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The Influence of Gene–Environment Interactions on the Development of Alcoholism and Drug Dependence

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Abstract

Alcoholism and drug dependence are common psychiatric disorders with a heritability of about 50%; therefore genetic and environmental influences are equally important. Early-life stress is a predictor of adolescent problem drinking/drug use and alcohol/drug dependence in adulthood, but moderating factors governing the availability of alcohol/drug are important. The risk–resilience balance for addiction may be due in part to the interaction between genetic variation and environment stressors (G×E); this has been confirmed by twin studies of inferred genetic risk. Measured genotype studies to detect G×E effects have used a range of alcohol consumption and diagnostic phenotypes and stressors ranging from early-life to adulthood past year life events. In this article, the current state of the field is critically reviewed and suggestions are put forth for future research.

Keywords

Childhood maltreatment; Sexual abuse; Physical abuse; Gene–environment interactions; Alcoholism; Drug dependence; Stressful life events; Crossover of risk; Differential susceptibility hypothesis; Alcohol dependence; Cocaine dependence; Adolescent problem drinking; HPA axis; Stress circuitry; Cortisol; Reward pathway; Dopamine; Corpus callosum; SLC6A4; 5-HTTLPR; MAOA-LPR; CRHBP; CRHR1; FKBP5; GABRA2; COMT; PER1; KCNJ6

Introduction

In most countries and throughout historical time, alcohol has been legally produced from a remarkable range of products and is consumed to enhance well-being and social relationships. However, a relatively large proportion of individuals are unable to remain within safe limits of consumption, with often devastating consequences for the afflicted individuals, their families, and society at large. Alcoholism is a common psychiatric disorder. Results from a nationally representative sample (NESARC [National Epidemiologic Survey on Alcohol and Related Conditions]) of 43,093 US adults have shown that the prevalence of lifetime *DSM-IV* alcohol dependence (AD) and alcohol abuse (together called alcohol use disorders [AUDs]) is 12.5% and 17.8%, respectively [1]. AUDs are twice as common in men as they are in women [1]. The same survey looked at all classes of illegal drugs, legal drugs, and inhalants/solvents and found that the prevalence of lifetime *DSM-IV* drug dependence (DD) was 2.6% and drug abuse was 7.7% [2]. Unlike AUDs, the

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prevalence of DD was similar in men and women [2]. Because alcoholism is a much more widespread problem in society, this addiction is the predominant focus of this review.

The essential features of addiction are loss of control over consumption, obsessive thoughts about the drug, and continuation of use despite knowledge of negative health and social consequences [3, 4]. It has been established, largely through twin and adoption studies, that the heritability (the genetic component of the variance) of all addictive substances lies between 40% and 70%, the heritability of alcoholism is about 50%, and that of cocaine and opiate addiction is about 60% to 70% [5]. Therefore, genetic and environmental risk factors for the development of addictive disorders are equally important. Moreover, alcoholism is a heterogeneous disorder. A latent class analysis of the NESARC dataset identified five homogeneous subtypes distinguishable by family history, age at AD onset, endorsement of *DSM-IV* AUD criteria, and comorbidity [6]. These subtypes are likely to differ in genetic and environmental risk factors.

There is accumulating evidence that variation in some genes may only increase the risk of the development of AUDs and DD in individuals who have experienced significant stress, perhaps particularly in childhood [7]. However, only a half or less of children exposed to severe maltreatment have developed psychopathology, including AUDs and DD, by early-adulthood [8]. This risk–resilience balance for psychopathology may be in part a result of the interaction between genetic risk and environmental stressors (G×E), and this topic is the focus of this review.

Characteristics of Early-Life Stress

Many studies have shown that early-life stress is a nonspecific predictor of many types of pathological behavior and psychopathology, including early-onset adolescent drinking and adult AUDs and DD [9•]. Early-life stress can be grouped into childhood maltreatment (childhood sexual abuse [CSA], physical and emotional abuse, physical and emotional neglect) and stressful life events (SLEs), although these two groups of stressors often co-occur [10]. Little specificity has been found for the association of particular types of childhood maltreatment and SLEs with particular psychiatric disorders [10, 11], and the severity is positively correlated with poorer outcomes in adulthood [9•].

Exposure to SLEs is common in the general population. The National Comorbidity Survey Replication (NCS-R) reported that 53% of adults had experienced some kind of stressor before age 18 [10], most commonly parental divorce or death, family violence, economic adversity, or mental illness. The NCS-R prevalence for childhood maltreatment subgroups was 8.4% for physical abuse, 6% for sexual abuse, and 5.6% for parental neglect [10]. However, higher prevalences have been reported in other studies (eg, in Native American tribes) [9•].

Although half of adults have been exposed to some kind of childhood stressor, according to the NCS-R, only 26% of substance use disorders and approximately 30% of mood and anxiety disorders with onset at ages 13 to 29 years are predicted by SLEs plus childhood maltreatment [10]. Not surprisingly, a high percentage (30%–80%) of treatment-seeking alcoholics and drug addicts have experienced childhood maltreatment, and the effect might be greater in women [12]. Therefore, G×E effects may be more likely to be detected in certain subtypes of alcoholics, such as the NESARC types 4 and 5: treatment-seeking, severe alcoholics with strong family histories and comorbid disorders [6].

The Influence of Early-Life Stress on Alcoholism and Drug Dependence

Many studies have demonstrated a link between retrospectively documented childhood stressors and AUDs and DD [13–20]. The NESARC community survey showed that experiencing at least two childhood SLEs significantly increased the risk of AD [19]. However, unlike other psychiatric disorders, there can be a gating effect between proximal stressor and distal outcome because access to alcohol/drug is essential for the development of AUDs and DD. Therefore, restrictive or permissive environments for alcohol/drug use are moderating influences on disease outcome.

A US longitudinal study of approximately 900 children with court-documented cases of childhood (0–11 years) sexual and physical abuse and neglect followed through to middle age showed that childhood maltreatment predicted the development of AD in women, but not men [21]. Moreover, in women, the pathway from childhood maltreatment to middle-aged drug use was moderated by negative risk factors [22, 23], but for men, there was no pathway from childhood maltreatment to adult drug use [23]. The ALSPAC (Avon Longitudinal Study of Parents and Children), a British, community-representative cohort study of 7,500 children followed from prebirth onward, showed that in both sexes, exposure to family adversity and SLEs in the first 3 years of life predicted hyperactivity and conduct problems at age 4, persisting until at least age 7 [24]. Some [25, 26], but not all [27] studies have shown that externalizing behavior in prepubertal children, particularly boys, predicts AUDs in early-adulthood. Therefore, by extrapolation, the ALSPAC study implies that early-life stress may predict adult AUDs.

Early-Life Stress Predicts Early-Onset Problem Drinking

Alcohol consumption is commonly initiated and drinking patterns established during adolescence and early-adulthood. Indeed, about 50% of alcoholics have developed their symptoms by age 23 [28]. Several studies have demonstrated the association between childhood stressors and early onset of drinking and binge drinking (≥5 drinks/occasion in any 2-week period) [29, 30]. Notably, a large study of adults showed that early-life stressors were strongly associated with early onset of alcohol use across four successive birth cohorts dating back to 1900, demonstrating the stability of this association over a long period of time [31]. Early age at onset (<15 years) of alcohol use predicts adult AD [26, 32]. Two large British longitudinal studies have shown that adolescent binge drinking at age 16 predicts AD and illicit drug use in adulthood [33], and frequent drinking at age 14 to 15 years predicts adult AD [34]. Moreover, individuals exposed to childhood maltreatment were substantially more likely to report that they drank to cope during the first year of alcohol use [29], another predictor of the development of alcohol problems [35]. Therefore, adolescent problem drinking may be one pathway from proximal stressors to distal development of AUDs and DD.

Neuroendocrine and Neurobiological Consequences of Early-Life Stress

Accumulating evidence from preclinical studies has shown that early-life stress at a time of developmental plasticity can result in widespread, enduring alterations in stress circuitry, including the hypothalamic-pituitary-adrenal (HPA) axis, the mesolimbic dopamine reward pathway, and brain morphometry. It is likely that genetic variation combined with stress exposure will increase the likelihood of physical changes that are potential risk factors for addiction. One such example is the interaction between *CRHR1* gene variation and childhood maltreatment as a predictor of HPA axis reactivity [36]. Another example is the finding that Met allele carriers of the functional *BDNF* Val66Met polymorphism were more sensitive than Val/Val homozygotes to the effects of early-life stress on gray matter volume shrinkage [37].

Effects of Early-Life Stress on Stress Circuitry and Mesolimbic Dopamine Reward Pathway

Stress induces activation of the HPA axis and secretion of the glucocorticoid hormone cortisol. Many studies have shown that early-life stress in humans, monkeys, and rodents results in alterations in behavioral and HPA axis responses to stress [9•, 38]. It is noteworthy that a blunted HPA axis stress response has been found in alcoholics as well as nonalcoholics from alcoholic families [39, 40], boys with persistent antisocial behavior [41], and women with high neuroticism, a predictor of psychopathology (including alcoholism) [42]. Thus, a blunted stress response may indicate vulnerability to addiction, perhaps due in part to exposure to early-life stress.

Studies in rats have shown that early-life stress (maternal separation or handling) has long-lasting effects on the mesolimbic dopamine pathway [9•] that is fundamental to the sensations of pleasure induced by natural rewards such as food and sex and also alcohol-/drug-related rewards. This “reward” pathway originates in the ventral tegmental area of the midbrain and projects to the nucleus accumbens, the limbic system, and the orbitofrontal cortex. Alcohol and drug intake is associated with increased synaptic dopamine in the nucleus accumbens and elsewhere in the reward pathway. Early-life stress in rats can result in profound and lasting changes in the responsiveness of dopamine neurons to stress and drugs in adulthood [43–45]. One congruent finding in humans was that a cortisol response to a psychosocial stress task was highly correlated with increased firing of dopamine neurons in the reward pathway, but only in young adults who had experienced poor parental care [46]. Exposure to early-life stress in rats also results in alterations in opiate and γ-aminobutyric acid $(GABA)_A$ receptors, and long-term changes in *BDNF* expression [45, 47, 48].

Effects of Early-Life Stress on Brain Morphometry

Childhood maltreatment is associated with abnormalities in brain development [9•, 38], most consistently with decreased volume of the corpus callosum together with other white tract abnormalities [49–51]. Notably, AUDs in adults are associated with white matter volume loss and demyelination, particularly in the corpus callosum, and this has implications for efficiency in interhemispheric processing [52, 53]. Disrupted corpus callosum microstructure is also found in adolescent binge drinkers [54] and those with adolescent-onset AUDs [55]. It remains to be seen whether this might be a consequence of childhood maltreatment and/ or the effects of alcohol on the developing brain.

Later-Life Stressors

Longitudinal studies have shown that maltreatment at an age younger than 5 years is related to greater psychopathology in adulthood than maltreatment experienced later in childhood [27, 56, 57]. It has not yet been determined whether stressors experienced in adolescence or adulthood are sufficient to detect a G×E effect on AUDs or DD. For example, Binder et al. [58] showed that childhood maltreatment, but not adult life stressors, had an interactive effect with *FKBP5* gene variation to predict post-traumatic stress disorder. However, it has been observed that proximal stress can beget distal stress. For example, childhood maltreatment has been associated with increased risk of physical assault and rape in adulthood [59]. Therefore, stress measured in adulthood could to some extent be a proxy for stress exposure in childhood.

Gene–Environment Correlations

A history of parental addiction is a strong predictor of AUDs and DD in their offspring and is associated with more severe symptoms [60]. Although the genetic risk of externalizing disorders transmitted from parents to child influences the likelihood that the child will be

exposed to early-life stress and will develop the disorder, several studies have shown that childhood stressors have an independent effect on the risk of adult externalizing disorders, including AUDs and DD [20, 61]. A longitudinal study of twins and their parents illustrates this point by demonstrating that there is a direct causal effect of childhood adversity on child conduct disorder over and above any indirect genetic correlation [62].

Gene–Environment Studies Using Inferred Genetic Risk

Results from twin studies suggest that there may be two pathways for genetic influence on the development of AUDs: an early-onset pathway driven in part by genetic risk of externalizing disorders and a later, adult-onset pathway driven by genetic risk factors that are specific to AUDs [63, 64•]. Twin studies have also shown that environmental moderation (principally alcohol availability, peer deviance, and low prosocial behaviors and parental monitoring) of genetic effects on alcohol consumption is more pronounced in adolescence than in adulthood [64•]. Several twin and adoption studies have analyzed ways in which environmental factors interact with aggregate genetic effects to influence drinking behaviors. Most of these G×E studies have looked at moderating factors such as parental and peer influences and marital and religious status. Few studies have looked at early-life stressors. Exceptions include a large study of twin pairs aged 5 years that found that the effect of physical maltreatment increased the risk of conduct problems by 24% in children at high genetic risk, but by only 2% in children at low genetic risk [65]. The Minnesota Twin Family Study also showed that at age 17 years, genetic factors become more important as predictors of externalizing disorders, including substance abuse, in the context of environmental adversity [66]. For a comprehensive review of other studies of inferred genetic risk, see the article by Young-Wolff et al. [67•].

Measured Gene–Environment Effects

G×E interactive effects are likely for stress- and anxiety-related genes. These include HPA axis genes such as those encoding corticotropin-releasing hormone (*CRH*), its receptor (*CRHR1*) and binding protein (*CRHBP*), the glucocorticoid receptor (*NR3C1*), and its co-chaperone (*FKBP5*). GABAergic pathway genes, such as *GABRA2*, are likely candidates, as are those genes with a glucocorticoid response element located within their promoters (regulatory region). Examples of the latter are the monoamine oxidase A (*MAOA*) gene that encodes an enzyme involved in the degradation of central nervous system serotonin and norepinephrine; the catechol-*O*-methyltransferase (*COMT*) gene that encodes the enzyme that is implicated in central nervous system dopamine and norepinephrine metabolism; and *SLC6A4*, the gene encoding the serotonin transporter that regulates synaptic serotonin availability. To date, many papers have been published showing interactive effects between stress genes and childhood stressors on depression phenotypes, post-traumatic stress disorder, and suicidal behavior, but there have been relatively few studies demonstrating G×E effects on AUDs and DD. There are, however, studies showing G×E effects on alcohol consumption phenotypes, on behaviors such as childhood conduct/hyperactivity disorders that often predate adult AUDs and DD, and on antisocial behavior that is often comorbid with AUDs and DD.

Specific Genes

Several G×E papers focusing on stress-related genes and alcohol consumption phenotypes in the Mannheim Study of Children at Risk have been published recently. This is an epidemiologic cohort study originally of 384 German children followed since they were in utero. Environmental stressors include family adversity during the year before birth, a measure derived from parental interview at 3 months after birth, and recent SLEs.

PER1

The circadian rhythm gene period 1 (*PER1*) is activated by stress hormones and, as was shown in mice, influences stress-related alcohol consumption [68•] and was associated with AD in a large sample of adults [68•]. In a group of 273 individuals aged 18 years, there were G×E effects of adversity and a *PER1* promoter single nucleotide polymorphism (SNP) rs3027172 shown to be functional [68•] on drinking behavior such that carriers of the minor C allele who were also exposed to high family adversity had an increased frequency of heavy drinking [68•].

KCNJ6

The *KCNJ6* gene encodes a potassium channel (GIRK2) with inhibitory effects on dopaminergic tone that is enhanced by *CRH*. Individuals (age 19) exposed to high family adversity and more severe recent SLEs (assessed separately, not cumulatively) who were also carriers of the minor homozygote (GG) of SNP rs2836016, previously associated with adulthood AD, had the highest AUDIT (Alcohol Use Disorders Identification Test) scores [69].

CRHR1

Increased severity of adolescent SLEs was associated with earlier age at first drink and heavier alcohol consumption, but only in carriers of the *CRHR1* rs1876831 CC major homozygote. Similar results were obtained at ages 15 and 19 years [70, 71]. Corresponding results were found in a group of more than 1,000 adults from the Nicotine Addiction Genetics project. In this sample, CSA was associated with greater lifetime alcohol consumption and AD only among adults homozygous for the haplotype (chromosomal region) that included the rs1876831 C allele [72].

FKBP5 and CRHBP

Recent studies have shown interactive effects between *FKBP5* and childhood maltreatment on violent behaviors, including suicidality, that are often comorbid with AUDs and DD. In a group of Italian prisoners, *FKBP5* variation had a significant effect on aggressive and violent behavior, but only in individuals exposed to childhood trauma, particularly physical abuse [73]. *FKBP5* and *CRHBP* variation were shown to predispose individuals—independently and additively—to suicidal behavior in a sample of African Americans who had experienced considerable childhood maltreatment [74, 75].

SLC6A4

The *SLC6A4* gene that encodes the serotonin transporter has a repeat promoter polymorphism, 5-HTTLPR. The “L” long allele is associated with increased gene activity and therefore increased reuptake of serotonin from the synaptic cleft compared with the “S” short allele. In the Mannheim Children at Risk Study, male (but not female) LL homozygotes with significant adversity consumed more drinks and had more heavy drinking days than S allele carriers and individuals unaffected by adversity. This G×E interaction was present for both early family adversity and recent SLEs (separate analyses), but the effects were stronger for recent SLEs [76]. In contrast, in a small study from the United States, the S allele predicted early alcohol use in maltreated children entering out-of-home care [77]. Likewise, the S allele predicted the use of illicit drugs in Italian adolescents who had experienced poor maternal care [78]. The S allele has also been associated with increased drinking and drug use in US college students who had experienced multiple past year SLEs [79]. Sex-specific effects also have been detected in rhesus macaque monkeys, but in contrast to the Mannheim study, only S allele carrier females with exposure to early-life stress (peer rearing vs maternal rearing) consumed more alcohol and progressively increased

levels of consumption over time compared with non–S allele carriers [80]. Finally, COGA (the Collaborative Study on the Genetics of Alcoholism) found no evidence for any interactive effect between 5-HTTLPR genotype and past year SLEs on AD risk [81]. Therefore, G×E results for 5-HTTLPR have thus far been mixed, but this may not be surprising because there is considerable variability in the different studies of both stressors and alcohol-related phenotypes.

MAOA

The X-linked *MAOA* gene has a repeat promoter polymorphism (MAOA-LPR) that influences gene activity. Several studies have shown G×E effects on childhood conduct and hyperactivity disorders, predictors of AUDs and DD [25], and on antisocial behavior that is often comorbid. Longitudinal G×E studies have shown that childhood maltreatment [82–84] and family adversity [85] interact with the MAOA-LPR low-activity variant to predict childhood conduct disorder and adult antisocial behavior. In the ALSPAC longitudinal study, the low-activity variant was associated with increased hyperactivity at age 7 years in children exposed to multiple SLE in the first 3 years of life [24]. One retrospective study showed an effect on AD: in women from a Southwestern American Indian tribe, the low-activity allele was associated with AD, particularly antisocial alcoholism, but only in women exposed to CSA [86]. Other retrospective studies have yielded mixed G×E results for antisocial behavior [9•]. Further studies have looked at G×E effects on drinking behaviors. In a large Swedish study of high school students, psychosocial risk (quality of family relations, sexual abuse) was associated with high alcohol consumption in boys with the low-activity variant and, in contrast, with high alcohol consumption and criminal activity in girls with the high-activity variant [87, 88].

GABRA2

The *GABRA2* gene has been implicated in AUDs and DD [89]. In a study of treatment-seeking, substance-dependent African American men, one common *GABRA2* haplotype that tags African ancestry appeared to confer resilience to the development of addiction (AD/heroin/cocaine) in individuals exposed to severe childhood maltreatment. Moreover, one unlinked, potentially functional intron 2 SNP rs11503014 increased the risk of addiction (particularly to cocaine), but only in association with severe childhood maltreatment [90•]. It remains to be seen whether these rs11503014 G×E effects play a role in risk–resilience for development of substance dependence in other ethnic groups.

Gene–Environment Moderating Factors

Several studies have looked at developmental trajectories for externalizing disorders using the Child Development Project, a longitudinal study of a community-based sample from age 5 to early-adulthood. These studies found a moderating effect of perceived parental monitoring at age 11 and age 14, respectively, on the association of *GABRA2* and *CHRM2* (encoding the cholinergic muscarinic 2 receptor) with externalizing trajectories [91, 92]. The genetic risk was manifest in a low parental monitoring environment that in and of itself may be a proxy for childhood stressors.

Gene–Environment Crossover of Risk

G×E crossover of risk has been observed in longitudinal studies [24, 82, 83, 85]. For example, in the ALSPAC study, girls with the low-activity MAOA-LPR variant showed both increased hyperactivity after stress exposure and decreased hyperactivity after little or no stress exposure compared with girls without the low-activity variant [24]. Another example comes from the Mannheim Children's Study in which adolescents were genotyped for the functional *COMT* Val158-Met polymorphism. In Met/Met homozygotes only, low

perceived parental supervision at age 15 was associated with increased drinking activity at age 19, but favorable parental supervision was associated with lower drinking activity compared with the other two genotype groups [93]. Thus, one genotype might confer both risk of behavioral disinhibition in the presence of stress and behavioral inhibition in the absence of stress. Genetic background may therefore make some individuals more susceptible to good and bad environmental influences—the so-called differential susceptibility hypothesis [94]. However, it should be noted that some have questioned whether the crossover effect might actually be a statistical artifact [92].

Conclusions

Studies of inferred genetic risk indicate that G×E effects are indeed likely to underlie the risk of AUDs and DD. However, the challenge is to detect G×E effects in human studies using measured genotypes. The limited number of studies have so far largely focused on a range of alcohol consumption phenotypes in non-AUD/DD adolescents or young adults, whereas a better population to detect G×E effects might be treatment-seeking, severe alcoholics [6] or drug addicts, many of whom have a history of childhood maltreatment. Studies have included a range of stressors from childhood maltreatment to past year SLEs in adults. It has yet to be determined whether recent SLEs in adults without a history of childhood maltreatment are strong enough to unmask G×E effects. The neurobiological changes resulting from early-life stress may be influenced by genetic variation and may confer vulnerability to addiction. Whether the availability of alcohol/drug, particularly in adolescence, is sufficient to promote onset of disease or whether later stress exposure, perhaps resulting in drinking to cope, is a requirement remains to be determined. Clearly, it is important to have longitudinal studies, starting in early-childhood, that look at the effect of cumulative stress. As it is generally accepted that the genetic risk of AUDs and DD is likely to derive from numerous genes, each with small to moderate effects, the number of potential G×E interactions is large, therefore G×E interactive effects are not likely to contribute to a major part of the variance. Finally, important phenotypes with relevance for treatment that should be explored in G×E studies are craving and stress-induced relapse.

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