

FIGHTING NEURODEGENERATIVE DISORDERS: Effect of Memantine on NMDA glutamate receptors

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BACKGROUND

L-Glutamate is the major excitatory neurotransmitter in the central nervous system. Glutamate receptors called NMDA (N-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) have been associated in playing a role in synaptic plasticity and various types of memory. Excessive activation of NMDA receptors is thought to mediate the calcium-dependent neurotoxicity associated with trauma, epilepsy, and several neurodegenerative diseases like Parkinson's and Alzheimer's. Various NMDA antagonists have been investigated for their therapeutic potential in these diseases, but heretofore none have proven to be both effective and safe. However, the drug memantine, which blocks the channels activated by NMDA stimulation, is deemed to be both effective and clinically tolerated. In this study, we will investigate the effect of drug Memantine in blocking activity of open channel NMDA glutamate receptors.

THE GLUTAMATE RECEPTORS

There are 3 types of ligand-gated (ionotropic) glutamate receptors, namely NMDA, AMPA and Kainate receptors, collectively called GluRs. These receptors activate a cation-selective ion channel permeable to key ions like sodium and potassium, the NMDA receptors also being permeable to calcium and magnesium. Calcium influx through NMDA channels sets off a chain of events that establish long-term potentiation: a long lasting enhancement in signal transmission between two neurons.

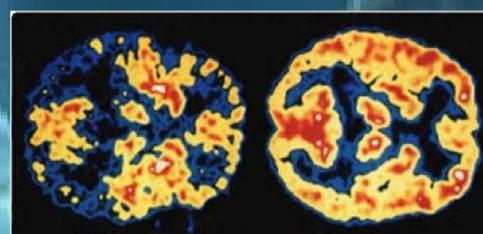
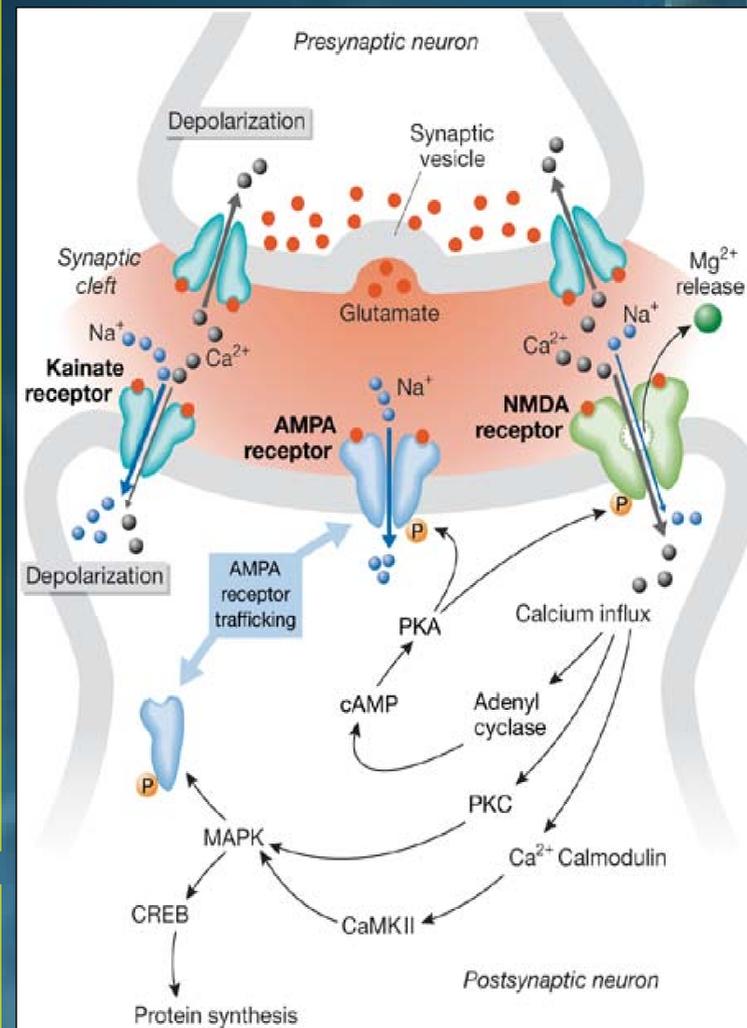
Long term potential takes place as follows:

- 1) Glutamate is released from the pre-synaptic terminal.
- 2) It binds to the GluR receptors to allow sodium influx.
- 3) Initiation of post-synaptic depolarization by AMPA and Kainate initiate release of magnesium ion block (due to size) from the NMDA receptors.
- 4) Calcium then enters the NMDA receptor making the cell more sensitive to glutamate.

GLUTAMATE RECEPTOR DYSFUNCTION

Although glutamate is very important, excessive activation of glutamate receptors is neurotoxic. Endogenous glutamate and other agonists can kill neurons through the 'excitotoxicity' of glutamate. While calcium plays a central role in synaptic plasticity, it can be cytotoxic in excess. An excess calcium influx results in the death of the neuron, releasing the glutamate present in the neuron into the interstitial spaces. This glutamate then binds to adjacent NMDA receptors, perpetuating neuronal death. This can lead to various neurodegenerative disorders such as Parkinson's, Huntington's, Alzheimer's and schizophrenia.

MECHANISM OF GLUTAMATE RECEPTORS



Neurodegenerative Brain PET (Alzheimer's) Normal Brain PET scan

MEMANTINE

- **Mechanism:** While how it accomplishes this effect is still unclear, past research indicates that memantine blocks the NMDA channel, thereby preventing calcium-induced cytotoxicity.

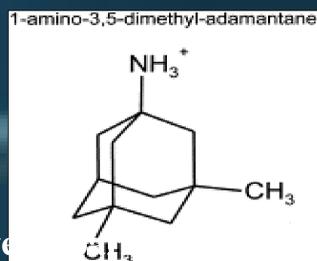
- **Advantages:**

1. Proven to produce positive results devoid of significant side-effects.

Why?

It has moderate potency and rapid, voltage-dependent blocking kinetics.

2. Also, it preferentially blocks neurotoxicity mediated by excessive NMDA receptor activity, while relative neurotransmission.



FUTURE RESEARCH

While an extensive amount of research has been done on glutamate receptors and their role in neurodegenerative disorders, there is a vast scope of possibilities that yet remain undiscovered. The next big step in research should be seeking a more effective analog of memantine, which we believe can be accomplished by gaining a full understanding of the underlying mechanism of action memantine itself.

References:

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