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Nitric oxide mediates cardiovascular symptoms in alcohol withdrawal

Seppo Kähkönen [a,b,*], Bondarenko Boris [c], Zvartau Edwin [d]

[a] BioMag Laboratory, Helsinki University Central Hospital, Finland
[b] Cognitive Brain Research Unit, Helsinki University, Finland
[c] Cardiologic Research Institute, St. Petersburg Russia
[d] Department of Psychopharmacology, Valdman Institute of Pharmacology, Pavlov State Medical University, St. Petersburg, Russia

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Abstract

We studied whether nitric oxide is involved in cardiovascular symptoms in alcohol withdrawal. Cardiovascular effects of isosorbide dinitrate (ISDN; 20 mg sublingually), a nitric oxide donor were compared in 21 alcohol-dependent subjects during alcohol withdrawal ($n=11$) on days 1, 2, 3, and 10 to those during remission (n=10; duration=60.7±10.5 days). Cardiovascular parameters were measured non-invasively. The levels of systolic and diastolic blood pressure, total peripheral resistance were significantly higher in patients with withdrawal than in remission. Same cardiovascular parameters showed different response to ISDN during withdrawal when compared to remission. The differences were largest during the initial phase (1–2 days) of withdrawal. Nitric oxide may mediate at least some cardiovascular symptoms in withdrawal.

Keywords: Alcohol dependence; Alcohol withdrawal; Blood pressure; Cardiac output; Heart rate; Hemodynamics; Isosorbide dinitrate

1. Introduction

Alcohol withdrawal syndrome (AW) is a short-lasting, but severe complication of alcohol dependence characterizing psychiatric symptoms and changes in autonomous nervous and cardiovascular systems. Tachycardia, arterial hypertension and elevated cardiac output (CO) are usual symptoms of AW (Beckman et al., 1981; Saunders et al., 1981; Kähkönen and Bondarenko, 2000), which correlate with AW severity (Potter et al., 1984) and with the amount of alcohol taken during the most recent last hard-drinking period (Clark and Friedman, 1985).

Mechanisms underlying cardiovascular abnormalities in AW are poorly understood, but changes in catecholamine metabolism are shown to be associated with changes in the circulatory system (for review, see Kähkönen, 2004). Nitric oxide (NO) mediates biological messages in several physiological systems including the central nervous and cardiovascular systems in normal state and pathological conditions (McCall and Vallance, 1992; Moncada et al., 1991). Acute and chronic ethanol treatments have shown to change NO function in rats (Uzbay et al., 1997; Lallemand and De Witte, 1997; Adams and Cicero, 1998). The level of NO was increased in heavy alcohol consumers (Soardo et al., 2005). Increased serum nitrate/nitrite levels in male alcoholic patients (Yuksel et al., 2005) were observed. These studies suggest that NO function may be impaired also in humans. However, studies linking NO function with different symptoms of alcohol dependence are almost lacking. To our knowledge, only one study explored whether NO impairment is linked to the symptoms of alcohol dependence in humans (Kähkönen and Zvartau, 2003). This study showed that isosorbide dinitrate (ISDN)-related cardiovascular responses differ between withdrawal and early remission.

ISDN is a NO donor which is a widely used as vasodilatator for treatment of ischemic heart disease. ISDN undergoes bioformation to NO and *S*-nitrosothiol, resulting in activation of guanylate cyclase to produce cyclic GMP, which initiates relaxation of vascular smooth muscle (Brien et al., 1987; Gruetter et al., 1981). ISDN is subject to extensive hepatic metabolism resulting in formation of physiologically active metabolites, isosorbide-5-mononitrate and isosorbide-2-mononitrate (Dollery, 1991). ISDN relaxes most smooth muscle including that in veins and arteries.

* Corresponding author. BioMag Laboratory, Helsinki University Central Hospital, P.O. Box 340, FIN-00029 HUS, Finland. Tel.: +358 9 47175579; fax: +358 9 47175781.
E-mail address: Seppo.Kahkonen@helsinki.fi (S. Kähkönen).

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Rapid administration of ISDN decreases systolic (SBP) and diastolic blood pressure (DBP) and CO and activates compensatory sympathetic reflexes. Tachycardia and peripheral arteriolar vasoconstriction tend to maintain systemic vascular resistance (Dollery, 1991; Murad, 1990). ISDN challenge can be used to study NO function in humans (Kähkönen and Zvartau, 2003). Impedance cardiography has been shown to be a reliable method for measuring changes in stroke volume (SV) and CO, and is thus suitable for studies of cardiovascular drug challenge (Sherwood et al., 1990; Newman and Callister, 1999). It has been used to study cardiovascular system in patients with alcohol dependence during withdrawal (Kähkönen and Zvartau, 2003; Bär et al., 2006) and after drug administration (Kähkönen and Zvartau, 2003).

In this study we aimed to investigate whether NO is involved in alcohol withdrawal by studying cardiovascular effects of ISDN in different phases of alcohol withdrawal compared to those in remission.

2. Material and methods

2.1. Patients

Twenty-one male patients with alcohol dependence, eleven during AW admitted to a specialized in-patient unit for treatment of AW and ten during remission, were examined. The experimental procedures were approved by the local ethical committee, and all subjects gave their written informed consent. All patients fulfilled the DSM-IV criteria for alcohol dependence and for uncomplicated alcohol withdrawal (American Psychiatric Association, 1994). Patients with other psychiatric pathology and substance-abuse, complicated forms of AW, and alcoholism, as well as evident cardiologic diseases were excluded. Relevant laboratory tests commonly used to evaluate liver and kidney functions and blood and urine examination, and an electrocardiogram were included. Patients reported that last alcohol intake exceeded 24 h before the first experiment. All were under 50 years of age. Characteristics of the patients studied in AW and at remission did not differ ($p>0.05$) (Table 1).

20 mg of ISDN was sublingually administered and cardiovascular effects were assessed before and after the drug intake: in 15, 30, 45, 60 and 120 min. Pharmacological tests were carried out in AW on the 1, 2, 3 and 10 days after admission to hospital. Control group consisted of patients admitted to the rehabilitation center. Duration of remission was 60.7±10.5 days. The severity of AW was studied at approximately the same time of the day with the aid of the rating scale described earlier (Kähkönen and Bondarenko, 2000). Patients were at day 1 and remission drug-free. Withdrawal symptoms were treated with oral diazepam 10–20 mg per day as needed. Diazepam was not given at least three days before the examination on day 10. All experimental sessions were carried out between 8 and 2 a.m. in a fasted state during the study.

Table 1
Summary of the characteristics of alcoholic patients

	In withdrawal	In remission
	Mean±SD	Mean±SD
Age (yr)	37±7.8	37±9.8
Duration of heavy drinking (yr)	13±6.0	16±8.1
Duration of WS (yr)	10±6.8	9.9±6.6
Daily alcohol consumption (g)	336±102	319±88
Duration of last alcohol-abuse period (days)	27±20.6	

2.2. Cardiovascular measurements

SV were measured by an impedance cardiograph system (RPG 2–02, Russia) using four band-electrodes as described by Kubicek et al. (1966). The parameters of impedance cardiography were measured with the patient in supine position after a 10-minute rest separately in the state of unforced breathing, of inspiration, and of expiration (at least 10 epochs for each), and the mean value was taken.

The following parameters were measured or calculated as follows:

(1) Heart rate (HR; beat/min) from the electrocardiogram
(2) Systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg) measured in supine position with sphygmomanometer by Korotkoff. Mean blood pressure (MBP; mmHg) calculated from the formula: MBP=(SBP+2×DBP) / 3
(3) SV (ml) of the heart by impedance cardiography utilizing the formula of Kubicek–Gundarov (Gundarov et al., 1983)
(4) CO (l/min) refers to HR×SV
(5) Total peripheral resistance (TPR; dynećs/cm^{-5}) calculated from the formula TPR=MBP/CO

2.3. Statistics

Results were expressed as the mean±standard deviation (M±SD). Data for multiple observations were analyzed by analysis of variance (ANOVA) for repeated measures.

3. Results

3.1. Severity of AW symptoms

The level of AW symptoms showed rapid decline in severity: 16.4±4.3 scores on day 1, 9.9±3.7 scores on day 2, 7.1±3.4 scores on day 3, and 3.6±3.2 scores on day 10.

3.2. Effects of AW on cardiovascular system

The results are summarized in Fig. 1. When cardiovascular parameters during AW and remission were compared with one-way ANONA, significant main effects on SBP ($df=4, 35$; $F=4.4$; $p=0.005$) and DBP ($df=4, 35$; $F=3.8$; $p=0.012$) were found. The effects were due differences between day 1 and remission ($p=0.001$) and day 2 and remission ($p=0.01$) for SBP and day 1 and remission ($p=0.01$), day 2 and remission ($p=0.018$), day 3 and remission ($p=0.028$) for DBP. ANOVA revealed significant main effect on TRP ($df=4, 34$; $F=2.8$;