

RESEARCH PAPER

Gender-specific vascular effects elicited by chronic ethanol consumption in rats: a role for inducible nitric oxide synthase

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Background and purpose: Epidemiological data suggest that the risk of ethanol-associated cardiovascular disease is greater in men than in women. This study investigates the mechanisms underlying gender-specific vascular effects elicited by chronic ethanol consumption in rats.

Experimental approach: Vascular reactivity experiments using standard muscle bath procedures were performed on isolated thoracic aortae from rats. mRNA and protein for inducible NO synthase (iNOS) and for endothelial NOS (eNOS) was assessed by RT-PCR or western blotting, respectively.

Key results: In male rats, chronic ethanol consumption enhanced phenylephrine-induced contraction in both endothelium-intact and denuded aortic rings. However, in female rats, chronic ethanol consumption enhanced phenylephrine-induced contraction only in endothelium denuded aortic rings. After pre-incubation of endothelium-intact rings with L-NAME, both male and female ethanol-treated rats showed larger phenylephrine-induced contractions in aortic rings, compared to the control group. Acetylcholine-induced relaxation was not affected by ethanol consumption. The effects of ethanol on responses to phenylephrine were similar in ovariectomized (OVX) and intact (non-OVX) female rats. In the presence of aminoguanidine, but not 7-nitroindazole, the contractions to phenylephrine in rings from ethanol-treated female rats were greater than that found in control tissues in the presence of the inhibitors. mRNA levels for eNOS and iNOS were not altered by ethanol consumption. Ethanol intake reduced eNOS protein levels and increased iNOS protein levels in aorta from female rats.

Conclusions and implications: Gender differences in the vascular effects elicited by chronic ethanol consumption were not related to ovarian hormones but seemed to involve the upregulation of iNOS.

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Abbreviations: eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; L-NAME, N^G-nitro-L-arginine methyl ester; 7-NI, 7-nitroindazole; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; OVX, ovariectomy; SNP, sodium nitroprusside

Introduction

Chronic ethanol consumption has been implicated as a causative factor in a variety of cardiovascular abnormalities (Altura and Altura, 1982). Long-term ethanol intake is

associated with hypertension in humans (Moore *et al.*, 1990) and increased blood pressure in rats (Utkan *et al.*, 2001; Resstel *et al.*, 2006). Previous reports suggest that enhanced vascular reactivity to vasoconstrictor agents (Tirapelli *et al.*, 2006a,b) or impairment of vascular relaxation (Kahonen *et al.*, 1999; Tirapelli *et al.*, 2006b) contributes to cardiovascular complications associated with chronic ethanol consumption. For instance, enhanced vascular reactivity to α_1 -adrenoceptor agonists was demonstrated in different arteries from ethanol-treated rats (Chan and Sutter,

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