Central and Peripheral N-Methyl-D-Aspartate (NMDA) Receptors: Sites, Actions, Modulators and Possible Clinical Applications

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by

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To My Family

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Contents :

List of abbreviations

Abbreviation	Meaning
Aβ	β-amyloid peptide
ACPC	1-amino cyclopropane carboxylic acid
AD	Alzheimer's disease
ALF	Acute liver failure
ALS	Amyotrophic lateral sclerosis
AMPA	Alpha-amino-3-hydroxy-5- methyl-4-isoxazole propionate
AMPARS	AMPA receptors
AP5	2-amino-5-phosphonopentanoate
AP7	2-amino-7-phosphonoheptanoic acid
CaMKii	Ca^{2+}/calmodulin dependent kinase ii
CDK5	Cyclin-dependent Kinase 5
CNS	Central nervous system
CPPene	(3-[(R)-2 carboxypiperazine- 4yl]-prop-2enyl-1-phosphonic acid)
DAB1	Disabled 1
DCKA	5,7- dichlorokynurenic acid
DXM	Dextromethorphan
EAA	Excitatory amino acid
EPSP	Excitatory post synaptic potential
ERK1/2	Extracellular signal related kinases
GABA	Gamma-amino butyric acid
GRIN1	Glutamate receptor, ionotropic, N-methyl D-aspartate 1
HD	Huntington's disease
Ica	Calcium current
IGluRs	Ionotropic glutamate receptors
Ke	Ketamine
LIVBP	Leucine/isoleucine/valine binding protein
LTP	Long-term potentiation
MAPK	P38 mitogen activated kinase
MDD	Major depressive disorder

MeF2C	Myocyte-specific enhancer factor 2C
MEM	Memantine
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
NO	Nitric oxide
N_2O	Nitrous oxide
NOS	NO synthase
NR	NMDA Receptor
NTD	N-terminal regulatory domain .
PD	Parkinson's disease
PCP	Phencyclidine
PSD-95	Postsynaptic density 95
PG	Prostaglandin
ROS	Reactive oxygen species
RT-PCR	Reverse transcriptase polymerase chain reaction
SNGFR	Single nephron glomerular filtration rate
SP	Substance P
TGF	Tubuloglomerular feedback

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Introduction & Aim of the work

"Protocol of The Study"

Introduction

The NMDA receptor (NMDA-R), a glutamate receptor, is the predominant molecular device for controlling synaptic plasticity and memory function. The NMDAR is a specific type of ionotropic glutamate receptor. NMDA (*N*-methyl *D*-aspartate) is the selective agonist that binds to NMDA receptors but not to other glutamate receptors. Activation of NMDA receptors results in the opening of an ion channel that is nonselective to cations. A unique property of the NMDA receptor is its voltage-dependent activation, a result of ion channel block by extracellular Mg^{2+} ions. This allows voltage-dependent flow of Na^{+} and small amounts of Ca^{2+} ions into the cell and K^{+} out of the cell.[1-2]

Activation of NMDA receptors requires binding of glutamate or aspartate (aspartate does not stimulate the receptors as strongly). In addition, NMDARs also require the binding of the co-agonist glycine for the efficient opening of the ion channel, which is a part of this receptor.[3]

The NMDA receptor is a non-specific cation channel which can allow Ca^{2+} and Na^{+}, to pass into the cell. The excitatory postsynaptic potential produced by activation of an NMDA receptor increases the concentration of Ca^{2+} in the cell. The Ca^{2+} can in turn function as a second messenger in various signaling pathways. However, the NMDA receptor cation channel is blocked by Mg^{2+} at physiological levels. To unblock the channel, the postsynaptic cell must be depolarized.

The NMDA receptor therefore functions as a "molecular coincidence detector". Its ion channel only opens when the following two conditions are met simultaneously: glutamate is bound to the receptor, and the postsynaptic cell is depolarized (which removes the Mg^{2+} blocking channel). This property of the NMDA receptor explains many aspects of long term potentiation (LTP) and synaptic plasticity.

NMDA receptors are modulated by a number of endogenous and exogenous compounds and play a key role in a wide range of physiological (e.g. memory) and pathological processes (e.g. excitotoxicity).

Antagonists of the NMDA receptor are used as anesthetics for animals and sometimes humans, and are often used as recreational drugs due to their hallucinogenic properties, in addition to their unique effects at elevated dosages such as dissociation. When NMDA receptor antagonists are given to rodents in large doses, they can cause a form of brain damage called Olney's Lesions.[4-5]. Mg^{2+} not only blocks the NMDA channel in a voltage-dependent manner but also potentiates NMDA-induced responses at positive membrane potentials. Magnesium treatment has been used to produce rapid recovery from depression. Na^{+}, K^{+} and Ca^{2+} not only pass through the NMDA receptor channel but also modulate the activity of NMDA receptors.[6-7]

Glutamate is the major central nervous system excitatory neurotransmitter found in approximately 60% of synapses. While monoamines have been historically emphasized as causal factors in depression, there is growing evidence that glutamate neurotransmission plays a major role. This new evidence has significant implications for the etiopathogenesis and treatment of major depressive illness**.**[8]

Increasing evidence suggests that glutamate, the major excitatory neurotransmitter in the CNS,[9] may also be a neurotransmitter in the peripheral nervous system. Excitatory effects of glutamate on peripheral tissues have long been described. Binding studies have demonstrated the presence of NMDA glutamate receptors in the myenteric plexus,[10] ileal longitudinal muscle [11], bronchi [12], adrenal glands[13], and cardiocytes[14]. There is also physiological and electrophysiological evidence for the existence of AMPA and kainate subtype of glutamate receptors in pancreatic islets[15].

Recently, it has been reported that kidney NMDA receptor expression is conditioned by protein intake, and this receptor may play an important role in the kidney vasodilatory response to glycine infusion and protein feeding in rats[16].

Aim of the work

The aim of this work is to review the current medical literatures addressing the subject of central and peripheral N-methyl-D-aspartate (NMDA) receptors: sites, actions, modulators and possible clinical applications .

Methods

MEDLINE search to define: nomenclature, Sites, Action, Classification

Search Strategies:

Search engine: PubMed

DataBase: Medline

- MeSH terms: N-methyl-D-aspartate (NMDA) Receptors, N-methyl-D-aspartate receptors agonist, N-methyl-D-aspartate Receptors antagonists, N-methyl-D-aspartate receptors modulators.

- Limits: Humans/ animals; English, core clinical journals.
- Limits for section on drug therapy also include randomized controlled trials, systematic reviews, meta-analysis, practice guidelines.

• Review Outline

I- Structure & Variants of NMDA-receptors

II- Ligands : Agonists and Antagonists of NMDA-receptors

III- Modulators of NMDA-receptors

IV- Functional role of NMDA-receptors

V- Novel therapeutic targets of NMDA-receptors

VI- Summary and Conclusion

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Structure and variants of NMDA-receptors

Structure and variants of NMDA-receptors

***N*-Methyl-D-aspartic acid** or ***N*-Methyl-D-aspartate** (NMDA) is an amino acid derivative which acts as a specific agonist at the NMDA receptor mimicking the action of glutamate, the neurotransmitter which normally acts at that receptor. Unlike glutamate, NMDA only binds to and regulates the NMDA receptor and has no effect on other glutamate receptors (such as those for AMPA and kainate). NMDA receptors are particularly important when they become overactive during withdrawal from alcohol as this causes symptoms such as agitation and, sometimes, epileptiform seizures. NMDA is a water-soluble synthetic substance that is not normally found in biological tissue. It was first synthesized in 1960s. NMDA is an excitotoxin; this trait has applications in behavioral neuroscience research. The body of work utilizing this technique falls under the term "lesion studies." Researchers apply NMDA to specific regions of an (animal) subject's brain or spinal cord and subsequently test for the behavior of interest, such as operant behavior (Madaan et al., 2009).

The NMDA receptor (NMDAR) is the predominant molecular device for controlling synaptic plasticity and memory function. The NMDAR is a specific type of ionotropic glutamate receptor. Activation of NMDARs results in the opening of an ion channel that is nonselective to cations. A unique property of the NMDA receptor is its voltage-dependent activation, a result of ion channel block by extracellular Mg^{2+} ions. This allows the flow of Na^{+} and small amounts of Ca^{2+} ions into the cell and K+ out of the cell to be voltage-dependent (Fei and Joe., 2009).