Overview

Medicobiological and genetic studies on alcoholism

Role of metabolic variation and ethnicity on drinking habits, alcohol abuse and alcohol-related mortality

D.P. Agarwal and H.W. Goedde
Institut für Humangenetik der Universität Hamburg

Alcohol abuse and alcohol dependence pose serious human behavioral disorders in most of the developed as well as developing countries of the world. Besides socioeconomic, cultural, and biobehavioral factors, certain biological and environmental components are among the major determinants of alcohol-seeking behavior in a society [3, 26, 27]. A series of factors interact in predisposing or protecting an individual against alcoholism and alcohol-related disorders: the availability of alcohol and its price, an individual's sociocultural, psychological, physiological, and genetic make-up. The three alcoholic subtypes described by Bohman et al. [9] may represent a cluster of different metabolic and mental disorders and behavioral traits grouped together artificially by a "clinical model" of alcoholism. Family, twin, and adoption studies unambiguously indicate a genetic basis for the familial aggregation of alcoholism [5, 27].

To understand the nature of the susceptibility factors responsible for the development of alcoholism, elucidation of the following aspects, among others, is essential: (a) predisposing factors which influence alcohol drinking habits; (b) genetic vulnerability to acute toxic effects of alcohol; and (c) variations in alcohol metabolism. Liver alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), primarily responsible for the oxidative degradation of ethanol and acetaldehyde, respectively, are genetically polymorphic [4].

In the past few years, several informative reviews have appeared which focus on genetic and biochemical factors relevant to alcoholism [18, 73, 82, 85]. In this overview, we have compiled part of the most current information on the biomedical aspects of alcoholism and discuss the influence of racial/ethnic and environmental factors in the establishment of drinking habits and in the susceptibility to or protection against alcoholism. Specifically, the role of the polymorphic forms of the alcohol-metabolizing enzymes in modulating the rate of ethanol and acetaldehyde degradation, individual drinking pattern, and vulnerability to alcoholism is critically examined. The principal findings from the biological and epidemiological studies are summarized, and some conclusions drawn. If validated in future studies, these findings may have major public health consequences. Moreover, the assessment of drinking norms and beliefs in relation to drinking practices may also help in a better understanding of the problems associated with drinking in a particular ethnic or racial group.

Medicobiological consequences of alcoholism

Both clinical and epidemiological studies have implicated the excessive use of alcohol in the risk of developing a variety of organ, neuronal, and metabolic disorders. Alcohol abuse-related metabolic derangements affect almost all body organs and their functions. Many physiological and degenerative metabolic processes including the endocrine system are adversely altered by chronic alcohol abuse, leading to short- and long-term impairments.

Organ damage

The liver is one of the prime target organs of alcohol-induced diseases. Alcohol in large amounts is
directly toxic to the liver, although nutritional deficiencies may play a secondary and accelerating role. Chronic alcohol abuse provokes successive hepatic changes consisting of hepatic steatosis (fatty liver), fibrosis, alcoholic hepatitis, and cirrhosis [50]. The major functional and structural cardiac abnormalities related to chronic alcohol abuse include hypertrophy, dilatation, fibrosis, cellular swelling, fatty infiltration, and inflammation [45].

**Neuronal effects**

Ethanol is a primary and continuous depressant of the central nervous system (CNS), although some behavioral stimulation is observed at low blood alcohol levels. The stimulation is largely due to a lowering of the normal restraining functions, but there may be some direct facilitation of motor processes and respiration. The behavioral symptoms show individual differences according to temperament and circumstances, but they tend to run an ascending course with increasing doses through euphoria, comfort, and enjoyment to elation and vivacity then downward through loquacity and garrulity, emotionalism either affectionate or quarrelsome or both, to violence, then stupor, and finally coma. Motor symptoms run through a similar but not necessarily parallel course. Obviously, the CNS is more affected by alcohol than any other system of the body. Typical alcohol-related CNS effects are reinforcement, intoxication, functional tolerance, physical dependence, and brain damage. Several neurologic syndromes including dementia, Wernicke-Korsakoff syndrome, pontine myelinolysis, and corpus callosum degeneration have been well-described in alcoholics. Other neurologic sequel of long-standing alcohol abuse include malnutrition, subdural hematoma, multiple infarction, hepatic encephalopathy, and cerebellar degeneration.

The exact mechanisms of action of ethanol on nervous tissues are still not fully understood because even modest doses simultaneously change many neurotransmitters and increase the fluidity of neuronal cell membranes. Accordingly, the levels, turnover, and synthesis of several neurotransmitters including norepinephrine, dopamine, serotonin, acetylcholine, and γ-aminobutyric acid (GABA) have been extensively studied [79]. The N-methyl-D-aspartate (NMDA) receptor has recently been implicated to play a role in the cognitive impairment produced by ethanol, the psychological deficits associated with the fetal alcohol syndrome, and the occurrence of ethanol withdrawal seizures [79].

**Metabolic changes**

Alcohol consumption, acute or chronic, results in a plethora of in vivo events, many of which influence different metabolic pathways. The alterations are organ-specific and influenced by genetic predisposition, nutritional status, hormone imbalance, and the presence or absence of prior alcohol-induced or associated organ damage.

The accumulation of lipids in the hepatocytes is the most striking initial manifestation of alcoholic liver injury [50]. The lipids that accumulate are mainly triglycerides originating from dietary lipids, adipose tissue lipids, and lipids synthesized in the liver itself. The altered redox state with the generation of excess reduced NADH from NAD via ethanol oxidation in the liver affects the “free energy” transfer potentially needed for protein synthesis and urea production. Ethanol affects the carbohydrate metabolism via its metabolite acetate, change in the NAD/NADH ratio, and directly (ethanol and acetaldehyde) on the intermediary metabolism in the liver. The redox changes associated with the oxidation of ethanol result in a shift of pyruvate to lactate, leading to increased lactate levels in the blood. Both short- and long-term ethanol consumption have significant effects on hormones and hormone-releasing factors from the anterior and posterior pituitary. Ethanol not only influences neurohormones, it also directly affects the neurotransmitters, thereby changing their metabolic influences on the body.

**Fetal alcohol syndrome**

Clinical studies have clearly demonstrated a correlation between maternal alcohol abuse during pregnancy and fetal abnormalities [1]. The principal features of fetal alcohol syndrome (FAS) are prenatal and postnatal growth deficiency, particularly in length; craniofacial abnormalities, especially microcephaly, short palpebral fissures, and maxillary hypoplasia, joint abnormalities and altered palmar crease pattern; cardiac anomalies; fine motor dysfunction; and impaired mental development. Epidemiological data show that the worldwide incidence of FAS is 1.9 births per 1000 live births [1].

**Genetics of alcoholism**

The current evidence strongly suggests that alcoholism may be a genetically influenced, complex,