Pharmacological perspective of neurotransmission basis of alcohol intoxication

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ABSTRACT

Alcohol in the human body appears to have an extensive impact on molecular targets in the nervous system. The wide spectrum of physical behavioural abnormalities express by alcoholics is traced to its ability to cross the blood-brain barrier (BBB), intercalates into cell membranes and affects the information processing activities in the brain membranes potential. It is also viewed that the far reaching effects of ethanol in the nervous system which is mediated via the ion channels, receptors and enzymes are primarily caused by its interactions with neurotransmitters. The molecular basis of neurotransmitter mediated alcohol induced behavioural effect is the main focus of this review. In this article the term alcohol is used as a generic name for ethanol (ethyl alcohol), which is the main subject of this discussion.

Keywords: Alcohol, Neurotransmitter, Psychoactive, Pharmacodynamics, BBB, CNS

Introduction

Alcohol, a chemical name for a group of organic compounds with hydroxyl (OH) as their main functional group is also used as a generic name for ethanol (ethyl alcohol) which is the most common member of the group with chemical formula CH₃CH₂OH. Alcohol is a psychoactive agent that acts at many sites, including the reticular formation, spinal cord, cerebellum and cerebral cortex, mostly via many neurotransmitter systems. Effects of alcohol intoxication range from sedation, characterized by decreased awareness and inability to function, to even death. Little wonder, George Bernard Shaw described it as “the anaesthesia by which we endure the operation of life”. Because of its very small molecular structure and ampiphatic nature, alcohol gets into the bloodstream easily and crosses the BBB to bring about some neurochemical effects in the brain.

After crossing the BBB, alcohol interacts with several neurotransmitter systems both agonistically and antagonistically to alter the normal neurochemical processes and produce some untoward effects. By neurotransmitter interaction, alcohol affects a number of different neurotransmitter systems through its action on the nerve cell membranes and the ion channels, especially those for calcium and chloride. Hence it tends to mimic the action of neurotransmitters, by altering the activities of receptors, acting on activation of second messengers, or directly affecting intracellular
processes that control normal neuronal functions to produce abnormal neurochemical effects like magnifying the effects of gamma amino butyric acid (GABA), glycine, serotonin and endorphins alongside antagonising effects on glutamate activities, increased turnover of norepinephrine and dopamine, decreased transmission in acetylcholine⁵. These abnormal neurotransmitter effects of alcohol are majorly the molecular basis behind alcoholics, drinking to achieve ecstatic mood or to relieve a moody state and in the process, increasing the frequency and quantity to achieve the same effect as well as the unsuccessful attempts to stop its consumption without experiencing negative physical symptoms.

**Alcoholism**

Alcohol intoxication - alcoholism, is manifested when the alcohol consumed by a person produces physical with concomitant intrinsic abnormalities or when the quantity measured in the blood exceeds a given threshold level and it mostly manifest as abnormal behavioural reactions. It occurs due to neurotransmission mediated depressive effects of alcohol on various areas of the central nervous system leading to states of euphoria, ataxia, amnesia, vomiting, confusion and disorientation, progressive lethargy, coma, shut down of respiratory centres and even death. Studies have established that drug dependence and tolerance are features of an organic brain disease caused by continual and cumulative impacts of psychoactive drugs on neurotransmission⁶. Drugs that cross the BBB like ethanol can alter important brain areas that are necessary for life-sustaining functions and can drive the compulsive drug abuse that marks addiction⁶,⁷,⁵. Alcohol addiction is viewed from its brain function alteration where it interacts with multiple neurotransmitter systems and positively reinforces drinking through several neurochemical systems that lead to dependence, tolerance and withdrawal syndromes. Abnormal stimulation of neurotransmission by drugs like ethanol, however, produces a rewarding effect, which strongly influences the user to repeat it unconsciously. Pharmacological investigations have shown that dopamine transmission, particularly in the medial part of the ventral tegmentum area (VTA) - dopamine system, plays a major role in this self-stimulation process⁸,⁹ as it energizes approach and induces conditioned approach arousal¹⁰,¹¹. It is believed to indirectly stimulate neuronal dopamine cell firing effects through various dopamine receptors⁶. Large and fast dopamine release caused by alcohol consumption (up to 10 times the natural level) leads to excitatory effect of dopamine in the nucleus accumbens from ventral tegmental neurons¹²,¹³. This resulting effects on the brain’s pleasure circuit influence those produced by naturally rewarding behaviour¹⁴,¹⁵ that produces a very strong motivation for the drugs. Reports of several studies have also shown that dopamine is involved in the reinforcing effects of alcohol where dopamine inhibitor drugs reduce alcohol self-administration in rats¹⁶,¹⁷.

However, this resultant strong motivation in taking this abuse drug (alcohol), dopamine’s impact on the reward circuit of the brain becomes abnormally low, as the ability to experience any pleasure is reduced thereby arising the need to constantly and increasingly take the drug to come to the normal dopamine level. At this point, tolerance - the need for higher drug dosages to produce an effect and addiction – the uncontrollable craving for alcohol as an indispensable food occurs¹⁸.

Initial exposure to intoxicating concentrations of alcohol appears to inhibit both N-methyl-D-aspartate (NMDA) and non-NMDA receptor activity, potentially resulting in sedation¹⁹. This in effect shifts the equilibrium toward inhibition by both enhancing the function of inhibitory neurotransmitters and neuromodulators (like GABA, glycine, and adenosine respectively) and declining the function of excitatory neurotransmitters (like glutamate and aspartate) while prolonged use has the reverse effects²⁰,¹⁹. The reduction in GABA function by long term consumption may result from a decrease in receptor levels or a change in the protein composition of the receptor, leading to decreased sensitivity to neurotransmission. Also, glutamate receptors tend to adapt to the antagonistic effects of alcohol by increasing their excitatory activity²¹,¹⁹.
On the other hand, alcohol withdrawal, most times is difficult and may require detoxification medication – a concept referred as assisted withdrawal. During alcohol withdrawal, these compensatory changes are no longer antagonised by the presence of alcohol and the equilibrium shifts toward a state of excessive excitation which is characterized by seizures, delirium, and anxiety. At the cellular levels, continual alcohol consumption causes brain cells adaptations via neurotransmitter balance process, so making the brain to produce more functional NMDA receptors as part of the normal excitatory system. When alcohol is stopped, these excess receptors combine to cause excessive influx of calcium into the cells coupled with the removal of alcohol mediated inhibitory actions through GABA receptor, leads to hyperexcitability. Consequently, the increase in excitatory glutamate coupled with a sharp decline in the brain’s inhibitory systems combine to give noradrenergic stimulation giving rise to hyper-sympathetic activity. Most alcoholics who stop drinking experience a spectrum of different withdrawal symptoms.

Pharmacokinetics of alcohol

The fundamental hypothesis of pharmacokinetics is the pharmacologic relationship between the effect (therapeutic or toxic) and concentration of the drug in a readily accessible site of action in the body which are dependent on these three pharmacokinetic variables –bioavailability, distribution and clearance. These variables are a function of absorption, metabolism and elimination. In simple terms, pharmacokinetics refers to what the drug is subjected to, in the body which as well affect the action and response of the drug at the site of action.

Alcohol enters the body through the mouth after ingestion and passes directly into the stomach where about 20% of it is absorbed by passive diffusion through the walls while the remaining 80% enters the blood stream through the walls of the intestine. Shortly, as the heart pumps blood throughout the body, alcohol is circulated to all parts of the body, including the brain and the longer the alcohol remains in the stomach, the slower it will be absorbed and the lower the blood alcohol concentration (BAC). Alcohol interaction with food has a lot of implications as the presence of food slows the rate of BAC. Alcohol irritates the gastro-intestinal system, increasing acid secretion by the stomach and interferes with nutrients absorption. Its metabolism by the liver uses niacin, thiamine and other B vitamins, which dispossess the body of these vitamins.

Elimination of alcohol out of the body is achieved majorly through metabolism which gets rid of over 90% alcohol by bio transforming them into metabolites. Ethanol distributed in the body fluid space is metabolized mainly through the hepatic oxidation catalyzed by the ADH, ALDH, cytochrome P450 2E1 (CYP2E1) and catalase enzymes.

The liver is the primary site of alcohol metabolism where several biochemical agents called enzymes help to convert it to other compounds (or metabolites), which can be easily processed by the body. Alcohol is also metabolized in non-liver (extrahepatic) tissues that do not contain ADH, such as the brain, by the enzymes cytochrome P450 and catalase. Alcohol metabolism can be categorised into two pathways viz; oxidative and non-oxidative pathways. The oxidative pathways involves either addition of oxygen or removal of hydrogen through pathways involving ADH, cytochrome P450 2E1 (CYP2E1) and catalase enzymes. ADH, present in the cytosol, converts alcohol to acetaldehyde (CH$_3$CHO) via the electron transfer chain (ETC) of nicotinamide adenine dinucleotide (NAD$^+$) / NADH system. The acetaldehyde is generally short-lived as it is quickly metabolised to a less toxic acetate (CH$_3$COO$^-$) by another enzyme called aldehyde dehydrogenase (ALDH). Acetate causes an increase in blood flow into the liver and is metabolized to acetyl CoA, which is involved in fatty acids, amino acids and steroids synthesis in addition to oxidation in the Krebs cycle, with CO$_2$ and water as the end-products. The activities of these enzymes may lead to variation in alcohol elimination rates among individuals. The catalase process is a minor pathway of alcohol
oxidation that occur mostly in the fasted state and utilise hydrogen peroxide to oxidize alcohol\textsuperscript{38}. Cytochrome P\textsubscript{450} 2E1 (CYP2E1) is useful in metabolizing ethanol to acetaldehyde at elevated ethanol concentrations\textsuperscript{39}. Studies on rat brain homogenates suggest that ethanol metabolism proceeds here through catalase and cytochrome P450 (CYP2E1), which inactivate about 60–70\% and about 20\% of ethanol, respectively, via oxidation\textsuperscript{40}. Acetaldehyde (ethanal) is metabolized mainly by aldehyde dehydrogenase 2 (ALDH2) in the mitochondria to form acetate and NADH. The non oxidative metabolism of alcohol is a two arm metabolism pathway, though minimal, but its products have some pathological and diagnostic applications. While one arm leads to the formation of fatty acid ethyl esters (FAEEs) from the reaction of alcohol with fatty acids, the other arm leads to the formation of a type of phospholipid known as phosphatidyl ethanol and requires the enzyme phospholipase D\textsuperscript{41}. FAEEs are detectable in serum and other tissues after alcohol ingestion and persist long after alcohol is eliminated. The role of FAEEs in alcoholics is thought to be implicated in "beerbelly" concept.

\[ \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CHO} \rightarrow \text{CH}_3\text{COO}^- \]

Oxidative and nonoxidative pathways for metabolism of alcohol are interconnected in that, inhibition of the oxidative pathway (by ADH, CYP2E1 and catalase inhibitors) leads to increase in the products of the non oxidative pathway like FAEEs in the liver\textsuperscript{42}. Finally, about 5\% is excreted into the urine while \textless 5\% is eliminated through sweat pore the lungs during exhalation which forms the basis for breath analyzer testing.

**Alcohol-neurotransmitters pharmacodynamics**

Drugs acting on the CNS are the most widely used group of pharmacologic active agents and most of them that have extensive effects are majorly due to their neurotransmitter interactions which are extremely of medical importance\textsuperscript{43}. Nerve cells or neurons communicate by releasing chemical messengers called neurotransmitters, which bind to receptor proteins on the surface of other neurons. This process is called neurotransmission. Sometimes other chemical messengers called neuromodulators modify the effects of neurotransmitters.

Diseases and drugs effects on neurotransmitters can exert different negative impacts on the body. Disease such as Alzheimer’s and Parkinson’s are associated with deficits in certain neurotransmitter\textsuperscript{44}. The effect of alcohol on specific neurotransmitter substances is one of the important findings\textsuperscript{45} as evidence suggests that alcohol affects neurotransmitter substances by interacting with multiple neurotransmitter systems, thereby altering the existing equilibrium between inhibitory and excitatory neurotransmitters\textsuperscript{46}.

The nervous system, which is one of the major means by which the human body functions are controlled through high level integration in the brain, relies not only on rapid electrical transmission of information over nerve fibres but importantly on chemical transmission between nerve cells and between nerve cells and their effector cells. This chemical transmission takes place through the release of small amount of transmitter substances called neurotransmitters or neuromediators from the nerve terminals into the synaptic cleft. These chemical transmitters cross the synaptic cleft by diffusion and cause a post synaptic action by binding to a specialised receptor molecule leading to either inhibitory or excitatory action\textsuperscript{47}. Neurotransmitters are chemical messengers that carry and modulate signals between neurons and other cells in the body. They are categorized by their excitatory or inhibitory effects on the effector cells. Some of the major excitatory neurotransmitters are epinephrine and norepinephrine\textsuperscript{48} while in the brain, the major excitatory neurotransmitters are the amino acids; aspartates and glutamates, which act through both N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors. GABA and serotonin are the major inhibitory neurotransmitters. Some neurotransmitters such as acetylcholine and dopamine can have both excitatory and inhibitory effects depending upon the type of the
Molecular basis of neurotransmission

The events in the communication between neurones in the CNS involve in the release of neurotransmitters from presynaptic terminal have been studied extensively at the vertebrate neuromuscular junction and at the giant synapse. A detailed description of synaptic transmission was not possible until 1950’s with the use of glass microelectrode that permitted intracellular recording was developed.

An action potential in the presynaptic fibre propagates into the synaptic terminal and activates voltage sensitive calcium channels in the membrane of the terminal leading to increase in the intra terminal calcium concentration that promotes the fusion of synaptic vesicles with synaptic membrane causing the release of neurotransmitters contained in the vesicles into the synaptic cleft which diffuses into the receptors on the post synaptic membrane. This communication process is maintained for normal transmission but the entrance of a psychoactive drug like ethanol leads to a dramatic malfunction of the process beyond limits. Membranes of nerves cells contain two types of channels, voltage sensitive gating and chemically activated gating. The voltage sensitive gateings are concentrated on the initial segment of the neurones and the axon and are responsible for fast action potential which transmits the signals from cell body to nerve terminals while the chemically activated channels sometimes called receptor operated channels are concentrated on the sub synaptic membrane e.g. nicotinic neuromuscular receptor of the skeletal muscle endplate. They are insensitive to membrane potentials but are opened by the activation of neurotransmitters and other chemical agents with actions leading to stimulation of either excitatory or inhibitory pathway. When an excitatory pathway is stimulated, a small depolarization or excitatory post synaptic potential (EPSP) is recorded due to increase in sodium and potassium permeability as the resultant EPSP depolarises the post synaptic cells to produce an action potential. When an inhibitory pathway is stimulated, the post synaptic membrane is hyperpolarised producing an inhibitory postsynaptic potential (IPSP) to alter the membrane potential. Alcohol affect the brain by connecting into its neurotransmitters communication system, affecting the complex interplay between excitatory and inhibitory pathways and interfering with its information processing pattern to produce abnormal EPSP or IPSP. The numerous transmitters involved in alcohol’s action explain its diverse effects and the large number of drug interactions.

Alcohol interaction with specific neurotransmitters

In the brain, alcohol affects the brain’s neurons in several ways. It alters their membranes conductance as well as their ion channels, enzymes, and receptors. Alcohol binds directly to the receptors for acetylcholine, serotonin, GABA, and the NMDA receptors for glutamate. Some reports suggest that short-term alcohol exposure increases the inhibitory effect of GABA receptors by exhibiting positive allosteric binding properties to GABA receptors. GABA’s effect is to decrease neural activity by allowing chloride ions into the post-synaptic nerves. These ions have negative electrical charge, which helps to make the neuron less excitable. This physiological effect is amplified when alcohol binds to the GABA receptor, expectedly because it causes the ion channel to be open longer and thus letting in more chloride ions into the cell. Dopamine is a neurotransmitter for natural rewards of everyday life. Alcohol also helps to increase the release of this neurotransmitter through stimulation of the mesolimbic pathway by binding to D4 receptors in the caudate nucleus and the
putamen, activating the beta-endorphins that innervate the ventral tegmental area and the nucleus accumbens, thereby producing a net effect of excitation\(^56\). According to\(^{57,58}\) stimulation of the function of serotonin receptors and medications that act on these receptors after alcohol consumption in humans and animals have been observed. Serotonin has also been implicated in the rewarding effect of alcohol dependence through an indirect effect on dopamine release\(^{59}\). Researches have shown that alcohol can directly act on different nicotinic acetylcholine receptor (nAChR) subtypes by opening the voltage gated channels, thereby allowing Na\(^+\) and/or Ca\(^{2+}\) to enter into a neuron. The resulting transient change in the internal ion concentration enhances the neuron’s excitatory ability and by extension causes the release of neurotransmitters that act on other neurons\(^{60}\). Alcohol acts on NMDA receptors, inhibiting their functions and thereby opposing glutamate-mediated neurotransmission\(^55\). Interestingly, alcohol also acts on some receptors for norepinephrine\(^{61,21,19}\) and causes the release of norepinephrine in the brain which is one reason why alcohol also acts as stimulant and not only as a depressant. It has been shown that alcohol increases the function of glycine receptors in laboratory preparations\(^{19}\) which is a pointer to the strong agonistic property of alcohol to glycine, a major inhibitory neurotransmitter in the spinal cord and brain stem.

Summarily, alcohol depressant effect is viewed to be achieved by either increasing inhibitory neurotransmission or by decreasing excitatory neurotransmission or through a combination of both while its excitatory actions by suppression of inhibitory neurotransmitter systems\(^{62}\).

**Conclusions**

Regardless of the beneficial effects of alcohol, this review however gives a pharmacological perspective of interactions involved in alcoholism from neurotransmission angle which depicts the pathophysiology of many alcohol related problems since most vital functions of the CNS especially the brain depend on the internal equilibrium between excitatory and inhibitory neurotransmitters which when affected by alcohol consumption, is the main basis behind the numerous alcohol induced abnormal behavioural manifestations.

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