Gender Differences in Animal Studies

Implications for the Study of Human Alcoholism

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Abstract. The reasons for gender differences in alcohol intake, responses to alcohol, and consequences of alcohol abuse in humans and in animals are poorly understood. Animal models for the study of alcoholism have been focused primarily on the study of male rodents, although researchers have observed that female rodents drink more alcohol than males and have sex-related differences in drinking patterns and responses to alcohol. In humans, the difference between the sexes is the opposite of rodents, with males drinking more than females. These results suggest differences between the sexes and differences between humans and rodents in drinking behavior and responses to alcohol which may be based on a complex interaction of social, genetic, hormonal, neurobiologic, and environmental factors. Four new studies are introduced to identify sex-distinct genetic influences in alcohol-related phenotypes, sex-based differences in behavioral responses to alcohol, sex differences in responses of brain reward systems to alcohol, and interactions of the anxiolytic effects of alcohol with steroids and the estrous cycle.

1. Gender Differences in Response to Alcohol

Alcohol research involving humans and animals has been dominated by investigations of males. Only recently the problems and mechanisms for alcoholism in female animals have been studied; and recently, interest has increased in including women in study populations. Increasingly, clinical and...
experimental studies are showing that women have higher blood alcohol levels than men after drinking the same amount of alcohol based on body size\(^1\) and greater vulnerability to damage by alcohol than men.\(^2\) Women, within a shorter period of time and with lower alcohol intake, are more likely to develop alcohol-induced liver disease and brain damage.\(^3\)–\(^5\) Liver damage and shrinking of the brain from loss of white matter have been detected in women categorized as moderate drinkers.\(^6\) These insidious effects of alcohol intake remained largely undetected until recent improvements in the technology of brain imaging and new interest in including female subjects in study populations.\(^7\)

The reasons for the differences in pattern of drinking and the differential risk for consequences of alcohol intake for males and females are poorly understood.\(^8\) Social factors, which have played a part in concealing problems associated with alcoholism of women, and the research focus on males, have limited the study of women, resulting in a deficit of information regarding drinking practices for women in our society.\(^9\) In the past, when most women did not work outside the home, they were able to conceal problems with alcohol and were enabled by family members to continue drinking.\(^10\) With changes in social roles, women are more likely to experience some of the work-related problems of alcoholism previously experienced predominantly by men.\(^11\) However, hypotheses that alcohol intake by women would converge to meet levels consumed by men when women began working outside the home have not been proved.\(^12\) Although women make up about half the work force, women still drink significantly less than men.\(^13\)

Currently, animal models for the study of alcoholism, alcohol preference, and voluntary alcohol intake are focused primarily on the study of male rodents, although researchers have observed that female rodents will drink more alcohol than males\(^14\),\(^15\) and have sex-related differences in drinking patterns and responses to alcohol.\(^16\) In humans, the difference between the sexes is the opposite of rodents, with males drinking more than females.\(^17\) These results suggest differences between the sexes and differences between humans and rodents in drinking behavior and responses to alcohol, which may be based on a complex interaction of social, genetic, hormonal, neurobiologic, and environmental factors.

1.1. Genetics and Environment

Gender differences in heritability of alcoholism suggest that women are more likely to experience type I alcoholism, which is environmentally influenced and associated with adult onset of alcohol abuse in either biological parent.\(^18\) Type II alcoholism, male-limited and having strong genetic transmission from father to son, is not thought to be experienced by females.\(^19\) However, scientific evidence to explain this protection of females from type II alcoholism remains unclear. A preliminary study of incarcerated female alcoholics suggests that some female alcoholics in families with a history of alco-