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Effects of alcohol on the brain biomembranes: A review

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SUMMARY
Alcohol consumption is a worldwide spread phenomenon influence of which on a human organism may even be fatal. Consequences of alcoholism are not only medical but also social and economical. The basic principles of alcohol dependence development remain still unclear.
Submitted article offers a short review of alcohol's effects mechanisms and it's interaction with neurotransmitters.

Keywords: alcohol – biomembranes fluidity – GABA – dopamine – serotonine – neurotransmitters.

Efekt alkoholu na biomembrány v mozku: Přehled

SOUHRN
Požívanie alkoholu je celosvetovo rozšírený fenomén, ktorého dopad na ľudský organizmus môže byť fatálny. Dôsledky alkoholizmu sú nielen zdravotné ale aj sociálne a ekonomické. Podstata vzniku závislosti na alkohole ostáva naďalej neúplne objasnená. Predložený článok je venovaný objasneniu mechanizmov pôsobenia alkoholu na centrálny nervový systém na molekulárnej úrovni a jeho interakciám s neurotransmitermi.

Kľúčové slová: alkohol – fluidita biomembrán – GABA – serotonín – dopamín – neurotransmitery.

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Alcohol is one of the oldest and most widely used and abused of all psychoactive drugs. Although alcohol ingestion impacts most organ systems, its effects on the brain are of considerable interest, given alcohol's many neuropharmacological actions, including its intoxicating, sedative, anxiolytic, hypnotic, and addictive properties. However, elucidating the cellular and molecular targets for alcohol's important pharmacological actions has proven challenging. Alcohol has a relatively simple chemical structure and has pleiotropic effects in disordering membrane lipids and proteins. Thus, it is unlikely that any single molecular mechanism (or target for that matter) will explain all of the relevant pharmacology of this important drug (1).

PRINCIPLES OF INTERACTION BETWEEN ETHANOL AND CENTRAL NERVOUS SYSTEM

Despite the generally held view that alcohol is an unspecific pharmacological agent, recent molecular pharmacology studies demonstrated that alcohol has only a few known primary targets. These are the NMDA, $GABA_A$, 5-hydroxytryptamine (serotonin) and other receptors as well as ion channels. Following this first hit of alcohol on specific targets in the brain, a second wave of indirect effects on a variety of neurotransmitter systems is initiated that leads subsequently to the typical acute behavioral effects of alcohol, ranging from disinhibition to sedation and even hypnosis, with increasing concentrations of alcohol (2).

1. Ethanol and biological membranes

The interaction of alcohol with biological membranes forms an important area of exploration because of the role of alcohol in metabolism, membrane fusion, drug delivery, alcohol toxicity, alcohol tolerance, and general anesthesia. Of particular interest is fundamental understanding of the molecular mechanism of alcohol action on the lipid portions of biomembranes (3).

Ethanol changes typical composition of biological membranes and thus its basic physical properties. Alcohol as well as other lipolytic molecules interacts directly with lipid bilayer. On the molecular level of considerations this means influencing degree of mobility of lipid molecules in the biomembrane and thus changing its fluidity (4).

The emerging paradigm is that alcohol primarily confines itself to the hydrophilic headgroup region instead of the hydrocarbon core. It's location in the headgroup region disturbs the natural microstructure of the lipid membrane and is apparently responsible for observed increases in membrane fluidity or disorder the membrane lipid lateral mobility, decreases in the main phase transition temperature, and the formation of an interdigitated gel phase. Past works have also shown that alcohols increase membrane permeability, induce shape transformations of vesicles, and influence membrane thermodynamic parameters (3). It is concluded that alcohol acts mainly as hydrogen bond donor whose binding to the polypeptide chain is stabilized by hydrophobic interactions. Binding at these sites may alter the

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local protein structure or displace bound solvent molecules and perturb the function of key proteins (5).

2. Ethanol and NMDA function

N-methyl-D-aspartate (NMDA) function was inhibited by ethanol in a concentration-dependent manner over the range of 5–50 mM, a range that also produces intoxication. What is more, the potency for inhibition of the NMDA-activated current by several alcohols is linearly related to their intoxicating potency. This suggests that ethanol-induced inhibition of responses to NMDA receptor activation may contribute to the neural and cognitive impairments associated with intoxication (6). NMDA-receptors appear to play a central role in alcohol dependence and alcohol-induced neurological disorders. Hence, NMDA receptor antagonists may have multiple functions in treating alcoholism. One of the new family of NMDA receptor antagonists, such as DETC-MESO, which regulate the redox site of NMDA receptors, may prove to be the drug of choice for treating alcoholism as well as many neurological diseases (7). Besides the NMDA receptor, other receptors or ion channels expressed within the CNS also have putative alcohol-binding sites (6)

3. Ethanol and GABAergic neurotransmission

GABAergic neurotransmission and $GABA_A$ receptors in particular have long been implicated in mediating at least some of the pharmacological actions of alcohol. $GABA_A$ receptors are also the molecular targets for benzodiazepines and anesthetic barbiturates, both of which share neuropharmacological properties and show cross-tolerance and cross-dependence with alcohol (3). The $GABA_A$ receptors are pentameric receptors which have a multitude of subunits. They have a rich pharmacology and this is dependent upon the particular subunits. These are arranged in a radial fashion such that they surround a central ion pore that opens in the presence of ligand. Once the ion channel opens, ion transport follows the electrochemical gradient that is established across the neuronal membrane. In the case of $GABA_A$ receptors, the ion pore conducts chloride ions. GABA is classified as an inhibitory amino acid neurotransmitter because the influx of chloride ions into the postsynaptic cell after the activation of these receptors moves the postsynaptic membrane potential further away from its firing threshold (8). Brain sites involved in the GABAergic component of ethanol reinforcement include the ventral tegmental area, elements of the extended amygdala and the globus pallidus (9). GABA has been associated with aggressive behavior (10). Recent studies have suggested that genetic variants of the $GABA_A$ receptor alpha2 subunit gene are associated with alcohol dependence (11). Results of a few scientific studies show that $GABA_A$ antagonists and inverse agonists reduce ethanol self-administration under limited-access conditions. $GABA_A$ receptor antagonists have been shown to increase ethanol-induced conditioned place preference and conditioned taste aversion and decrease ethanol-induced conditioned taste aversion in rodents (12).

4. Ethanol and neurosteroids

Interactions of ethanol with GABAergic neurotransmission system is tightly connected with neurosteroids (NS). These are endogeneous neuromodulators being synthetised de novo in the brain and also in the ovaries/ testicles and adrenal glands. Among biochemical substances with neuromodulatory properties belong 3,5-THDOC (alotetrahydrodeoxykortikosterone) and 3,5-THP (3-hydroxy-5-pregnan-20-one or alopregnenolone) (13). Presence of steroid neuromodulators in the blood stream of the central nervous system (CNS) induces anxiolysis and has anticonvulsive, sedative and hypnotic effects. Sensitivity of CNS on ethanol is grossly influenced by positive GABAergic acting of NS in the CNS. Experiments on rodents showed that increase in NS in the CNS increases CNS sensitivity to ethanol and thus it might cooperate on alcohol excessive consumption development. On the other hand, low ethanol sensitivity in CNS together with low plasmatic and brain NS levels enhances consumption of higher alcohol doses and so the risk of chronic alcoholism (14). NS could through their GABAergic actions inhibit craving for alcohol in humans (15). Each action of human organism on ethanol consumption can be blocked by former adrenalectomy or finasterid administration which is inhibitor of NS synthesis. Administration of 3,5-THP is able to renew ethanol's effects on CNS even in animals after adrenalectomy (16–18). Dysregulation of hypothalamus-hypophysis-adrenal glands system is also of big importance in developing alcohol dependence (19). All drugs of abuse have been shown to act either directly or indirectly by increasing dopamine neurotransmission within the limbic system. Thus, alcohol has been shown to increase dopamine transmission primarily by activating dopamine cell spike activity (20).

DISCUSSION

The dopaminergic brain reward system, physiologically mediating pleasure, seems to play a fundamental role in the mechanisms of alcohol intake and craving. This system is activated by physiological stimuli (like food, sleep, sexual activity) or non-physiological ones like behaviour provoking strong emotions (i.e. gambling, consumption of food followed by vomiting as in bulimia, sex addiction) or the consumption of psychoactive substances (i.e. alcohol, opioids, benzodiazepines, cannabinoids, cocaine). All these substances increase dopamine levels in the nucleus accumbens, which has been defined as the reward center of the brain (21). Several studies in animal brain have shown that changes in levels of dopamine, serotonin, gamma-aminobutyric acid (GABA), endogenous opioid peptides, and noradrenalin are associated with activation of the reward center in the brain. In particular endogenous opioid peptides have an important role in alcohol reinforcement, while GABA mediates the effects of alcohol. Serotonin is increased in the hypothalamus; this neurotransmitter causes an indirect activation of opioid receptors determining the release of encephalines into the ventral egmental region, projecting dopaminergic endings into the limbic system (nucleus accumbens, amigdala, tuberculum, olfattorium), the hippocampus, and the prefrontal cortex (22). The encephalines inhibit the release of GABA from the substantia nigra. The reduction in GABA concentrations and their interaction with GABA receptors (in particular $GABA_B$) determine a variation in dopamine levels. It has been shown that low doses of ethanol reducing the production of GABA lead to a rise in dopamine levels in the former mentioned brain regions. This activation reduces the excessive desire for alcohol and transmits the release of noradrenalin in the region of the locus ceruleus from which fibres branch out directed to a group of cells called CAx taking part in the mechanisms of gratification. In the presence of high concentrations of neuropeptid called diazepam-bound-inhibitor and betacarboline (GABA inhibitor) in the hippocampus, levels of GABA-inhibiting noradrenaline are reduced and the desire for alcohol is increased. On the other hand, when levels of GABA are increased, benzodiazepine receptors (against anxiety) can be stimulated, determining a reduction in alcohol consumption. This cascade mechanism leads to a state of well-being as a specific effect on the brain reward areas; when this system is interrupted by a deficit or an unbalance it transforms this sensation

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into a perception of anxiousness or anguish and into an excessive desire to consume a substance able to relieve these unpleasant feelings. This may suggest that patients born with a defect of these receptors are not able to respond normally by a release of dopamine and are predisposed to increase the activity by taking substances, e.g. alcohol, thus stimulating its release. A consensus of the literature suggests that when there is a dysfunction in the brain reward cascade, which could be caused by certain genetic variants. This trait leads to multiple drug-seeking behaviours and has been called reward deficiency syndrome (21,22).

CONCLUSION

Alcohol consumption is an integral part of daily life in many societies. The benefits associated with the production, sale, and use of alcoholic beverages come to an enormous cost to these societies. Impact of high doses of ethanol on human behavior and it's fatal consequences have been detaily analysed in a few studies including Slovak republic (23–26). The World Health Organization ranks alcohol as one of the primary cases of the global burden of disease in industrialized countries. Alcohol-related diseases, especially alcoholism, are the result of cumulative responses to alcohol exposure, the genetic make-up of an individual, and the environmental influences. This complex gene/environment interaction, which has to be seen in a life-span perspective, leads to a large heterogeneity among alcohol-dependent patients, in terms of both the symptom dimensions and the severity of this disorder. Therefore, a reductionistic approach is not very practical if a better understanding of the pathological processes leading to an addictive behavior is to be achieved. Instead, a systems-oriented perspective in which the interactions and dynamics of all endogenous and environmental factors involved are centrally integrated, will lead to further progress in alcohol research (6).

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