Genetic and Environmental Influences on the Development of Alcoholism

Resilience vs. Risk

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ABSTRACT: The physiological changes of adolescence may promote risk-taking behaviors, including binge drinking. Approximately 40% of alcoholics were already drinking heavily in late adolescence. Most cases of alcoholism are established by the age of 30 years with the peak prevalence at 18–23 years of age. Therefore the key time frame for the development, and prevention, of alcoholism lies in adolescence and young adulthood. Severe childhood stressors have been associated with increased vulnerability to addiction, however, not all stress-exposed children go on to develop alcoholism. Origins of resilience can be both genetic (variation in alcohol-metabolizing genes, increased susceptibility to alcohol's sedative effects) and environmental (lack of alcohol availability, positive peer and parental support). Genetic vulnerability is likely to be conferred by multiple genes of small to modest effects, possibly only apparent in gene–environment interactions. For example, it has been shown that childhood maltreatment interacts with a monoamine oxidase A (MAOA) gene variant to predict antisocial behavior that is often associated with alcoholism, and an interaction between early life stress and a serotonin transporter promoter variant predicts alcohol abuse in nonhuman primates and depression in humans. In addition, a common Met158 variant in the catechol-O-methyltransferase (COMT) gene can confer both risk and resilience to alcoholism in different drinking environments. It is likely that a complex mix of gene(s)—environment(s) interactions underlie addiction vulnerability and development. Risk–resilience factors can best be determined in longitudinal studies, preferably starting during pregnancy. This kind of research is important for planning future measures to prevent harmful drinking in adolescence.

KEYWORDS: MAOA; HTTLPR; COMT; polymorphism; adolescents

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INTRODUCTION

Adolescent alcohol misuse is a major factor in teen car crashes, homicides, and suicides, the three leading causes of death for 15–24-year olds. Drinking tends to start in the teenage years; the average age of the first drink is 11 years for boys and 13 years for girls. In 2004, 19%, 35%, and 48% of 8th, 10th, and 12th graders, respectively, admitted drinking in the previous month.[1] Binge drinking (≥5 drinks/occasion in any 2-week period) is common at this age. Approximately 60% of all adolescents who drink alcohol indulge in this harmful drinking pattern: in 2004 the percentages of binge drinkers were 11%, 22%, and 29%, respectively, for 8th, 10th, and 12th graders.[1] The main reasons teenagers give for drinking to excess are sheer enjoyment and the relief of social anxiety: that is, the perceived improvement of social skills. Thankfully, not all adolescent heavy drinkers become addicted to alcohol: the prevalence of 12-month alcohol use disorders (abuse + dependence) (AUD) is 5% in both boys and girls aged 12–17 years with a peak prevalence at age 18–23 years: 20% in men and 10% in women.[2] By the ages of 23–30 years, 50–75%, respectively, of all AUDs have been diagnosed.[3] Thus the key time frame for the development of alcoholism lies in adolescence and young adulthood.

HERITABILITY OF ALCOHOLISM

Alcoholism has been described as the interminable cycling of preoccupation and anticipation, binge–intoxication, and withdrawal–negative affect.[4] A recent meta-analysis of twin studies has shown that the heritability (the genetic component of interindividual variability) of all addictive substances ranges from 40% to 60%.[5] The heritability of alcoholism, derived from nearly 10,000 twin pairs, is 50%.[5] Thus genetic and environmental factors are almost equally important in alcoholism risk, although the proportions will vary in different populations. Genetic vulnerability to alcoholism is likely to be due to numerous genes of small to modest effects in many neurotransmitter systems (e.g., opioid, serotonin, dopamine, GABA, glutamate, and cannabinoid) and signal transduction pathways within the mesolimbic dopamine reward pathway[6] and interacting stress response systems.[7] Some individuals may be more vulnerable to the development of long-term or permanent neurobiological changes in response to heavy alcohol use resulting in addiction.

RISK FACTORS FOR THE DEVELOPMENT OF ALCOHOLISM

Alcoholism runs in families. A child with an alcoholic parent has a 4- to 10-fold increased risk of developing alcoholism themselves. This can be due to both genetic and environmental factors. Environmental influences, such as

alcohol availability, parental attitudes, and peer pressure, strongly influence if and when a child starts to drink. Not surprisingly, frequent drinking in adolescence has been shown to independently increase the risk for alcoholism (OR = 3 [95% CI: 1–8]).[8] Starting to drink before the age of 15 years is associated with a fourfold increased risk for lifetime alcoholism compared with starting at the age of 21 years.[9] One reason for this may be that heavy drinking during adolescence can impair brain development (particularly the hippocampus) and function (particularly learning and memory).[10,11] Animal studies have demonstrated permanent changes in adult brain resulting from adolescent binge drinking.[12] Two important neurotransmitter systems that are affected by alcohol consumption and undergo substantial changes during adolescence are dopamine, implicated in the rewarding effects of alcohol, and GABA, implicated in alcohol's sedating effects and the development of tolerance.[11] For developmental reasons, adolescents are less influenced by the sedating effects of alcohol than adults. Longitudinal studies starting with young adults have shown that a heritable trait, a low level of response to the sedating effects of alcohol, predicts a fourfold increased risk of future alcoholism.[13] Thus vulnerable, low-response individuals who start drinking when very young may be at even greater risk for addiction.

Severe childhood stressors, especially emotional (harsh, inconsistent discipline, hostility, rejection), physical, and sexual abuse, have been associated with increased vulnerability to addiction. Childhood sexual abuse is associated with a fourfold increase in the lifetime prevalence of alcoholism and other drugs of abuse in women.[14] Among female drug users, 70% report childhood sexual abuse.[15] In populations, such as some American Indian tribes that have a high prevalence of both adverse childhood events and alcoholism, childhood abuse and neglect is associated with a twofold increase in risk for alcoholism for one exposure, increasing to a three- to sevenfold increased risk for $\geq$4 exposures.[16]

Children of depressed mothers experience increased antisocial behavior and conduct problems, thought to be predominantly due to impoverished nurturing.[17] Teacher-rated hyperactive and conduct problems in boys aged 8 years have been shown to predict frequent drunkenness 10 years later.[18] Childhood antisocial behavior predicts regular alcohol use in early adolescence and the development of alcoholism later on.[8]

In rodents it has been shown that poor maternal contact in early life results in several neurobiological changes that persist into adulthood. These include effects on the hippocampus that are due to alterations in gene transcription.[19] It is not known whether these same permanent changes occur in humans but if so, the combination of these epigenetic effects and drinking at a young age may account for some aspect of increased addiction vulnerability.

Not all children who experience adverse events subsequently develop psychopathology predictive of alcoholism or take up drinking. What makes some children resilient, despite experiencing severe stressors?

RESILIENCE FACTORS

Genetic: Alcohol-Metabolizing Enzymes

Genetic variation in alcohol-metabolizing genes, seen in Asian and Jewish populations, provides protection against the development of heavy drinking and subsequent alcoholism (FIG. 1). Alcohol dehydrogenases (ADH) metabolize ethanol to acetaldehyde, a toxic intermediate, which is then converted to acetate by aldehyde dehydrogenases (ALDH). Approximately half of Japanese, Chinese, and Koreans, together with other East Asian individuals, have functional polymorphisms at four different genes: ADH2, ADH3, ALDH1, and ALDH2. The most important genetic variants are ALDH2∗2 (Glu487Lys), which dominantly inactivates ALDH2, the mitochondrial enzyme responsible for most acetaldehyde metabolism in cells, and ADH2∗2 (Arg47His), a superactive variant. ADH2∗2 and ALDH2∗2 act independently and additively to increase acetaldehyde levels: ADH2∗2 increases the rate of synthesis and ALDH2∗2 decreases the rate of metabolism.[20,21] Therefore when individuals with the ALDH2∗2 and ADH2∗2 genotypes drink even small amounts of alcohol they experience a very unpleasant reaction characterized by facial flushing, headache, hypotension, palpitations, tachycardia, nausea, and vomiting. The ALDH2∗2 variant causes a stronger flushing reaction than ADH2∗2; the ALDH2∗2/2 homozygous genotype is nearly completely protective against heavy drinking and the heterozygous genotype is partially protective. The ADH2∗2 allele has been shown to account for 20–30% of the alcohol intake variance between light drinking and heavy drinking Jews, and it has been suggested that the relatively high frequency of the ADH2∗2 allele might be implicated in the lower levels of alcohol consumption and increased sensitivity to alcohol observed among Jews.[22,23]

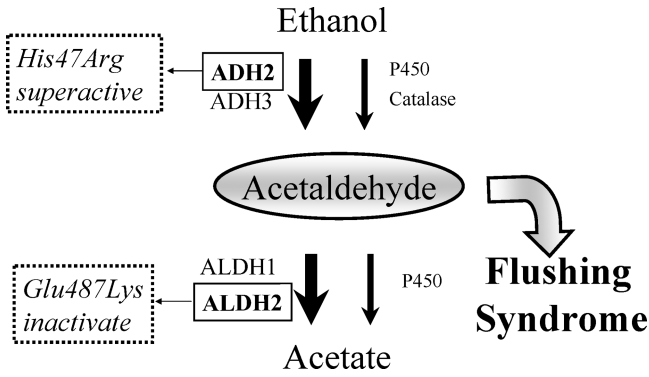

FIGURE 1. Functional polymorphisms in ethanol metabolism confer resilience to the development of alcoholism.

Environmental Factors

Parental mental health and family interaction strongly influence the child's own mental health. Good family functioning, good parent–child relationships and close parental monitoring, higher socioeconomic status, and educational aspiration have been shown to protect against heavy drinking in adolescence.[24]

Gene × Environment Interactions

There are likely to be multiple genes, as well as gene–gene and gene–environment interactions, underlying a complex, heterogeneous disorder, such as alcoholism (FIG. 2). So far, relatively few common, functional genetic polymorphisms have been discovered. However, recent studies have demonstrated that three common polymorphisms that have significant effects on central nervous system (CNS) availability of the neurotransmitters serotonin, dopamine, and norepinephrine, interact with childhood environmental factors to predict alcoholism and associated psychopathology.

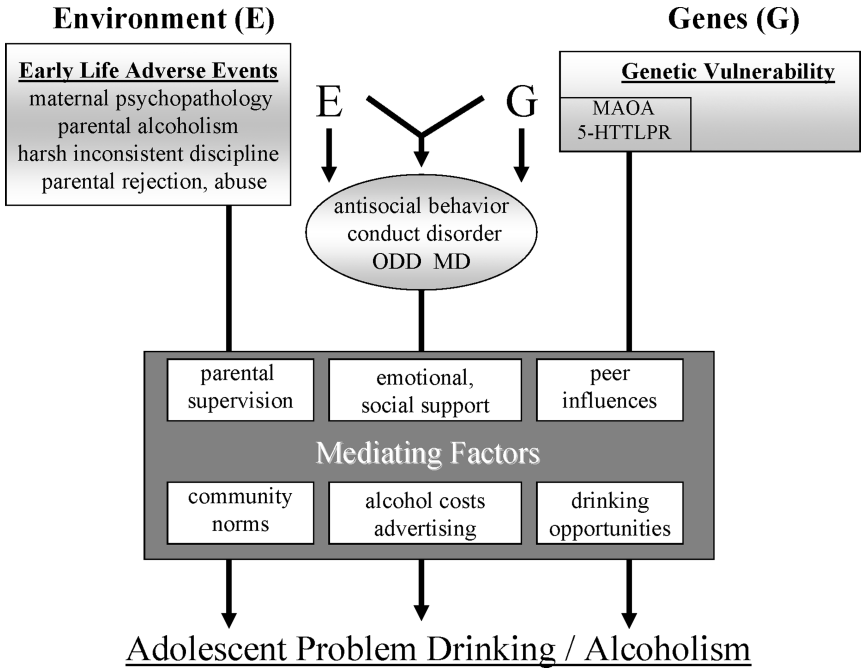

FIGURE 2. Individual and interactive effects of genetic vulnerability and early childhood adverse events on the development of problem drinking and alcoholism in adolescence. MD = major depression, ODD = oppositional defiant disorder.

The neurotransmitter serotonin (5-HT) plays an important role in mood control and is implicated in impulsivity, anxiety–dysphoria, and alcoholism. Monoamine oxidase A (MAOA) is primarily responsible for 5-HT degradation. Recent studies have shown that maltreatment (parental rejection, harsh discipline, physical and sexual abuse) and family adversity (interparental violence, neglect) experienced by young boys interact with a genotype conferring low levels of MAOA expression to predict childhood conduct disorder and adult antisocial behavior, often antecedents for addiction.[25,26] Thus the gene variant that produces high MAOA levels confers resilience against the development of alcoholism-related psychopathology in maltreated boys.

5-HT actions are terminated by the serotonin transporter (5-HTT) through reuptake at the synaptic cleft. 5-HTTLPR is a common 44-base-pair insertion/deletion in the 5-HTT promoter region; the short "S" allele is associated with an approximately 50% reduction in transporter availability and consequent increase in synaptic 5-HT compared with the longer "L" allele. Individuals with the S allele show greater amygdala activation in response to fearful stimuli[27] as well as greater coupling between the amygdala and the ventromedial prefrontal cortex,[28] a limbic brain area implicated in major depression.[29] Depression is predicted by the interaction between the S allele and cumulative stressful life events in young adults and adolescents.[30,31] In addition, it has been shown that maltreatment combined with the S allele in children who had poor social support was associated with increased depressive symptoms, however, good social support protected children from the adverse effects of the maltreatment–genotype interaction.[32] Depressive symptoms in childhood are often antecedents for adult alcoholism. Indeed, the interaction between early life stress (emotional deprivation) and the S allele has been shown to predict increased alcohol consumption in female rhesus macaque monkeys.[33] Thus the 5-HTTLPR L allele can be regarded as a resilience factor.

Catechol-O-methyltransferase (COMT) plays a major role in the metabolism of CNS dopamine and norepinephrine. A common polymorphism, Val158Met, is responsible for three- to fourfold variation in enzyme activity. The lower activity Met158 allele has been associated with greater activation in emotion-modulating brain regions, including the limbic system and connected prefrontal areas, in response to unpleasant visual stimuli.[34] COMT Met158 has also been associated with a more anxious, sensitive, cautious personality.[35–37] Both COMT Val158Met alleles have been implicated in alcoholism but in different populations. The Met158 allele has been associated with increased social drinking and late onset alcoholism in European Caucasian men.[38–40] However, Met158 is associated with protection against alcoholism in Plains American Indians.[41] The explanation may lie within the differing drinking environments. European alcoholics tend to drink on a daily basis, however, alcoholics within many American Indian tribes, such as the Plains Indians, tend to drink heavily but episodically.[41] Thus the Met158 allele may be a vulnerability factor for anxiety-relieving maintenance drinking in some societies, such as Europeans, but in other societies, such as American Indians, the anxious, cautious

personality associated with the Met158 allele may protect against excessive bouts of heavy drinking. Adolescents tend to have the same binge-drinking pattern; it remains to be seen whether COMT Met158 is a resilience factor against heavy drinking in adolescents.

FUTURE DIRECTIONS

Longitudinal research is the best way of tracking the influences of parental psychopathology and other early childhood adverse events on the emergence of behavioral problems and psychopathology in the child as well as the child's own eventual alcohol use. We are undertaking gene–environment interaction studies in a cohort of 7,500 children from Avon, UK, intensively followed from conception in 1991–1992 onward (Avon Longitudinal Study of Parents and Children (ALSPAC)) (www.alspac.bris.ac.uk). Results will be forthcoming in the near future.

CONCLUSION

Adolescence is a critically vulnerable time for the development of risky drinking habits that may lead to permanent neurobiological changes with significant consequences including the development of addiction. Environmental risk–resilience factors have been well documented and have so far been the main focus for preventive measures. However, recent studies indicate that genetic vulnerability in combination with environmental factors may affect the risk–resilience balance. Thus it is likely that a complex mix of gene(s)–environment(s) interactions are likely to underlie addiction vulnerability and development. This fact should be taken into account when planning future measures to prevent harmful drinking in adolescence.

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