Published in final edited form as:

Life Sci. 2010 July 31; 87(5-6): 133–138. doi:10.1016/j.lfs.2010.06.002.

Sex Difference in Alcoholism: Who is at a Greater Risk for Development of Alcoholic Complication?

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Abstract

Aims—Alcohol abuse and alcoholism are among the major medical problems afflicting both men and women. While men display a higher prevalence for alcoholism, it is women who suffer a much greater risk for alcoholism-associated bodily damage. Although women generally consume less alcohol compared to men, females usually suffer more severe brain and other organ damage following binge or chronic alcohol abuse. Main methods and key findings: Although many biological (i.e., genetic risk and neurological abnormalities) and psychosocial (i.e., impact of positive drinking expectancies, personality characteristics and deviance proneness) factors appear to impact men and women equally. These factors especially social and environmental, physiological, genetic and neurobiological ones have been demonstrated to contribute to the sex difference in response to alcohol intake, as well as the development of alcoholic complications. A number of neurotransmitters and growth factors may be partially involved in these differences between men and women. The mesolimbic dopamine system is implicated in the development of addictive behaviors. Differences in dopamine receptor density are found between sexes where gonadal steroid hormones may play a role. Inhibitory GABAergic and stimulatory glutamatergic systems also act as neuromodulators in the brain and differences in their specific receptors have been identified between men and women (particularly GABA_A receptors and NMDA receptors).

Significance—Given the variety of factors contributing to the sex difference in response to alcohol intake, alcoholism treatment should take sex dimorphism into consideration. Furthermore, future research needs to be directed towards a better understanding of the mechanism of action of alcohol in both men and women.

Keywords

Sex differences; dopamine; GABA receptors; NMDA receptors; alcoholism

INTRODUCTION

Alcohol abuse and alcoholism are major health problems and the cost for society and the individual is tremendous. Not surprisingly, a majority of clinical and experimental

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approaches has been focused on male subjects. However, drastic differences have been identified between men and women not only in the propensity for alcohol abuse but also in their bodily response to alcohol. As a matter of fact, the pattern of drinking and the amount of alcohol consumed varies between men and women, which imposes a major challenge for alcohol research and the proper management against alcoholism (Devaud et al., 1999; Piano et al., 2005). Epidemiological evidence suggests that nearly 20% of adult males have alcohol abuse or suffer from alcoholism-related complications. On the other hand, only about 5–6% of adult females are alcoholic or abuse alcohol on the regular basis (Devaud et al., 1999). In general, women tend to consume less alcohol than men and appear to be less likely to manifest certain risk factors for alcohol use and health problems. Nonetheless, women perceive greater social and health sanctions for drinking while alcohol and alcoholism may counter desirable feminine traits (e.g., nurturing). Moreover, women are less likely to display characteristics associated with excessive drinking including aggressiveness, drinking to alleviate distress, behavioral undercontrol, sensation-seeking and antisociality (Nolen-Hoeksema, 2004). However, the consequence of heavy alcohol use as well as alcoholic complications may be more problematic in women than men, at least in some domains. Women tend to suffer from alcohol-related physical illnesses and display more severe cognitive and motor impairment with significantly lower alcohol exposure compared with men. Heavy alcohol use in women is known to be associated with a range of reproductive problems and fetal alcohol syndrome (Bradley et al., 1998; Hommer, 2003; Nolen-Hoeksema, 2004; Prendergast, 2004). Despite a recent effort towards sex difference under both physiological and pathophysiological conditions, the sex disparity in alcohol abuse and alcoholic complications has not been clearly elucidated. Moreover, the sex difference in pharmacokinetics of alcohol may determine the time course of blood alcohol levels following alcohol ingestion and thus the degree of organ exposure to alcohol. There is proven variability in alcohol absorption, distribution and metabolism between men and women, as a result of hormonal, genetic and environmental factors (Ramchandani et al., 2001). Finally, alcohol abuse is often associated with increased sexuality, heightening the risk for HIV/AIDS and other sexually transmitted diseases, resulting in a secondary health effect of alcoholism (Kalichman et al., 2007). This mini-review will examine some of the more recent clinical and experimental findings in sex difference of alcohol-related implications, which should be used for both proper management of alcoholic injury and public health education campaign.

Sex Difference in Alcohol Metabolism and Alcohol Detoxification

The pharmacokinetics of alcohol determines the time course of alcohol level in blood following alcoholic intake and the degree of organ exposure to alcohol. The interplay between the metabolism and organ distribution of alcohol is rather important for the pharmacodynamic response to alcohol (Ramchandani et al., 2001). Alcohol is mainly detoxified by alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH2) in liver (Chrostek et al., 2003; Crabb et al., 2004). These enzymes display various genetic polymorphism in human although their contribution to differential risk of alcoholism is still debatable (Crabb et al., 2004). The first step of alcohol metabolism is the oxidation of ethanol into acetaldehyde catalyzed by the class I ADH isoenzymes (ADH1a, ADH1b and ADH1c). ALDH2 then catalyzes the subsequent irreversible reaction in oxidation of acetaldehyde into acetate and water. Although the total ADH and class I and II ADH activities are significantly higher in males than in females, the class III and IV ADH as well as total ALDH activities are not significantly different between men and women (Chrostek et al., 2003). Kishimoto and colleagues examined the acute effect of ethanol in mice and revealed lower serum levels of ethanol, acetaldehyde and acetate in females compared with males (Kishimoto et al., 2002). Upon injection of β -estradiol, the primary female reproductive hormone, the activity of hepatic mitochondrial ALDH was found to be

significantly increased in males. Meanwhile, ALDH activity in cytosolic fraction of the liver was decreased in females following treatment of the primary male hormone testosterone (Kishimoto et al., 2002). These data favor a sex disparity in ALDH2 isoform activity. Given that stomach in particular gastric mucosa is involved in the first-pass ethanol metabolism through ADH, the sex disparity in gastric mucosal ADH activity may likely contribute to the blood level of alcohol and alcoholic complications following alcohol intake. An age-associated decline in gastric mucosal ADH activity has been reported in men. In contrary, women 41–60 years of age display much higher gastric mucosal ADH activity than those women 20–40 or 61–80 years of age (Parlesak et al., 2002). These findings favor a possible role of sex difference in ethanol metabolism in the sex disparity in alcoholic complication. Further study from our group revealed that females may be more sensitive to the ethanol metabolic product acetaldehyde-induced cardiac contractile depression, which may attribute to the sex difference in alcoholic cardiomyopathy (Duan et al., 2003). When transgene encoding ADH enzyme was overexpressed in myocardium from both males and females, the ethanol exposure-induced depression in cardiomyocyte contraction was significantly augmented in female but not male ADH mice (Duan et al., 2003), suggesting that females are more sensitive to the ADH enzymatic product acetaldehyde-induced cardiac depression.

Sex Difference in Alcohol Consumption

Drinking is associated with pleasure, leisure and reward. Chronic stress has also been shown to play a pivotal role in the continued alcohol abuse by addicts (Koob and Le Moal, 2001; Sinha, 2001). In human alcohol addiction, one of the essential factors underlying addiction is a need for mood enhancement or relief from stress. As the stress- and reward-systems in the brain are influenced by sex hormones, the development of alcohol dependency, and approaches to recovery, may also be sex dependent and exhibit sex disparity. Although men have a greater tendency toward alcoholism than women, (Isralowitz et al., 2009; Tadic et al., 2009), evidence has demonstrated a greater incidence of alcohol-related damage, especially neurological damage, in women. Though heavy drinking is less prevalent among women, it can also be more damaging because drinking during pregnancy leads to increases in prenatal ethanol exposure, which may cause severe permanent birth defects, including neurotoxicity (Mancinelli et al., 2009). It is worth mentioning that the U-shaped relationship can be found for both sexes with regards to the overall health prevalence. For example, the relative risk for type 2 diabetes in men is protective when consuming 22 g/day alcohol and becomes deleterious at > 60 g/day compared with lifetime abstainers. In women, consumption of 24 g/day alcohol is considered most protective and becomes deleterious at > 50 g/day compared with lifetime abstainers (Baliunas et al., 2009).

Recent epidemiological study revealed a trend of alcohol use starting at early ages. One recent study in adolescents reveals that certain biological and psychosocial factors impact boys and girls in similar ways (Schulte et al., 2009). However, the two sexes quickly diverge when it comes to both behavioral and physiological responses to alcohol. Boys have a greater risk for disruptive drinking because of a low response to alcohol, later maturation in brain structures and socialization toward heavier drinking. On the other hand, courtesy of the stereotypical female characteristics, girls tend to have reduced alcohol involvement. In adulthood, sex difference in response to alcohol is more dramatic. According to data from “National Institute on Alcohol Abuse and Alcoholism” (<http://alcoholism.about.com/cs/alerts/l/blnaa46.htm>), female alcoholics have greater death rates than male alcoholics. Women alcoholics experience an increased risk for liver diseases, circulatory disorders, breast cancer, fertility impairment and early menopause.

Insulin-Like Growth Factor and Alcohol-induced Neurodegeneration

Alcoholism is a rather complex disorder representing an important contributor to health problems. In particular, alcohol influences the function of many hormonal and neurotransmitter systems, with the interaction at γ -aminobutyric acid (GABA) receptors which is integral for the reinforcing and withdrawal-related effects of ethanol (Finn et al. 2010). Among a wide cascade of hormones and neurotransmitters, insulin-like growth factors (IGF) I and II regulate neuronal survival, energy metabolism and plasticity in the central nervous system. The major targets for ethanol-induced neurotoxicity are the hypothalamus, temporal lobe and cerebellum, in which the greatest levels of IGF polypeptide and receptor genes are expressed (de la Monte and Wands, 2005). *In vivo* and *in vitro* studies showed that IGF-I improves dopaminergic survival (Clarkson et al., 2001; Chung et al., 2005). It has also been demonstrated that inhibition of insulin and IGF by ethanol in cultured neuronal cells and immature brains results in apoptosis via a PI-3 kinase-Akt pathway (Zhang et al., 1998; Ramachandran et al., 2001; de la Monte and Wands, 2002). On the other hand, the ethanol-induced impairment of neuronal survival could be prevented by IGF-I treatment (de la Monte et al., 2000; Patel, 2004). In a recent study, the mean levels of insulin, IGF-I and IGF-II receptor bindings have been found to be decreased in chronic alcoholic patients (de la Monte et al., 2008). Additionally, the adverse effects of ethanol were believed to be mediated by interrupted insulin receptor binding and inhibition of insulin gene expression in the central nervous system (de la Monte and Wands, 2005; Soscia et al., 2006). Results favor the notion that the region-specific effects of ethanol in neuronal loss seen in alcohol drinkers may be associated with the ethanol-induced inhibitory effects on insulin and IGF gene expression. Nonetheless, insulin and IGF-I levels do not seem to differ between males and females although administration of estrogen in post-menopausal women suppresses hepatic IGF-I production leading to lower IGF-I concentrations. Moreover, there is circumstantial evidence indicating that testosterone stimulates IGF-I production, and a threshold level of androgens required for hepatic IGF-I production (Jorgensen et al., 2004; Jorgensen et al., 2005). These data clearly depict an interaction between sex steroids and IGF-I production, which may underscore the sex difference in tissue IGF-I levels and growth hormone sensitivity. Further study is warranted to determine the precise role of sex difference in IGF-I in the sex disparity in alcoholic organ damages.

Alcohol Consumption and Risk of Dementia

The correlation between alcohol intake and risk of dementia, a complex disease with mysterious pathological machinery, is somewhat ambiguous. Evidence has suggested that health behaviors like smoking, alcohol drinking, diet, physical activity and body mass index are important factors for cognition and dementia. While some findings have confirmed a positive correlation between alcohol intake and risk of dementia (Tanev et al., 2008), others indicated that alcohol drinkers in late life have reduced risk of dementia. It is unknown at this point whether the beneficial effect of alcohol on dementia reflects selection effects in cohort studies commencing in late life, a protective effect of alcohol consumption throughout adulthood, or a specific benefit of alcohol in late life (Anstey et al., 2009). Alzheimer's disease (AD) as an important type of dementia and one of the leading causes of death in women and men above the ages of 65 in the U.S. (Chen et al., 2009). Moderate alcohol consumption can lower the risk of dementia (Mukamal et al., 2003). Between 1997 and 2008, 19 longitudinal cohort studies and 25 cross-sectional or case-control reports of cognitive decline or dementia indicated that the dementia risk factors were decreased with moderate alcohol consumption, a phenomenon known as "preconditioning". Alcohol-related preconditioning was also examined in rat hippocampus-entorhinal cortex (HEC) complex (Collins et al., 2000). The finding revealed that moderated alcohol consumption may protect

HEC slice and cerebellar cultures against glycoprotein 120 (the potent neurodegenerative agent)-induced neurodegeneration. In a postmortem study focused on the relationship between alcohol consumption and neurodegenerative lesion, heavy and chronic alcohol consumption was unable to lead to the obvious neuropathologic lesions (assessed by vascular lesions or the accumulation of amyloid- β peptide, hyperphosphorylated τ protein and α -synuclein) (Aho et al., 2009). On the other hand, epidemiological survey has shown that excessive alcohol consumption can result in overt cognitive dysfunction (Saunders et al., 1991; Hillbom, 1998; Letenneur, 2004). Numerous studies indicate alcohol consumption has little effect on the development of AD (Graves et al., 1990; Rosen et al., 1993; Huang et al., 2002; Tanaka et al., 2002), though contradictory results have been reported (Fratiglioni et al., 1993). Although direct toxic effect of ethanol on the neurological system has been mainly manifested as alcohol-related dementia, the specific pathologic mechanisms remain unclear.

A large volume of clinical evidence has indicated that estrogen plays an important role in the improvement of cognitive function and neurodegenerative conditions (Henderson et al., 1996; Sherwin, 1996; Kawas et al., 1997; Wise et al., 2001). Estrogen replacement has beneficial effects in delaying the onset of AD and Parkinson's disease (Cho et al., 2003). 17 β -estradiol, a physiologically significant estrogen, activates MAP kinase pathway, attenuates NMDA receptor activation and/or activates the cAMP/PKA/CREB pathway in addition to its classical genomic actions (Kajta et al., 2001; Wise et al., 2001). Using the SK-N-SH cells, Keller and colleagues demonstrated that moderate concentrations of estradiol and ethanol protected the cells against the manganese-induced toxicity. In particular, estrogen protection has been speculated through its antioxidant property (Keller et al., 2005). Given the multifactorial nature of AD and clinical senile dementia, the sex dimorphism of the diseases may also depend on factors independent of sex hormones (i.e., a gender behavioral effect). In fact, difference in dementia mortality between men and women may be attributed to not only the biological sex difference but also the "socially constructed sex or gender" (i.e., the characteristics that a society or culture delineates as masculine or feminine) (Candore et al., 2010). Therefore, it is essential to take the role of hormones, socio-behavioral and educational levels into account regarding the different propensity between males and females in alcohol dementia.

The Dopamine System

The mesolimbic dopamine system, with dopaminergic projections from ventral tegmental area (VTA) to the nucleus accumbens and other forebrain areas, has been implicated in the development and maintenance of many addictive behaviors including drug and alcohol abuse (de Bruin et al., 2005). Given the key role of this system in alcohol-associated changes in behavior, the sex difference in dopaminergic system may be responsible for certain aspects of the differences between men and women following alcohol intake. Although dopaminergic neurotransmission appears to be similar between sexes, women tend to have lower dopamine levels and higher levels of dopamine metabolites, including homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) (Pohjalainen et al., 1998; Devaud et al., 1999). In addition, a sex difference in the D₂ receptor, which is important in the development of addiction and alcoholic complications, has been demonstrated (Pohjalainen et al., 1998). Imbalance of the homeostatic responses of D₃ following elevated synaptic dopamine concentrations, in reference to D₁ and D₂ dopamine receptors, may contribute to the development of behavioral sensitization (Richtand et al., 2001; Wodarz et al., 2003). It is well established that the density and binding potential of D₂ receptors decline rapidly with aging in striatum. This age-associated decline occurs much faster in men than women with alcoholic men possessing decreased densities of striatum D₂

receptors (Pohjalainen et al., 1998). This sex disparity in D₂ receptor should help to explain the increased incidence of alcoholism in men compared with women.

The dopamine receptor D₂ (DRD2) in particular the A₁ allele has been associated with alcoholism. Subjects carrying this allele have decreased D₂ receptor levels in the brain (Berman et al., 2003). Genetic evaluation in children of alcoholics have identified distinct sex difference in children carrying the DRD2 A₁ allele (Berman et al., 2003). Girls with this allele displayed increased novelty seeking compared to boys. This personality trait has been linked to substance abuse, particularly in adolescence, and may predispose women with this genotype to alcoholism. Female offspring with this allele exhibited decreased visuospatial ability compared to males, which may represent a cognitive deficit and act as a marker for substance abuse in adulthood (Berman et al., 2003). Males carrying this allele showed changes in event-related potential (ERP) responses. In alcohol-dependent individuals following chronic alcohol consumption, latency is prolonged and amplitude is reduced for multiple ERP components, including a large positive deflection, the P300. Interestingly, following an extended period of alcohol abstinence, most alcohol-associated abnormalities disappeared with the exception of P300 (Berman et al., 2003). Boys carrying the DRD2 A₁ allele showed low P300 scores similar to an alcoholic, indicating a genetic risk factor for alcoholism (Berman et al., 2003). Males with this allele also possessed poor harm avoidance, which may contribute to the increased risk-taking and impulsive behavior, traits usually associated with addiction. This evidence suggests that genetically related dopamine dysfunction in both sexes may play a role in the development of alcohol addiction, although this may manifest itself in different ways.

To date, the scenario behind the sex difference in dopaminergic system remains elusive. Endogenous dopamine levels in the striatum may be affected by gonadal steroid hormones. Furthermore, synthesis, circulating levels, degradation, uptake, and receptor density of dopamine may fluctuate during the estrous cycle (Pohjalainen et al., 1998), indicating a possible role of estrogen in the regulation of dopaminergic system. Estrogen is believed to possess potent anti-dopaminergic properties. Nonetheless, the underlying mechanisms are still poorly understood while inconsistent results have been seen displaying both stimulatory and inhibitory effects of estrogen in modulating dopamine neurotransmission (Pohjalainen et al., 1998).

GABA Receptors

Considerable evidence has demonstrated the importance of the mesolimbic dopamine system in the development of drug addiction and alcoholism. It is well known that this system is modulated by both inhibitory and stimulatory inputs, including GABAergic and glutamatergic neurons (Johnson, 2005). Chronic alcohol usage may be associated with alteration in the subunit composition of the GABA receptors in human (Dodd et al., 2006). The GABA_A receptor in particular may be pivotal in the sex disparity in response to alcohol intake. Alcohol is known to alter GABAergic neurotransmission through GABA_A receptor, which plays an essential role in acute response to alcohol, alcohol dependence and self-administration (Grobin et al., 1998; Dodd et al., 2006). Activation of the GABA_A receptor also mediates behavioral responses including, motor ability, anxiolytic responses, and sedating responses to alcohol (Grobin et al., 1998; Abramov et al., 2006). Additionally, female gonadal hormones affect many neurobiological responses through the GABA_A receptor. It has been well known that neuroactive steroids can influence the actions of ethanol at GABA_A receptors (Grobin et al., 1998). Therefore, the sex difference in dopamine function may be regulated in part through the GABA_A receptor (Devaud et al., 1999; Raud et al., 2003; Raud et al., 2005).

Sex is an important factor for GABA_A receptor subunit peptide expression in alcoholics (Devaud et al., 1999; Raud et al., 2003; Raud et al., 2005). In cortical regions, alcohol dependent male rats display decreased $\alpha 1$ subunit expression, whereas these levels are not altered in females (Devaud et al., 1998). In hypothalamus, chronic alcohol exposure increased $\alpha 1$ subunit peptide expression in males. Male rats also showed increased levels of $\alpha 4$ and $\alpha 3$ subunits, whereas females had increased peptide levels of $\alpha 2$ and $\alpha 3$ subunits in hypothalamus (Devaud et al., 1999). This sex dimorphism in the up- or down-regulation of receptor subunits in various brain regions may have important physiological effects, such as manipulation of neuronal inhibition in specific brain areas. Other alterations in GABA_A receptors which may affect responses to alcohol also include changes in subunit assembly, altered postranslational modification, conformational changes in structure, or dissociation of receptor subunits (Grobin et al., 1998; Devaud et al., 1999). These factors may also participate in the GABA_A receptor-mediated sex difference in dopamine function although further investigation is warranted.

Administration of exogenous neuroactive steroid hormones, such as the progesterone derivative $3\alpha,5\alpha$ -THP, also affects the alcohol actions on GABA_A receptors (Grobin et al., 1998). Given that females possess higher levels of progesterone, they also have higher levels of $3\alpha,5\alpha$ -THP than males, although levels fluctuate with the estrous cycle (Grobin et al., 1998; Devaud et al., 1999). In addition GABA_A receptor stimulation can be affected by estrous cycle and (Grobin et al., 1998). Female rats display variations in the amount of alcohol consumed over the estrous cycle, with the lowest alcohol intake coinciding with proestrus, when progesterone and its derivative $3\alpha,5\alpha$ -THP levels are elevated in the brain (Grobin et al., 1998). Finally, males are more responsive to both the depressant and the stimulatory actions of acute alcohol consumption, suggesting sex difference in the responsiveness to alcohol (Grobin et al., 1998).

NMDA Receptors

Excitatory glutamatergic inputs are important modulators of the mesolimbic dopamine system and have been implicated in the development of alcohol dependence. Chronic alcohol exposure is associated with increased NMDA receptor responsiveness and decreased GABA_A receptor activation, which may be due to alterations in the receptor subunit expression for both alcohol target systems (Devaud and Morrow, 1999; Dodd et al., 2006). In glutamatergic system, neuroadaptations in the NMDA receptor system appear to be important in sex dimorphism following alcohol intake (Devaud and Morrow, 1999; Johnson, 2005). Female rats chronically exposed to alcohol displayed greater levels of the NR1 subunit of NMDA receptor in the cortex and hypothalamus, whereas male rats exhibited increased NR1 and NR2A subunit levels in the hippocampus (Devaud and Morrow, 1999). It has been suggested that neuroadaptation in alcoholics might be resulted from NMDA and/or GABA_A receptors with different subunit assemblies rather than expression in the naïve state (Devaud and Morrow, 1999). Further study revealed that the differential adaptations of GABAergic and glutamatergic neurotransmission between male and female are associated with the sex difference in alcohol withdrawal recovery, suggesting that selective withdrawal-induced neuroadaptations in regulation of these two alcohol target systems may underlie, at least in part, sex difference in alcohol withdrawal recovery between male and female (Alele and Devaud, 2005). Other neurotransmitter systems, such as the serotonergic system, the endogenous opioids, and norepinephrine may also be involved in differences in addictive responses to alcohol, although little data is available on these systems.

Sex Difference and Overall Effect of Ethanol in the Brain

The medical consequences of alcoholism generally develop much more rapidly in women than in men. It is well known that cirrhosis and alcohol-induced cardiomyopathy as well as peripheral neuropathy can be developed after fewer years of heavy drinking in women than men. (Hommer, 2003). In addition, women seem to be more vulnerable to brain damage and the neurotoxic effects of alcohol than men (Hommer, 2003; Prendergast, 2004). Both men and women alcoholics display reduced brain volume in comparison to the nondrinking individuals. Interestingly, brain shrinkage and cognitive dysfunction appears to develop much more quickly in women (Hommer, 2003; Prendergast, 2004). To the contrary, it was also reported that higher levels of alcohol consumption may be associated with smaller brain volume in men (Paul et al., 2008). These authors found that women showed larger total cerebellar brain volume compared to men at any given level of alcohol consumption and these women were much more susceptible to the undesirable effects of alcohol. Such sex difference in the brain volume between women and men may be interpreted as a much faster alcohol absorption rate in women compared with men. Neuroimaging examination has also depicted that both gray and white matter is shrunk more in female brains while the female alcoholics may present a greater short-term memory impairment than alcoholic men (Prendergast, 2004).

Treatments for Alcoholism

Treatment for alcoholism encompasses social, psychological and pharmacotherapeutic strategies (Kiefer and Mann, 2005). In clinical practice, pharmacological intervention has been widely used for treatment of withdrawal symptoms of alcohol, while other strategies have been used for treatment of relapse and cravings, such as psychosocial intervention. Drug therapy may be useful to reduce cravings and to reduce the risk of relapse (Kiefer and Mann, 2005). A few of the drugs currently available include naltrexone, an opiate receptor antagonist, acamprosate, which restores glutamatergic tone, and disulfiram, which prevents the breakdown of alcohol and increases the negative effects of alcohol withdrawal, hopefully preventing alcohol intake (Kiefer and Mann, 2005). Drugs not yet received approval but are in clinical trials include “drugs acting on dopaminergic (tiapride, lisuride and flupenthixol) and serotonergic mechanisms (buspirone, fluoxetine nefazodone, ritanserin and ondansetron) (Kiefer and Mann, 2005). In addition, drugs that stabilize mood and anticonvulsant drugs (e.g. carbamazepine and topiramate) are being tested. Sedative-anxiolytics drugs, such as benzodiazepines and γ -hydroxybutyric acid may also be beneficial (Johnson, 2005; Kiefer and Mann, 2005). Other targets for drug development may include opioid receptors, cannabinoid receptors, cholinergic receptors, calcium channel blockers, or compounds that modulate GABAergic and glutamatergic systems (e.g. baclofen, gabapentin, valproic acid, and vigabatrin). Of the drug therapies currently available, naltrexone and acamprosate seem to be most effective in preventing relapse and decreasing consumption, respectively, when used in conjunction with psychotherapy (Kiefer and Mann, 2005).

Because men and women respond differently to alcohol, treatments for alcoholism also need to take into account sex difference in alcoholic complications. Differences in the influence of gonadal steroid hormones, neurotransmitter systems, patterns of behavior, increased brain and organ damage in women, and a variety of other factors need to be taken into consideration when treating alcohol dependent patients. In addition, psychological and social factors need to be taken into consideration when treating alcoholic patients. Women are often passive in seeking help and are less likely to enter treatment groups due to the associated social stigma. Women are also less likely to be encouraged by a partner to seek assistance. The middle-aged alcoholic women are more likely to be depressed, use psychoactive drugs, and express more family-related problems than alcoholic men (Walter

et al., 2003). It seems clear that sex difference in alcoholic addition and complication are likely due to many other contributing factors, including neurobiology, physiology, genetics, gonadal hormones, social factors and environmental factors (Walter et al., 2003), which should all be taken into consideration for treatment of alcoholism.

CONCLUSION

As with many areas of science, basic research on the effects of alcohol has focused primarily on male subjects. Society has also had the long held belief that alcoholism and alcohol-related problems are predominantly a male phenomenon, because rates of alcohol dependence are greater in men than in women. However, alcohol dependence does affect an estimated 5% of women in the United States with rather serious consequences. Accumulating evidence has made it apparent with regards to the sex dimorphism in response to alcohol consumption including neuroadaptations leading to the development of alcoholism and the medical consequences of alcohol abuse. Continued research focused on the sex difference in alcohol dependence is needed to better our understanding of this devastating health problem in order to develop appropriate individualized treatment for both men and women.

Acknowledgments

The research in the Ren laboratory is supported by NIH R15 AA13575 and NIH/NIAAA 1R01 AA013412. We sincerely express our apology to those authors whose important work cannot be cited here due to space limitation.

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