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Cardiovascular alterations at different stages of hypertension development during ethanol consumption: Time-course of vascular and autonomic changes

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ABSTRACT

The aim of the present work was to establish a time-course correlation between vascular and autonomic changes that contribute to the development of hypertension during ethanol ingestion in rats. For this, male Wistar rats were subjected to the intake of increasing ethanol concentrations in their drinking water during four weeks. Ethanol effects were investigated at the end of each week. Mild hypertension was already observed at the first week of treatment, and a progressive blood pressure increase was observed along the evaluation period. Increased pressor response to phenylephrine was observed from first to fourth week. α_1-adrenoceptor protein in the mesenteric bed was enhanced at the first week, whereas β_2-adrenoceptor protein in the aorta was reduced after the second week. In the third week, ethanol intake facilitated the depressor response to sodium nitroprusside, whereas in the fourth week it reduced nitrate content in aorta and increased it plasma. The bradycardic component of the baroreflex was impaired, whereas baroreflex tachycardia was enhanced at the third and fourth weeks. AT_{1A} receptor and C-type natriuretic peptide (CNP) mRNAs in the nucleus tractus solitarius were increased at the fourth week. These findings suggest that increased vascular responsiveness to vasoconstrictor agents is possibly a link factor in the development and maintenance of the progressive hypertension induced by ethanol consumption. Additionally, baroreflex changes are possibly mediated by alterations in angiotensinergic mechanisms and CNP content within the brainstem, which contribute to maintaining the hypertensive state in later phases of ethanol ingestion. Facilitated vascular responsiveness to nitric oxide seems to counteract ethanol-induced hypertension.

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Introduction

Among several alcohol use-related disorders, it is well documented in clinical and experimental studies that cardiovascular dysfunctions and hypertension are associated with long-term ethanol consumption (Chan et al., 1985; Corrao et al., 2004; Resstel et al., 2008). Indeed, preclinical studies have demonstrated a positive correlation between the duration of ethanol consumption and the development of hypertension (Abdel-Rahman and Wooles, 1987; Resstel et al., 2006; Russ et al., 1991).

Ethanol acts directly on blood vessels (Altura and Altura, 1987; Puddey et al., 2001). Moreover, several mechanisms are thought to be involved in ethanol-induced cardiovascular dysfunctions, including neuroendocrine changes and sympathetic nervous system activation (Chan et al., 1985; Da Silva et al., 2013; Resstel et al., 2008). Furthermore, clinical and experimental studies have demonstrated that long-term ethanol exposure affects baroreflex activity (Abdel-Rahman et al., 1985, 1987; Fazio et al., 2001; Resstel et al., 2006), and this effect has been implicated in ethanol-induced hypertension (Russ et al., 1991). Changes in baroreflex activity following chronic ethanol consumption are mainly characterized by changes in the baroreflex control of the heart rate (HR) (Abdel-Rahman and Wooles, 1987; Abdel-Rahman et al., 1985; Resstel et al., 2006), since baroreflex-mediated changes in sympathetic nerve activity are not affected by ethanol (Russ et al., 1991; Zhang et al., 1988). Although a central site of action for ethanol-evoked baroreflex changes has been proposed (Li et al., 2005; Varga and Kunos, 1992; Zhang et al., 1989), the mechanisms underlying baroreflex changes are still poorly understood.

It has been demonstrated that ethanol-induced hypertension is also followed by changes in vascular responsiveness to vasoactive agents (Abdel-Rahman et al., 1987; Resstel et al., 2006; Tirapelli et al., 2008).

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Indeed, chronic exposure to ethanol increases vascular reactivity to α-adrenoceptor agonists in aorta rings and in segments of superior mesenteric arteries (Ladipo et al., 2002; Pinardi et al., 1992; Tirapelli et al., 2006, 2008), whereas the relaxation response to acetylcholine is impaired in these vessels (Husain, 2007; Tirapelli et al., 2007, 2008). In vivo studies have also demonstrated that both, pressor response to the α_1-adrenoceptor agonist phenylephrine and hypotensive response to the nitric oxide donor sodium nitroprusside (SNP), are facilitated following long-term ethanol ingestion (Resstel et al., 2006; Russ et al., 1991). Based on evidence that NO synthase (NOS) inhibition abolishes the changes in vascular reactivity to vasoconstrictor and vasodilator agents and that endothelial NOS (eNOS) protein levels and NO content are reduced in the vessels of ethanol-treated animals (Husain, 2007; Husain et al., 2011; Tirapelli et al., 2008), it is proposed that changes in the vascular responsiveness are mediated by a reduced endothelial NO formation.

Taken together, the evidence mentioned above clearly demonstrates that ethanol-induced hypertension is followed by changes in baroreflex activity and vascular responsiveness to vasoactive agents. However, most of the studies conducted so far have only evaluated hypertension after long periods of ethanol exposure, when large blood pressure changes are detected. Therefore, the mechanisms involved at the early stages of hypertension development during ethanol exposure are unclear. Therefore, the main aim of the present study was to establish a time-course correlation between baroreflex and vascular changes that contribute to the development of hypertension during ethanol intake in rats.

Material and methods

Animals and ethical approval

Male Wistar rats (250 g) were used in the present study. Animals were housed collectively in plastic cages (4 per cage) in a temperature-controlled room at 24 °C in the Animal Care Unit of the Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo. They were kept under a 12:12 h light–dark cycle (lights on at 6 AM, lights off at 6 PM) and had free access to water and standard laboratory food. Experimental procedures were carried out following protocols approved by the Ethics Committee for Animal Use of the School of Medicine of Ribeirão Preto, and are in accordance with the international guidelines for animal use and welfare.

Ethanol treatment

Ethanol treatment regimen was based in a protocol previously reported by our group (Da Silva et al., 2013; Resstel et al., 2008). Briefly, animals received increasing concentrations of ethanol in their drinking water for four weeks (first week: 5%, second week: 10%, third and fourth weeks: 20% *v/v*). In the present study, animals were randomly divided into four groups of control and ethanol-treated rats. Groups receiving ethanol included**:** i) *first week ethanol*: 5% ethanol in the drinking water for one week; ii) *second week ethanol*: 5% ethanol for one week followed by one week of 10% ethanol in the drinking water; iii) *third week ethanol*: 5% ethanol for one week, one week of 10% ethanol, and a third week of 20% ethanol in the drinking water; and iv) *fourth week ethanol*: first week 5% ethanol, second week 10% ethanol, and third and fourth weeks 20% ethanol in the drinking water. Control groups received water ad libitum for the same period that the ethanol-treated groups.

Functional evaluation of cardiovascular activity

Surgical preparation and measurement of cardiovascular parameters. Twenty-four hours before the trial, rats were anesthetized with tribromoethanol (250 mg/kg, i.p.) and a catheter was inserted into the abdominal aorta through the femoral artery for cardiovascular recording. A second catheter was implanted into the femoral vein for the infusion of vasoactive agents to evoke arterial pressure changes. Both catheters were tunneled under the skin and exteriorized on the animal's dorsum. After the surgery, rats were treated with a streptomycin and penicillin polyantibiotic formulation (0.27 mg/kg, i.m.; Pentabiotico®; Fort Dodge, Brazil) and received the non-steroidal anti-inflammatory drug flunixine meglumine (0.025 mg/kg, i.m.; Banamine®; Schering Plough, Brazil) for postoperative analgesia.

On the trial day, the arterial cannula was connected to a pressure transducer and the pulsatile arterial pressure was recorded using an HP-7754A pre-amplifier (Hewlett Packard, Palo Alto, CA, USA) and an acquisition board (MP100A, Biopac Systems Inc, Goleta, CA, USA) was connected to a personal computer. Systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressure and heart rate (HR) values were derived from pulsatile arterial pressure recordings.

Infusion of vasoactive agents. Intravenous infusion of the selective α_1-adrenoceptor agonist phenylephrine (50 μg/ml at 0.32 ml/min/kg) and of the nitric oxide (NO) donor sodium nitroprusside (SNP) (70 μg/ml at 0.8 ml/min/kg) was performed using an infusion pump (K.D. Scientific, Holliston, MA, USA) (Crestani et al., 2011; Resstel et al., 2006). Phenylephrine and sodium nitroprusside caused incremental pressor and depressor responses, respectively. Infusions of vasoactive drugs were randomized and lasted for 30–40 s, resulting in the injection of a total dose of 8–10 μg/kg of phenylephrine and 20–25 μg/kg of sodium nitroprusside.

Method of baroreflex evaluation. Baroreflex curves were constructed matching MAP variations evoked by vasoactive agents with reflex HR responses. Paired values of MAP and HR variations were plotted to create sigmoid curves, which were used to determine baroreflex activity (Crestani et al., 2010; Head and McCarty, 1987; Resstel et al., 2006). Baroreflex analysis using sigmoid curves were characterized by five parameters: (i) P_1 (bpm), lower HR plateau; (ii) P_2 (bpm), upper HR plateau; (iii) HR range (bpm), difference between upper and lower plateau levels; (iv) median blood pressure (BP_{50}, mm Hg), mean arterial pressure at 50% of the heart rate range; and (v) average gain (G, bpm/mm Hg), average slope of the curves between +1 and −1 standard derivations from BP_{50}. To analyze bradycardic and tachycardic responses separately, HR values matching MAP changes were plotted to create linear regression curves and their slopes were compared to test changes in baroreflex gain (Crestani et al., 2010; Resstel et al., 2006).

Dose–response arterial pressure curves. The graded rises and falls in MAP evoked respectively by increasing concentrations of phenylephrine and SNP were used to generate dose–response curves. In this manner, it was possible to generate dose–response curves that demonstrated the effect of ethanol treatment on pressor and depressor responsiveness (Engi et al., 2012; Resstel et al., 2006). Dose–effect curves were generated for each vasoactive agent using MAP values corresponding to cumulative recording times (each 2 s) after starting the infusion. The maximal effect (E_{max}) and the dose at 50% of the mean arterial pressure range (ED_{50}) for each vasoactive agent were compared in all experimental groups.

Experimental procedures. Independent groups of animals were evaluated at the end of each week of the 4-week treatment protocol. For this, 24 h before the trial, rats were subjected to surgical preparation for cardiovascular recordings. In the trial day, animals were transferred to the experimental room in their home box. They were allowed to 60 min adaptation to the experimental room conditions, such as sound and illumination, before starting cardiovascular recordings. The experimental room was temperature controlled (24 °C) and was acoustically isolated from the other rooms. Cardiovascular recording was realized in unanesthetized, freely moving rats. Animals in all experimental groups were initially subjected to 30 min period of basal cardiovascular

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