TECHNICAL SCIENCE OF ADDICTION

Gamma aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the central nervous system. GABA is an amino acid but is not found in protein. GABA acts at inhibitory synapses in the brain. It binds to specific transmembrane receptors.

When your body is in balance it supports body function and greatly contributes to the re-regulation of the body's internal equilibrium (homeostasis) in response to sudden decrease in blood alcohol levels as well as in maintaining homeostasis.

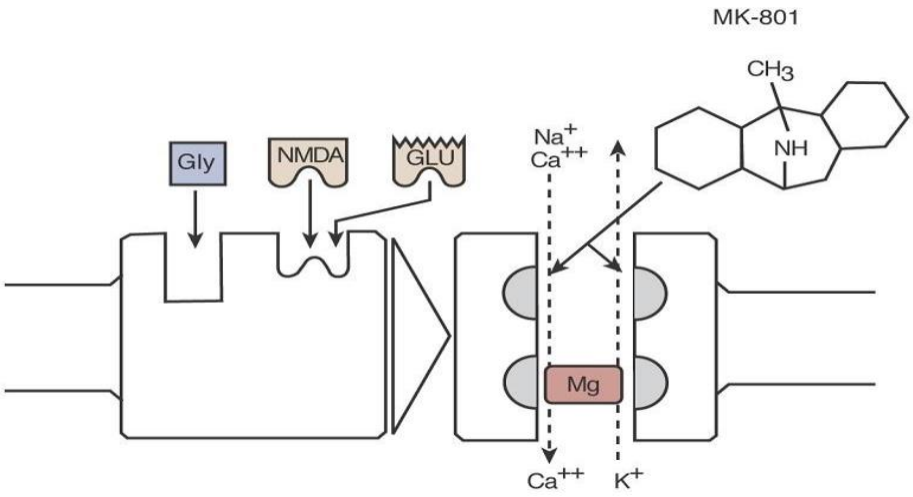
The balance of GABA and glutamate are important in understanding the neurobiological maintenance of both homeostasis and emotional control in response to chronic alcohol intake and acute alcohol withdrawal. The temporal and spatial dynamic balance of these neurotransmitters within specific brain regions leads to profound effects on the behavior, mood, memory, and function of the individual.

A balanced, healthy body creates a support opportunity benefitting the n-methyl-d-aspartate glutamate receptor's role in alcohol use disorders and alcohol withdrawal

Typically, chronic alcohol use disorders develop in individuals who consume excessive quantities of alcohol at regular intervals over an extended period of time. Individuals who drink excessive alcohol depend upon alcohol for normal function and perform more normally with high circulating levels of alcohol in the bloodstream than moderate users. Upon cessation of alcohol intake, physical and emotional symptoms characteristic of alcohol withdrawal, are experienced. The symptoms of alcohol withdrawal syndrome simply implies dysregulation of the body's internal equilibrium in response to a sudden decrease in blood alcohol content. The positive effects from a body made healthier assists the natural homeostatic principle which is regulated by the brain by supporting overall body function. We began researching the neurobiological maintenance of both homeostatic and emotional control in response to chronic alcohol intake and acute alcohol withdrawal in the early 90's as other research was also becoming available.

Ethanol, the primary alcohol molecule in consumable alcoholic beverages, is absorbed into the bloodstream during digestion and then travels throughout the body via the bloodstream. Most of the absorbed ethanol is metabolized in the liver to form carbon dioxide and water, but ethanol molecules can also escape into other organs and tissues. While some alcohol metabolism can be performed in these tissues, ethanol molecules can also interact with and affect the molecular machinery subtending normal function. This can bring about molecular changes in the brain that may explain alcohol's effect on the neurobiological maintenance of homeostatic and emotional control.

N-methyl-d-aspartate receptor



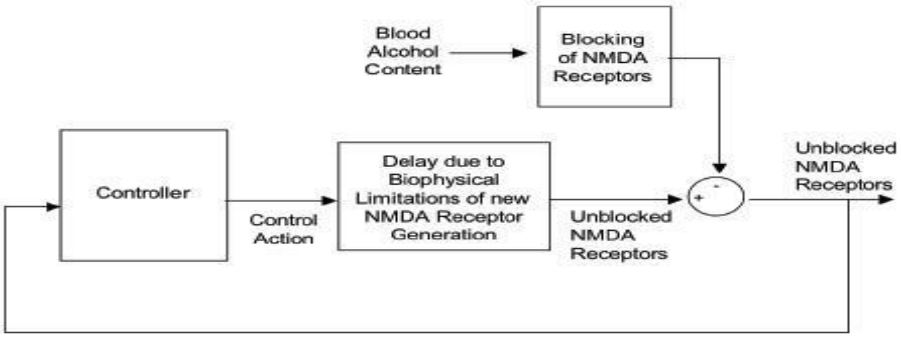
The N-methyl-D-aspartate receptor is a heteromeric ionotropic glutamate receptor found on neurons throughout the brain. NMDA (N-methyl-D-aspartate) is the name of its selective agonist. Each NMDA receptor is composed of two NR1 subunits and two NR2 subunits and the specific subtype compositions differ in functionality and brain region localization allowing for brain region variability and glutamate neurotransmission specificity. NMDA receptors form calcium channels that are blocked by magnesium under resting conditions. A decrease in the electrical potential across the neuron's outer membrane caused by a shift in the electrochemical gradient across the membrane, known as membrane depolarization, leads to the displacement of the magnesium blockade. The NMDA receptor is then activated by the binding of both glutamate (to the NR2 subunit) and the amino acid glycine (to the NR1 subunit). The NMDA receptor then allows an influx of calcium along with the release of glutamate and other neurotransmitters such as dopamine and norepinephrine. Since 1995, it has been hypothesized that it may be via the dysregulation of these and other neurotransmitters that NMDA receptors contribute to the dysregulation of the homeostatic and emotional control observed in alcohol withdrawal.

NMDA receptors have been shown to be high-affinity targets for ethanol in the brain. Like known NMDA receptor antagonists (a substance that acts against and blocks an action), ethanol molecules attenuate NMDA receptor function. Multiple studies have shown that to compensate for the chronic blockade of NMDA receptors by ethanol, chronic use induces some brain regions to generate new NMDA receptor subunits. Ethanol dissociates from the NMDA receptors during withdrawal, leading to an increased number of unblocked NMDA receptors. Unblocked NMDA receptors promote the release of additional glutamate via a positive feedback mechanism of glutamate-induced glutamate release. The excess glutamate from the additional unblocked NMDA receptors could then lead to excessive excitation known as excitotoxicity. Increased glutamate release is observed experimentally in chronic alcohol treated animals withdrawing from alcohol. NMDA antagonists have been shown to reduce withdrawal symptoms and provide dopamine in dependent euphoria comparable to that provided by ethanol consumption. Conversely, NMDA receptor agonists (a substance that initiates a physiological response when combined with a receptor) increase the magnitude of dysphoria (Dissatisfaction with life. The opposite of euphoria) and the symptoms of withdrawal.

Current scientific understanding is that, in some brain regions critical to homeostatic and emotional control, the number of NMDA receptors which are under feedback control increase with chronic alcohol

intake. In alcohol use disorders, the level of unblocked, viable NMDA receptors is controlled to maintain the desired level of glutamatergic inhibition and the amount of glutamate release. Because ethanol blocks these receptors, additional receptors are generated to compensate for the loss.

The Control of Unblocked NMDA Receptors



Observing the Control System Diagram, it can be understood how the feedback controller controls new NMDA receptor generation in order to maintain a certain number of unblocked NMDA receptors, or equivalently, to regulate the total amount of glutamate release.

The controller has an implicit set point and generates new unblocked NMDA receptors, however there is a delay. This delay is due to the biophysical limitations of the cell's transcription, translation, and post translational machinery.

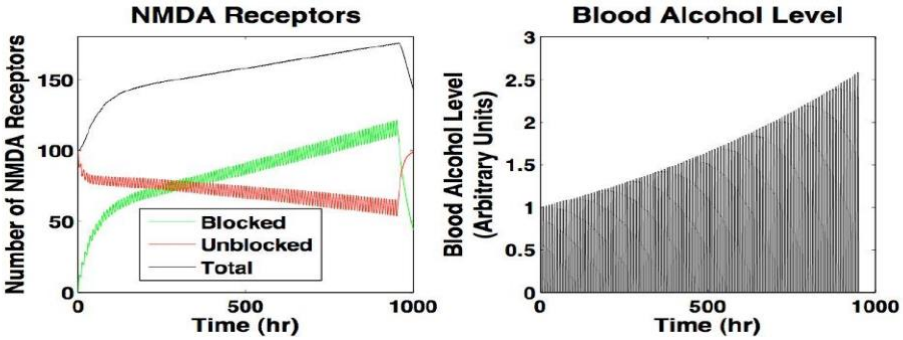
Alcohol intake is a disturbance to the process decreasing the number of unblocked NMDA receptors via ethanol blockage of NMDA receptors. Viewing this process from the control system perspective, the decrease in the number of unblocked NMDA receptors causes an increase in NMDA receptor generation consistent with experimental observations in certain brain regions.

Between drinking sessions and upon the initiation of withdrawal, the increase in the NMDA receptor response to extracellular glutamate brings increased physical and emotional discomfort. This drives the alcohol adapted individual to consume more alcohol to raise the blood alcohol level and repress the withdrawal symptoms.

In the case of a more prolonged withdrawal, the increase of unblocked, viable NMDA receptors leads to increased glutamate via the positive feedback system mentioned earlier and increased response to glutamate by virtue of the increased number of NMDA receptors – thereby contributing to the more severe withdrawal symptoms and dysphoria observed during such an episode of withdrawal. It is important to note that more recent research shows that in some brain regions, kinases and phospotases act at modulatory sites on the NMDA receptor, but the ultimate result is a sensitization of NMDA receptors to ethanol, and the present analysis of increased receptor number is analogous to any such increase in sensitization.

The anti-alcohol effects of a botanical material was first reported in November 1993 in the Proceedings of the National Academy of Sciences. The progression of hundreds of studies on the causative role of N-methyl-D-aspartate receptors can be now clearly demonstrated with an analysis of the number of unblocked, blocked and total NMDA receptors over a 1,000 hour period along with the input blood alcohol level function. In the demonstration, the sharp increase in the number of unblocked NMDA receptors during the final withdrawal period agrees with experimental observation of increased glutamate response.

The dynamics of blocked, unblocked, and total NMDAR's in response to a growing periodic alcohol input function.



In the depiction of the dynamics of blocked, unblocked, and total NMDA receptors in response to a growing periodic alcohol input function, it is clear that the number of NMDA receptors increases with each dose of alcohol as well as throughout the simulation and also drops abruptly during withdrawal as expected. Similarly, the number of blocked receptors increases until the alcohol input is removed, when it then drops rapidly. Conversely, the number of unblocked receptors decreases until the point when the alcohol input is removed, when it then increases leading to the excitotoxicity observed chemically.

Although the mechanism is not fully understood, it has been theorized that body function can be affected via an action that changes the NMDA receptor effect by supporting a chemical nutritional event which results in the minimization of the available excitatory neurotransmitters and the natural occurring homeostasis of the glutamate/GABA balance.