Available online at www.sciencedirect.com
SCIENCE DIRECT®
Life Sciences 78 (2006) 2179 – 2187
Life Sciences
www.elsevier.com/locate/lifescie

Chronic ethanol consumption alters cardiovascular functions in conscious rats

Leonardo B.M. Resstel [a], Carlos R. Tirapelli [a], Vera L. Lanchote [b], Sérgio A. Uyemura [b], Ana M. de Oliveira [c], Fernando M.A. Corrêa [a,*]

[a] Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo (USP), Avenida dos Bandeirantes, 3900, 14090-090, Ribeirão Preto, SP, Brazil
[b] Department of Clinical, Toxicological and Food Science Analysis, Faculty of Pharmaceutical Sciences, USP, Ribeirão Preto, SP, Brazil
[c] Department of Physics and Chemistry, Laboratory of Pharmacology, Faculty of Pharmaceutical Sciences, USP, Ribeirão Preto, SP, Brazil

Received 17 June 2005; accepted 6 September 2005

Abstract

Chronic ethanol intake and hypertension are related. In the present work, we investigated the effect of chronic ethanol (20% v/v) intake for 2, 6 and 10 weeks on basal arterial blood pressure, baroreflex and heart rate levels, as well as on the cardiovascular responses to the infusion of vasoactive agents in unanesthetized rats. Mild hypertension was observed after 2 weeks, 6 weeks or 10 weeks of treatment. On the other hand, no changes were observed in heart rate after long-term ethanol intake. Similar baroreflex changes were observed in 2- or 6-week ethanol-treated rats, and affected all parameters of baroreflex sigmoid curves, when compared to the control group. These changes were characterized by an enhanced baroreflex sympathetic component and a reduction in the baroreflex parasympathetic component. No differences in baroreflex parameters were observed in 10-week ethanol-treated animals. The pressor effects of i.v. phenylephrine were enhanced in 2-week ethanol-treated rats; not affected in 6-week treated animals and reduced in 10-week ethanol-treated rats, when compared to respective control and isocaloric groups. The hypotensive response to i.v. sodium nitroprusside (SNP) was enhanced at all different times of treatment, when compared to respective control and isocaloric groups.

In conclusion, the present findings showed increased arterial pressure in the early phase of chronic ethanol consumption, which was consequent of rise in both systolic and diastolic pressures. Ethanol intake affected both the sympathetic and the parasympathetic components of the baroreflex. Vascular responsiveness to the pressor agent phenylephrine was initially enhanced and later on decreased during chronic ethanol intake. Vascular responsiveness to the depressor agent SNP was enhanced during chronic ethanol intake.

Keywords: Chronic ethanol; Blood pressure; Heart rate; Baroreflex

Introduction

Chronic ethanol consumption is associated with cardiovascular dysfunctions (Altura and Altura, 1982, 1987; Patel et al., 1997) and hypertension (Moore et al., 1990; Patel et al., 1997). However, the mechanisms involved in ethanol intake-related blood pressure increase are not yet completely understood. Current investigation in this field has been centered on mechanisms known to be involved in human hypertension. Several mechanisms have been postulated for the hypertensive response to chronic ethanol consumption, such as enhanced secretion of hormones and neurotransmitters, stimulation of the sympathetic nervous system (Chan et al., 1985) and a myogenic mechanism, which involves alteration of contractile properties of vascular smooth muscle (Chan and Sutter, 1982). Additionally, there is evidence that altered baroreceptor activity could contribute for the hypertensive state of chronically ethanol-treated rats (Abdel-Rahman et al., 1985). The arterial baroreflex system is regarded as one of the most powerful and rapidly acting homeostatic mechanisms regulating blood pressure. It is also known that baroreflex activity is significantly depressed in human (Goldstein, 1983) and experimental (Gordon et al., 1981) hypertension.

* Corresponding author. Fax: +55 16 633 2301.
E-mail address: fmdacorr@fmrp.usp.br (F.M.A. Corrêa).

0024-3205/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2005.09.021

Although chronic ethanol consumption has been usually associated with hypertension, there are reports that chronic ethanol consumption lowered (Hatton et al., 1992) or did not (Abdel-Rahman et al., 1985) affect blood pressure in rats. These reports state that two main points might account for the lack of hypertension in ethanol-treated animals. First, the 30-day exposure period may not be long enough and second, the anesthetic agent may have depressed the cardiovascular function more severely in ethanol-fed rats than in control rats yielding similar blood pressure values.

In fact, there are reports of a positive correlation between the extent of ethanol intake and the development of hypertension (Abdel-Rahman and Wooles, 1987; Strickland and Wooles, 1988), suggesting that the period of exposure to ethanol is the major factor in the development of hypertension. However, the duration of chronic ethanol treatment differs among several studies published (Abdel-Rahman et al., 1985; Chan et al., 1985; Utkan et al., 2001). Moreover, the majority of the experiments designed to study the effects of chronic ethanol consumption on cardiovascular functions used only one period of treatment to evaluate arterial blood pressure, baroreflex activity, heart rate basal levels and hemodynamic responses to vasoactive agents (Abdel-Rahman et al., 1985; Utkan et al., 2001).

It has also been reported that anesthesia alters cardiovascular parameters in normal animals (Haskins et al., 1986; Sumitra et al., 2004) and consequently the lack of effect of experimental chronic ethanol consumption on cardiovascular functions described in some studies could be related to the use of anesthetized rats (Abdel-Rahman et al., 1985).

Considering the above-mentioned controversies, it is relevant to study the time-course of the effects of chronic ethanol intake on the cardiovascular functions in age-matched unanesthetized rats.

In the present study we compared the effect of the intake of ethanol (20% v/v) for 2, 6 and 10 weeks on the arterial blood pressure and heart rate basal levels; the baroreflex activity and the hemodynamic responses to vasoactive agents in conscious rats, with data obtained from age-matched control untreated rats or rats receiving an isocaloric sucrose solution.

Methods

Chronic ethanol treatment

Fifty-one male Wistar rats were used in the present experiment. Rats were housed in individual plastic cages, under standard laboratory conditions with free access to food and water and under a 12 h light/dark cycle (lights on at 06:30 h), in the Animal Care Unit of the Department of Pharmacology of the School of Medicine of Ribeirão Preto, University of São Paulo. The Institution's animal ethics committee approved housing conditions and experimental protocols.

The rats initially weighing 300–350 g (80–100 days old) were randomly divided into three groups: control, isocaloric and ethanol-treated animals. Control rats received tap water ad libitum. Rats from the isocaloric group received a solution containing sucrose (290.5 g/L) instead of ethanol. Rats from the ethanol group received 20% (v/v) ethanol in their drinking water (adapted from Chan and Sutter, 1983; Tirapelli et al., 2003). All animals had free access to Purina Lab Chow®. In order to avoid a considerable loss of animals, the ethanol-treated group was submitted to a brief and gradual adaptation period. The animals received 5% ethanol in their drinking water in the first week, 10% in the second and 20% in the third week. At the end of the third week the experimental stage was initiated. The same procedure was adopted for the isocaloric group. The different groups were treated for 2, 6 and 10 weeks. Animals were weighted weekly and average food intake was calculated.

Blood ethanol and serum glucose measurements

Blood samples were collected for analysis of blood ethanol content at the completion of the 2nd, 6th or 10th week of ethanol feeding. Blood samples were collected during the morning period, from the aorta artery of anesthetized rats using heparinized syringes. Blood samples were transferred to tubes containing sodium fluoride (1 mg/mL). Ethanol analysis was carried out using a CG-17A gas chromatography (Shimadzu, Kyoto, Japan) equipped with a flame-ionization detector and an HSS-4A headspace sampler (Shimadzu). Injections were made in the split mode onto a Supelcowax 10 (Supelco, Bellenfonte, PA) column (30 m × 25 mm i.d. and 25 μm film thickness). The split ratio was 20:1 and the injector, column and detector temperatures were 150 °C, 50 °C and 150 °C, respectively. The samples were placed in 10 mL headspace vials by adding 1 g sodium chloride, 1.0 mL water, 100 μL of the internal standard (acetonitrile, 1 mL/L) solution, and 1 mL of blood. The samples were sealed using crimp top vial caps with septa and were placed in the headspace rack at the temperature of 60 °C and with equilibration time of 20 min. Calibrations standards were prepared in the same headspace vials (0.10–3.16 mg/mL). The results were expressed as mg of ethanol/mL of blood.

For glucose measurements, blood was collected from the aorta artery of anesthetized rats. The samples were centrifuged at 8000–10,000 × *g* for 10 min at room temperature. The serum was analyzed for glucose content using available commercial kits (Labtest Diagnóstica) and the auto-analyzer ABBOTT (model ABAA VP). The results are expressed as mg/dL.

Animal preparation

One day before the experiments, the rats were anesthetized with tribromoethanol and a catheter (a 4 cm segment of PE-10 heat-bound to a 13 cm segment of PE-50, Clay Adams, Parsippany, NJ, USA) was inserted into the abdominal aorta through the femoral artery for blood pressure and heart rate recording. Whenever intravenous administration of drugs was necessary, a second catheter was implanted into the femoral vein. Both catheters were tunneled under the skin and exteriorized at the animal's dorsum.