Consequences of Alcohol Consumption on Neurotransmitters - An Overview

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Abstract: Alcohol one of the important product of the global addiction alters brain function by interacting with multiple neurotransmitter systems thereby disrupting the delicate balance between inhibitory and excitatory neurotransmitters. Alcohol positively reinforces drinking by producing a mild euphoria. The reinforcing effects of alcohol are mediated by several neurochemical systems and are associated with some of the behavioral manifestations of intoxication. Alcohol consumption is initially accompanied by decreased attention, alterations in memory, mood changes, and drowsiness. Generally all vital functions of brain depend on a delicate balance between excitatory and inhibitory neurotransmission, which in turn dependent on short, and long term alcohol consumption. For detailed understanding of alcohol's mechanism of action on the neurotransmitters of brain is a prerequisite in discovering effective treatments for both alcohol abuse and alcoholism. This review covers the elaborate literature on the subject, and highlights the functions and interactions of neurotransmitters and alcoholism.

Keywords: Alcohol, GABA, glutamate, glycine, neurotransmitters.

INTRODUCTION

Alcoholic beverages, and the problems they engender, have been familiar in human societies since the beginning of recorded history. Accompanying the near ubiquity of alcoholic beverages in human history has been an appreciation of the social and health problems caused by drinking. Although the recorded per capita alcohol consumption has fallen since 1980 in most developed countries, it has risen steadily in developing countries. In the Asian subcontinent per capita alcohol consumption has increased by over 50% between 1980 and 2000, and alarmingly so in India. The per capita consumption of alcohol by adults above 15 years in India increased by 106.7% between 1970–72 and 1994–96. The pattern of drinking in India has changed from occasional and ritualistic use to social use. Today, the common purpose of consuming alcohol is to get drunk. These developments have raised concerns about the health and the social consequences of excessive drinking **(**Das *et al.*, 2006).

Ethanol induces a number of effects, such as disinhibition, a feeling of general well being, tolerance and physical dependence. Being a depressant drug, alcohol has major effects on higher nerve centers. Its first effect is to reduce feelings of worry, and thereby to promote a feeling of wellbeing. It also loosens powers of imagination. Alcohol even in small doses impairs judgment and inhibits the skills necessary for fine movements (Passmore & Eastwood, 1986). When alcohol is consumed above recommended levels, it makes the nervous system alcohol-dependent. Once the actions of alcohol are over, the opposite effects (rebound symptoms) begin to appear. If one carries on drinking in spite of reverse or rebound symptoms, tension, nervousness, restlessness, etc., can creep on the individual, depending on the tolerance of the body (Gianoulakis, 1993)

Clinical and experimental evidence has demonstrated that ethanol is a teratogen, and central nervous system dysfunctions are the most severe and permanent consequence of maternal alcohol intake and can occur in absence of gross morphological defects associated with fetal alcohol syndrome (FAS). Alcohol interferes with many molecular, neurochemical and cellular events occurring during the normal development of the brain. Some brain areas are more affected than others, and even within a given region; some cell populations are more vulnerable than others. The neocortex, hippocampus and cerebellum are especially susceptible to alcohol and have been associated with behavioural changes. These effects may be associated with ethanol-induced alterations in both neurotrophic support, and the expression of cell adhesion molecules, which affects cell-cell interactions and cell survival. Experimental evidence also shows that alcohol disrupts radial glial and astroglial development that may lead to alterations in cell migration and neuronal survival and differentiation. Impairment of several neurotransmitter systems and/or their receptors, as well as changes in the endocrine environment during brain development, are also important factors involved in the neurodevelopmental changes observed after in utero alcohol exposure (Guerri, 2002).

Alcohol mainly affects the *frontal lobe* region of the brain, causing thinking and problem-solving difficulties. Alcohol's effects on the cerebellum cause motor-coordination problems. Alcohol can cause memory loss by damaging the *hippocampus.* Large doses of alcohol can cause a person's heart to stop beating through its effects on the *medulla oblongata* and the *pons.* Alcohol has specific effects on certain

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receptors and neurotransmitters in the brain. Alcohol interrupts the normal functioning of other neuro-transmitters, and can prevent the neurotransmission that would normally affect certain types of behavior. For example alcohol increases dopamine release, which is responsible for the pleasurable aspects of drinking (Guerri, 2002) (Table **1**).

Table-1. Neurotransmitters Alteration in Acute and Chronic Alcohol Consumption

Neurotransmitters	Acute consumption	Chronic consumption
Acetyl Choline	Decreases	Increases (AChE muscarinic receptors)
Noradrenergic	Decreases	Increases (β-NA receptors)
Serotonin	Increases	Decreases (5-HT)
Opiates	Decreases	Increases
Inhibitory amino acids (GABA, Taurine)	Increases	Excitatory amino acids(glutamate, aspartate) increases.
Neuronal excitability	Decreases	Increases

AchE- acetylcholineesterase, NA- Noradrenergic, 5-HT- serotonin (DeWitte, 1996)

SEROTONIN

Serotonin (5-hydroxytryptamine, 5-HT) is assumed to play a role in the pathophysiology of different psychiatric disorders including alcoholism. Since platelets and central serotonergic synaptosomes share similar pharmacodyna-mics of 5-HT, it is seen that alterations in 5-HT system might be related to alcoholism (Pivac *et al*., 2004). Serotonin (5-hydroxy-tryptamine, or 5-HT) regulates alcohol intake and the development of alcoholism (LeMarquand *et al.*, 1994). Central and peripheral levels of serotonin and of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) are modified by alcoholism (Daoust *et al*., 1992) Fig. (**1**).

Alcohol interacts with serotonergic synaptic transmission in the brain in several ways. Even single episode (i.e acute) alcohol exposure alters various aspects of serotonin's synaptic functions. In humans, the levels of serotonin metabolites in urine and blood increase after a single drinking session, indicating increased serotonin release in the nervous system (Lovinger, 1999). Dorsal striatum is regulated by the serotonergic system, and it is a brain area with a role in the development of obsessive thought patterns, which may be related to addiction. The Serotonin Transporter (SERT)

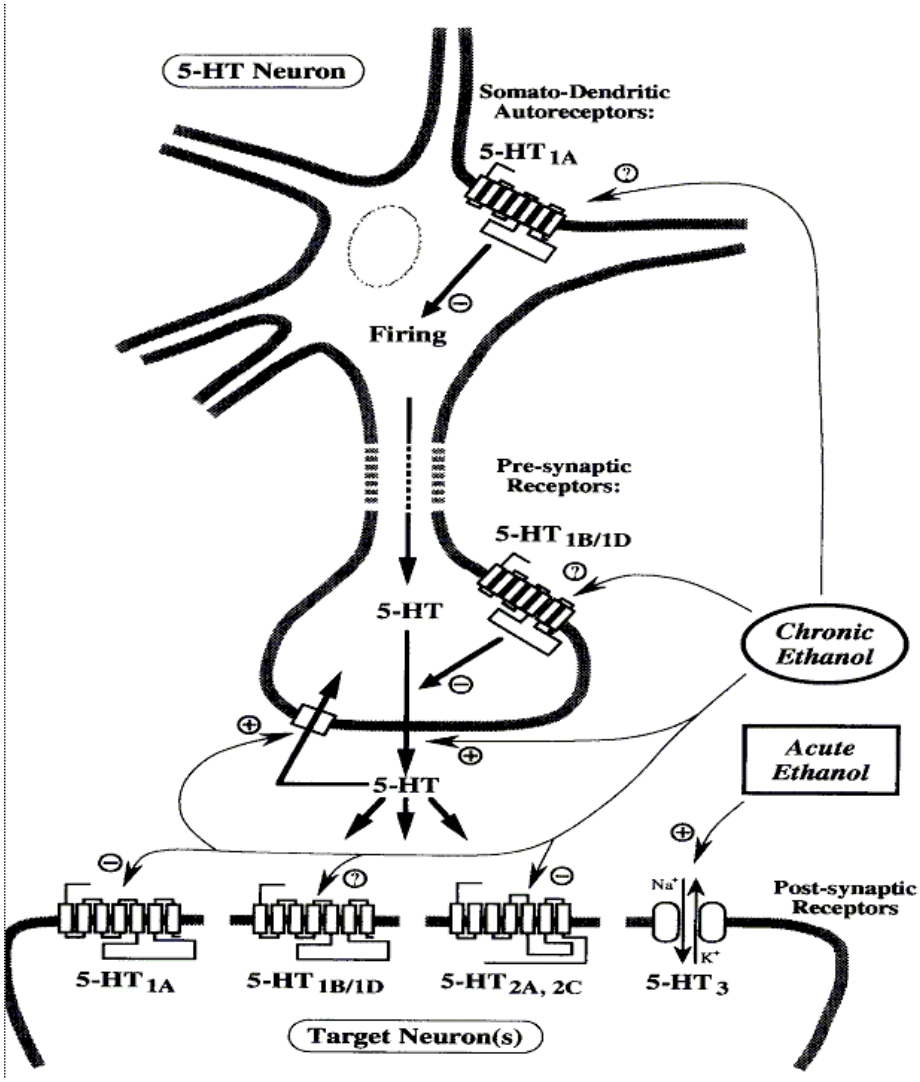

Fig. (1). Effect of chronic and acute effect of ethanol on the various 5-HT receptor subtypes, (+) positive effect and (-) negative effect. (Nevo and Hammon, 1995).

binding was significantly lower in alcoholics. The SERT binding tended to be lower also in the other parts of the dorsal striatum in alcoholics, and the serotonergic system may be affected in cortical and striatal areas simultaneously. The cortico-striatal-thalamic axis may have an important role in fully developed addictions and the characterization of these correlations within the serotonergic system may lead to a better understanding of the anatomical dynamics underlying the neurochemistry of alcoholism (Storvik *et al.*, 2006).

GLUTAMATE

Brain glutamate increases during the first cycle of ethanol withdrawal, and this increase is much higher during the third cycle of ethanol withdrawal. The elevated glutamate released in the hippocampus during the first cycle of ethanol withdrawal episode was exacerbated in subsequent withdrawal episodes (De Witte, 2004).

Glutamate, the excitatory neurotransmitters increase the activity of signal receiving neurons and play a major role in controlling brain function (Gonzales and Jaworski, 1997). Neurophysiological and pathological effects of ethanol may be mediated, to an important extent, *via* the glutamatergic system (Tsai *et al.*, 1998). Glutamate exerts its effects on cells in part through three types of receptors that, when activated, allow the flow of positively charged ions into the cell (Gonzales and Jaworski, 1997). Moreover, alcohol-induced impairment of the NMDA receptor may contribute to alcohol-related learning disabilities, neuronal losses, as well as to some of the manifestations of alcohol withdrawal (Gonzales and Jaworski, 1997). The acute effects of ethanol disrupt glutamatergic neurotransmission by inhibiting the response of the N-methyl-D-aspartate (NMDA) receptor. Persistent attenuation of glutamatergic neurotransmission by chronic ethanol exposure results in the compensatory up-regulation of NMDA receptors. The augmentation of excitatory neurotransmission may lead to enhanced oxidative stress, which, in concert with reduced inhibitory neurotransmission, may contribute to the symptoms of ethanol withdrawal and associated neurotoxicity in humans (Tsai *et al.*, 1998).

GABA

Alcohol affects gamma amino butyric acid (GABA) receptors and GABA. GABA is an inhibitory neurotransmitter; it decreases the activity of neurons. Excess GABA may cause decreased attention, memory alterations, mood changes, and drowsiness. Both catecholaminergic and GABAergic mechanisms control ethanol-induced motor impairment and the regulation of the receptors (Kiianmaa, 1990).

Acute ethanol facilitates GABAergic transmission by enhancing chloride conductance through the $GABA_A$ receptor, and inhibits glutamatergic function by decreasing cationic conductance through the NMDA receptor. Conversely, the development of tolerance associated with chronic ethanol consumption leads to a reduced GABAergic and increased glutamatergic function. Interactions between ethanol and the monoaminergic transmitter systems are complex. Dopaminergic and noradrenergic mechanisms, along with the endogenous opioid systems of the brain, seem to be implicated in the rewarding effects of ethanol *via* activation of positive reinforcement pathways, while the serotonergic system mediates negative reinforcement. Central cholinergic activity has been reduced in alcohol-dependent patients (Nevo & Hamon, 1995).

Alcohol facilitates gamma-aminobutyric acid (GABA) function, and suppresses alcohol withdrawal symptoms. Alcohol increases GABA release, raises neurosteroid levels, and may potently enhance the function of a $GABA_A$ receptor subclass that shows high affinity for GABA and neurosteroids, relative insensitivity to benzodiazepines, low chloride conductance, and an extrasynaptic location (Krystal, 2006). GABA inhibits the activity of signal-receiving neurons by interacting with the $GABA_A$ receptor on these cells. The $GABA_A$ receptor is a channel-forming protein that allows the passage of chloride ions into the cells. Excessive $GABA_A$ activation may play a role in mediating the sedative effects of alcohol and other sedating and anesthetic agents. Alcohol enhances the $GABA_A$-mediated chloride flow into cells and may thereby enhance neuronal inhibition. Alcohol's effects on the $GABA_A$-receptor function likely involve other molecules (*e.g.*, other neurotransmitters and proteins that add phosphate groups to the receptor [i.e., protein kinases]) (Mihic and Harris, 1997). Variation in $GABA_A$ receptor subunit genes may contribute to the vulnerability to alcoholism, particularly in the context of environmental risk factors. Alcohol dependence is associated with time-dependent changes in brain $GABA_A$ receptor density and subunit gene expression levels that contribute to a withdrawal-related deficit in $GABA_A$ receptor function. However, cortical GABA levels are not reduced during acute withdrawal (Krystal, 2006).

GLYCINE

Glycine accomplishes several functions as a transmitter in the central nervous system (CNS). As an inhibitory neurotransmitter, it participates in the processing of motor and sensory information that permits movement, vision, and audition. This action of glycine is mediated by the strychnine-sensitive glycine receptor, whose activation produces inhibitory post-synaptic potentials. In some areas of the CNS, glycine seems to be co-released with GABA, the main inhibitory amino acid neurotransmitter. In addition, glycine modulates excitatory neurotransmission by potentiating the action of glutamate at N-methyl-D-aspartate (NMDA) receptors (López-Corcuera *et al.*, 2001). The synaptic action of glycine ends by active recapture through sodium- and chloride-coupled glycine transporters (GLYT1 and GLYT2) located in glial and neuronal plasma membranes (Aragón and López-Corcuera, 2003), whose activities and subcellular distributions are regulated by phosphorylation and interactions with other proteins **(**Eulenburg *et al.*, 2005). Glycine transporters may become major targets for therapeutic of pathological alterations in synaptic function (López-Corcuera *et al.*, 2001).

OTHER ACTIVATORS

Neurotransmitters such as acetylcholine, glycine, glutamate and γ- aminobutyric acid (GABA), have an “inherent” biological activity that increases the conductance of certain

ions by binding to ligand-activated ion channels at the postsynaptic membrane. Other neurotransmitters, such as norepinephrine, dopamine and serotonin have no direct activity but act indirectly *via* second messenger systems to bring about the postsynaptic response. These second messengers systems involve cAMP, cGMP, ionosine triphosphate (ITP), diacylglycerol (DAG), prostaglandins, leukotrienes, epoxides and Ca^{2+}. These second messengers activate preexisting target proteins, including protein kinases, which in turn act on substrates such as ion channels etc., to produce that effect. A single neurotransmitter may have different effects at receptors on different neurons, different effects at receptors on the same neuron, and similar effects at different receptors on the same neuron. In addition to acetylcholine, the catecholamines such as dopamine, norepinephrine and epinephrine are also been shown convincingly to be neurotransmitters in the peripheral and central nervous systems. Other primary amines such as histamine, octamine, phenylethylamine and polyamines such as putrescine, spermine and spermidine may also act as neurotransmitters. A number of amino acids such as glutamic and aspartic acids, glycine, β-alanine, GABA, taurine and possibly proline function as neurotransmitters (Gonzales and Jaworski, 1997).

Abnormalities in the mesolimbic dopamine pathway, and/or the serotonin, opioid, and GABA systems that regulate the pathway may underlie vulnerability to the abnormal alcohol-seeking behavior in the genetic animal models (McBride and Li, 1998).

Animal studies have demonstrated that alcohol changes neurotransmitter concentrations in the brain. Compared with alcohol-avoiding rats, rats with an affinity for alcohol have a greater sensitivity to the stimulatory effects of low to moderate doses and a reduced sensitivity to the negative effects of high doses. Rats that voluntarily drink large quantities of alcohol also acquire tolerance to alcohol's aversive effects. In addition, these rats differ from their alcohol-avoiding counterparts in the levels of several chemical mediators (i.e., neurotransmitters) found in the brain, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and the endogenous opioids (Stewart and Li, 1997). These changes of dopamine, serotonin, gamma-aminobutyric acid (GABA), endogenous opioid peptides, and noradrenaline are associated with activation of reward centres in the brain. Alcohol is believed to be responsible for the reinforcing effect of alcohol consumption in rats. One class of neurotransmitters, the endogenous opioid peptides, is believed to play an important role in alcohol reinforcement. The widely distributed inhibitory neurotransmitter GABA is also believed to play a fundamental role in mediating the effects of alcohol (De Witte, 1996). Development of tolerance towards alcohol seems to be accompanied by changes in neuronal membrane structure that, in turn, affects the function of membrane-bound dopaminergic receptors. On the other hand, changes in cholinergic receptor number in certain brain areas may be responsible for certain signs of physical dependence during ethanol withdrawal (Tabakoff *et al*., 1980).

Ethanol appears to interact with ethanol-sensitive elements within neuronal membranes that convey the specificity of neurochemical action. Ethanol reinforcement appears to be mediated by an activation of $GABA_A$ receptors, release of opioid peptides, release of dopamine, inhibition of glutamate receptors, and interaction with serotonin systems. These neurocircuits may be altered by chronic ethanol administration as reflected by opposite effects during acute ethanol withdrawal and by the recruitment of other neurotransmitter systems such as the stress neuropeptide corticotropin-releasing factor (Koob *et al.*, 1998).

AFFINITY FOR ALCOHOL

Several disciplines suggest a three-pathway psychobiological model of craving for alcoholism. Essential to this model is the appreciation of the role of individual differences in affect regulation strategies or personality styles, conditionability, sensitivity to alcohol's effects, and related dysregulations in distinct neural circuitries or neurotransmitter systems. As a first pathway, it is suggested that reward craving or desire for the rewarding, stimulating and/or enhancing effects of alcohol might result from either dopaminergic/ opioidergic dysregulation or a personality style characterized by reward seeking or a combination of both. As a second pathway, it is suggested that relief craving or desire for the reduction of tension or arousal might result from either gamma-aminobutyric acid (GABA) ergic/glutamatergic dysregulation or a personality style characterized by stress reactivity or a combination of both. Obsessive craving, the result of the third pathway, can be defined as lack of control over intrusive thoughts about drinking resulting in impaired functioning. This type of craving might result either from a serotonin deficiency or a personality style characterized by low constraint or disinhibition or a combination of both (Verheul *et al.*, 1999).

ALCOHOLISM AND ALCOHOL WITHDRAWAL SYNDROME

Alcoholism is a chronic relapsing disorder characterized by compulsive drinking, loss of control over intake, and impaired social and occupational function (Koob, 2003). Alcohol dependence is considered to be two types. These are psychological dependence, in which the rewarding effects of alcohol play a primary role, and chemical dependence, in which adaptive changes in the brain initiate punishing effects on withdrawal of alcohol, and suppression of these becomes the primary motive for using the drug (Littleton and Little, 1994). Specific neurochemical mechanisms in specific brain reward and stress circuits that become dysregulated during the development of alcohol dependence are important. The brain reward system implicated in the development of alcoholism comprises key elements of a basal forebrain macrostructure termed the extended amygdala that includes the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and a transition zone in the medial (shell) part of the nucleus accumbens. There are multiple neurotransmitter systems that converge on the extended amygdala that become dysregulated during the development of alcohol dependence (Koob, 2003). Neurotransmitter-gated and receptor-coupled ion channels, as well as neurotransmitter receptor coupled with intracellular mediator systems, such as phosphatidylinositides

and cyclic nucleotide-generating systems are suppressed during alcohol dependence (Kuriyama and Ohkuma, 1990). Both acute and chronic alcohol consumption alter the activities of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and the excitatory neurotransmitters glutamate, dopamine, and serotonin. These alterations may contribute to the reinforcing and rewarding effects of alcohol as well as to symptoms of alcohol withdrawal (Wong *et al.*, 2003).

Chronic alcohol treatment induces a variety of effects on the metabolism of neurotransmitters and the function of their receptors. Neurotransmitter-gated and receptor-coupled ion channels, as well as neurotransmitter receptor coupled with intracellular mediator systems, such as phosphatidylinositides and cyclic nucleotide-generating systems, are invariably suppressed during alcohol dependence. The central actions of alcohol and on alcohol dependence should therefore be directed at the molecular changes in synaptic membrane-bound components such as neurotransmitter receptors, as well as on neurotransmitter release and relevant membrane-bound enzymes (Kuriyama and Ohkuma, 1990).

Alcohol positively reinforces or rewards drinking by producing a mild euphoria. In alcohol-dependent individuals, chronic exposure to alcohol may alter the function and communication between the liver, brain and other vital organ systems involved in hunger and the maintenance of nutrition (Lewis, 1996).

Acute and chronic administration of ethanol has multiple effects on several neurotransmitters in the basal ganglia especially dopamine. Acceleration of dopaminergic activity is observed at low doses of ethanol. However, at high doses the reverse is observed. During the ethanol withdrawal syndrome that develops after chronic treatment, whether from presynaptic or postsynaptic origin dopaminergic responses are reduced, Evidence also indicates that cholinergic and GABAergic processes may be implicated in actions of ethanol. Ethanol apparently induces a variety of alterations in neurotransmitter function as a result of its disruption of membrane structure and associated electric properties (Hunt, 1981).

There are, however, two major hypotheses or groups of hypotheses on the basic mechanism of the alcohol withdrawal syndrome (AWS). Adaptive changes in membrane lipids and/or proteins in response to prolonged high alcohol concentrations, which might cause abnormal function after withdrawal of alcohol in general, or more specifically in certain receptor sites. Changes in the formation or concentration of some receptor ligands as a consequence of alcohol metabolism are, however, also possible. Both can cause changes in neurotransmission, and these have been found in several systems. There seems to be some reduction in GABAergic, enkephalinergic, and possibly in dopaminergic function and increase in glutaminergic, adrenergic, cholinergic and possibly in serotoninergic and tryptaminergic activity at least in some neurons during AWS (Airaksinen and Peura, 1987).

The neurochemical basis for the rewarding effects of alcohol may be the potentiation of GABA at $GABA_A$ receptors (causing relaxation) and release of dopamine from mesolimbic neurones (causing euphoria). The adaptive changes that cause

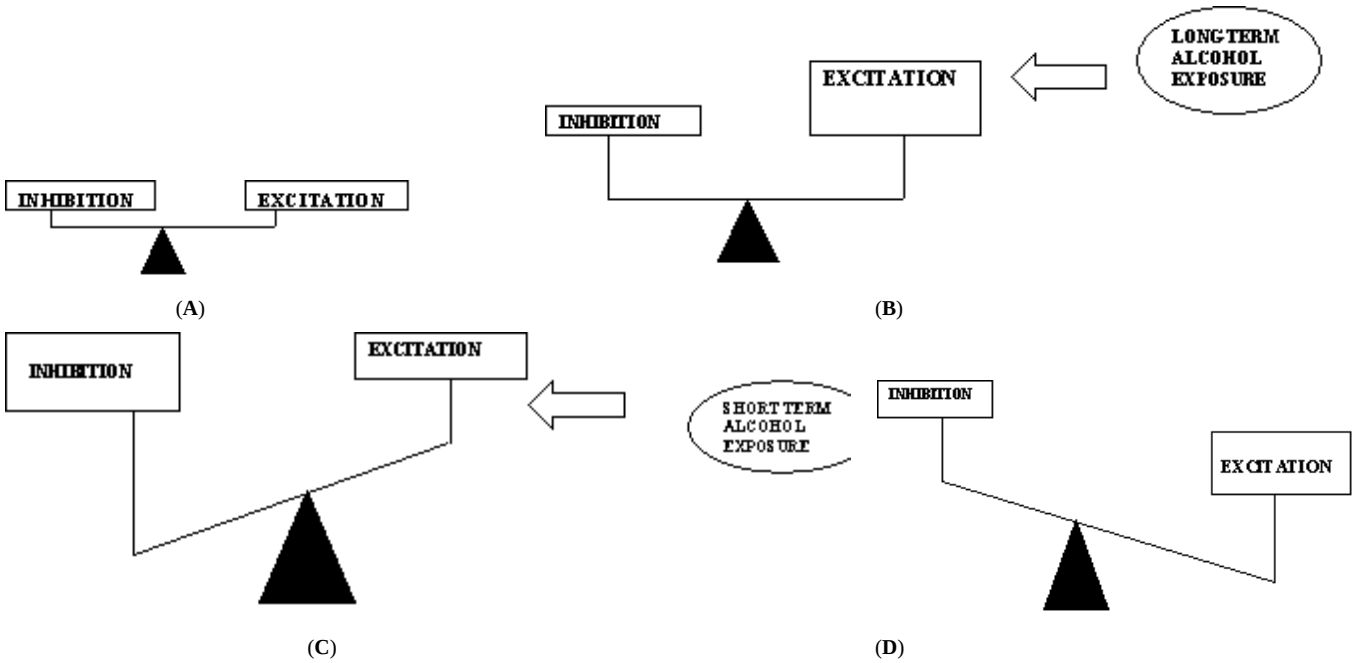

Fig. (2). (**A**). Under normal conditions, a balance exists between excitatory and inhibitory neurotransmission in the brain. (**B**). In long-term alcohol exposure, the brain attempts to restore equilibrium by compensating for the depressant effects of alcohol; thus, the brain decreases inhibitory neurotransmission and enhances excitatory neurotransmission. (**C**). Short-term alcohol exposure tilts the balance toward inhibition by both enhancing the function of inhibitory neurotransmitters and neuromodulators (i.e., GABA, glycine, and adenosine) and decreasing the function of excitatory neurotransmitters (i.e., glutamate and aspartate). (**D**). During alcohol withdrawal, the compensatory changes are no longer opposed by the presence of alcohol and the balance shifts toward a state of excessive excitation. This state of hyperexcitation is characterized by seizures, delirium, and anxiety in alcoholism. (Valenzuela, 1997).

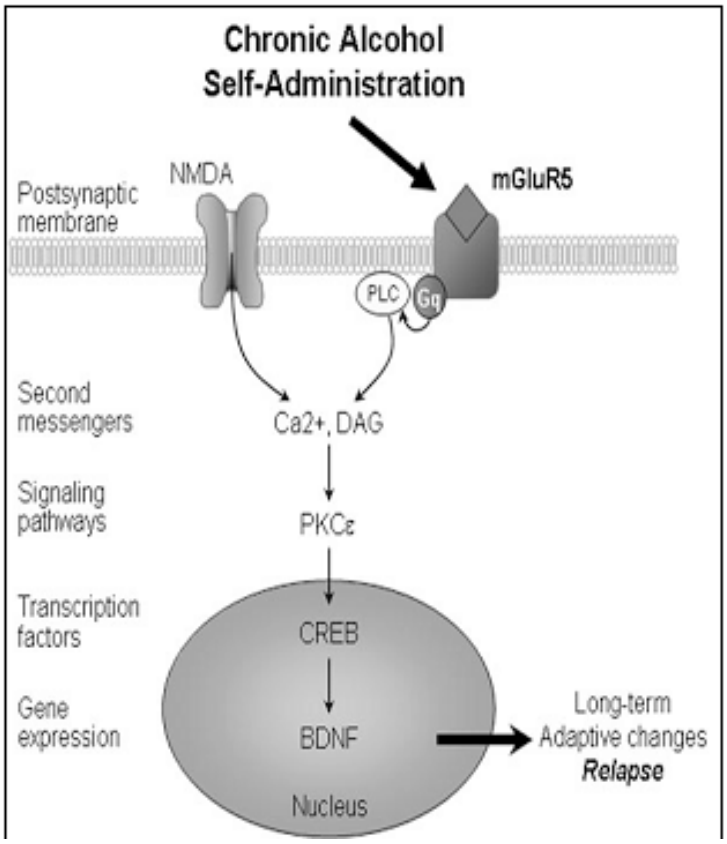

Fig (3). Overview of the effects of ethanol consumption on the signaling pathways.

the alcohol withdrawal syndrome are not known, but alterations in $GABA_A$ receptors, NMDA receptors and voltage-operated calcium channels all have a claim. However, it is distinctly doubtful whether these all contribute to the negatively reinforcing effects of alcohol that are important in chemical dependence, although they may be important in other pathological effects of alcohol abuse (Littleton and Little, 1994).

Short-term alcohol consumption depresses brain function by altering the balance between inhibitory and excitatory neurotransmission. Alcohol's depressant effect on neurons may be associated with some of the behavioral manifestations of intoxication: Alcohol consumption is initially accompanied by decreased attention, alteration in memory, mood changes, and drowsiness. Continued acute consumption may result in lethargy, confusion, amnesia, loss of sensation, difficulty in breathing (Draski and Deitrich, 1995).

After long-term alcohol ingestion brain attempts to restore equilibrium. After short-term alcohol consumption, $GABA_A$ receptor function is increased, but prolonged drinking cause the opposite effect. This decrease in $GABA_A$ function may result from a decrease in receptor levels or a change in protein composition of the receptor, leading to decreased sensitivity to neurotransmission. Similarly, glutamate receptors appear to adapt the inhibitory effects of alcohol by increasing their excitatory activity (Valenzuela and Harris, 1997).

Long-term exposure to ethanol leads to an imbalance in different excitatory and inhibitory amino acids. When ethanol consumption is reduced or completely stopped, these imbalances in different amino acids and neurotransmitters are behaviorally expressed in the form of ethanol withdrawal. Glutamate, a major excitatory amino acid, and GABA, a major inhibitory amino acid, are responsible, at least in part, for ethanol withdrawal symptoms. The hypofunction of $GABA_A$ receptors and enhanced function of NMDA receptors are suggested to be responsible for the increase in the behavioral susceptibility during ethanol withdrawal. This imbalance between receptors may be exacerbated by repeated withdrawal. Because multiple and repeated periods of chronic ethanol consumption and withdrawal often occur in alcohol abusers (De Witte, 2004) Fig. (**2**).

CONCLUSION

Alcohol affects multiple neurotransmitter systems in brain and brain functions depend on a delicate balance between excitation and inhibitory neurotransmission. Therapeutic interventions and de-addictive measures will intervene on this delicate balance of the neurotransmitter systems in combating the defense against alcoholism and alcohol related toxicity Fig. (**3**).

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