Alcoholism: the dissection for endophenotypes

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Alcohol is a common "addictive" substance. As a psychoactive compound, it can elicit a spectrum of behavioral effects, which include gregariousness, aggression, loss of executive function, and cognitive deficits. While pharmacokinetic factors (absorption, distribution in the tissues, and rate of metabolism, primarily in the liver) contribute to the intensity and duration of ethanol's actions, the behavioral manifestations are a consequence of the effects of ethanol on the brain. The spectrum of behavioral effects is attributed to the ability of ethanol to inhibit or activate multiple neural pathways, and how one responds to alcohol will ultimately depend on how the neural pathways are

Alcohol dependence (alcoholism) is a complex disorder attributed to the interaction of genetic and environmental factors that form a collage of "disease" predisposition, which is not identical for every alcohol-dependent individual. There is considerable evidence to demonstrate that genetic predisposition accounts for roughly half the risk in the development of alcohol dependence. Both family and population studies have identified a number of genomic regions with suggestive links to alcoholism, yet there have been relatively few definitive findings with regard to genetic determinants of alcoholism. This ambiguity can be attributed to a multitude of complications of studying complex mental disorders, such as clinical heterogeneity, polygenic determinants, reduced penetrance, and epistatic effects. Complex mental disorders are clinical manifestations described by combinations of various signs and symptoms. One approach to overcoming the ambiguity in studying the association between genetic risk factors and disease is to dissect the complex, heterogeneous disorder by using intermediate phenotypes—or endophenotypes—to generate more homogeneous diagnostic groupings than an all-encompassing definition, such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*–derived term "alcohol dependence" or the commonly used term "alcoholism." The advantage of using endophenotypes is that the number of influential factors that contribute to these characteristics should be fewer and more easily identified than the number of factors affecting the heterogeneous entity of alcohol dependence (alcoholism). A variety of alcohol-related characteristics have been investigated in epidemiological, clinical, and basic research as potential endophenotypes of alcohol dependence. These include phenotypes related to alcohol metabolism, physiological and endocrine measures, neural imaging, electrophysiology, personality, drinking behavior, and responses to alcohol and alcohol-derived cues. This review summarizes the current literature, focused on human data, of promising endophenotypes for dissecting alcoholism.*

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organized in an individual, and the extent to which certain pathways are inhibited or activated. It is known that there is substantial variability in the response to alcohol, and differences in cognitive evaluation of ethanol's effects are likely to play a significant role in the predisposition to alcohol abuse and dependence.

Although the diagnoses for alcohol use disorders are based on a range of reported symptoms, they are typically treated as a binary outcome (affected or unaffected). As early as the 1960s, it was conceptualized that alcoholism was not a single entity and that various types of alcoholism existed. Jellinick originally identified five "species" of alcoholism characterized by psychological and physiological dependence.[1] Researchers have utilized and refined such typological schemes in order to identify more etiologically homogeneous subtypes as a means for studying, diagnosing, and treating alcoholism.[2-4]

As with all complex diseases, alcoholism can be thought of as a clinical outcome that has been generated by a combination of many risk factors, and the alcohol-dependent population represents a spectrum of individuals displaying different sets of symptoms and severity of disease. Genetic factors that affect susceptibility to alcohol dependence may be involved in only certain components of the spectrum of alcohol dependence, such as alcohol metabolism, personality, cognitive function, and neurophysiology.[5] An approach for identifying alcohol susceptibility genes is to focus on the particular components of the dependence spectrum, ie, intermediate phenotypes that influence susceptibility to alcohol dependence, also known as endophenotypes. With reference to genetic theories in schizophrenia research, Gottesman and Shields[6] originally defined endophenotypes as internal phenotypes, not obvious to the unaided eye, which can fill the gap between the gene and the available descriptors of disease. More recently, Tsuang et al[7] established the following criteria for evaluating endophenotypes[8]:

- *Specificity*. The endophenotype is more strongly associated with the disease of interest relative to other psychiatric conditions.
- *State-independence*. The endophenotype is stable over time and not merely indicative of the disease process or its treatment.
- *Heritability*. Variance in the endophenotype is associated with genetic variance.
- *Familial association*. It is more prevalent among the relatives of ill probands compared with the appropriate control group.
- *Cosegregation*. The endophenotype is more prevalent among the affected relatives compared with the unaffected relatives of affected probands.
- *Biological and clinical plausibility*. The endophenotype bears some conceptual relationship to the disease.

The advantage of using endophenotypes is that the number of genetic and environmental factors that contribute to these should be easier to identify because the number of factors influencing each is fewer than the number affecting the undifferentiated clinical syndrome.[9] Endophenotypes have been utilized extensively when nonhuman animals have been used to study alcohol use–related phenomenon. Animal models have proven to be an ideal tool for identifying genetic and environmental factors that influence alcohol-related traits due to the ability to conduct studies under controlled environmental and genetic conditions. Furthermore, animal models provide an opportunity to assess quite specific alcohol-related endophenotypes, such as alcohol preference, sensitivity, tolerance, and dependence. For example, selected lines of mice produced from breeding animals for certain endophenotypes have been widely used in mapping quantitative trait loci (QTL), an analytical method utilized to identify regions of the genome influencing a specific trait by comparing genetic markers that are shared by lines or strains displaying extremes in quantitative endophenotypes. Several selected lines that differ with respect to various alcohol-related traits have been developed to identify genetic differences contributing to differences in the effects of alcohol. This area of research has recently been reviewed.[10]

Although animal models provide for "proof of concept," which indicates that the definition and utilization of endophenotypes can lead to a better understanding of the etiology of the endophenotype and provide a means for identifying which genetic factors would be of interest to study in humans, not all observations in the nonhuman animal are necessarily applicable to humans. Thus, it is essential to conduct studies with human populations in order to elucidate the pathophysiology of human disease. Recent research efforts with humans have focused on the identification and incorporation of endophenotypes to study risk factors for alcoholism. Schuckit recently proposed that the majority of genetically related markers of alcoholism risk were represented by five relatively independent overarching categories (endophenotypes), which include level of response, neuronal or behavioral disinhibition, independent axis I major psychiatric disorders,

the opioid system, and alcohol-metabolizing enzymes.[11] A variety of additional traits have been investigated in epidemiological research as potential endophenotypes for alcohol dependence. These include endophenotypes related to endocrine measures, electrophysiology, personality, and drinking behavior.

Behavioral and physiological traits

Low alcohol response

Researchers have investigated the significance of sensitivity to intoxication with respect to the development of alcohol dependence.[12-15] Low response to alcohol is a well-characterized biological measure, which is indicative of alcohol sensitivity, specifically the need for more alcohol to produce an effect.[11] It has been hypothesized that low response increases the risk of alcohol dependence by increasing the probability of heavy drinking and acquisition of tolerance and dependence.[11]

Historically, level of response (ie, a low response) has been assessed through various measurements, which include level of change in subjective feelings of intoxication, motor performance, hormone levels, and/or electrophysiological measures observed at specific blood alcohol concentrations, or by a self-report of the number of drinks required for specific effects.[16-18] The effects of ethanol can be measured by the use of the alcohol challenge test, where subjects are typically given three to five standard drinks to be consumed over approximately 10 minutes.[13,14,16]

A low response has been found to be a predictor of future alcohol use disorders among various populations, including Native Americans and Koreans.[19,20] However, contradictory results have been observed in other studies. These inconsistencies have been attributed to differing methods of alcohol administration and limited sample size.[21-23] An estimated 40% of offspring of alcoholics have a low response to alcohol, and prospective studies have shown that it may be a predictor of future development of alcohol use disorders among alcoholic offspring.[24-26] Both animal and human twin studies have found that response is genetically influenced.[15] Genetic factors are estimated to account for 60% of the variance in response to alcohol.[12,27] Among certain populations, low response could explain up to 50% of the relationship between family history of alcohol use disorders and risk of alcoholism.[11] In a recent review, data from various animal and human studies were summarized and various candidate genes involved were implicated in influencing level of response to alcohol.[15] These include genes related to the second-messenger system (adenylyl cyclase [AC]/cyclic adenosine-3´,5´-monophosphate [cAMP] system), neurotransmitters (endogenous opioids, serotonin, γ-aminobutyric acid [GABA], adenosine, dopamine), and alcohol metabolism (alcohol dehydrogenase, catalase, cytochrome P450 enzyme CYP 2E1). For example, a recent study by Ray and Hutchison[28] has found an association between the A118G single nucleotide polymorphism (SNP) of the μ-opioid receptor gene and sensitivity to the effects of alcohol. Specifically, individuals with at least one copy of the G allele, which codes for the more potent μ-opioid receptors, displayed higher sensitivity to the stimulatory, sedative, mood-altering, and subjective feelings of intoxication.[28] Furthermore, previous studies have implicated a polymorphism in the promoter region of the serotonin transporter gene (*5´HTLPR*, locus ID *SLC6A4*) with subjective feelings of intoxication during an alcohol challenge protocol using a nonclinical sample.[29] Taken together, these studies underscore the importance of evaluating individual differences in alcohol sensitivity, particularly with regard to the quality of the alcohol intoxication, as a potential endophenotype for alcohol use disorders. Some of the strengths of this endophenotype include its specificity, state-independence, heritability, and biological and clinical plausibility. Further information is needed regarding familial association and cosegregation applied to alcohol response endophenotype.

Alcohol metabolism

The Australian Alcohol Challenge Twin Study, initiated over 20 years ago, has provided substantial contributions to understanding the genetics of alcohol metabolism in relation to alcohol use disorders, such as heritability of various alcohol-related traits including alcohol consumption habits and pharmacokinetic measures.[30,31] Initial studies have demonstrated genetic influences on peak blood alcohol concentrations, rate of decrease in blood alcohol concentration, and alcohol dependence.[32] More recently, Whitfield et al analyzed the relationship between blood or breath alcohol values after an alcohol challenge test, a reflection of pharmacokinetics, and risk of alcohol dependence over a 10-year period of follow-

up.[33] They observed a two- to threefold increased risk in individuals who demonstrated blood or breath alcohol concentrations in the highest quartile of values compared with those in the lowest.

Genetic variation among alcohol-metabolizing genes has been well studied with respect to their role in affecting predisposition to alcohol dependence.[34] A functional variant in aldehyde dehydrogenase type 2 (*ALDH2*), predominantly observed among Asian populations, produces a reduced capacity to metabolize acetaldehyde and a physiologic flushing response and is believed to contribute to the aversion to alcohol consumption.[35] Genetic variants among the class I alcohol dehydrogenases have also been implicated in modulating levels of alcohol intake.[35] These findings suggest that alcohol metabolism does influence susceptibility to alcohol use disorders. Prospective studies have been pursued to evaluate the role of variation in alcohol metabolism on risk of alcohol dependence.[13,33] Overall, there is evidence suggesting that genes that affect alcohol pharmacokinetics are likely to contribute to the levels of alcohol consumption by individuals.

Electrophysiological measures

Various electrophysiological measures of the brain have been implicated in predisposition to alcohol use disorders. Evidence from twin studies suggests that a substantial proportion of the variance in electroencephalographic (EEG) patterns is genetically determined.[36-39] Studies investigating the EEG of chronic alcoholics have reported the alcoholic EEG to be of lower voltage, to be deficient in α activity, to be higher in β activity, to contain some θ activity, and to have an excess of fast activity.[19,40-44] Studies conducted on offspring of alcoholic fathers suggest that certain EEG variants may be potential endophenotypes for development of alcohol dependence.[19,45]

A biological trait that has received considerable attention is the P_{300} waveform, also known as P3, of the event-related brain potential (ERP). The P3 waveform represents the largest positive peak voltage of the event-related potential occurring between 250 and 500 ms after presentation of a stimulus.[46] This component is believed to depict several aspects of cognitive function, including attention and maintenance of working memory.[47] It has been suggested that diminished P3 amplitudes or shorter latencies reflect problems in attending and interpreting subtle environmental events.[48,49] Research has shown that alcoholic individuals also have reduced P3 amplitude and that offspring of alcoholics with low P3 amplitude are more likely to develop an alcohol use disorder.[50]

A low-voltage α resting EEG trait has also been previously associated with alcoholism and anxiety disorders.[51] Alpha (8-13 Hz) represents the EEG waveform that predominates in an individual who is awake and alert, while relaxed.[51] Typically, α oscillations will greatly diminish or disappear during periods of high arousal. Individuals with the low-voltage α resting EEG trait appear to have an atypical EEG characterized by few or no α oscillations, resembling an EEG of increased arousal. Alcoholics tend to have low-amplitude α.[52] However, high-voltage α has also been suggested as a potential risk factor for alcohol dependence. In two different studies, men with alcoholic fathers were more likely to have high-voltage α than men with no alcoholic relatives.[53-55] This finding has also been observed in a sample of women at high risk for alcoholism.[56] Taken together, these studies suggest that subjects at high risk for the development of alcoholism may be characterized by an *atypical* variation of α.

Various other attributes of EEG have also been implicated. In one study, young children (11 to 13 years old) of alcoholic parents were found to have more relative fast (β, >18 Hz) activity in their EEG than children without alcoholic parents.[57] In a recent study examining older adults with alcoholic relatives, sons of alcoholics were found to have elevated β amplitudes in specific regions of the brain[58]; however, other studies have not observed this finding.[42,59] Both linkage and candidate gene analysis that incorporate various aspects of EEG are currently being explored in connection with certain subtypes (endophenotypes) of alcohol dependence.

Alcohol craving

Alcohol craving has been defined as a strong desire to consume alcohol and has been associated with loss of control over drinking, which is part of the alcohol dependence syndrome, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Although there has been some controversy over the definition and use of the term, the endophenotype of craving is a construct that is central to alcohol dependence and is often a target of intervention effort.[60-63] Although there has been controversy over the measurement of subjective "craving" in humans, craving and loss of control drinking

have been biologically linked to the actions of alcohol on the mesolimbic and mesocortical dopamine pathways in the brain (the neural substrates that putatively underlie the attribution of incentive salience to alcohol and other drugs of abuse), which is thought to be an important factor in the etiology of alcohol dependence. Individual differences in the development of loss of control drinking and the ability to stop drinking are likely to be related to genetic factors that influence the effects of alcohol on mesolimbic dopamine activation and craving.

A few studies have investigated the pharmacological and genetic underpinnings of craving for alcohol. For example, a study by Hutchison et al[64] has found that individuals with the "long" variant (7 or longer repeat allele) of the D_4 dopamine receptor gene (*DRD4 VNTR*) displayed higher craving after consumption of alcohol, as compared with the placebo beverage. In addition, a pharmacological trial of olanzapine in a nonclinical sample found that individuals with the long allele of the *DRD4 VNTR* demonstrated greater reduction in craving after alcohol consumption during the medication condition, as compared with individuals with the short allele.[65] These results were later expanded using a clinical sample, in which patients with the long allele of the *DRD4 VNTR* experienced greater reductions in craving for alcohol and reduced alcohol consumption during the course of treatment, as compared with individuals with the short allele.[66] The fact that craving has been linked to specific biological mechanisms and has both etiological and clinical implications demonstrates its utility as an endophenotype for studying genetic and pharmacological factors associated with alcoholism and its treatment.

Neuroimaging-derived endophenotypes

Advances in imaging technology have provided the field with an opportunity to refine and expand the conceptualization of phenotypes that lend themselves to the identification of genetic variations that influence the etiology of alcohol and drug dependence. For example, there have been a number of studies that have utilized functional magnetic resonance imaging (fMRI) technology to investigate craving for alcohol by examining the hemodynamic response of brain structures after exposure to alcohol cues.[67-69] Specifically, one study has found that alcohol-related stimuli increased activation in the prefrontal cortex and anterior thalamus,[67] whereas another study noted activation in the prefrontal cortex and anterior limbic areas.[68] Furthermore, a study utilizing alcohol odor as an alcohol cue found significant increases in activation of the cerebellum and amygdala in alcoholics, but not controls.[69] These differences, however, were not observed after treatment and no evidence of a correlation between brain activation and subjective craving was presented.

Imaging techniques provide the opportunity to examine endophenotypes that are more proximal to the biological mechanisms that underlie risk for the development of alcohol use disorders. For example, the interplay of the mesocortical and mesolimbic structures represents a potential endophenotype for alcoholism, given that these structures are putatively associated with alcohol craving. An important advantage of the neuroimaging approach is the fact that the output does not rely on subjective reports of effect, which can induce a great deal of experimental variability. Measuring a more biologically based expression of the incentive salience of alcohol provides an objective means of defining the endophenotype.

Major psychiatric disorders

Psychiatric disorders, such as mood disorders and anxiety, are common comorbidities of alcoholism.[70] An estimated two-thirds of people with antisocial personality disorder are alcohol-dependent.[11] Depending on the individual, psychiatric symptoms may be manifestations of intoxication and withdrawal, or be precursors for the development of alcohol abuse.[71,72] Diagnoses of psychiatric disorders, as well as alcohol dependence, are based on a range of symptoms, which potentially reflect distinct etiologies. There is substantial evidence indicating that most psychiatric disorders, similar to alcohol dependence, are complex disorders that have a substantial genetic component. It is likely that certain genetic components involved in the susceptibility to psychiatric disorders are also likely to contribute to the development of alcoholism. A prospective study of 11-year-old children found three traits related to different dimensions on a personality questionnaire—specifically high novelty-seeking, harm avoidance, and reward dependence—were predictive of later alcohol abuse.[73] Furthermore, certain genetic variants have been found to be associated with alcoholism as well as certain psychiatric disorders.[52,74] Several studies of the genetics of psychopathology have identified common genes that may be associated with a variety of disordered behaviors. For example, the D_4 dopamine receptor gene has been linked to attention deficit–hyper-

activity disorder (ADHD), schizophrenia, and alcohol craving.[64] Likewise, a polymorphism of the promoter region of the serotonin transporter gene (*5´HTLPR*, locus ID *SLC6A4*) has been associated with alcohol dependence,[75,76] suicide attempts,[77] anxiety symptoms,[78] and major depressive disorder.[79] These results however, are mixed, and several negative findings question the replicability of the positive findings.

Such investigations however, raise an important issue regarding the specificity of endophenotypes for alcoholism, given that a series of common genes may be associated with a host of psychopathological behaviors. It is possible that common factors may confer risk for several psychopathologies. For instance, personality factors, such as impulsivity and sensation/novelty-seeking, may also represent a common index of vulnerability to various psychopathologies. The hypothesis that common factors may confer risk or protection to more than one form of psychopathology led investigators to refine the endophenotypes such that they become better defined and possibly more psychopathology-specific. However, one should not cling thoughtlessly to current mental disease classifications when data regarding endophenotypes may be suggesting new relationships between causal factors and disease manifestations.

Biochemical traits

Monoamine oxidase

Monoamine oxidase (MAO) catalyzes the oxidative deamination of a number of neurotransmitters in the brain and peripheral tissues.[80,81] Two MAO enzymes, type A and B, were discovered and characterized on the basis of their substrate selectivity and inhibitor sensitivity.[82,83] The biochemistry and molecular biology of MAO have been studied extensively.[80] The finding of MAO activity differences in platelets of alcohol-dependent individuals versus controls was first reported approximately 40 years ago.[84] It was subsequently found that human platelets contained exclusively the B-type of MAO.[85] Early studies also suggested that low platelet MAO activity was associated with certain personality traits, such as impulsiveness, risk-taking behaviors, aggressiveness, and, in particular, predisposition to alcohol and drug dependence.[80,86] It has been hypothesized that low levels of platelet MAO activity may be an endophenotype for predisposition to alcohol and drug abuse; however, the results from several studies have not been consistent, and this discrepancy has been primarily attributed to the confounding effect of tobacco use.[80,86] Snell et al[87] examined the relationship between differences in platelet MAOB activity associated with alcohol dependence, cigarette smoking, and gender. The findings suggested that lower platelet MAO activity is attributed to cigarette smoking and may reflect reduced substrate accessibility to the MAO catalytic site in smokers. Prospective studies on platelet MAO activity are necessary to further evaluate its validity as an endophenotype for alcoholism.

Adenylyl cyclase

The enzymatic activity of AC has been proposed as a potential endophenotype for alcohol dependence. AC is responsible for the conversion of adenosine 5´-triphosphate (ATP) to the second messenger cAMP.[88,89] Other major components involved in AC/cAMP pathway are various extracellular signal receptors and heterotrimeric guanine nucleotide-binding regulatory proteins (G proteins) that couple the signals generated at receptors to the catalysis of cAMP formation. Nine isoforms of the mammalian AC enzyme (types I – IX), with differing regulatory properties, are known to exist.[88,90]

AC activity is regulated by different receptors, including dopamine, opiate, adenosine, muscarinic cholinergic, corticotropin-releasing factor (CRF) adrenergic, and serotonergic receptors. These receptors interact with either stimulatory (Gs) or inhibitory (Gi) G protein subtypes, resulting in stimulation or inhibition of AC.[89] On the other side of the cAMP signaling cascade, phosphodiesterases can inactivate cAMP through hydrolysis into AMP. There are two known targets of cAMP in mammals, the cAMP-dependent protein kinase (PKA) and the cAMP-gated ion channel (predominantly found in the olfactory neurons). The production of cAMP depresses the activity of PKA, which then modulates intracellular metabolism, receptor, or ion channel function, and gene expression in various cells and tissues.[88,90,91] cAMP-responsive binding element (CREB) is one example of a transcription factor that can be modulated in its function by the cAMP signaling cascade.

Many drugs, hormones, and neurotransmitters produce their physiological effects by stimulating or inhibiting the catalytic activity of AC, and thus affecting the concentration of cAMP within the cell.[92] AC activity in animal and human cells and tissues is altered by acute and

chronic ethanol treatment.[93] AC activity can be measured in both platelets and lymphocytes, although the results can differ depending on which in vitro model is used.[11] Lower cAMP production following chemical stimulation of platelets or white blood cells has been observed among alcoholics and individuals with a family history of alcoholism.[94] The production of cAMP in chemically stimulated cells has been investigated in children of alcoholics who might share lower levels of Gs protein–stimulated cAMP production with their alcoholic relatives. The children of alcoholic parents were found to have lower platelet AC activity in comparison to children of nonalcoholic parents.[95] The risk of alcoholism could be a result of low innate activity of AC, with acute alcohol causing a temporary stimulation and subsequent abstinence producing the opposite effect. Thus, this might promote more alcohol intake in attempt to compensate for low AC activity in individuals predisposed to alcohol dependence or already dependent individuals.[95-97]

As already mentioned, several studies have shown that AC activity in platelets or lymphocytes of alcohol-dependent individuals is less responsive to various stimulations, such as that by forskolin, compared to non–alcohol-dependent individuals.[98-103] However, it is not completely clear if these differences are a consequence of alcohol drinking or an indicator of susceptibility to alcohol dependence. Recent studies have shown that platelet AC activity decreases after a period of abstinence from heavy drinking.[104] Furthermore, AC activity in alcohol-dependent subjects was lower for those who abstained for a period of time prior to testing.[104] Various alcohol-related factors that affect AC activity level may compromise its utility as an endophenotype to study predisposition to alcohol dependence.[104]

β-Endorphins

The endogenous opioids, which include β-endorphins, are proteins that bind to the opioid receptors. Alcohol is believed to stimulate the release of certain opioid peptides, which could interact with opioid receptors in regions of the brain associated with reward and positive reinforcement.[105] Increased activity of brain β-endorphin (enkephalin) opioid peptide systems may be important for initiating and maintaining high levels of alcohol consumption.[105] Subjects with a family history of alcoholism presented with lower concentrations of plasma β-enodorphin in the early morning hours and a more pronounced increase in pituitary β-endorphin release after ingestion of moderate doses of alcohol.[106,107] When examining the heritability of hormonal responses, a twin study found that β-endorphin response to alcohol was heritable.[108] Decreased β-endorphin has been noted in the cerebrospinal fluid (CSF) of abstinent alcoholics.[109] Opioid antagonists, such as naltrexone, have been shown to decrease the self-administration of alcohol in animals and humans.[110-112] This effect has been attributed to blunting the stimulatory effect of alcohol, enhancing the sedative effect, and/or decreased levels of reinforcement from alcohol.

Conclusions

The use of the current *DSM-IV* classification for alcohol use disorders has proven impractical in the pursuit of identifying predisposing genetic and environmental risk factors for the complex phenotype of dependence on alcohol. This can be attributed to the fact that many researchers have used *DSM-IV* criteria to arrive at binary classifications based on a range of symptoms and, thus, do not capture the heterogeneity of the disorder. The ability to study well the multiple factors that contribute to the development of "alcoholism" will depend on the creation of more homogeneous subgroups by use of endophenotypes. This can be achieved through the development of new classification schemes based on genetic/biological, physiological, and behavioral endophenotypes. Future research in the area of alcohol use disorders will continue to improve phenotypic definitions and ultimately contribute to the disentanglement and elucidation of the etiology of the various components that contribute to the multifaceted and complex syndromes currently encompassed by the *DSM-IV, the International Classification of Mental and Behavioral Disorders (ICD-10)*, and the lay public perceptions of alcohol use disorders. ❑

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Alcoholismo: la disección mediante endofenotipos

La dependencia de alcohol (alcoholismo) es un trastorno complejo que se atribuye a la interacción de factores genéticos y ambientales que forman un collage para la predisposición a la "enfermedad," lo que no es idéntico para cada individuo dependiente de alcohol. Existe una considerable evidencia que demuestra que la predisposición genética da cuenta aproximadamente de la mitad del riesgo para el desarrollo de la dependencia de alcohol. Tanto los estudios en familias como en población han identificado un número de regiones del genoma que sugieren asociaciones con el alcoholismo, pero han sido relativamente pocos los hallazgos definitivos en relación con determinantes genéticos del alcoholismo. Esta ambigüedad puede atribuirse a diversas complicaciones del estudio de los trastornos mentales complejos, tales como la heterogeneidad clínica, los determinantes poligénicos, la reducción de la penetración y los efectos epistáticos. Los trastornos mentales complejos son manifestaciones clínicas descritas por combinaciones de varios signos y síntomas. Una aproximación para superar la ambigüedad en el estudio de la asociación entre los factores de riesgo genético y la enfermedad es disecar el trastorno heterogéneo y complejo mediante el empleo de fenotipos intermediarios –o endofenotipos– para generar agrupaciones diagnósticas más homogéneas que la definición ampliamente abarcadora del término "dependencia de alcohol" derivada del Manual Diagnóstico y Estadístico de los Trastornos Mentales*, en su cuarta edición* (DSM IV) *o del término "alcoholismo" utilizado comúnmente. La ventaja de utilizar endofenotipos es que el número de factores que pueden ser determinantes en la contribución a estas características debe ser menor y de más fácil identificación que el número de factores que afectan la heterogénea entidad de la dependencia de alcohol (alcoholismo). A través de estudios epidemiológicos, clínicos y básicos se ha investigado una variedad de características relacionadas con el alcohol como potenciales endofenotipos de la dependencia de alcohol. Estos incluyen fenotipos relacionados con el metabolismo del alcohol, mediciones fisiológicas y endocrinas, neuroimágenes, electrofisiología, personalidad, conducta para beber y respuestas para señales para el alcohol y derivadas del alcohol. Esta revisión, focalizada en resultados en seres humanos, resume la literatura actual de prometedores endofenotipos que permitan hacer una disección del alcoholismo.*

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Alcoolisme : le découpage des endophénotypes

La dépendance alcoolique (alcoolisme) est un trouble complexe attribué à l'interaction de facteurs génétiques et environnementaux qui forment un ensemble de prédispositions à la " maladie " différentes pour chaque individu alcoolodépendant. Il existe des arguments solides pour démontrer que les prédispositions génétiques participent pour à peu près la moitié du risque dans le développement de la dépendance alcoolique. Des études de population et familiales ont identifié un certain nombre de régions du génome présentant des liens évocateurs avec l'alcoolisme ; il y a eu jusqu'à maintenant relativement peu de résultats définitifs en ce qui concerne les déterminants génétiques de l'alcoolisme. Cette ambiguïté peut être attribuée à une multitude de complications dans l'étude des troubles mentaux complexes, tels que l'hétérogénéité clinique, les déterminants polygéniques, la pénétrance réduite et les effets épistatiques. Les troubles mentaux complexes se manifestent cliniquement par des associations de signes et symptômes variés. Découper ces troubles complexes, hétérogènes en utilisant des phénotypes intermédiaires – ou endophénotypes – pour former des groupes de diagnostic plus homogènes qu'une définition globale, telle que celle de " dépendance alcoolique " ou celle courante d' " alcoolisme " du DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) *peut permettre de surmonter l'ambiguité qui existe dans l'étude de l'association des facteurs de risque génétiques et la maladie. L'avantage des endophénotypes est que le nombre de facteurs influents qui les caractérisent devrait être moins important et plus facilement identifiable que le nombre des facteurs affectant l'entité hétérogène de la dépendance alcoolique (alcoolisme). Nous avons recherché de multiples caractéristiques liées à l'alcool aux niveaux standard, clinique et épidémiologique, comme endophénotypes potentiels de la dépendance alcoolique. Ceux-ci comprennent des phénotypes liés au métabolisme de l'alcool, à des mesures endocrines et physiologiques, à l'imagerie nerveuse, à l'électrophysiologie, à la personnalité, aux comportements vis-à-vis de la boisson et aux réponses aux signaux alcooliques et dérivés de l'alcool. Cet article résume la littérature actuelle, mise au point sur des données humaines, concernant des endophénotypes prometteurs dans l'analyse fine du phénomène de l'alcoolisme.*

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