INTRODUCTION

Alcohol is the most widely used and frequently abused psychoactive drug in the world with serious social and health implications. Global status report on alcohol-2004 (WHO) revealed that more than 2 billion people have been consuming alcohol worldwide with a periodical increase in the number with the addition of new drinkers every year including teenaged boys and girls. While the majority of alcohol consumers are able to enjoy benefit from the positive psychological and healthy effects of moderate alcohol consumption, a large number of individuals suffer from alcohol related diseases and disorders. An estimated 2 million deaths and 60 million people with alcohol disorders and many millions with Disability Adjusted Life Years (DALY) were reported in literature. Moreover, nearly 60 diseases are directly attributable to alcohol and a number of diseases with alcohol relatedness have been recognized. Alcohol dependence and its disorders are an area of growing concern in India. Alcoholism is perceived as male problem till now, but there has been a clear indication of dramatic rise in alcoholism among women in recent years with increased number of female alcoholics worldwide including India. Consequently an increased number of female alcoholics with disorders who turned up for treatment recently at NIMHANS at Bangalore was evident.

Research evidences revealed that women alcoholics respond differently in comparison to men on behavioral and physiological responses as well in biochemical aspects. There exists a gender difference in females and males due to differential hormonal milieu, differential anatomical, physiological, and biochemical aspects of brain, sex organs as well metabolism and body mass and composition. There is a need for better understanding of the biological mechanisms underlying sex differences related to the effects of alcoholism. Understanding the molecular events as well
Gender differences in pharmacokinetics of alcohol revealed that women achieve rapid higher blood alcohol levels due to decreased volume of ethanol distribution compared to men as they have lower proportion of body water to fat. Moreover women have reduced gastric alcohol dehydrogenase activity. Interestingly women can develop alcohol induced liver disease after consuming lower amounts of alcohol over shorter period of time than men. Further, the biomarkers of alcoholism used for males such as gamma-glutamyl transferrin, carbohydrate deficient transferrin are not sensitive and suitable in screening female alcoholics. Female alcoholism has not been thoroughly investigated as male alcoholism. Very few isolated studies are available using females as models in alcohol research. Those experiments were also designed at scientists' discretion. Hence scientists strongly emphasized a need for research on female alcoholism to obtain essential information for understanding the impact of gender. Of late, various aspects of biochemistry and physiology related to females are being focused.

Recent studies on alcoholism clearly indicated that gender differences play a major role in alcohol intoxication as well as damage and other beneficiary or adverse effects of alcohol use. Further, studies also revealed that there are a number of possible mechanisms underlying these gender differences in ethanol sensitivity and toxicity. Emerged evidences suggest that women respond differently to alcohol. There are multiple explanations for the differential response such as differential body composition and size, water content, structural and functional differences in brain, size of liver and differences in other physiological processes. Generally, women are
smaller than men. So the same dose of alcohol leads to higher blood alcohol levels in women than men. Further, women body water content per kilogram of body weight is smaller and higher percentage of fat than men. Thus, a dose of ethanol will be distributed in smaller volume of water in women than in men leading to somewhat higher concentrations of ethanol in women’s blood. Also the alcohol metabolizing enzyme content as well as the activity of gastric alcohol dehydrogenase (ADH) was found to be lower in women than men leading to high blood alcohol levels of women18. Moreover, females exist under a different hormonal milieu than males and gonodial steroids affect γ-amino butyric acid (GABA) receptors. As GABA receptors are known to mediate the actions of alcohol, regulation of these receptors and consequent effects depend on gender9.

It is also well known that therapeutic dosages of drugs, their pharmacokinetics and toxico-dynamics are gender dependent20. Although women consume less alcohol than men, they are more vulnerable to many of the medical consequences of alcohol use8. Female susceptibility to toxic effect of alcohol has been observed in hepatic, cerebral, cardiac and muscular alterations21. Investigating the mechanisms underlying these adverse effects of alcohol consumption in humans is impractical for alcohol related disease develops only after many years of heavy drinking. Moreover it would be unethical to conduct studies in humans. Therefore, researchers have been forced to use various animal models to gain insight into the processes responsible for alcohol effects on the body and to determine new ways to prevent or treat alcohol related diseases22. Enhanced oxidative stress and decreased antioxidant status induced by ethanol metabolism appear to play a major role in causing alcohol toxicity and damage23,24. Recent studies revealed involvement of nitric oxide (NO) in alcohol-induced physiological and pathophysiological effects25,26. Though the precise mechanisms of
action of alcohol-induced characteristic intoxication effects as well as injury are not fully understood, studies clearly revealed that biophysical and biochemical changes in membranes are wholly, if not, largely responsible for the above. But, the impact of gender and how these biophysical and biochemical changes lead to alcohol toxicity remain unknown. The precise relationship between membrane fluidity and oxidative stress as well as the role of NO in the causation of these changes are not known. Therefore, the present study has been designed to understand the impact of gender on the effects of alcohol and alcohol-induced biophysical as well as biochemical mechanisms at molecular level in female rats at selected doses in comparison to male rats. Further this study has been designed to understand the sex differences in the mechanism(s) of alcohol toxicity which facilitates the development of therapeutic strategies. Hence, the present study is aimed at the following objectives:

Objectives:

- to evaluate the impact of gender on biophysical and biochemical changes related to membranes and other components of cells of the chosen tissues viz., the liver, brain and blood from alcohol-fed female rats to compare them with those of males with special emphasis on biomembranes [erythrocyte, hepatic (mitochondrial and microsomal) and brain mitochondrial membranes] to find out the precise mechanism(s) of toxicity.

- to assess the antioxidant status as well as oxidative stress in female alcoholic rats in comparison with males,
to understand the role of NO in the causation of alcohol toxicity in females with a view to compare with males,

to understand the differences in various molecular interactions and physico-chemical properties of biomembranes at the molecular level especially changes in membrane fluidity using anisotropic as well as changes in membrane lipids, and

to evaluate histopathology of female alcoholic rats as to compare them with that of controls.
References


