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## Oxidation of ethanol to acetaldehyde and free radicals by rat testicular microsomes

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**Abstract** A large number of epidemiological studies evidencing that excessive alcohol consumption is associated with impaired testosterone production and testicular atrophy are available in the literature. One hypothesis to explain the deleterious action of alcohol involves the *in situ* biotransformation to acetaldehyde, but it strongly suggests the need to learn more about the enzymatic processes governing alcohol metabolism to acetaldehyde in different cellular fractions since limited information is available in the literature. In this article we report studies on the metabolic conversion of alcohol to acetaldehyde and to 1-hydroxyethyl radicals in rat testicular microsomal fractions. The oxidation of ethanol to acetaldehyde in rat testes microsomal fraction was mostly of enzymatic nature and strongly dependent on the presence of NADPH and oxygen. Several compounds were able to significantly decrease the production of acetaldehyde: SKF 525A; diethyldithiocarbamate; esculetin; gossypol; curcumin; quercetin; dapsone; and diphenyleiiodonium. Microsomal preparations in the presence of NADPH were also able to produce both hydroxyl and 1-hydroxyethyl free radicals. Their generation was modulated by the presence of diphenyleiiodonium, gossypol, and deferoxamine. Results show that rat microsomal fractions are able to metabolize alcohol to deleterious chemicals, such as acetaldehyde and free radicals, that may be involved in ethanol toxic effects. Enzymes involved could include CYP2E1, P450 reductase, and other enzymes having lipoxygenase- /peroxidase-like behavior.

**Keywords** Alcohol · Ethanol · Acetaldehyde · 1-hydroxyethyl · Testes · Radicals · Microsomes

### Introduction

A large number of epidemiological studies evidencing that excessive alcohol consumption is associated with impaired testosterone production and testicular atrophy are available in the literature (Adler 1992; Emanuele and Emanuele 1998). Similar findings were observed in experimental studies in ethanol-treated rats (Akane et al. 1988; Van Thiel et al. 1987; 1989). Mechanistic *in vitro* studies on the testosterone production by isolated testes revealed that ethanol acts at least in part directly on the testes to affect this hormone production (Badr et al. 1977; Cobb et al. 1978).

One hypothesis about how alcohol may contribute to testosterone decreasing effects on those *in vitro* studies involved the metabolic transformation of ethanol to acetaldehyde. The rationale behind that hypothesis is that in some studies acetaldehyde was found to be more potent than alcohol in suppressing testosterone release (Badr et al. 1977; Cobb et al. 1978). Acetaldehyde might harm testicular function by directly inhibiting steroidogenic enzymes or indirectly by decreasing antioxidant defenses (e.g., GSH levels) and enhancing lipid and protein oxidation to cause damage as suggested by others (Rosenblum et al. 1989; Nordmann et al. 1990; Emanuele et al. 2001). Alternatively, the metabolism of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) could also result directly in the formation of free radicals by changing the NADH level and the NADH/NAD<sup>+</sup> redox ratio, which in turn modulates the activity of the free-radical-generating enzyme xanthine oxidase (Mantle and Preedy 1999). Still, another possibility could be that the biotransformation of alcohol to acetaldehyde in the testes competed for cofactors with the process involved in testosterone production thereby preventing testosterone production (Ellingboe and Varanelli 1979; Gordon et al. 1980). In fact, Akane et al. (1988) reported that ethanol inhibited testicular steroidogenesis by suppressing at least two steps in the pregnenolone-to-testosterone pathway, the pregnenolone-

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