REVIEW

Alcoholism: Recent advances in epidemiology, biochemistry and genetics

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Abstract: Countries traditionally consuming beer and wine have high alcohol consumption as compared to East Asia, where the fact of low alcoholism prevalence can be attributed to a defect in metabolic degradation of ethanol. Dependence on alcohol is multifactorial and is related to a complex interplay of metabolic, genetic, social and environmental factors. Repetitive alcohol ingestion and its resulting dependence is associated with false euphoria triggered by an inhibition of glutamate receptors and other brain neurotransmitters, namely dopamine and serotonine. Genetic polymorphisms of genes encoding the alcohol metabolism enzymes and neurotransmitter signaling molecules in dopamine, gamma aminobutyric acid, opioid and serotonin systems, are involved in individual variations for susceptibility to alcohol dependence. Prominent progress has been achieved toward identification of genes related to alcoholism. Six genes were described on chromosomes 4, 7, 8, 11, 15 and 20, which are known to have influence on neuronal signal transfer and generation of dopamine receptors. It is suggested that such genes carry the risk for alcoholism. In the last years, the role of (GABA) receptors in the development of alcoholism is studied in detail. In future it may be possible to separate the genetic, enzymatic and environmental factors that are responsible for increased vulnerability of some individuals to alcohol abuse *(Fig. 2, Tab. 1, Ref. 19).* Full Text (Free, PDF) *www.bmj.sk*.
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The National Council on Alcoholism defines alcoholism as "a primary, chronic disease characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking" (1). The consequences of alcohol misuse are life-threatening in many cases and in many countries. Heavy drinking can increase the risk for certain cancers. Heavy drinking can also cause liver cirrhosis, immune system problems, brain damage, and harm the fetus during pregnancy. Both homicides and suicides are more likely to be committed by alcoholics. The (WHO) estimates that more than 200 million people throughout the world suffer from alcohol dependence (2,3). In purely economic terms, the cost of alcohol-related problems borne by society amounts to many billions of dollars per year. In human terms, the costs cannot be reckoned. This review outlines recent data related to ethylalcohol (A) consumption in different parts of the world, as well as includes information on both, ethanol metabolism and interplay between genetic and environmental factors leading to alcoholism.

Alcohol consumption and dependence prevalence

Data on A consumption widely differ. Rather than accurate values, these are more-or-less estimates. Table 1 includes data from three internationally respected institutions (3−5). Since these are only estimates, Table 1 includes the probability intervals of consumption. Figure 1 shows schematically the geography of alcohol consumption.

Reports on A dependence are very sparse. However, it can be assumed that in countries with extreme A consumption the dependence is higher. A good example is the Russian Federation where the present mean life expentancy of population, especially of males is similar to that in developing countries (or even shorter). Russian scientists are in agreement that one of the main causes is the extremely high A consumption. High rate of alcoholism in Russia is related to the Russian tradition of binge consumption of large amounts of distilled A. Such drinking raises A blood level to extreme values, such as those achieved after a fast consumption of 250 to 500 ml of vodka.

Alcoholism is surprisingly high also in the United States: statistics indicate that more than 13.8 million Americans, about 7−8.5 % of the population at age of 18 and older, have problems with drinking (6). In the Slovak Republic, the prevalence of alcoholism is very similar. It should be noted that the USA criteria for the diagnosis of alcoholism are very strict. On the contrary, alcohol dependence is low in Japan and China due to decreased capacity of Asians to metabolize A (see next part of this review). Alcoholism is very rare in Muslim countries where the production, importing and consumption of A are forbidden.

Metabolism of ethylalcohol

More than 90 per cent of A is metabolized by the human body to acetate. The remaining 10 per cent is not metabolized

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Tab. 1. Estimated consumption of pure ethanol in liters per person aged over fifteen per year.

| Group	Country	Remarks
1. extremely high consumption (over 15 l)	Russian Federation, Ukraine, Latvia, Belarus, Estonia, Lithuania, Moldova, Czech Republic, Luxembourg	Former USSR shows low official figures (illegal production, smuggling are not included). High values for the Czech Republic are related to traditional beer drinking.
2. high consumption (10–15 l)	Slovakia, Hungary, Poland, Denmark, Finland, Switzerland, Ireland, United Kingdom, Slovenia, Austria, Germany, Belgium, Croatia, Spain, Italy, France, Portugal	Data from Slovakia, Hungary and Poland do not include illegal production and smuggling from Ukraine. High values in the Mediterranean are related to wine consumption
3. medium consumption (5–9,9 l)	USA, Australia, Canada, New Zealand, Japan, South Africa, South Korea, Argentina, Greek, Bulgaria, Netherlands, Brazil, Chile, Romania, Sweden, Norway, Iceland	Mostly a high consumption of spirits and especially wine in Argentina, Chile, Bulgaria and Romania.
4. low consumption (2–4,9 l)	Mexico, Azerbaijan, Kazakhstan, Kyrgyzstan, Albania, Bolivia, China, Congo, Cuba, Salvador, Mongolia, Georgia, Israel, Libanon	Asians typically have deficiency of alcohol-degrading enzymes, limiting consumption of alcohol
5. minimum consumption (under 2 l)	Turkey, Armenia, Ghana, Maroco, Tajikistan, Turkmenistan, Uzbekistan, Algiers, Bangladesh, Egypt, Etiopia, India, Indonesia, Iran, Irak, Jordan, Kuwait, Lybia, Oman, Pakistan, Tunis, Yemen	There is a strong religious influence, especially of Islam, limiting alcohol consumption
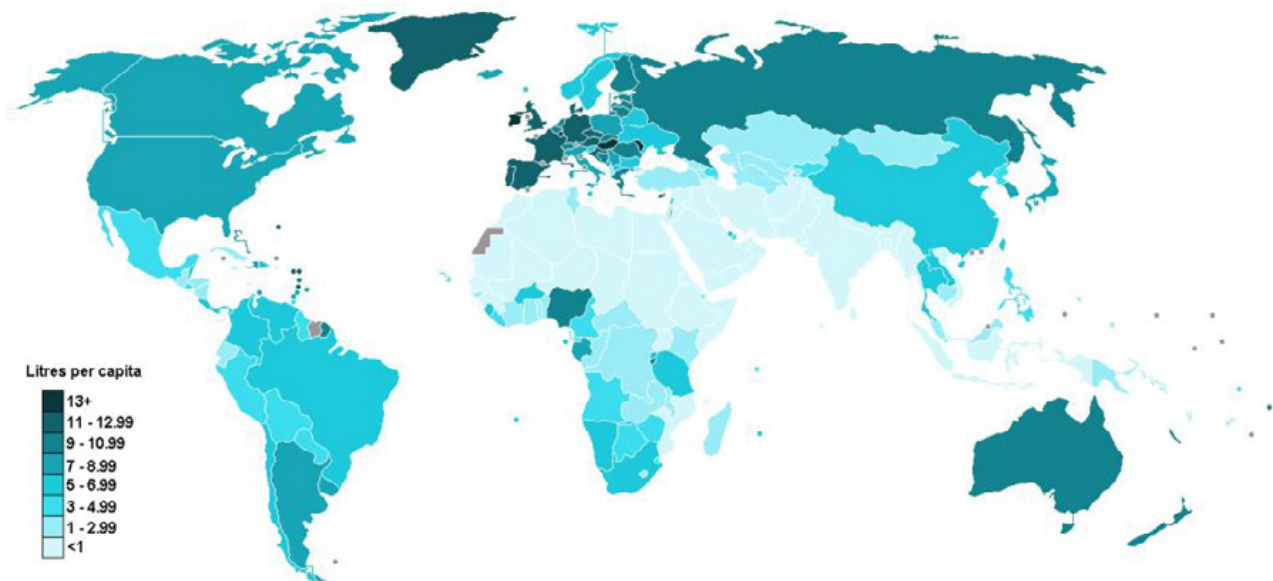
Fig. 1. Geography of alcohol consumption.

and it is excreted in urine, sweat and breath. Oxidation of A occurs predominantly in the liver and its first step includes conversion of A into a highly toxic acetaldehyde. This process is catalyzed by alcohol dehydrogenase (ADH). It is not a solitary enzyme; there exist five different ADH genes, of which two are polymorphic (having different variations), namely ADH2 and ADH3. Each person's capability to oxidize A depends on such genetic outfit. People with specific alleles (variants) of ADH2 and ADH3 may act as being more sensitive (and less tolerant) to

A because they oxidize A more promptly. Such genetic variants are frequent in Japanese and Chinese populations. After starting to drink A they rapidly accumulate the toxic aldehyde that triggers unpleasant side effects. Degradation of A occurs, especially at high blood levels of A, also through the microsomal cytochrome P 450 (also called MEOS). In the stomach, a small proportion of A is oxidized by catalase.

The next step in A breakdown, ADH oxidation is catalyzed by the enzyme acetaldehyde dehydrogenase (ALDH). The ac-

etaldehyde is converted to acetate, which is a normal metabolite and thus not toxic. Acetaldehyde is a reactive and highly toxic compound. The liver has two types of ALDH. One is the cytoplasmic ALDH 1, the other is ALDH 2 in the mitochondria. The degradation of aldehyde occurs much faster than the oxidation of A. Because of this, the concentration of the toxic acetaldehyde in the cells is thousand times lower than the level of A. There exists a genetic polymorphism of ALDH genes (7). A genetic variant of the mitochondrial ALDH called ALDH2*2, carries a message for generating a mostly inactive enzyme. Such a non-functioning system occurs in 50 per cent of the Japanese and Chinese populations, both, on mainland and in Taiwan. Because of this, they have a delayed detoxification of acetaldehyde. After ingesting the alcoholic drink, these people respond by the reddening of face, similarly as patients given Antabuse. Populations with deficient ALDH are aware of these side effects and they avoid A. Consequently, A consumption in Japan and China is much lower than in Europe or in the USA. Regretfully, Slavic populations with high intake of A obviously do not benefit from such dysfunctional degradation of acetaldehyde.

Development of alcohol dependence

The development of A dependence is very variable. While a part of population is easily vulnerable, the other segment may be resistant due to differences in their metabolic and genetic outfit but also because of the type of environment in which they live. However, neither the specificity of metabolism and genes, nor the social factors can reliably predict which individual is to develop A dependence. This is a complex disorder that results from an interplay of various metabolic, genetic and environmental factors. The risk of dependence of an individual seems to be independent from a simple gene-environment mechanism. Recent progress in molecular biology has facilitated the identification of numerous genes associated with alcoholism. It is predictable that in the future this genetic know-how will continue to grow.

The brain with its regulatory functions is central for the development of A dependence. Various brain components coordinate their activities mediated with the assistance of 100 billions of neurons. This vast amount of nerve cells communicates by using electric signals. The site of transfer of signal from one neuron to another occurs at a synapse which consists of a pre-synaptic terminal, synaptic space and post-synaptic membrane. The transfer takes place via specific molecules, neurotransmitters that bind to specific receptors at the post-synaptic membrane. There are many various neurotransmitters but regarding the effect of A, most important are the following four: glutamate, gamma aminobutyric acid (GABA), dopamine and serotonine.

Glutamate is the main excitatory neurotransmitter in the brain. Receptors for glutamate are inhibited by A, thus reducing the excitatory effect of glutamate. GABA is the main inhibitory neurotransmitter in the brain and ethanol activates its receptors. The overall result is the inhibitory effect of A on the brain. This process contributes to the development of A dependence. The other two transmitters, dopamine and serotonine also contribute to the
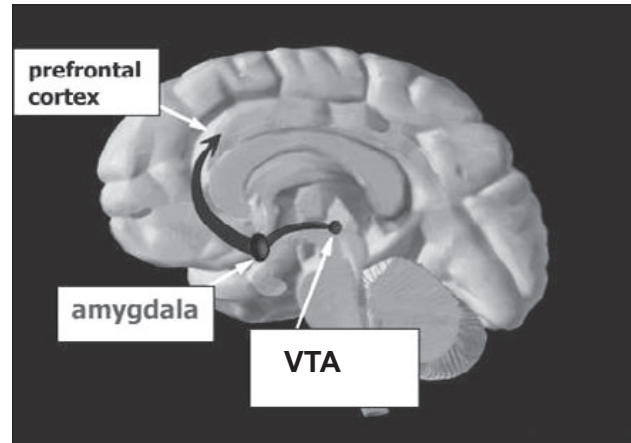

Fig. 2. Ventral tegmental area (VTA) plays an important role in the development of alcoholism. This structure directs the human behavior when we are motivated to seek reward.
According to www.youthbingedrinking.org/images/brain3parts.jpg.

psychologically pleasant "reward" effect, further enhancing the potential for abuse of A.

In addition to various anatomic structures there is a specific system in the base of the brain that contributes to A dependence. There is a "reward" system in the deep segment of the brain called the ventral hypothalamic area (VTA) (Fig. 2). Recent reports described a process located in the nucleus accumbens where A releases dopamine that triggers pleasant perceptions. These are transferred to the brain cortex where they are fixed (coded) and thus written in the memory. This mechanism stimulates the desire to repeat the intake of A.

Psychologically, such memory reminiscence is associated with the site where A was consumed. No wonder that this may initiate the cycle: the location of drinking heightens the desire for further consumption of A.

Genetic mechanism of alcohol dependence

It has been known for some time that alcoholics come from families that have numerous members dependent on A. This observation is frequently used by some investigators when stating that alcoholism is a consequence of social stigma. However, geneticists are actively exploring the possibility that the vulnerability to A in an individual is related to a genetic trait transferred between generations. This research attempts to identify in specific chromosomal regions the genes that increase or decrease the risk of alcoholism. The predisposition to alcohol dependence is affected by multiple environmental and genetic factors in a complicated way. Family and twin studies estimated the hereditary rate for aloholism to be about 60 %. These studies have shown that the genetic polymorphisms of genes encoding alcohol metabolism enzymes and neurotransmitter signaling molecules in dopamine, GABA, opioid and serotonin systems were substantially involved in individual variations of susceptibility to alcohol dependence (8).

Genetic analysis discovered the gene ALDH1 located on chromosome 4. In above paragraphs, ALDH1 was noted as an agent that is required to generate aldehyde dehydrogenase that has a protective effect preventing the dependence on A (7). Variants of three genes encoding the alcohol-metabolizing enzymes, namely the aldehyde dehydrogenase gene ALDH2 and alcohol dehydrogenase genes ADH1B and ADH1C have been associated with reduced rates of alcohol dependence. The prevalence of these genes varies in general samples of different Asian ethnic groups. The ALDH2*2 allele appears to be most prevalent in Chinese-American, Han Chinese and Taiwanese, Japanese, and Korean people. Much lower rates have been reported in the Thais, Filipinos, Indians and Chinese as well as in Taiwanese aborigines. ADH1B*2 is highly prevalent among Asians with the exception of Indians. ADH1C*1 is also highly prevalent in Chinese and Korean samples (9). In addition, six genes were described on chromosomes 4, 7, 8, 11, 15 and 20. These are known for influencing the neuronal signal transfer and the generation of dopamine receptors. It is suggested that these genes carry the risk for alcoholism.

In the past years, several papers described the role of (GABA) receptors in the development of alcoholism (10–18). The GABA receptors are membrane-bound proteins that respond to the, the chief inhibitory neurotransmitter in the central nervous system. When GABA binds to ubiquitous GABA receptors on neurons, chloride channels are activated and there is a rapid increase in chloride conductance that depresses the excitatory depolarisation. There are three classes of GABA receptors: A, B, and C. GABAA and GABAC receptors are G-protein-coupled receptors, while GABAB receptors are neurotransmitter. The GABAAA receptors are responsible for mediating the effects of (GABA), the major inhibitory ligand-gated ion channels in the brain. These receptors undergo allosteric modulation by ethanol, and have been implicated in chronic effects of A including tolerance, dependence and withdrawal. Two large genetic studies in the US population have reported an association between the genetic variation in gamma-amino butyric acid alpha2 receptor subtype (GABRA2) and the risk for alcohol dependence (12, 13). Genetic variants of GABRA2 increase the risk for alcoholism also in the Russian population (18).

Polymorphic variation at GABRA2 locus plays an important role in the predisposition to alcohol dependence. The dopamine mesolimbic reward pathway originating in the ventral tegmental area (VTA) (Fig. 2), and interacting stress circuitry play an important role in the development of alcoholism. VTA GABAergic interneurons are the primary inhibitory regulators of dopamine neurons, and a subset of VTA GABAA receptors may be implicated in the switch from heavy drinking to dependence. The GABAA receptor subunit genes clustered on chromosome 4 are highly expressed in the reward pathway. Variation in one of chromosome 4 genes, namely GABRA2, has been associated with alcohol abuse. GABRG1 haplotypes were significantly associated with alcoholism. It is likely that there are independent, complex contributions to alcoholism from both GABRG1 and GABRA2 (12, 13). The very strong association of GABRA2 with both alcohol dependence and beta frequency of electroencephalogram, combined with biological evidence for the role of this gene in both phenotypes suggest that GABRA2 might influence the susceptibility to alcohol dependence by modulating the level of neural excitation.

New methods are used in alcoholism research. Recent whole-genome association examination using 500K gene-chip revealed that a set of genes of adhesion and cytoarchitecture molecules were also involved in alcohol dependence. These new findings by gene-chip technology will probably bring about a breakthrough in the investigation of neural mechanisms of alcohol dependence and innovative therapy (8). Proteomics is a large-scale study of proteins, particularly their structure and functions. Proteomics is often considered the next step in the study of biological systems, after genomics. Proteomic studies on human hippocampus, an important region for neurocognitive function and psychiatric illnesses are still sparse, and further investigation is warranted to understand the underlying mechanisms (19).

Conclusion

The development of alcoholism is not a case of genetics versus the environment; it is that of genetics and the environment. However, our understanding of the dependence is far from complete. Geneticists are not in possession of a crystal ball with a magic potential to predict alcoholism. Genes do not function per se but in coexistence with a potentially harmful background that includes A abuse and unfavorable social or family conditions. Some carriers of a genetic risk may be vulnerable but other individuals with similar genetic constellation may remain resistant to alcoholism. If we hypothesize that half of the risk for alcoholism has a genetic basis, the other half must have other root causes. One fact is certain: no A dependence develops in people who do not drink A. Clearly, while being exposed to a similar risk, some individuals are more prone to alcoholism than others. Additional research is needed to provide definitive answers for this important question. There are gaps in our knowledge of alcoholism relative to other medical conditions. In part, the gaps can be explained by the complexity of the phenomena of alcoholism. Alcoholism research is very active and there are good reasons to believe that mechanisms of vulnerability to A will be further elucidated in order to bring about more effective prevention and management of alcoholism.

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