Obstetrics

Analgesics, Case Reports and Obstetrical Pain: NMDA Receptor Antagonists

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In recent years, NMDA receptor antagonists have emerged as viable alternatives to conventional pain relief therapies. Read on to know more about their mechanism of action and their potential uses.

Introduction

N-Methyl-D-aspartate (NMDA) is an amino acid derivative comparable to glutamate. Glutamate is the primary excitatory neurotransmitter of the brain found in most synapses of the central nervous system. There are several glutamate receptors in the brain. The pharmacologic distinction between the different receptors is possible with the help of various drugs, of which NMDA is one.

NMDA is synthetically formulated and it selectively binds to NMDA sub-type of excitatory glutamate receptors. NMDA induced over-excitation is lethal for nerve cells and this led to its discovery as an ‘excitotoxin’.
NMDA Receptors (NMDAR)

There are a number of ionotropic glutamate receptors, of which NMDA receptor is one. NMDA receptor has a high affinity towards glutamate, a high electrical conductance, and a high permeability for calcium ions and a voltage-dependent block by magnesium ions.

NMDA receptors perform a vital role in brain functioning which includes not only their role as an excitatory neurotransmitter but also in learning and memory. It is thus thought of as an essential neurotransmitter receptor in the brain.

At the time of excitatory neurotransmission, there is activation of glutamate receptors present in the postsynaptic membrane due to the pre-synaptic release of glutamate. Consequently, there is a generation of excitatory postsynaptic potential (EPSP).

There are two types of glutamate receptors that bring about the generation of EPSP. They include NMDA receptors and non-NMDA receptors, i.e., AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors.

Whenever synaptic transmission takes place, there is a release of neurotransmitters and resultant rapid depolarization in response to the neurotransmitters because of the non-NMDA glutamate receptors. The duration of the synaptic current is established by the NMDA receptors.

**NMDA receptor types**

NMDA receptors are of two types: central and peripheral receptors.

**Peripheral NMDA Receptors**

NMDA receptors have been identified on the unmyelinated, as well as myelinated axons, of the peripheral somatic tissues. They have been associated with chronic pain. These receptors are expressed on nerves in the human tendons, along with an elevated concentration of glutamate; thus, peripheral administration of the NMDAR antagonists has various clinical implications, which include:

- Local anesthetic-like effects.
- Inhibition of hyperalgesia.
- Attenuation of inflammatory pain (NMDARs on peripheral nerve fibers increases during inflammation, and this may contribute to peripheral sensitization in inflammation).

**Central NMDA receptors**

These are of two types: spinal and supraspinal NMDA receptors.

**Spinal NMDA receptors**

After an injury, there occurs a series of changes in the periphery that lead to peripheral sensitization and hyperalgesia. These are thought to have an associated central component which is known as central sensitization. In central sensitization, there is an amplified dorsal horn excitability. This results in the facilitation of its response to sensory input.

Studies have demonstrated that persistent pain and spinal hyperexcitability occur as a result of activation of the NMDARs. The properties of NMDARs in the spinal dorsal horn might be altered due to peripheral inflammation.
Supraspinal NMDA receptors

NMDARs are thought to cause supraspinal sensitization as well. In response to the inflammation, there is an induction of neuronal hyperexcitability which, in turn, leads to an increased NMDAR activation.

Activation of NMDA receptors

NMDA receptor has NR1 subunit/s along with NR2 and NR3 subunits. Whenever the synthesized amino acid binds to an NR2 subunit, activation of the excitatory channel takes place.

NMDA receptors’ functioning occurs in three steps as follows:

- **Opening or closing of NMDA receptor** requires the binding with two ligands – glutamate and D-serine/glycine at the same time and thus is ligand gated.
- **At resting membrane potential**, magnesium or zinc ions block the receptor pores. These are released because of the depolarizing potential.

Further, there is the initiation of the non-specific cation exchange and resultant influx of calcium and sodium ions and co-dependent outflow of potassium ions. NMDA possesses three important properties which include excitotoxicity, synaptic plasticity, and memory functioning.

The induction of these is due to an influx of calcium ions. The damaging effects of NMDA are attributable to an excessive influx of calcium ions across the cell. They could range from minor alcohol withdrawal symptoms and schizophrenia to severe life-threatening epileptic seizures.

NMDA Receptor Antagonists

NMDAR antagonists are the chemical molecules which target the NMDA receptor in particular. Eventually, this results in the deactivation of the NMDA receptors. These NMDAR antagonists are classified depending upon the mechanism of deactivation as follows:

- **Competitive antagonism**: As the name suggests, there is competition between the molecule and glutamate for binding to the NMDA receptor.
- **Glycine specific antagonism**: These molecules bind specifically to the glycine binding sites and thus the attachment of the original amino acid is blocked.
- **Allosteric antagonism**: There is binding of molecules to an allosteric site instead of competing for or binding to the original site; thus, the receptor configuration is changed, leading to a failure in the identification of the receptors by the concerned ligands.
- **Non-competitive antagonism**: Some chemicals selectively bind to voltage-gated ion channels thereby altering the pathway. On the other hand, ligand-dependent receptor opening is completely operational.

The blockade of NMDAR by their antagonists is **dose-dependent**. When the conduction of electrical impulses is considerably diminished, there is a disconnection between the neurons and consequently dissociation.

NMDAR antagonists cause induction of a state of **dissociative anesthesia**. This ability of
the NMDAR antagonists is important and is responsible for their clinical use. Dissociative anesthesia is characterized by analgesia, amnesia, and catalepsy.

Thus, there are certain synthetic compounds that are produced specifically for the above purpose. They include Ketamine, Dextromethorphan (DXM), Phencyclidine (PCP), Methoxetamine (MXE), Kynurenic acid, Amantadine, and Memantine.

**Ketamine** is a strong dissociative drug. It possesses euphoriant and hallucinogenic properties, making it an exceedingly addictive recreational drug also known as ‘Special K’. The metabolism of ketamine and phencyclidine takes place in the liver and thus their prolonged use leads to the development of a gradual tolerance to the drug.

### Association of NMDA Receptors and Visceral Pain

A probable role of NMDARs in the mediation of pain from internal organs has also been suggested. Studies have found NMDARs on peripheral terminals of the primary afferent nerves which innervate the colon.

**Ketamine** has been experimentally used for pain originating in the urinary bladder and has been found to be effective. On administration of i.v. ketamine, a direct inhibitory effect on the cardiovascular as well as visceromotor responses to urinary bladder distention was seen.

**Dextromethorphan** and **memantine** also show similar responses, thus suggesting a spinally mediated effect.

A study was conducted to assess spinal cord dorsal horn neuronal responses to urinary bladder distention in acutely spinalized decerebrate rats. The results of this study established that the site of action of ketamine appears to be localized in the spinal cord.

In another study, systemically administered NMDAR antagonists reduced the visceral pain due to cyclophosphamide-induced cystitis in rats; thus, the currently available experimental evidence is suggestive of NMDAR antagonists being a useful analgesic in the treatment of visceral pain such as in Irritable Bowel Syndrome.

### Management of Pain by NMDAR Antagonists

The state of chronic pain has been neurologically linked to the arrest of NMDA receptors in open configurations. This results in an over-sensitization of the central nervous system. Hyperalgesia and neuropathic pain follow this excessive excitation. This is where NMDAR antagonists come into the picture.

The actions of NMDAR antagonists are as follows:

- **Deactivation of explicitly functioning NMDA channels** through direct or allosteric inhibition.
- **Anti-nociceptive action**, which leads to a gradual reduction in the perception of pain.
- **Co-analgesic action**: When used in combination with an opioid analgesic as a co-analgesic, it increases the sensitivity of opioid receptors that were desensitized due to prolonged therapy for chronic pain.
Ketamine

Developed in the mid-1960s, ketamine is a phencyclidine (PCP) and cyclohexamine derivative that possesses a distinctive anesthetic property called dissociative anesthesia.

Dissociative anesthesia is characterized by a dissociation between the thalamocortical and limbic systems. Upon use, it makes the patients unconscious and cataleptic (partially conscious).

Depending on the dose administered, patients become unresponsive to purposeful physical stimulation or verbal command. The vital reflexes of the patients are usually intact. Ketamine thus produces a state between deep sedation and general anesthesia.

Ketamine is the favored drug in emergencies like major trauma or burns; where the patient history is unknown or incomplete. This is attributable to its properties to minimally depress respiration and circulation while maintaining an appropriate state of analgesia.

Several post-operative benefits have been ascribed to the use of ketamine in place of opioids for the management of pain. These include early ambulation, a lesser degree of postoperative sedation and a reduced requirement of morphine to treat operative pain.

Methadone

It is an NMDAR antagonist having a long and variable half-life of 8—59 hours. Patient monitoring using an ECG is necessary during the administration of this drug. With higher doses, ECG monitoring for possible QTc prolongation becomes mandatory. It can produce adverse effects like CNS depression, respiratory depression, QTc prolongation, constipation, nausea, vomiting, and disorientation.

NMDA Receptor Antagonists in Obstetrics

Ketamine is primarily used as an induction agent to induce anesthesia in the pregnant woman. A dose of 1 mg/kg is required for the same. Lower doses (0.2—0.3 mg/kg) are known to produce analgesia and sedation in a pregnant woman just before delivery; thus, it is used for the management of obstetric pain.

As compared to thiopental that may produce hypotension, ketamine has no such effect and can be safely used in cases of acute hemorrhage. It should be avoided in women with pre-eclampsia and may produce hallucinations and delirium as side effects.

Side-Effects of NMDAR Antagonists

These compounds have a comparatively narrow therapeutic window. Optimal analgesia can be produced by a cautiously titrated dose, while a sub-anesthetic dose is a mild stimulant. Higher doses can lead to agitation, hallucinations and paranoid delusions.

Ketamine-induced cell death has only been observed in animals, but the consistent and non-medicated use of ketamine and phencyclidine has been shown to result in short-term or even permanent cognitive impairment.

Care should be taken to not use NMDAR antagonists other than ketamine for patients who cannot provide a complete medical history. Amantadine and phencyclidine are
known to cause depression of the respiratory center and elevation of the heart rate; thus, careful **ECG monitoring** and an **arterial blood gas analysis** is indispensable with their use.

### Other Uses of NMDAR Antagonists

#### Alzheimer’s disease and schizophrenia

NMDA receptors play a crucial role in **memory formation and recollection**. Impairment of this receptor with age has been linked to senile memory deficits, the most common being **Alzheimer’s disease**.

A synthetic NMDA channel blocker, memantine, is currently used for the treatment of Alzheimer’s disease. The glutamate theory of **schizophrenia** states the relevance of NMDA receptor over-firing in the etiopathogenesis of schizophrenia.

The clinical importance of NMDA receptor antagonists cannot be doubted in these cases, but an overwhelming occurrence of **‘psychomimetic’ symptoms** has limited their use. These symptoms include precipitation of hallucinations, delusion and personality deficits in schizophrenia patients.

#### Depression

Depression was earlier thought to be a pharmacotherapy resistant disorder, with only cognitive behavioral therapy (CBT) being used in the past. Recent studies have established the efficacy of ketamine to provide a rapid reversal of symptoms of depression.

This effect is, however, only observed with **ketamine**. Theories put forward to explain this peculiar phenomenon suggest that ‘differential affinity’ of non-competitive NMDA receptor ligands is responsible for not obtaining similar results with other NMDA receptor antagonists. Ketamine selectively binds to the GluN2B subunit of NMDA receptors and this is how its anti-depressant action is achieved.

Other selective positive and negative allosteric site modulators have also shown promise in the same direction. While research continues, several implications of these antagonists are possible for treatment of such neuro-psychiatric conditions.

### Conclusion

It has been observed that after certain noxious events, NMDARs induce and maintain **neuronal hyperexcitability**. The role of NMDARs in pain management is increasing day by day. Earlier, only central NMDARs were thought to be clinically effective. However, extensive research is being carried out today about the utility of peripheral somatic and visceral NMDARs in various clinical settings.

### References


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