the day. They were instructed to sleep from 11:00 p.m. on the test day to 7:00 a.m. on the following morning in the clinical laboratory unit. All behaviors, including diet and sleep, were monitored by two psychiatrists during the experimental period, and no serious violation was observed. The subjects were asked to keep a sleep diary. The average duration of sleep was 7.7 ± 0.3 h.

To evaluate the degree of a hangover, the subjective hangover scale and somatic hangover scale were evaluated at 7:50 a.m. on the test day and at the same time on the following day (Ylikahri et al., 1974). For the subjective hangover scale, each subject was asked to rate the subjective degrees of fatigue, headache, dizziness, nausea, thirst, tension, depression, and general discomfort from 0 to 4 points. For the somatic hangover scale, two psychiatric specialists rated paleness, tremor, perspiration, nystagmus, vomiting, and general appearance by observing each subject and using a three-point scale from 0 to 2. The total hangover score was calculated by summing the values obtained for subjective hangover scale and somatic hangover scale.

2.2.2. Measurement of blood alcohol levels

Blood samples were obtained at 8:00 a.m. on the first day, 1 h after consumption of alcohol, and at 8:00 a.m. on the following day. After 10 µl of the blood sample was added to 3 ml of reagent [nicotinamide adenine dinucleotide (NAD), 2.8 mmol/l; alcohol dehydrogenase (ADH) (yeast), 200,000 U/l],

the mixture was reacted at 25ºC for 10 min. This mixture was subsequently placed in a spectrophotometer within 10 min, and the absorbance was read at 340 nm. The alcohol concentration was calculated by using the absorbance obtained from the blood sample and the standard absorbance obtained from the standard (ethanol: 80 mg/dl, 0.08%).

2.2.3. Measurement of cytokine concentrations

The PBMCs were isolated from blood samples by using Ficoll-Hypaque fractionation. After aliquotting 1.5×10^6 ml of the PBMC sample into complete medium, phytohemagglutinin [(PHA); 6.25 µg/ml] was added. Stimulation of PBMCs with PHA was done immediately after PBMCs were isolated. All supernatants were evaluated in one assay, and the sampling was performed in duplicate. After absorbance was read at 450 nm and 570 nm by using an enzyme-linked immunosorbent assay (ELISA) reader (Behring ELISA Processor 11, Behring, Marburg, Germany), the quantitative ELISA was done by using interleukin (IL)-1β, IL-4, IL-6, IL-10, IL-12, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) ELISA kit (Endogen Inc., Woburn, MA, USA). IL-12 is represented as total IL-12 (p40+p70).

2.3. Statistical analyses

Paired *t* test (two-tailed) was applied to compare the cytokine production in normal conditions with that during the hangover state (i.e., 13 h after alcohol consumption). The scale scores were also compared between normal and hangover states. Statistical analysis was performed by using the SPSS for Windows (version 10.0). A *P* value of .05 was considered to be significant. Pearson correlation coefficients were used to examine the correlation between changes in the hangover scales (subjective, somatic, and total hangover scales) and changes in cytokine concentrations in normal and hangover conditions.

3. Results

Blood alcohol levels for the subjects were 1.57 ± 1.08 mg/dl at 8:00 a.m. on the test day before alcohol consumption, 74.49 ± 21.86 mg/dl 1 h after alcohol consumption, and 2.87 ± 2.09 mg/dl at 8:00 a.m. on the following day, 13 h after alcohol consumption.

The total subjective hangover scale scores were 3.0 ± 3.7 before alcohol consumption and 7.5 ± 5.4 during the hangover state (95% CI, *P* = .00) (Table 1). The total somatic hangover scale scores also increased significantly from 0 to 1.2 ± 0.8 points (95% CI, *P* = .00) (Table 1). Therefore, the total hangover scale scores showed a significant increase from 3.0 ± 3.7 to 8.7 ± 5.6 (95% CI, *P* = .00) (Table 1).

Concentrations for the cytokines IL-10, IL-12, and IFN-γ significantly increased 13 h after alcohol consumption. In

contrast, those for the cytokines IL-1β, IL-4, IL-6, and TNF-α showed no increase during the hangover state compared with findings for normal (control) conditions (Table 2).

As can be seen from examining the data displayed in Table 3, the IFN-γ concentration was positively correlated with the subjective hangover scale ($P = .042$) and total hangover scale ($P = .036$) values. The IL-12 concentration was also correlated with the somatic hangover scale ($P = .049$) and total hangover scale ($P = .034$) values.

4. Discussion

For the current study, we induced a hangover state in healthy subjects 13 h after alcohol consumption and examined the change in cytokine production by the PBMCs. We found a significant increase in the production of cytokines IL-10, IL-12, and IFN-γ during the hangover state compared with production of these cytokines in a normal condition. In contrast, there were no changes detected in production of IL-1β, IL-4, IL-6, and TNF-α. In addition, changes in hangover scale scores were correlated with changes in cytokine (IFN-γ and IL-12) concentrations.

Interleukin-10 is a typical T helper cell subtype 2 (T_H2) cytokine that inhibits the production of cytokines in macrophages and cellular immunity. Because IL-10 is thought to play a significant role in the mechanism of decreased cellular immunity induced by alcohol (Mandrekar et al., 1996; Szabo et al., 1996), an increase in production of IL-10 during hangover states supports the suggestion that impaired cellular immunity persists into the hangover state.

On the other hand, IL-12 is a proinflammatory cytokine that induces proliferation of natural killer cells and T lymphocytes and activates cytotoxicity. Furthermore, IFN-γ produced in T helper cell subtype 1 (T_H1) lymphocytes is responsible for stimulating natural killer cells and macrophages. They increase the cell-mediated immune responses. Thus, an increase in the production of IL-12 [total IL-12 (p40+p70)] and IFN-γ during the hangover state supports the suggestion that hangovers are associated with immune functions.

Injection of healthy volunteers with IL-10 shows a dose-related adverse effect, including a flu-like syndrome characterized by fever with chills, headache, and myalgia (Huhn et al., 1996). With intravenous injection of recombinant human IL-12, similar toxicities, such as fever, chills, fatigue, nausea, vomiting, and headache (Atkins et al., 1997), are also exhibited. Wiese et al. (2000) have demonstrated that symptoms arise from abnormal immune functions due to viral infection, and the side effects of IFN-α administration for hepatitis are similar to hangover symptoms. We found that the scores for items on hangover scales, such as fatigue, headache, thirsty, discomfort, general appearance, and vomiting, exhibited a significant increase during hangover states with an increase in production of IL-10, IL-12, and IFN-γ.

In the current study, there are a few limitations that warrant further discussion. First, the number of subjects was

Table 1
Hangover scale scores in control and alcohol hangover conditions
($N = 20$)

		Mean (S.D.) score		
		Control	Hangover	*P*
Subjective hangover scale	Fatigue	0.6(0.9)	1.5(0.8)	.001
	Headache	0.1(0.3)	1.2(1.0)	.000
	Dizziness	0.4(0.7)	0.9(1.1)	N.S.
	Nausea	0.5(0.9)	0.6(0.9)	N.S.
	Thirsty	0.7(0.7)	1.8(0.8)	.000
	Tension	0.4(0.6)	0.3(0.7)	N.S.
	Depression	0.2(0.4)	0.1(0.3)	N.S.
	Discomfort	0.3(0.5)	1.2(0.8)	.000
	Total	3.0(3.7)	7.5(5.4)	.000
Somatic hangover scale	Paleness	0.0(0.0)	0.1(0.3)	N.S.
	Tremor	0.0(0.0)	0.0(0.0)	
	Perspiration	0.0(0.0)	0.3(0.4)	N.S.
	Nystagmus	0.0(0.0)	0.0(0.0)	
	Vomiting	0.0(0.0)	0.2(0.4)	.042
	General appearance	0.0(0.0)	0.8(0.4)	.000
	Total	0.0(0.0)	1.2(0.8)	.000
Total hangover score		3.0(0.4)	8.7(5.6)	.000

N.S. = Not significant; S.D. = standard deviation.

Table 2
Changes in cytokine production in control and alcohol hangover conditions ($N = 20$)

Cytokine	Mean (S.D.) (pg/ml)		*P*
	Control	Hangover	
IL-1β	269.4 (218.6)	290.9 (221.5)	N.S.
IL-4	0.3 (0.5)	0.4 (0.6)	N.S.
IL-6	724.2 (86.2)	743.5 (46.5)	N.S.
IL-10	68.2 (52.9)	98.1 (68.5)	.001
IL-12	323.7 (72.4)	770.4 (352.5)	.003
IFN-γ	505.00 (553.53)	955.71 (721.77)	.001
TNF-α	1,174.40 (346.11)	1,212.44 (345.15)	N.S.

IFN = Interferon; IL = interleukin; TNF = tumor necrosis factor; N.S. = Not significant; S.D. = standard deviation.

Table 3
Correlation coefficients and *P* values for changes in subjective and somatic hangover scale scores and changes in cytokine concentrations ($N = 20$)

Cytokine	Subjective hangover scale score		Somatic hangover scale score		Total hangover score	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
IL-1β	0.04	.882	0.03	.905	0.04	.875
IL-4	−0.32	.174	−0.19	.421	−0.32	*.166*
IL-6	−0.13	.589	0.20	.398	−0.08	.731
IL-10	0.41	.070	0.26	.261	0.42	.062
IL-12	0.44	.055	0.45	.049	0.48	.034
IFN-γ	0.46	.042	0.30	.195	0.47	.036
TNF-α	0.18	.440	0.48	.032	0.25	.285

IFN = Interferon; IL = interleukin; TNF = tumor necrosis factor.

relatively small. To draw more reliable conclusions, replication is needed with larger samples. In addition, the congener content of Soju might be an important confounder. The IL-10 response is possibly due to the congeners in Soju, as opposed to pure vodka as an example.

Results of the current study support the suggestion that alcohol interferes with immune functions, particularly the cytokine pathway. Changes in the T_H1-associated cytokine IFN-γ and in the T_H2-associated cytokine IL-10 might be involved in the mechanism underlying physiologic changes during hangover states. In aspects of the T_H1/T_H2 balance, the changes in IFN-γ and IL-10 during hangover states might affect the balance of the immune system. In conclusion, we suggest that the dysregulated cytokine pathway (IL-10, IL-12, and IFN-γ) is associated with the symptoms of a hangover.

Acknowledgments

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