

# Era of Glutamate

Zoran M Pavlovic MD

Medical Affairs

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## XCV. STUDIES ON BRAIN METABOLISM.

### I. THE METABOLISM OF GLUTAMIC ACID IN BRAIN.

By HANS WEIL-MALHERBE.

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*(Received February 26th, 1936.)*

It has long been realised that glutamic acid differs from most amino-acids, since it is oxidised in organs whose metabolism is supposed to be mainly concerned with carbohydrate and which are quite inert towards most of the other amino-acids. This suggests a connection between glutamic acid and carbohydrate metabolism.

Thunberg [1920] first showed that glutamic acid was the only amino-acid in presence of which washed frog muscle decolorised methylene blue. Harrison [1925] described aerobic oxidation of glutamic acid by washed frog muscle. Needham [1930] showed that glutamic acid is oxidised to succinic acid by the muscle of ox, rabbit, pigeon and frog. Holmberg [1934] prepared extracts from washed muscle which reduced methylene blue in presence of glutamic acid.

Thunberg [1923] demonstrated oxidation of glutamic acid by minced peripheral nerve and Quastel and Wheatley [1932] by brain. Krebs [1935, 1] observed increased respiration of brain and retina in the presence of glutamic acid.

The probable oxidation of glutamic acid by tumour tissue was indicated by the observation of Fleisch [1924] that a preparation of washed, minced Jensen rat sarcoma reduces methylene blue in presence of glutamic acid and by unpublished experiments of Dickens and Weil-Malherbe.

#### METHODS.

Respiration was measured by the manometric method of Warburg [1926]. Unless otherwise stated, brain slices (grey matter only) of rats or guinea-pigs were used. The tissue (10–15 mg. dry wt.) was suspended either in phosphate saline [Krebs, 1933] or in bicarbonate saline [Krebs and Henseleit, 1932]. When phosphate saline was used, the manometer was filled with oxygen and the respiratory  $\text{CO}_2$  was absorbed by 0.2 ml. of 10% NaOH in the inner cup of the vessel. For the experiments with bicarbonate saline a gas mixture containing 5%  $\text{CO}_2$  was used. Any substrate added was neutralised to litmus paper. All experiments were done at 37.5°.

Ammonia and glutamine were determined according to Krebs [1935, 1, 2] with the apparatus of Parnas and Heller.

*Units.* The amount of metabolites formed or disappearing is expressed in  $\mu\text{l.}$  (1 millimol = 22400  $\mu\text{l.}$ ) or in  $Q$ -values  $\left( \frac{\mu\text{l.}}{\text{mg. dry weight} \times \text{hours}} \right)$  with a corresponding index.

*Nomenclature.* The nomenclature of the amino-acids is that of Freudenberg and Karrer [cf. Krebs, 1935, 1].

Further experimental details will be given in the following sections.

( 665 )



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## Review

# Towards a glutamate hypothesis of depression An emerging frontier of neuropsychopharmacology for mood disorders

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## ABSTRACT

Half a century after the first formulation of the monoamine hypothesis, compelling evidence implies that long-term changes in an array of brain areas and circuits mediating complex cognitive–emotional behaviors represent the biological underpinnings of mood/anxiety disorders. A large number of clinical studies suggest that pathophysiology is associated with dysfunction of the predominant glutamatergic system, malfunction in the mechanisms regulating clearance and metabolism of glutamate, and cytoarchitectural/morphological maladaptive changes in a number of brain areas mediating cognitive–emotional behaviors. Concurrently, a wealth of data from animal models have shown that different types of environmental stress enhance glutamate release/transmission in limbic/cortical areas and exert powerful structural effects, inducing dendritic remodeling, reduction of synapses and possibly volumetric reductions resembling those observed in depressed patients. Because a vast majority of neurons and synapses in these areas and circuits use glutamate as neurotransmitter, it would be limiting to maintain that glutamate is in some way ‘involved’ in mood/anxiety disorders; rather it should be recognized that the glutamatergic system is a primary mediator of psychiatric pathology and, potentially, also a final common pathway for the therapeutic action of antidepressant agents.

A paradigm shift from a monoamine hypothesis of depression to a neuroplasticity hypothesis focused on glutamate may represent a substantial advancement in the working hypothesis that drives research for new drugs and therapies. Importantly, despite the availability of multiple classes of drugs with monoamine-based mechanisms of action, there remains a large percentage of patients who fail to achieve a sustained remission of depressive symptoms. The unmet need for improved pharmacotherapies for treatment-resistant depression means there is a large space for the development of new compounds with novel mechanisms of action such as glutamate transmission and related pathways.

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## 1. Introduction. Do we need a glutamate hypothesis of depression?

The fields of neuropsychopharmacology and biological psychiatry have been dominated for over half a century by the monoamine hypothesis, which has driven the research on pathophysiology of neuropsychiatric disorders, in particular mood/anxiety disorders, as well as the development of therapeutic drugs. The basic version of the hypothesis, with regard to depression, speculated that pathology was due to (or accompanied by) reduced availability of monoamines, particularly serotonin and noradrenaline, and that

antidepressants exerted their therapeutic action by increasing extracellular availability of monoamines, particularly at synaptic level (Bunney and Davis, 1965; Schildkraut, 1965). The early hypothesis was intrinsically tautological, in that the main evidence was based on the mechanism itself of monoamine oxidase inhibitors and tricyclic antidepressants, drugs that acutely increase the availability of monoamines.

In subsequent years and decades the hypothesis has registered several modifications in the attempt to solve its inherent inconsistencies, the main one being the temporal discrepancy between the immediate effects of drugs on monoamines availability (minutes, hours) and their therapeutic effects (several weeks) (Heninger et al., 1996; Hyman and Nestler, 1996; for a historical perspective, see: Racagni and Popoli, 2008). The roots of a ‘glutamate hypothesis’ can be traced back to the early 1990s,

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A paradigm shift from monoamine hypothesis of depression to a neuroplasticity hypothesis focused on glutamate may represent a substantial advancement. The unmet need for improved pharmacotherapies for treatment-resistant depression means there is a large scale for the development of new compounds with novel mechanisms of action such as glutamate transmission  
**(Sanacora 2012)**

# Glycine Transport Inhibitors for the Treatment of Schizophrenia

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**Abstract:** Multiple lines of evidence indicate that hypofunction of glutamatergic neurotransmission via *N*-methyl-D-aspartate (NMDA) receptors might be implicated in the pathophysiology of schizophrenia, suggesting that increasing NMDA receptor function via pharmacological manipulation could provide a new strategy for the management of schizophrenia. Currently, the glycine modulatory sites on NMDA receptors present the most attractive therapeutic targets for the treatment of schizophrenia. One means of enhancing NMDA receptor neurotransmission is to increase the availability of the obligatory co-agonist glycine at modulatory sites on the NMDA receptors through the inhibition of glycine transporter-1 (GlyT-1) on glial cells. Clinical studies have demonstrated that the GlyT-1 inhibitor sarcosine (*N*-methyl glycine) shows antipsychotic activity in patients with schizophrenia. Accordingly, a number of pharmaceutical companies have developed novel and selective GlyT-1 inhibitors for the treatment of schizophrenia. This paper provides an overview of the various GlyT-1 inhibitors and their therapeutic potential.

**Keywords:** Schizophrenia; NMDA receptor; Glutamate; Glycine; Transporter; Glia.

## INTRODUCTION

A growing body of evidence suggests that the *N*-methyl-D-aspartate (NMDA) receptors (Fig. 1) play a role in the pathophysiology of schizophrenia [1-12]. Subanesthetic doses of the non-competitive NMDA receptor antagonist phencyclidine (PCP; Fig. 2) have been shown to produce a wide range of transient schizophrenia-like symptoms, including estrangement, loss of body boundaries, formal thought disorder, hallucinations, and psychosis [1,13,14]. In addition, PCP is known to dramatically exacerbate the symptoms of schizophrenia [1,13,14]. In a randomized, double-blind, placebo-controlled study, Krystal and co-workers [15] reported that the non-competitive NMDA receptor antagonist ketamine (Fig. 2) produced positive and negative symptoms in a dose-dependent manner. A high dose of ketamine elicited significant perceptual effects, including altered perceptions of the body, environment, and time. In another double-blind, placebo-controlled study, Malhotra *et al.* [16] reported that ketamine produced brief psychosis marked by thought disorder and withdrawal-retardation in healthy volunteers. Furthermore, a double-blind, crossover-design study revealed that ketamine alters mood in healthy volunteers [17]. Moreover, in a double-blind, placebo-controlled study, Lahti *et al.* [18] reported that ketamine induced a brief (less than 30 minutes), dose-related worsening of positive symptoms in schizophrenic patients maintained on haloperidol. In contrast, Zarate *et al.* [19] demonstrated the robust and rapid (within 2 h) antidepressant effects of a single dose of ketamine (0.5

mg/kg, i.v. infusion for 40 min) in treatment-resistant major depression, suggesting the role of NMDA receptors in the rapid antidepressant activity of ketamine [20-22].

In addition to glutamate, the NMDA receptors are modulated by glycine, D-serine, polyamines, and specific divalent cations, including magnesium and zinc [9-12] (Fig. 1). Glycine and D-serine (Fig. 3) act as obligatory co-agonists at the glycine modulatory sites on the NMDA receptors to regulate glutamatergic transmission. Currently, the glycine modulatory sites on the NMDA receptors are the most attractive therapeutic targets for schizophrenia. This review article provides an overview of glycine transporter-1 (GlyT-1) inhibitors as a potential therapeutic approach to the treatment of schizophrenia.

## GLYCINE

Glycine (Fig. 3) was first proposed to act as a neurotransmitter in the mammalian spinal cord in 1965 [23]. Glycine is now among the well-characterized amino acid neurotransmitters in the mammalian CNS, where it is known to act as an inhibitory transmitter via its interaction with strychnine-sensitive glycine receptors [24-29]. It also plays an important role in excitatory neurotransmission via strychnine-insensitive glycine sites located on the NMDA receptors [26-29].

The plasma levels of total serine (L- and D-serine) and glycine in patients with schizophrenia are higher than those of controls [30], and the levels of serine and glycine in the brains of schizophrenic patients are higher than those of controls [30,31], suggesting a possible abnormality in serine hydroxymethyltransferase, by which glycine is converted to L-serine [10]. Interestingly, it has been reported that serum D-serine levels and the D-serine/total serine ratio in patients with schizophrenia are significantly lower than those of

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Thinking about schizophrenia from glutamate perspective versus dopamine perspective gives us new receptor targets that we can think about as being etiologic and in particular NMDA receptors. It gives us new conceptual opportunities in which we focus on sensory as well as higher cortical dysfunction and on bottom-up contributions to social cognition and executive processing impairments in which basic sensory processing contribute to social cognition and executive dysfunction along with deficit in the frontal brain regions that we're more used to thinking about impaired in schizophrenia

**(Javitt 2012)**



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## Review

## Glutamatergic medications for the treatment of drug and behavioral addictions

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## ABSTRACT

Historically, most pharmacological approaches to the treatment of addictive disorders have utilized either substitution-based methods (i.e., nicotine replacement or opioid maintenance) or have targeted monoaminergic or endogenous opioidergic neurotransmitter systems. However, substantial evidence has accumulated indicating that ligands acting on glutamatergic transmission are also of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling. The purpose of this review is to summarize the pharmacological mechanisms of action and general clinical efficacy of glutamatergic medications that are currently approved or are being investigated for approval for the treatment of addictive disorders. Medications with effects on glutamatergic transmission that will be discussed include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. We conclude that manipulation of glutamatergic neurotransmission is a relatively young but promising avenue for the development of improved therapeutic agents for the treatment of drug and behavioral addictions.

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There is a strong body of preclinical evidence arising over two decades of animal studies suggesting a critical role for glutamate transmission and glutamate receptors in drug reward, reinforcement and relapse. There is overwhelming evidence that all drugs of abuse interact with glutamate transmission and can cause long-lasting neuroadaptations of glutamate systems in the brain. These adaptations somehow lead in compulsive drug use, loss of volitional control over drug intake and hypersalience of drug-associated environmental cues or contexts

**(Olive 2012)**



**Two case reports  
of successful use of Lamotrigine  
in substance use disorders:  
Confirmation of Glutamatergic  
neurotransmission involvement ?**

Presented by:  
Zoran M Pavlovic MD  
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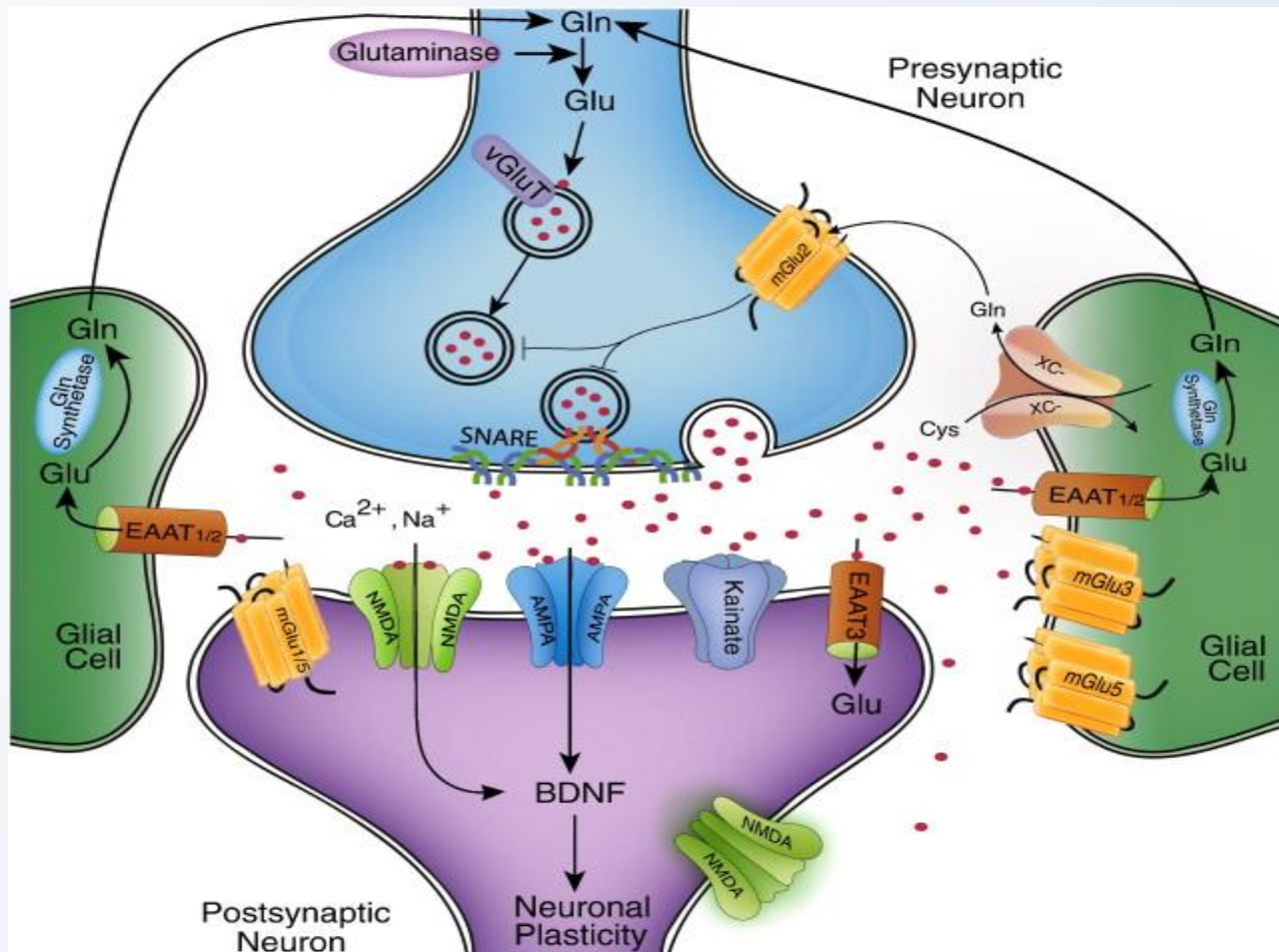
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- Glutamate is packaged into synaptic vesicles in the presynaptic terminal by vesicular glutamate transporters (vGluTs) using a proton gradient generated by the hydrolysis of adenosine triphosphate (ATP)
- Once released into the synaptic cleft, glutamate can bind to one of three different types of ionotropic glutamate receptors (iGluRs) located on the head of the postsynaptic spine: the N-methyl-D-aspartate (NMDA) receptor, the  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, and the kainic acid (kainate, KA receptor). iGluRs are ligand-gated ion channels that mediate fast excitatory neurotransmission.
- Glutamate can also bind to metabotropic glutamate receptors (mGluRs) located in perisynaptic regions or on the presynaptic terminal

- mGluRs, G-protein coupled receptors (GPCRs) that mediate slower, modulatory glutamatergic transmission
- located either in the perisynaptic annulus or on presynaptic terminals
- mGluRs can be divided into three distinct groups, based on their pharmacological and signal transduction properties
- Group I mGluR receptors (mGluR1 and mGluR5)
- Group II (mGluR2 and mGluR3)
- Group III (mGluR4, mGluR6, mGluR7, and mGluR8)
- G-proteins and are negatively coupled to adenylyl cyclase (AC) activity, and upon stimulation result in decreased intracellular levels of cyclic adenosine monophosphate(cAMP)
- Presynaptically localized Group II and Group III mGluRs, particularly mGluR2 and mGluR3, are thought to represent the classical inhibitory autoreceptor mechanism that suppresses excess glutamate release
- mGluR3 and mGluR5 have been localized to glial cells such as astrocytes

- Together, the simultaneous activation of iGluRs and mGluRs activates a host of intracellular signaling pathways that result in protein phosphorylation of ion channels, other kinases, and transcription factors and eventually leads to the molecular events underlying neural plasticity
- Such events include initiation and/or regulation of dendritic mRNA translation and de novo protein synthesis, changes in gene expression in the nucleus, and cytoskeletal remodeling
- neuroplasticity linked to long term potentiation (LTP), long term depression (LTD)

# Regulation of Glutamate Neurotransmission



# Dopamine and Glutamine interconnections

- Historically, research into the neurobiological substrates that underlie the rewarding and reinforcing effects of drugs of abuse has focused on the mesolimbic dopamine reward circuitry, comprised primarily of dopaminergic neurons in the ventral tegmental area (VTA) that project rostrally to forebrain and limbic regions such as the nucleus accumbens

- Dopaminergic cell bodies in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC), and glutamate (GLU) projections from the PFC to both the VTA and NAc, generally define the fundamental circuitry of the mesocorticolimbic reward system.
- Other important brain structures associated with emotional memories and drug taking and dependence include the amygdala, hippocampus and hypothalamus
- VTA receives glutamatergic projections from the FC, Amyg, pedunculo-pontine tegmentum (PPT), and laterodorsal tegmentum (LDT)
- The NAcc receives a convergence of glutamatergic input from the FC, Amyg, hippocampal formation (Hipp), and various nuclei of the thalamus (Thal)
- The FC cortex receives glutamatergic input from the Hipp, Amyg and Thal

**Thus, there is a robust excitatory glutamatergic innervation of the mesolimbic dopamine reward circuitry which proves and anatomical basis for dopamine-glutamate interactions in regulating the addictive properties of drugs of abuse as well as synaptic plasticity**

# **Lamotrigine Reduces Craving and Depressive Symptoms in Cocaine Dependence**

J Neuropsychiatry Clin Neurosci 23:1, Winter 2011

- Recent preclinical studies reveal that GLU projections from the PFC to the NAc are critical for cue-, stress- and cocaine-primed reinstatement of previously extinguished cocaine self-administration in animals
- The GLU ionotropic receptor agonist AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) infused into the NAc reinstates cocaine self-administration, whereas blocking translation and expression of the AMPA receptor subunit, GluR1 (by antisense oligonucleotides) attenuates this behavioral effect
- Glutamate levels were also positively correlated with years of cocaine use suggesting that the changes in GLU developed as a result of exposure to cocaine

- Repeated cocaine exposure can lead to a phenomenon called “behavioral sensitization” (sometimes termed “reverse tolerance”), which is a progressive increase in the behavioral (i.e., locomotor) response to cocaine in response to repeated exposure to the same dose
- Behavioral sensitization to cocaine is paralleled by adaptive changes in mesolimbic dopamine system function as well as the responsiveness of this system to glutamate
- In the primary target field of VTA DA neurons, the NAcc, it has been demonstrated that multiple cocaine exposures result in a sensitized increase in extracellular levels of glutamate

- A role for glutamatergic transmission in the rewarding and reinforcing effects of cocaine has been clearly demonstrated by pharmacological studies utilizing iGluR antagonists. Systemic administration of NMDA antagonists attenuate cocaine reinforcement
- The ability of iGluR antagonists to reduce cocaine reinforcement are likely mediated, at least in part, by NMDA and/or AMPA receptors in the NAcc and dorsal striatum

- Dampening glutamate transmission via stimulation of presynaptic mGluR2/3 receptors or activating glutamate transporters attenuates cocaine reinforcement, cue- and cocaine-induced reinstatement, “incubation” of cocaine craving (i.e., a progressive increase in the magnitude of cue-induced reinstatement over time following cocaine self-administration)
- The NAcc and amygdala appear to be important mediators of some of these effects

# Cocaine use and craving

- Administration of cocaine to human addicts during abstinence can increase craving for the drug
- Cocaine-induced craving is important to understand as it may be a critical factor in relapse and may contribute to continued drug dependence
- Individuals with high levels of craving show a higher probability of relapse upon discharge after treatment

# Impulsivity and craving in cocaine users

- Craving appears to be closely related to certain aspects of impulsivity
- The data show that craving before drug use was significantly correlated with total impulsivity as well as craving after use

# Cocaine-primed craving and its relationship to depressive symptomatology

- Depressive symptomatology affects cocaine-primed craving and that this relationship is relatively specific to symptoms defined by the HRSD

- Three patients diagnosed with cocaine dependence according to the DSM-IV criteria
- They had used cocaine for an average of 5.4 years, and
- They had made an average of 3.1 quit attempts in their lifetimes
- Patients had used cocaine for an average of 12.10 days during the 30 days before completing the baseline assessment battery
- Their average baseline Cocaine Craving Questionnaire—Brief10 score was 48
- Beck Depression Inventory (BDI) score was 17

- After 12 weeks on lamotrigine monotherapy, 200 mg/day, the respective scores decreased to
- 7 on the BDI and
- 21 on the Cocaine Craving Questionnaire, with no reports of relapse

# **Long-Term Treatment and Relapse Prevention of Alcohol and Benzodiazepine Dependence with Lamotrigine**

J Neuropsychiatry Clin Neurosci 22:2, Spring 2010

- Ethanol was long thought to exert its actions on the brain solely via potentiation of GABAergic transmission and/or increases in plasma membrane fluidity. However, in the late 1980's and early 1990's, a series of reports were published indicating that ethanol also acts by inhibiting neuronal NMDA receptor function
- Ethanol appears to inhibit NMDA receptor function via a non-competitive mechanism and induces the phosphorylation and internalization of NR2 subunits
- NMDA receptors in many brain regions are sensitive to inhibition by ethanol, including the cerebral cortex , NAcc , amygdala, hippocampus, locus coeruleus, VTA and cerebellum
- As a result, ethanol inhibits the induction of several forms of neural plasticity such as LTP in the hippocampus, dorsal striatum and bed nucleus of the stria terminalis while enhancing LTD in the hippocampus

- Chronic ethanol upregulates NR1 expression in the VTA and amygdala, regions that are critical for the reinforcing effects of ethanol
- Chronic ethanol also increases NMDA receptor functionality (i.e., conductance, cation influx, etc.) and synaptic clustering of the receptor
- Infusion of NMDA receptor antagonists systemically into the cerebral ventricles or directly into regions such as the NAcc or dorsal striatum attenuates oral ethanol consumption in rats
- As a result of ethanol-induced up-regulation of NMDA receptor expression, the central nervous system enters a state of hyperexcitability upon acute withdrawal from ethanol exposure

- NMDA or AMPA/KA ligands also attenuate sucrose or saccharin reinforcement indicating that such compounds may not be selective for reducing ethanol intake, but may rather attenuate general appetitive responding
- Attenuation of glutamatergic transmission by mGluR ligands also appears to reduce the rewarding and reinforcing effects of ethanol as well as relapse-like behaviors

- Thus, a paradoxical effect of ethanol on glutamatergic transmission exists, with acute exposure to low doses of ethanol as well as withdrawal from chronic exposure increasing extracellular levels of this neurotransmitter, while ethanol simultaneously acts to inhibit the function of one of its primary cognate receptors (i.e., the NMDA receptor).

- Group I and II mGluRs are highly expressed in the mesocorticolimbic system
- mGluR5s and mGluR2/3s are abundant in regions such as the nucleus accumbens, lateral septum, striatum, amygdala, and hippocampus
- mGluR1s show low expression in most but are highly expressed in the cerebellum where they regulate motor coordination
- Ethanol self-administration is modulated by activity of specific brain regions, including the nucleus accumbens and frontal cortex, that express high levels of mGluR5 and mGluR2/3

- mGluR5 activity in the nucleus accumbens is required for the full expression of ethanol's reinforcing effects in individuals with a genetic predisposition for heavy alcohol-drinking
- mGluR5 but not mGluR2/3 activity specifically in the nucleus accumbens reduces the maintenance of ethanol-reinforced responding
- Disrupting glutamate neurotransmission either through blockade of postsynaptic ionotropic NMDA or metabotropic mGluR5 in the nucleus accumbens is sufficient to prevent the full expression of ethanol's reinforcing properties.
- mGluR5 regulate firing rate of mPFC neurons, which is a neural correlate of reward prediction
- mPFC sends glutamatergic projections to the nucleus accumbens, and inactivation of them PFC reduces the firing rate of nucleus accumbens neurons in response to reward-predictive cues
- Inhibition of mGluR5 activity in the nucleus accumbens, a key component of the brain's reward pathway, specifically reduces operant ethanol self administration.
- The importance of mGluR5 activity in the nucleus accumbens in regulating drug reinforcement might be translated in their therapeutic utility in individuals with genetic risk for excessive drinking

Mrs. N is a 45-year-old woman who was diagnosed with alcohol and benzodiazepine dependence according to DSM-IV criteria and had a 5-year history of alcohol and benzodiazepine addiction at the time she was referred to our clinic.

She experienced nightly insomnia and, during the previous 2 weeks, persistent vomiting.

She presented with severe withdrawal symptoms, manifested as constant nausea and vomiting, extensive sweating, tactile disturbances on her scalp in the form of “electric cap,” and severe tremor

- Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA)11 score 38
- Severity of Dependence score was 9 for alcohol (cutoff for dependence is 3) and 12 for benzodiazepines (cutoff 7)
- Alcohol craving score according to the Penn Alcohol craving scale was 25 (maximum score 30)

- Lamotrigine was uptitrated according to manufacturer's instructions to a final dose of 200 mg/day
- During the next 2 weeks of full dosage treatment, she reported moderate improvements, which correlated with a decrease on her CIWAscore. The symptoms continuously diminished during the following weeks, and
- After 16 weeks of active treatment, during the last assessment, she was only mildly anxious, with moist palms and moderate tremor (CIWA score 10)
- Severity of Dependence score of 2 for alcohol and 4 for benzodiazepines
- Penn Alcohol craving score decreased to 12
- She also reported complete abstinence during the aforementioned period

- Lamotrigine which was uptitrated according to manufacturer's instructions to a final dose of 200 mg/day
- During the next 2 weeks of full dosage treatment, she reported moderate improvements, which correlated with a decrease on her CIWA score
- The symptoms continuously diminished during the following weeks, and after 16 weeks of active treatment, during the last assessment, she was only mildly anxious, with moist palms and moderate tremor (CIWA score 10) and Severity of Dependence score of 2 for alcohol and 4 for benzodiazepines
- She also reported complete abstinence during the aforementioned period, while her Penn Alcohol craving score decreased to 12



*A Clear Difference*