

ALCOHOL PHARMACOLOGY

Alcohol is one of the oldest and most widely used drugs on earth. Its use predates recorded history and may go back as far as the Paleolithic age, around 8000 B.C. References to its use appear in the Bible, in ancient Egyptian pictograms, and alcohol has been a part of American culture since the Pilgrims landed in Plymouth Rock, Massachusetts. In the last decade, neuroscience has significantly increased our understanding of the neuropharmacological effects of this drug. As a psychoactive drug, alcohol-induced changes brain chemistry to produce a wide range of behaviors.

What is Alcohol?

The modern use of the term "alcohol" describes various compounds composed of carbon, hydrogen and oxygen. The three most commonly encountered alcohols are: methyl alcohol (methanol), isopropyl alcohol (isopropanol) and ethyl alcohol (ethanol). All alcohols have a similar chemical structure and always contain a hydroxyl group, "OH", attached to a carbon molecule, which itself is connected to various combinations of carbon and hydrogen molecules.

Methanol is found in windshield wiper fluids and de-icers, antifreeze, glass cleaner, canned heat, paints, varnishes, and paint thinners and removers. Its toxicity is the result of its metabolism to formaldehyde and then to formic acid, a cellular toxin that is extremely poisonous. The accumulation of formic acid produces severe metabolic acidosis. Six to seven ounces of methanol is lethal for most adults, and much smaller quantities can cause permanent damage to the retina.

Isopropanol, common rubbing alcohol, is also quite toxic. Small amounts, as little as several ounces, can cause permanent damage to the visual system, and eight ounces is usually lethal. Some alcoholics may consume methanol or isopropyl alcohol, intentionally or unknowingly, with potentially lethal consequences.

Ethanol, the subject of this review, is the alcohol in alcoholic beverages consumed by many people. From this point, the term "alcohol" will be used to denote ethanol.

Alcohol is a relatively simple compound, with the general chemical formula C_2H_5OH . It is a clear, relatively odorless liquid that is infinitely miscible in water. Alcohol is metabolized by the enzyme alcohol dehydrogenase to acetaldehyde, a sympathomimetic toxin, which in turn is rapidly metabolized by another enzyme, aldehyde dehydrogenase, to acetic acid, and eventually to carbon dioxide and water. Understanding the biochemistry of alcohol metabolism has helped to develop treatments for alcohol abuse. For example, the drug Antabuse® inhibits aldehyde dehydrogenase allowing a toxic accumulation of acetaldehyde to occur when alcohol is consumed. Acetaldehyde causes nausea and discomfort. This aversive reaction is the basis of some aversion therapies.

Alcohol Concentrations

When yeast, water, and sugar are present together, the yeast recombines carbon, hydrogen, oxygen, and water to form alcohol and carbon dioxide. Each molecule of glucose (a simple sugar) is converted to two molecules of alcohol. Different alcoholic beverages are derived from the use of different fermenting ingredients. For wines, sugar-rich fruits provide necessary sugar for fermentation. This process continues naturally until alcohol concentrations of about 15-20% are reached. At that concentration, alcohol is so high that the yeast dies. Beers are manufactured with a different source of sugar; namely, the starch found in cereal grains, which is enzymatically converted to sugar through a malting process that allows fermentation to occur. For beers, fermentation is intentionally stopped when the alcohol concentration reaches about 3-6 percent, and for wines, the process is typically terminated at concentrations of about 11-13%. Since alcohol boils at a lower temperature than water, the two can be separated through distillation. In this process, fermented alcohol is heated, and the escaping alcohol vapors are cooled, so that they condense and can be collected. Distilled spirits can be made to very high alcohol concentrations (typically 50-60% in some beverages and up to nearly 100% in other products). The percent of alcohol by volume is $\frac{1}{2}$ the listed proof (e.g., 80 proof = 40% v/v).

From a scientific perspective, a 5-ounce glass of wine (12% v/v), a 12-ounce beer (4.9% v/v) and a shot or mixed drink containing $1\frac{1}{2}$ ounces of 80 proof spirits (e.g., whiskey, vodka, gin) each contain the same amount of absolute (100%) ethanol. However, the ultimate concentration of alcohol in the human body is a function of the number of grams of alcohol consumed, the amount of body water in the person, and other biological factors, such as absorption and metabolism.

Blood Alcohol Concentrations

The concentration of alcohol in blood, serum, water or any other liquid is the quantity by weight of absolute alcohol in a fixed volume of fluid. For example, 0.08% (w/v) is the same as 80 milligrams per 100 cc of fluid. Some clinical laboratories (hospitals) may report alcohol concentrations in serum, rather than whole blood. Because of differences in water content, in most cases, serum alcohol is *about* 18% higher than whole blood alcohol concentrations.

Neurochemistry of Acute Alcohol Intoxication

Regardless of the type of alcoholic beverage consumed, it is the psychoactive drug, ethanol, which produces effects on the brain with subsequent alteration of behavior, and the influence on virtually all cells within the body. The degree of alcohol's effects is determined by the concentration in blood, which is influenced by the amount and rate of alcohol consumption, bioavailability due to factors such as rate of absorption, the biotransformation of alcohol, which may be influenced by genetic factors, and drinking experience. All of these factors ultimately result in

individual differences in the exposure and response of various cells to alcohol.

Two specific neurochemical systems in the brain have been strongly implicated in mediating alcohol intoxication: 1) gamma aminobutyric acid (GABA) and its receptor; and 2) glutamate, and one of its receptors, which is termed N-methyl-D-aspartic acid (NMDA). GABA is the major inhibitory neurotransmitter in the brain, and interacts with a family of receptors that recognize anxiolytic and sedative benzodiazepines and other drugs. GABA receptors form ion-selective channels, or ligand-gated ion channels. When these receptors are activated by their specific neurotransmitter, cellular activity changes. For example benzodiazepines, which share many biobehavioral properties with alcohol, enhance chloride ion transport through the GABA_A receptor, causing a decrease in neuronal activity.

Drugs that mimic the effects of GABA enhance and prolong the behavioral effects of alcohol. Those drugs that block the effects of GABA have the opposite effects. For example, benzodiazepine receptor inverse agonists antagonize (block) many alcohol-induced cognitive, behavioral and neurophysiological effects of alcohol in animal models. Such research suggests that alcohol produces its effects by enhancing chloride ion transport resulting in a decrease in neuronal activity within neurons that use GABA.

Glutamate, the major excitatory neurotransmitter in the brain, is also believed to play an important role in alcohol intoxication and behavior. Blocking NMDA receptors has similar behavioral effects to alcohol and electrophysiological studies have shown that alcohol antagonizes or counteracts the NMDA-induced behavioral responses. Together, such findings suggest that the inhibition of NMDA receptors is an important mechanism by which acute alcohol consumption affects brain function and behavior.

Neurochemistry of Chronic Alcohol Intoxication

Since alcohol shares pharmacological actions with benzodiazepines and barbiturates, including cross-tolerance and dependence, this suggests that all three drugs share some neuropharmacological mechanism(s) of action. Possibly tolerance to the sedative and intoxicating effects of alcohol is the result of a compensatory decrease in GABA-mediated inhibition in the brain. Recent studies suggest that alterations in the function of the GABA_A receptor chloride channels also contribute to the signs and symptoms of the ethanol withdrawal syndrome.

Decreases in GABA mediated inhibition of neurons, and increased sensitivity of NMDA receptors may account for important characteristics of alcohol withdrawal. Moreover, several studies have revealed that supersensitive NMDA stimulated calcium flux occurs after only a few days of chronic alcohol exposure, and may contribute to the hyperexcitability and seizures that accompany withdrawal. It has been suggested that chronic alcohol consumption can induce NMDA supersensitivity by increasing NMDA receptor density, composition or increased release of glutamate (the neurotransmitter that stimulates NMDA receptors).

Naltrexone, a drug that antagonizes opiate receptors, has been shown to be effective in reducing relapse. This suggests that alcohol and opiates share some common mechanisms. Another drug, acamprosate, a drug that modulates both glutamate and GABA systems, decreases craving and may be a promising treatment for alcoholism.

Decades of research lead to the conclusion that the behavioral effects of acute and chronic alcohol intoxication occur as a result of changes in brain chemistry and that alcoholism is a brain disease. With a clearer picture of when and where neuropharmacological changes occur in the brain, future research on the neurophysiological mechanisms that mediate these effects may lead to effective pharmacological adjuncts to treatment and prevention of alcohol-related problems.

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