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GLUTAMATE IN ALCOHOLISM: A REVIEW

Medical Science

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ABSTRACT

Alcoholism is a major public health problem and a devastating disorder for affected individuals, their families and society. Advances in understanding the nature of alcoholism over the last 25 years have stimulated innovative treatment approaches in managing this devastating major public health problem. In the past decades, the scientific community has come to a better understanding of the neurobiological actions of alcohol in the brain, and the potential neurochemical disruptions associated with chronic, uncontrollable and excessive alcohol drinking.The neurotransmitter receptors commonly affected are those with a transmembrane ion channel, such as γ-aminobutyric acid (GABA) -benzodiazepine and glutamatergic N-methyl-D-aspartate (NMDA) receptors. Accumulating evidence suggests that neurophysiological and pathological effects of ethanol are mediated to a considerable extent through glutamatergic system. Acute effects of ethanol disrupt glutamatergic neurotransmission by inhibiting the response of the N-methyl-D-aspartate (NMDA) receptor. Prolonged inhibition of the NMDA receptor by ethanol results in development of supersensitivity and acute removal of ethanol causes marked augmentation of activity of postsynaptic neurons, such as those in the noradrenergic system, and, in the extreme, glutamate-induced excitotoxicity. Therefore, drugs modulating NMDA receptor action has been hypothesized to be effective in different domains of alcohol use disorder. Also treatments directed at altering glutamatergic transmission may be important for enhancing our understanding of the pathophysiology of human alcoholism. They will also expand our therapeutic options for the treatment of the various complications of alcoholism. Memantine, a NMDA receptor blocker, has been used in attenuating alcohol withdrawal symptoms in two different studies and have been found to be well tolerated and efficacious.

KEYWORDS

Alcohol Dependence, Glutamate, Memantine

Glutamate is the neurotransmitter at the majority of excitatory synapses in the mammalian CNS. Two broad subclasses of glutamate receptors exist: **ionotropic receptors**, which are ligand-gated ion channels; and **metabotropic receptors**, which are coupled to second messenger pathways through G proteins (1, 2). The ionotropic receptors are further subdivided (3) on the basis of their sensitivity to the exogenous agonists N-methyl-D-aspartate (NMDA receptors), DL-a-amino – 3 – hydroxyl – 5 – methylisoxazole – 4 - propionate (AMPA receptors) and kainate (KA receptors). The NMDA receptors are assembled from NR1 and NR2 subunits, while the non-NMDA receptors comprise GluR1±7 and KA1±2 subunit types (1). Numerous heteromeric receptors can be formed, which can have distinctive properties with respect to ligand gating, modulation, and function.

(a) NMDA receptors

The NMDA receptor channel has slower kinetics than AMPA/KA receptors and mediates Na+ and Ca2+ infux. The slow kinetics of channel opening allows both summation of glutamate responses and a large infux of calcium into the cell. This increase in intracellular calcium concentration is believed to be critical for many of the proposed roles of the NMDA receptor. Ion influx through the NMDA receptor is voltage-dependent. When the cell is at resting potential, Mg2+ binds within the ion channel and blocks the cation influx. It is likely that synaptically released glutamate first activates AMPA/KA receptors, thereby causing depolarization of the post-synaptic cell and release of the Mg2+ ion such that other cations can move through the NMDA receptor ion channel (4, 5).

NMDA receptor ion channel comlpex

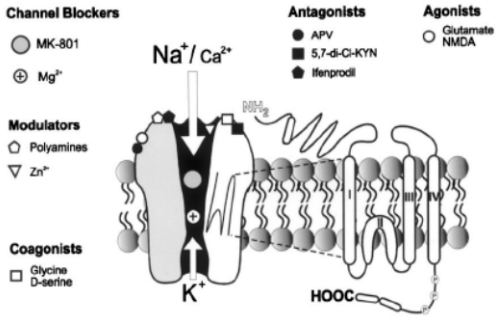

Figure-1 Diagram representing NMDA receptor ion channel with its various regulatory sites. The receptor is activated by agonists such as glutamate or NMDA. APV is a competitive antagonist, 5,7-di-Cl-KYN binds to a strychnine insensitive glycine site, ifenprodil is a polyamine site antagonist. The open NMDA channel is blocked by Mg^{2+} and by uncompetitive antagonists such as MK-801. Glycine and D-serine act as coagonists. Additionally, polyamines and Zn^{2+} ions modulate the NMDA receptor. There are phosphorylation sites (P) that modulate responses of the receptor to agonists and may play a role in synaptic plasticity. Each subunit is believed to have four regions (I, II, III, and IV) within the cell membrane

The NMDA receptor complex exhibits five main domains:

(1) A glutamate recognition site where the agonist NMDA also binds
(2) A Mg2+ binding site within the channel pore
(3) A binding site for (+)- 5 – methyl - 10, 11 – dihydro - 5H –dibenzo [a,d] cyclohept - 5, 10 - imine maleate (MK801; dizocilpine) and dissociative anaesthetics (phencyclidine, ketamine) within the channel pore that interacts with the cation binding site and has a requirement for agonist binding to open the channel for ligand access
(4) A glycine-binding co-agonist site that modulates the agonist recognition site and
(5) A polyamine modulatory site (6, 7, 8). There are also sites which bind Zn2+, protons, and redox reagents (9).

Table-1 Neuronal Functions and Plausible Clinical Roles of Glutamate-Related Neurotransmission

Neuronal Function	Plausible Clinical Role
Fast excitatory transmission	Arousal and pathway-dependent activity
Excitotoxicity and neuronal degeneration	Region-dependent neuropathology
Neurotrophic effects	Neurodevelopment
Regulation of neuronal growth	Neuronal differentiation
Synaptic plasticity	Compensation and homeostasis
Long-term potentiation	Memory

NMDA receptors are heavily glycosylated multi-subunit complexes (10, 11). Early sequence analysis suggested four transmembrane segments (M1-M4) within each subunit typical of transmitter-gated ion channels; the subunit sequences have homology with each other

and with subunits of AMPA and KA receptors (10). More recently, the model was revised to accommodate a transmembrane segment 2 that does not cross the membrane but rather forms a kink within the membrane analogous to the pore-forming domain of the voltage-activated K^+ channels. Inclusion of this P-element domain in the model predicts that the COOH terminal of the subunit protein is intracellular and potentially subject to post-translational modification (12). An NR1 subunit (10, 13) is absolutely required, since mutants lacking this allele die as neonates even though their overall neuroanatomy appears normal (14, 15). Incorporation of the NR2A±D (mouse e1±4 respectively) subunits reconstitute many properties of native NMDA receptors (16, 17, 18). The NR2A±D subunits range in size from 133 to 163 kDa (19, 18). Homomeric expression of NR1 subunit cDNA does not generate glutamate-gated ion channels in mammalian cells (20). Major determinants of glutamate binding reside in the extracellular domain of the NR2 subunits, consistent with the low efficiency and unusual properties of glutamate binding to homomeric NR1 subunits (21). Other potential subunits have been identified, including the glutamate-binding protein and NR±L (22).

The total number of subunits in native NMDA receptors is not known, but may be five, as occurs in nicotinic receptors (23), or four, as in ion channels with pore loops. Natively expressed NMDA receptors are likely to include at least one member of the NR2 class. Immunoprecipitation studies under non-denaturing conditions suggest that at least a sub-population of native receptors contains two different NR2 subunits (24). Using more selective and quantitative antibodies, Luo et al. (1997) concluded that the form of NMDA receptor with highest abundance in adult rat cerebral cortex contains all three (NR1, NR2A, NR2B) subunits in a single ternary structure, with binary species (NR1/NR2A and NR1/ NR2B) being present at much lower levels. In contrast, the co-association of NR1, NR2A and NR2B subunits in the same receptor was shown directly, and the triple combination was identified as a minor sub-population, compared with binary NR1/NR2A, NR1/NR2B and homomeric NR1 receptors (25).

Radioligand binding studies in rat forebrain delineated four distinct populations of heteromeric NMDA receptors. Agonist-preferring receptors, defined by L-[3H] glutamate binding that is weakly inhibited by D-AP5, were found predominantly in brain regions that contained both NR2B and NR1 mRNA moieties. The distribution of antagonist-preferring NMDA receptors, defined by 3-[3H] (carboxypiperazine-4-yl)-propyl-1-phosphonate binding, was virtually identical to that of NR2A subunits, while cerebellar NMDA receptors with a distinctive pharmacological profile corresponded anatomically to the distribution of the NR2C subunit : co-expression of NR2C and NR1 mRNA in ooÈ cytes yields receptors pharmacologically similar to native cerebellar receptors. A pharmacologically distinct NMDA receptor was identified in the midline thalamus; its anatomical distribution was virtually identical to that of the NR2D subunit (26).

NMDA receptors are distributed throughout the brain (1). The anatomical organization of NR2 subunits is highly heterogeneous in rat fore-brain, which would result in regionally functional diversity of the receptor (27). In contrast, in situ hybridization histochemical and immunocytochemical studies have demonstrated that NR1 is present in most neurones in all regions of the brain. The most densely stained cells include pyramidal and hilar neurones of the CA3 region of the hippocampus.

NMDA receptor activation allows the influx of Ca2+ from the extracellular milieu. This raises the intracellular concentration of Ca2+ ions, principally in the apical dendrites in the vicinity of the afferent synaptic input. This in turn may promote activation of protein kinase C by its translocation from the cytosol to the cell membrane, or activation of other Ca2+-dependent signalling pathways including Ca2+/calmodulin-dependent kinase, tyrosine kinase, protein phosphatases, proteases and phospholipases such as phospholipase A2. Activation of phospholipase A2 and subsequent prostaglandin production may then stimulate protein kinase A and bring about an increase in cyclic AMP levels. Finally, glycine serves as an obligatory facilitator of channel opening.

However, excitatory amino acids are a double-edged sword. The excitatory amino acids also may cause neuronal damage when there is persistent or excessive stimulation of their receptors, a phenomenon known as “excitotoxicity”. Excessive activation of Glutamate receptors has been implicated in the neurodegeneration found in a variety of conditions, such as stroke, ischemia, and epilepsy, and in degenerative disorders, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Glutamate receptor antagonists exhibit neuroprotective effects in the animal models of these disorders. In addition to their primary role of effecting neurotransmission and excitotoxicity, Glutamate receptors regulate neuronal differentiation, synaptic plasticity, and memory. Evidence indicates that alcohol affects glutamatergic transmission in three ways: by interfering with fast excitatory neurotransmission, by promoting excitotoxicity and by impairing neurodevelopment.

Ethanol and glutamate - NMDA sites

The NMDA receptor may mediate phenomena which include long term potentiation, synaptic plasticity, excitotoxicity through excessive Ca2+ influx, ischaemic brain damage, and epilepsy (28). These postulated roles suggest that the NMDA receptor may be involved in some of the acute and chronic effects of ethanol, including cognitive defects, seizures, and neuronal degeneration.

Acute effects

Acute ethanol application in vitro inhibits NMDA-stimulated Ca2+ influx and the resultant cyclic GMP accumulation in cultured cells. Ethanol at intoxicating doses (5±50 mM) inhibits NMDA-induced increases in intracellular Ca2+ in dissociated foetal brain cells, the NMDA-receptor-activated ion current in hippocampal neurones, NMDA-receptor-evoked [3H] catecholamine, [3H]acetylcholine and [3H]noradrenaline release in rat striatal and cortical slices, respectively (29), and NMDA-induced excitotoxicity in cerebral cortical slices and primary neuronal cultures from rat brain. Ethanol also caused a selective attenuation of K+ evoked glutamate and aspartate release from hippocampal CA1 slices (30).

Ethanol interferes with the access of MK801 to its intra-channel site by reducing the average probability of channel opening. Although a relatively small effect, the resulting reduction in Ca2+ influx and subsequent alteration in the associated intra-neuronal response would be sufficient to lead to aberrant neurotransmission. The potency for inhibition of NMDA-activated current by several alcohols linearly correlates with their intoxicating potency (31). In vivo application of ethanol to the inferior colliculus and hippocampus, but not the lateral septum, potently inhibits NMDA-evoked neuronal activity in a current-dependent manner. NMDA-evoked neuronal activity in the medial septum (32), glutamate-, NMDA-, and quisqualate-induced excitation of rat locus coeruleus neurones and NMDA-induced seizure activity are inhibited by acute ethanol administration. Ethanol inhibits NMDA-induced increases in cyclic GMP production (33). Presynaptic inhibition by ethanol has also been demonstrated. The precise site of ethanol's action at the NMDA receptor is not known. Ethanol in vitro has little effect on [3H] MK801 binding to well-washed rat brain membranes, which suggests that the inhibition of function is not mediated by direct competition in the channel. Ethanol does not appear to compete at NMDA, channel (33), polyamine) or Mg^{2+} sites, but may alter the kinetics of channel opening. The effects of ethanol are reversed by glycine in cerebellar granule cells (33) and in cortex and hippocampus, although an interaction with glycine is not always observed in the latter regions.

Several lines of evidence suggest that ethanol acts on the glycine modulatory site of the NMDA receptor ionophore (figure 1). Glycine is a co-agonist of the NMDA receptor and thus is absolutely required for NMDA receptor activation by Glutamate (34). Glycine reverses the inhibitory effect of ethanol on NMDA stimulated dopamine release. Magnesium, which blocks the NMDA channel ionophore, has a noninteractive additive effect with ethanol. Glycine and D-serine, a glycine modulatory site agonist, decrease ethanol-mediated inhibition of NMDA-stimulated calcium flux . Consistent with this finding, ethanol reduces glycine's enhancement of Glutamate stimulation of cGMP production in cerebellar granule cells, which is mediated by calcium influx through the NMDA receptor. However, in the hippocampus the inhibition of NMDA-activated current by ethanol does not involve a competitive interaction with glycine. Nor does glycine alter the inhibitory effects of ethanol on NMDA-stimulated norepinephrine release. The understanding of the mechanisms responsible for ethanol's diverse effects on NMDA and non-NMDA excitatory neurotransmission will require further clarification of the molecular heterogeneity of Glutamate receptors.

Chronic effects

Chronic exposure of the brain to ethanol leads to up-regulation of the NMDA receptor and its responses in vivo in the rat (35), and increases the number of glutamate binding sites in synaptosomal membranes prepared from rat brain . There is a modest (25±50%) increase in the number of MK801 binding sites in the hippocampus, and variable changes in cortex, striatum, and thalamus. Glutamate binding is also increased but CGS-19755 and glycine-site binding is not altered by chronic ethanol treatment. Expression of the mRNA encoding the NR1 subunit has been reported to be unaltered in rat brain following chronic ethanol administration, although NR1 subunit immunoreactivity is increased in the hippocampus, ventral tegmental area and cerebellum (36). In contrast, NR2A mRNA expression is either unchanged (36) or increased, while protein expression is increased (36), in rat cortex and hippocampus. These conflicting findings may be explained by translation control of NR2A protein expression. Expression of the NR2B mRNA is increased in the cortex and hippocampus. A recent study confirmed the increase in NR2B after chronic ethanol use.

Studies in vitro show that chronic ethanol increases the NMDA/glycine-induced Ca^{2+} influx and sensitizes cultured cerebral granule cells and cortical neurones to the excitotoxic effects of NMDA application. Increased MK801 binding in chronically ethanol exposed cultured cortical neurones is reflected by increased NR1 and NR2B subunit immunoreactivity. Chronic ethanol treatment of cultured cortical neurones enhances the NMDA- mediated increase in intracellular Ca2+ ion concentration and in parallel increased [3H] MK801 binding.

As the chronic attenuation of glutamate transmission results in the compensatory up-regulation of NMDA receptors, ethanol withdrawal would be expected to be associated with an increase in excitatory amino acid transmission. Withdrawal from chronic ethanol exposure generates seizures, especially after an audiogenic or handling stimulus. Hippocampal MK801 binding sites are increased at the initiation of ethanol withdrawal, remain elevated during the period of peak withdrawal hyperactivity, and return to control levels 24 h after withdrawal, although another study showed no change in [3H] MK 801 binding to hippocampal membranes from ethanol-dependent rats killed 3 h after the last ethanol exposure. Ethanol withdrawal in the rat also leads to a selective increase in extracellular glutamate release, which acamprosate blocks.

Administration of a glutamate antagonist, glutamate diethyl ester, attenuates withdrawal behaviours. MK801 suppresses spontaneous seizures and decreases the likelihood of audiogenically- induced seizures as can antagonists at the polyamine and glycine sites. Ethanol withdrawal potentiates NMDA-induced damage to the hippocampus. The increased number of MK801 binding sites in the hippocampus and elevated NR2 subunit mRNA expression return to control with the same time course as ethanol withdrawal seizures. The competitive NMDA receptor antagonist, CGP-39551, is a potent inhibitor of withdrawal seizures and hyperexcitability

Considerable increases in the severity of the withdrawal hyperexcitability and an increased incidence of seizures is seen if CGP-39551 is given chronically along with ethanol. These results suggest that chronic administration of CGP-39551 increases the adaptive changes that cause or contribute to ethanol-withdrawal hyperactivity. Just as glutamate antagonists reduce the severity of ethanol withdrawal, administration of agonists such as NMDA during the withdrawal period increased the severity of withdrawal. Ethanol withdrawal causes an up-regulation of glutamate transmission in the locus coeruleus (the major noradrenergic nucleus of the brain), increasing the activity of the noradrenergic system. This may contribute to the autonomic instability, behavioural agitation and psychosis seen during ethanol withdrawal in human cases.

Glutamate Dysregulation: As a Hypothesis of Alcoholic Brain Injury

Table 2 provides a summary of the relationships between Glutamate neurotransmission and ethanol's many acute, chronic, and delayed effects on the nervous system. The acute effects of ethanol disrupt Glutamate neurotransmission by inhibiting the response of the NMDA receptor. Prolonged inhibition of the NMDA receptor by ethanol results in the development of supersensitivity; acute removal of the "brake" of ethanol results in markedly augmented activity of postsynaptic neurons, such as those in the noradrenergic system, and, in the extreme, Glutamate -induced excitotoxicity. While the facilitory effect of ethanol on inhibitory GABA-ergic neurotransmission cannot be discounted, the net combined effect of enhanced inhibitory neurotransmission and attenuated excitatory neurotransmission is decreased neuronal activity in the acute phase and increased excitability upon ethanol withdrawal. Impaired cognition and the blackouts that occur with chronic ethanol abuse may be explained by ethanol's acute attenuation of NMDA transmission. NMDA transmission in the hippocampus is essential for longterm potentiation, a cellular analogue of recent memory. Ethanol-induced inhibition of NMDA transmission impairs hippocampal neuronal function, thereby impairing memory acquisition. In the ethanoldependent individual, large amounts of ethanol can induce blackouts in the context of an up-regulated NMDA receptor.

Table: 2 Glutamatergic Hypothesis of Alcoholic Brain Injurya

Clinical Presentation	Ethanol's Glutamatergic Effects
Ethanol intoxication; Impaired cognition Blackout	Acute attenuation of NMDA receptor neurotransmission Impaired long-term potentiation; acute attenuation of NMDA receptor neurotransmission in the context of chronic up-regulation of NMDA receptors
Wernicke-Korsakoff syndrome	NMDA receptor supersensitivity leading to excitotoxicity
Cerebrellar degeneration	Excitotoxicity
Fetal alcohol syndrome	Decreased glutamate receptor density and impaired neurodevelopment

[a]NMDA, N-methyl-D-aspartate.

The three distinct syndromes of uncomplicated ethanol withdrawal, ethanol withdrawal seizures, and withdrawal delirium (delirium tremens) may have in common a single underlying mechanism: the ability of chronic ethanol administration to produce up-regulation of NMDA receptors and consequent catecholaminergic activation. The increased density of NMDA receptors renders neurons more sensitive to their glutamatergic input. Under these circumstances, the postsynaptic transduction, e.g., catecholaminergic effects, will be amplified considerably. This hypersensitive state of NMDA-receptor-mediated neurotransmission may account for the occasional inability of GABA agonists, such as the benzodiazepines, to treat adequately severe cases of ethanol withdrawal delirium despite high doses (38). Therapeutic intervention targeting this hypersensitive state of glutamatergic transmission needs to be considered in the treatment of refractory complications of ethanol withdrawal.

The long-lasting memory deficit in Wernicke's encephalopathy can be the result of neuronal degeneration that is mediated by ethanol-induced excitotoxicity. Evidence suggests that excessive or persistent activation of Glu receptors causes neuronal degeneration. Increased density of NMDA receptors in chronic ethanol dependence appears to render the brain more susceptible to excitotoxic insults, such as anoxia or head trauma, in the excitatory neuronal circuitry. It is intriguing that the hippocampus, cerebral cortex, and cerebellum, all highly susceptible to ill effects from alcoholism, all exploit Glutamate as the major excitatory neurotransmitter. However, in the absence of a consensus for post-mortem neuropathology in chronic alcoholism, it is difficult to compare the anatomy of ethanol neurotoxicity with NMDA receptor distribution. For example, the neuropathology of the subcortical structures that receive abundant glutamatergic input from the cortex is unclear in chronic alcoholism. The overlap between the neuroanatomical profiles of NMDA receptors and ethanol-induced brain damage is most evident in the hippocampus. The hippocampus, which exploits Glutamate as the major transmitter for its input, output, and intrinsic circuitry, is the brain region most vulnerable to ethanol neurotoxicity. It has also been suggested that alcoholism is the most common cause of diffuse cerebral atrophy. The cerebral cortex contains abundant NMDA receptors, which serve an integral role in corticocortical and corticofugal transmission. NMDA receptor supersensitivity may thus account for the diffuse cerebral atrophy in chronic alcoholism. In summary, neuronal loss from chronic ethanol exposure not only can explain hippocampus-mediated learning and memory deficits but also can provide a plausible neural basis of the global cognitive impairment that is frequently encountered in alcoholic dementia. Animal models of fetal alcohol syndrome reveal

decreased density of Glutamate receptors and impaired neurodevelopment. Excitatory amino acids, including Glutamate and Aspartate, exert trophic influences on neuronal differentiation and are thus important for neurodevelopment. Excitatory amino acids regulate the formation of neuronal circuitry and synaptic plasticity, and activation of NMDA receptors enhances synaptogenesis in the hippocampus.

Glutamate exposure accelerates the maturation of synaptic profiles. Exposure to excitatory amino acid receptor antagonists may disrupt the maturational processes mediated by excitatory amino acids and interfere with normal neurodevelopment. Similarly, decreases in numbers of excitatory amino acid receptors due to fetal exposure to ethanol may disrupt neuronal differentiation during development and compromise synaptic plasticity throughout life.

Human studies

In animal model studies, increases in NMDA receptor binding such as those discussed above do not always occur under other chronic ethanol treatment protocols and in different animal strains. Although it is now realised that a wide range of paradigms may be applied to autopsied brain tissue (39), few studies on excitatory amino acid neurotransmission and the pathogenesis of alcohol-related brain damage have been carried out. NMDA receptor antagonists have been reported to have ethanol-like acute subjective effects in human subjects, and glutamate-mediated transmission in the brain has been strongly argued to play a part in alcoholism. Studies of human brain samples obtained at autopsy from chronic alcoholics have shown contrasting results. Dodd et al. (1992) found no difference from controls in [3H] MK801 binding to membranes from superior frontal cortex (39), while Freund and Anderson (1999) found no differences in an autoradiographic investigation of several brain regions (40). Michaelis et al. (1990) reported increased [3H] glutamate binding in the hippocampus of alcoholics (41).Michaelis et al. (1990) found an apparent increase in the total number of glutamate binding sites (41), but a decrease in NMDA receptor density. There is autopsy-based evidence that AMPA/KA receptor subunit expression differs in alcoholics and control cases, and that brain regions are selectively affected. It is clear that much more work is needed in this area. Studies of both NMDA and non-NMDA receptors will be markedly advanced by the systematic application of emerging molecular techniques.

Genetic linkages between glutamatergic neurotransmission and alcoholism in humans

Despite overwhelming evidence that glutamatergic transmission is involved in drug addiction and alcoholism, and the widely accepted notion that addiction has a strong genetic component, only a handful of genetic alterations in components of glutamate transmission (such as single nucleotide polymorphisms, SNPs) have been successfully linked to or associated with addictive behaviors. One of the first findings in this area was reported by Sander and colleagues, who found an increased allelic frequency of a silent SNP in exon 5 of the EAAT2 gene (G603A) in a population of German alcoholics with co-morbid antisocial personality disorder, but not in alcoholics without the co-morbid psychiatric diagnosis (43). Thus, in this population, the EAAT2 SNP may not have been associated with alcoholism per se, but in tendencies towards risk-taking behaviors that are occasionally found in alcoholic individuals. An additional study found an association between the G603A allele and alcoholic cirrhosis. One of the molecular targets of alcohol is the NMDA receptor, the function of which is inhibited by alcohol. Indeed, non-alcoholics with a family history of alcoholism have altered subjective responses to NMDA antagonists such as ketamine as compared with nonalcoholics without a family history of alcoholism.

Accordingly, several groups of investigators have attempted to identify allelic variations in the genes encoding one or more of the NMDA receptor subunit proteins that may confer susceptibility to alcoholism. However, the results of these studies have been mixed. Two groups of investigators have shown that alcoholics with a history of alcohol withdrawal seizures and delirium tremens were more likely to carry a G2108A SNP in exon 7 of the NR1 subunit gene than controls. An association of delirium tremens was also demonstrated to be associated with a Ser310Ala polymorphism in the GluR7 KA receptor gene (44), although this same polymorphism was not associated with alcoholism per se. With regards to other iGluR subunits, findings have been less consistent. For example, a decreased allelic frequency of a C2664T SNP in exon 13 of the NR2B subunit gene in early-onset alcoholics has been demonstrated (45), while other groups of investigators have shown no association between alcoholism and a C2873T SNP in the NR2B gene, even in early onset alcoholics. Given the present set of data, it appears that genetic variations in iGluR subunit genes may be related to the presence of delirium tremens or alcohol-withdrawal seizures in alcoholic patients, but further research is needed to clarify whether such polymorphisms are associated with risk for alcoholism itself. Group II and Group III mGluRs are often localized to presynaptic glutamatergic terminals where they regulate glutamate release via classic inhibitory autoreceptormechanisms. Therefore, genetic mutations in these mGluRs may result in a lack of inhibitory feedback tone on the presynaptic glutamatergic terminal, resulting in excessive glutamate release and the possibility of seizures. Preuss and colleagues hypothesized that since mice carrying a targeted deletion of the mGluR7 gene show increased seizure susceptibility, polymorphisms in one or more presynaptic mGluRs might confer susceptibility to delirium tremens during alcohol withdrawal. However, these investigators found no association of a Tyr433Phe polymorphism in the mGluR7 gene or a C2756T polymorphism in mGluR8 gene and seizures or delirium tremens in a population of alcoholic patients.

Memantine and addiction

Memantine has been hypothesized to be effective in alleviating alcohol withdrawal syndrome owing to hyperactivity of NMDA receptors during withdrawal state. Clinical studies have shown that memantine is efficacious in reducing withdrawal symptoms in detoxified alcoholics and opiate addicts, consistent the NMDA hyperactivity hypothesis of alcohol withdrawal. Several clinical trials have reported that memantine was superior to placebo in attenuating on-going drinking and/or craving for alcohol in alcoholics. This amelioration of craving for alcohol may be a result of the ethanol-like subjective effects that are produced by memantine . However, a larger placebo controlled study indicated that memantine does not appear to reduce on-going drinking behavior in alcohol-dependent patients. These data suggest that memantine may be of use in the treatment of alcohol or opiate withdrawal, but the disparate results that have been reported on its ability to reduce on-going alcohol consumption and/or alcohol craving need to be further evaluated.

Clinical studies of Memantine in addiction

N-methyl-d-aspartate (NMDA) is involved in receptor mediated glutamatergic neurotransmission which has been proposed to play a considerable role in alcoholism. Therefore it has been proposed that NMDA receptor antagonists may be effective in the treatment of alcohol withdrawal syndrome. Because of this many preclinical studies were performed to measure the efficacy of NMDA receptor antagonists in alcohol withdrawal syndrome in animals and Memantine, in particular, was found to be having beneficial effects on ethanol-induced glutamatergic hyperexcitability reflected in the ethanol withdrawal syndrome in rats, but there have been few studies in humans. In one study done in humans, Memantine was found to be more effective in reducing withdrawal severity as compared to placebo, whereas in another study combination of Diazepam and Memantine was found to be more efficacious than combination of Diazepam and placebo in controlling withdrawal symptoms (46).

Memantine has also been studied in a laboratory model of cocaine self-administration. Eight cocaine smokers were maintained for 8–11 days on memantine (20 mg daily) and placebo, using a double-blind crossover design. Under these conditions, memantine significantly increased subjective effects of cocaine, including ratings of 'high', 'potency', 'quality', and street value. Ratings of 'I want cocaine' were not significantly different under memantine versus placebo, but they were consistently higher during memantine maintenance across all doses. In spite of the increase in many of the subjective effects of cocaine, memantine did not alter the number of times participants chose cocaine over the monetary alternative. These results confirm some of the preclinical data showing that uncompetitive antagonists may potentiate acute effects of cocaine (47). Nonetheless, in the human laboratory paradigm memantine did not affect the reinforcing effects of cocaine. This observation is in contrast to the majority of animal data suggesting that NMDA antagonists reduce the reinforcing and other effects of cocaine that may contribute to the maintenance of cocaine dependence. The relevance of findings from the study by Cummings et al. (48) , to medication development is unclear. This study had several limitations (e.g. low dose of memantine, short duration of the treatment, population tested in laboratory has no

motivation for the treatment, and the predictive validity of laboratory model is unknown as there is no effective medication for the treatment of cocaine dependence). Only further laboratory studies and a clinical trial may help to determine whether memantine will have an advantage over amantadine for the treatment of cocaine dependence.

CONCLUSION

In producing its behavioral and toxic effects, ethanol interacts with numerous processes modulating signal transduction in the brain. The effects of ethanol on GABA-ergic neurotransmission are well known, but a host of findings from recent research converge to support a unifying mechanism of action of ethanol, i.e., interference with glutamatergic neurotransmission, especially through the NMDA receptor. In this regard, alcoholism may be considered the newest member of the expanding family of Glutamate related neuropsychiatric disorders. These insights should assist in improving understanding of the biologic vulnerabilities resulting in ethanol abuse and dependence and should lead to the development of more effective pharmacologic interventions that address acute intoxication, withdrawal, and neurodegeneration associated with chronic abuse.

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