History about the function of the N-methyl-D-aspartate (NMDA) receptor (data to the end of 1980s)

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Types and characteristics of nervous cells

Neurons are nerve cells that vary in size and shape, but they all have three parts; the dendrite(s), the cell body, and the axon. The dendrites receive information from other neurons and generally conduct nerve impulses toward the cell body. The axon on the other hand , conducts nerve impulses away from the cell body. The cell body contains the nucleus and other organnels typically found in cells. One of the main functions of the cell body is to manufacture neurotransmitters, which are chemicals stored in secretory vesicles at the ends of axons. When neurotransmitters are released, they influence the excitability of nearby neurons. Both, dendrite and cell body integrate (sum up excitatory and inhibitory inputs). There are three types of neurons;

(a) motor neurons, each with a long axon and short dendrites, messages from the CNS to muscle fibers or glands.

(b) Sensory neurons, each with a long dendrite and a short axon, messages from sense organs to the CNS.

(c) Interneuron, the third type of neurons is found within the CNS only. It conveys messages between various parts of the CNS , such as from one side of the brain or spinal cord to the other or from the brain to the cord , and vice versa.. An interneuron has short dendrites and either a long axon or a short axon.

The dendrites and axons of these neurons are called fibers, or processes. Most long fibers are covered by a white myelin sheat formed from the neurolemnocytes. These are one of the several types of neuroglial cells in the nervous system. Neuroglial cells service the neurons and have supportive and nutritive functions.

The nerve impulse moves from one neuron to another at a synapse, which has three components; a **presynaptic membrane, a gap called the synaptic cleft, and a postsynaptic membrane**. When nerve impulse traveling along an axon reach an axon bulb, the membrane **becomes permeable to calcium ions (Ca2+).** These ions enter and then interact with actin filaments, causing the actin filaments to pull synaptic vesicles to the presynaptic membrane. When the vesicles merge with this membrane, a neurotransmitter is discharged into the synaptic cleft. The **neurotransmitter molecules** diffuse across the cleft to the postsynaptic membrane, where they bind with a receptor in a lock- and – key manner. This binding process **alters the membrane potential of the postsynaptic membrane** in the direction of either **excitation or inhibition**. If excitation occurs, the membrane potential becomes **less negative**, and if inhibition occurs, the membrane potential becomes **more negative**. This could happen if the neurotransmitter were to cause only sodium gates to open and the axon gained sodium ions (Na+).

The pathways directly involved in **sensory perception** and **motor control** are included in hierarchical systems. In general the axons in these pathways are composed of large myelinated fibers that can often conduct action potentials in excess of 50 m/ s and form clearly delineated fiber tracts. In sensory systems the information is typically phasic and is

processed sequentially by successive integrations at each relay nucleus on its way to the cortex. The system is incapacitated by a lesion at any level. **There are two types of cells** within each nucleus and in the cortex; relay or **projection neurons** and local **circuit neurons**.

The projection neurons that form the interconnecting pathways transmit signals over long distances. The axons of projection neurons have relatively large cell bodies and usually emit collaterals that arborize extensively in the vicinity of the neuron. The synaptic potentials produced by these **neurons are excitatory** and very short lived. In contrast, the vast majority of local **circuit neurons are inhibitory**, and they release either GABA or glycine. Small peptides are often colocalized with these amino acids. The axons of local circuit neurons arborize only in the immediate vicinity of the cell body, and they synapse primarily on the cell body of the projection neurons but can also synapse on the dendrites of projection neurons and onto each other. Local circuit neurons are commonly involved in recurrent feedback and feed-forward pathways. In the spinal cord a special class of local circuit neurons forms axoaxonic synapses on the terminals of sensory axons. In some sensory pathways, local circuit neurons may actually release neurotransmitter from dendritic synapses in a graded fashion in the absence of action potentials and may entirely lack an axon.

The fact that a limited number of neurotransmitters is utilized by the neurons in these hierarchical systems indicates that a profound effect on the overall excitability of the CNS will occur after any major pharmacological manipulation of this system. For instance, generalized seizures occur when GABA receptors are selectively blocked by picrotoxin.

Receptors- ion channels- second messengers

The mechanism of action of putative neurotransmitters and specifically on the **coupling between receptors for neurotransmitters and the ion channels** that ultimately are opened or closed to produce an electrophysiological response- is following; **two major types** of coupling are throught to occur;

First, a receptor may be part of the ion channel molecule so that binding of ligand leads to a conformational change that opens the ion channel. Very fast excitatory or inhibitory synaptic transmission in the CNS utilizes the ligand- gated receptor , since it allows for a very rapid response to agonist. These channels most likely never open except in response to ligand.

The second major type of coupling involves a receptor molecule coupled to the effector channel through at least one other protein. In this situation, the gating of the ion channel is often controlled by changes in voltage. In some cases, voltage – dependent ion channels open and close even in the absence of agonist so that when ligand does bind, it may be considered a modulator of an already operating channel.

Hovewer, considerably more complicated schemes also exist. In particular, **receptors are often coupled through G proteins to membrane**- bound enzyme systems that generate soluble intracelular second messengers in response to ligand binding. **These second messengeres** , often acting through additional intracellular proteins, ultimately have a number of effects, including modulation of ion channels.

Three second messenger systems have been shown to be coupled to their receptors through G proteins. **First is adenylate cyclase**, the enzyme responsible for the generation of adenosine 3,5- cyclic monophosphate (cAMP). Receptors are coupled to this enzyme through two proteins; Gs mediates the coupling for receptors that activate adenylate cyclase , and Gi is its counterpart in inhibition of the enzyme. Activation of adenylate cyclase results in cAMP production , and cAMP then turns on cAMP- dependent protein kinase, an enzyme that acts by phosphorylating cell proteins (NESTLER et al., 1984).

A second major second messenger system involves activation of phospholipase C, an enzyme system that breaks down polyphosphoinositides from the membrane itself, a process that has also been shown to require a G protein (STRYER and BOURNE, 1986). Phospholipase C generates two second messengers molecules, inositol triphosphate(IP3) and

diacylglycerol (BERRIDGE, 1984; FISHER and AGRANOFF, 1987; HIRASAWA and NISHIZUKA, 1985; NISHIZUKA, 1984).

In many systems IP3 causes the release of intracellular Ca2+ from a variety of intracellular pools; this Ca2+ may then **become a „third“ messenger** by interacting with other cell proteins. Because Ca2+ (often released by IP3) enhances the activity of protein kinase C once it has bound diacylglycerol (NISHIZUKA, 1984), phosphatidyl- inositol (PI) turnover can strongly activate this kinase system.

Excitatory amino acids- NMDA receptors

For many years the excitatory amino acids (**glutamate and aspartate**) have been regarded as a relatively unexisting class of neurotransmitter beleived to mediate synaptic transmission at excitatory synapses throughout the nervous system. In the 1980s great strides have been made toward better undersanding the function of these neurotransmitters, in particular because of the application of voltage – and patch- clamp techniques to cultured neurons that express the receptors and because of the development of specific receptor antagonists (COLLINGRIDGE and LESTER, 1989; MAYER and WESTBROOK, 1987; MONAGHAN et al.,1989; STONE and BURTON, 1988). This surge in information has not only resulted in a detailed understanding of the currents that underlie the fast excitatory amino acid- mediated transmission at many central synapses but has unveiled an exciting **new receptor type, the N-methyl- D- aspartate (NMDA) receptor, the activity of which is gated in a unique manner both by ligand binding and by voltage.**

Table 1 Neurotransmitters receptors that are ligand- gated ion channels

Functional type	Ligand+	Ion channel
Excitatat.receptors		
	Acetylcholine (nicotinic receptor)	Na+/K+
	Glutamate (NMDA classs recept).++	Na+/K+ and Ca+
	Glutamate (non NMDA class recept.)+++	Na+/K+
	Serotonin (5HT3 class receptors)	Na+/K+
Inhibitory receptors		
	Gama-aminobutyric acid-GABA (A- class)	Cl-

Glycine Cl-

+ Most of these ligands also bind to receptors that are coupled to G proteins
Their receptors that are ion channels are indicated in parentheses.
++ Opening of the cation channel in these receptors requires a slightly depolarized membrane and binding of glutamate (or; N-Methyl-D-Aspartate, NMDA).
+++ Opening of the cation channels in these receptors only requires binding of glutamate

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Neurons from the spinal cord , cerebral cortex, and other brain regions share the properties of those in the hippocampus with one exception. **Excitatory amino acid receptors in the cerebellum** have been reported to exhibit a physiology and pharmacology quite **different from the other brain areas**, and for this reason the properties of excitatory amino acids in the cerebellum are desribed separately.

Because of, in large part, the work of WATKINS and EVANS (1981) in developing new and better glutamate analogues , the excitatory amino acid receptors have for many years been divided into three relatively selective agonists; NMDA, quisqualate, and kainate. These are all structural analogues of glutamate and appear to activate three separate receptor populations. The most clearly defined of these are the NMDA receptors, which are blocked quite selectively by a number of organic and inorganic antagonists. The quisqualate and kainite receptors differ considerably from the NMDA receptors in their susceptibility to antagonists.

Two observations clearly indicate that quisqualate and kainite receptors are distinct entities.

First, there are cases, e.g., primary afferent C-fibers , where kainate generates responses but amino-3-hydroxy-5methyl-4-isoxazolepropionic acid (AMPA), a very selective quisqualate receptor agonist. Is cca 100-fold less potent (AGRAWAI and EVANS, 1986).

Second, a functional kainate receptor has been cloned that is insensitive to quisqualate (HOLLMANN et al., 1989).

An important breakthrough in understanding excitatory amino acid receptors was the development of the NMDA receptor- specific antagonist, D-2-amino-5-phosphonovalerate (APV, or AP5) (DAVIES et al., 1980; DAVIES et al., 1981). With the use of APV or similar

compounds (AP7…) , it has been found in cortex , spinal cord, neostriatum, and hippocampus that NMDA receptors contribute only a amall and variable amount to the **excitatory postsynaptic potentials (EPSPs)** atresting membrane potentials, even though the blockade of the EPSPs by nonselective glutamate antagonists indicated that the synapses utilized glutamate (COLLINGRIDGE et al., 1983; GANONG et al., 1983; JAHR and JESSELL,1985; JAHR and YOSHIOKA,1986). Both L-glutamate and L-aspartate are mixed agonists at the three receptor types, with their actions being diminished at least partially in nearly all systems by all antagonists.

At many synapses it has been found that under physiological conditions NMDA receptors contribute a long-lasting component to EPSPs, primarily when the cell is substantially depolarized from rest (COLLINGRIDGE et al., 1988; JONES and BAUGMAN, 1988; KAUER et al., 1988; WIGSTROM and GUSTAFSSON, 1988). In addition to these competitive antagonists of receptor binding, several drugs block NMDA receptors noncompetitively , apparently by binding within the ion channel associated with this receptor. These compounds are of the dissociative anesthetic class; including ketamine, phencyclidine, MK- 801 (ANIS et al., 1983: MACDONALD et al., 1987: WONG et al., 1986) **and Mg2+ at physiological concentrations.**

Magnesium blockator, zinc modulator of NMDA channel

In the study by MacDONALD and WOJTOWICZ (1980) on cultured neurons, it was found that **in high Mg2+ (10mM) only the conductance increase was observed** , whereas in **ambient concentrations of Mg2+ both increases and decreases could be recorded**. Independently it was found in the isolated hemisected spinal cord that **physiological concentrations of Mg2+ (1 mM) severely depresed NMDA responses selectively** (AULT et al., 1980) .

With the use of cultured neurons NOWAK et al.(1984) and MAYER et al.(1984), both

reported that the **elimination of Mg2+ from the recording medium abolished** the voltage dependence seen in response to NMDA, essentially converting it to a linear current voltage (I-V) relation similar to that of the non- NMDA receptor agonists. Thus the ion channel itself has no intrinsic voltage dependence (ASCHER et al., 1988). Single –channel openings in response to NMDA demonstrated **that the presence of Mg2+ led to a rapid voltage-dependent on- and- off block of the channel** (NOWAK et al., 1984). **Magnesium concentrations as low as 10uM had significant effects on channel** gating properties, and since physiological levels in CSF are 1mM, NMDA channels in most cells at the resting potential (- 60 to – 80 mV) are likely to be largely blocked. **The Mg2+ block of the NMDA channel explained** the apparent decrease in conductance reported by MacDONALD and WOJTOWICZ (1980)

In neurons from a variety of brain regions, a surprising result was obtained; although each agonist tested did act primarily to open channels of a single conductance state , every agonist also caused openings to a lesser degree to several other conductance states. **Magnesium was found to block only the largest of the conductance** states, the 40- to 50 –pS conductance state (NOWAK et al., 1984).

In all; three to five basic conductance states were reported in **cerebellar Purkinje cells** and neurons from hippocampus, spinal cord, mesencephalon, striatum, and cortex, and every conductance was opened to some extent **by every agonist** (ASCHER et al., 1988; ASCHER and NOWAK, 1988; CULL-CANDY and USOWICZ, 1987; JAHR and STEVENS,1987; LLANO et al., 1988).

Zinc reduces the mean channel open time of the NMDA channel and may also decrease the conductance, **but unlike the block by Mg2+ , the effect of zinc is not dependent on voltage** (MAYER et al., 1988; MAYER et al., 1989; WESTBROOK and MAYER, 1987). Thus zinc may bind to an additional site on the NMDA receptor molecule that is unlikely to

be within the membrane electric field (KUSHNER et al., 1988). Indeed, zinc interferes with NMDA receptor binding, raising the possibility that this metal ion may uncouple the agonist site from the channel (REYNOLDS and MILLER, 1988). However, electrophysiological results suggest that **it is a noncompetitive antagonist** (MAYER et al., 1989). The lack of voltage dependence means, that unlike Mg2+ , **zinc will depress NMDA receptor function regardless of cell activity**. The finding that zinc depressed synaptic transmission between cultured hippocampal neurons (FORSYTHE et al., 1988; MAYER and VYKLICKY, 1989) is particularly exciting , since in the CA3 region of hippocampus, **zinc is present in synaptic boutons** (CRAWFORD and CONNOR, 1972; FREDERICKSON et al., 1983) and can be released during synaptic stimulation at levels sufficient to **modulate NMDA receptor function** (200 uM)(ANIKSZTEJN et al., 1987).

Zinc is also present in other cortical brain structures, and it will be of interest to determine its effects using tissue slices. Interestingly, it has been noted that zinc enhances cell responses to non- NMDA agonists, particularly quisqualate (KOH and CHOI, 1988; MAYER and WESTBROOK, 1987;MAYER et al., 1989; PETERS et al., 1987).

NMDA channels permeability to calcium

The ion channels coupled to both NMDA and non NMDA receptors (quisqualate and kainate receptors) are permeable nonselectively to monovalent cations, with a resulting reversal potential at 0 mV for all excitatory amino acids tested (MAYER and WESTBROOK, 1984). In contrast, NMDA and non- NMDA channels differ dramatically in permeability to divalent cations. Non- NMDA channels are relatively impermeant to divalent cations, **whereas NMDA channels are highly permeable to Ca2+** (MAYER and WESTBROOK, 1987). Therefore one of the more critical function of the NMDA channel may be to increase intracellular Ca2+. The permeability of the NMDA channel to Ca2+ has been demonstrated in a variety of ways.

The **application of NMDA caused Ca2+ influx into cultured spinal cord neurons** filled with the Ca2+ indicator dye, arsenazo III (MACDERMOTT et al., 1986; MAYER et al., 1987). The use of voltage clamping was particularly important here, since it excluded the entry of Ca2+ through voltage- dependent Ca2+ currents; thus it was certain that Ca2+ entered the cell only through NMDA channels. **Extracellular Mg2+ was able to block the Ca2+ increase in response to NMDA,** showing that the source of the Ca2+ was extracellular rather than intrecellular stores. To test the Ca2+ permeability in another way, Ca2+ concentrations were changed while monitoring the reversal potential of the responses to NMDA or non- NMDA agonists, and these experiments also show **that NMDA channels are significantly more permeable to Ca2+ than non- NMDA channels** (cca 70 times more permeable in physiological solution) (MACDERMOTT et al., 1986; MAYER and WESTBROOK, 1987). Single- channel recording confirmed that the large- conductance (50 pS) state of the ion channel , which was **preferentially activated by NMDA, shows significant permeability to Ca2+** (ASCHER and NOWAK, 1988a; JAHR and STEVENS,1987).

Although the non- NMDA receptor ion channels are not very permeable to Ca2+, glutamate and quisqualate (but not AMPA or kainite) act at receptors in cultured embryonic hippocampal neurons, **causing release of Ca2+ from intracellular stores** (MURPHY and MILLER,1988). This effect is likely mediated by a receptor linked to PI turnover (inositol phosphate), releasing Ca2+ through the generation of IP3 (inositol triphosphate). Thus at least **some non- NMDA receptors may directly influence intracellular Ca2+ levels**.

In summary, in contrast to to the non- NMDA receptor channel , the NMDA receptor channel has a binding site for divalent cations strongly reduces the flow of current at membrane potentials more negative than cca 40mV. The NMDA channel unlike the non-NMDA channel, is also permeable to Ca2+ . This may result from **rapid binding and release**

of Ca2+ from the same site at which Mg2+ exerts its voltage- dependent block.

Cerebellum - excitatory synaptic transmission

Recordings from Purkinje cells within cerebellar slices have presented a pharmacological profile for the excitatory amino acids different from that of other CNS regions. Early studies showed that the ionophoresis of glutamate or quisqualate produced a strong depolarization of Purkinje cell dendrites but not cell bodies, whereas in contrast to its effects in other brain regions , NMDA was relatively less potent (BUNZOW et al., 1988; CREPEL et al., 1982).

D-Glutamylglycine (DGG) and APV (D-2-amino-5-phosphonovalerate) blocked the response to aspartate and the synaptic response to activation of the climbing fibers, with almost no effect on the response to glutamate (KIMURA et al., 1985). This pharmacological profile suggests an action at NMDA receptors, but **early studies suggested that NMDA receptors were not present on Purkinje cells.**

SEKIGUCHI et al. (1987) prepared and maintained cerebellar slices in zero Mg2+ medium for several hours before recording. Under these conditions, they observed a rapid response to NMDA at iontophoretic currents comparable to those used to elicit responses to quisqualate. The NMDA- induced depolarization showed a voltage sensitivity similar to that in other neurons and was **exquisitely sensitive to Mg2+, being abolished** entirely within seconds after 1 mM Mg2+ was reintroduced into the bathing medium.

Aspartate appeared to act at the NMDA receptor as well as at additional sites, since **part of the aspartate response showed a Mg2+ sensitivity similar to that of the NMDA** response (SEKIGUCHI et al.,1987). These results suggest that cerebellar Purkinje cell dendrites do posses NMDA channels, but their functional role is still unclear. **The receptor pharmacology in cerebellum is apparently slightly different from other brain regions.**

First, APV does not entirely block NMDA responses (CREPEL et al., 1983; SEKIGUCHI et

al.,1987). **Second, aspartate** seems preferentially to activate NMDA- like receptors, some of which mediate effects **that are entirely blocked in 1 mM Mg2+** (SEKIGUCHI et al.,1987) and others at which NMDA may act as a competitive antagonist (CREPEL et al., 1983; KIMURA et al., 1985; SEKIGUCHI et al.,1987).

Finally, quisqualate may cross over to act at this „NMDA like" receptor much more than in other brain regions, since APV significantly affected the quisqualate response (CREPEL et al., 1983). In this regard, it is of interest that whole cell patch records from presumptive Purkinje cells in culture showed that currents induced by quisqualate were reduced by one – half in 1 mM Mg2+ , **suggesting strong crossover to a Mg2+- sensitive site** (CULL-CANDI and USOWICZ, 1987). In these studies, responses to aspartate **were entirely blocked in 1 mM Mg2+.**

In **neurons from spinal cord, 10 mM Mg2+ is required to block NMDA responses** at potentials negative to 0 mV (MAYER and WESTBROOK, 1985). It may be that the **NMDA channel in Purkinje cells has a more extreme sensitivity to Mg2+ than that in other brain regions.**

Consistent with the apparent lack of typical NMDA receptors is cerebellum, LLANO et al. (1988), using organotypiccultured slices , found no single- channel responses of Purkinje cells to NMDA, whereas the usual responses were observed to quisqualate (12-14pS) and kainate (2,5*4 pS). Interestingly, these authors also report that they **never observed the 50-pS (large conductance) channel openings reported in cultured neurons from other CNS areas.**

In contrast, the cultured cerebellar cells used by CULL- CANDY and USOWICZ (1987; 1987a) , which showed the 50- pS conductance state and were sensitive to NMDA, were tentatively identified as Purkinje cells. An explanation for this apparent discrepancy is that the **localization of NMDA receptors may change during development** , and, in particular, NMDA receptors disappear in the regions innervated parallel fibers (at cca 1 mo of age in

rats) (DUPONT et al., 1987; GARTHWAITE et al., 1986).

Synaptic transmission at the resting membrane potential in pyramidal cells of the CA1 region of the hippocampus is primarily mediated through non- NMDA receptors ; however, binding studies show the highest level of NMDA receptors in the brain (MONAGHAN and COTMAN, 1985). **Discovery of the voltage- dependent Mg2+ block of NMDA channels under physiological conditions** provided an explanation for this. In neurons from a variety of CNS regions, the EPSP at excitatory synapses has been found to **consist of two components**; a fast**, rapidly decaying non- NMDA receptor**- mediated component and a **late slow NMDA receptor**- mediated component, **which is unmasked in low Mg2+** and which can be blocked by APV (ANDREASEN et al., 1989; ARTOLA and SINGER, 1987; CHERUBINI et al., 1987; BLOOM, 1988; ROBERTS, 1985; FORSYTHE and WESTBROOK, 1988; GALLAGHER and HASUO, 1989; HABLITZ and LANGMOEN, 1986; HERRON et al., 1985; HUETTNER and BAUGHMAN, 1988; JONES et al., 1988; KAUER et al., 1988; MULLER et al., 1989; O´BRIEN and FISCHBACH, 1986;THOMSON, 1986; WIGSTROM and GUSTAFSSON, 1988).

NMDA receptors - properties and implications

As neuroscience has begun to define the central pathways in which NMDA receptors act, it is becoming clear that neurological damage caused by a variety of different pathological states can result when NMDA receptors are inappropriately activated. **The NMDA receptors differ in fundamental ways from the non- NMDA receptors**, and these properties relate directly to the functions conferred on cells that posses them.

The **first unique** property of the NMDA receptor **is the voltage dependence caused by Mg2+ binding within the ion channe**l. **Second**, EPSP mediated by NMDA receptors has a prolonged time course relative to that mediated by the non- NMDA receptors. **Third,** unlike non- NMDA channels , **NMDA channels are permeable to Ca2+.**

The voltage- dependent block of the NMDA receptor channel causes a region of negative slope conductance in the current – voltage relations of cells that posses it. This means that when glutamate is present, **depolarization of the cell causes Mg2+ to be expelled** from the channel. This in turn results in current flow into the cell through the previously blocked NMDA channel, causing further depolarization. Thus non- NMDA receptor- mediated responses above a certain threshold recruit current flow through NMDA receptors, acting as amplifiers for large EPSPs. This excitatory feedback presumably explains some of the regenerative behavior of a variety of neurons in response to NMDA receptor activation (FLATMAN et al., 1986; GRILLNER and WALLEN, 1985; SIGVARDT et al., 1985). In the absence of synaptic inhibition a small NMDA component to the EPSP can be detected at the resting potential in hippocampal neurons. In addition, ambient glutamate in the extracellular fluid tonically activates NMDA receptors and modulates hippocampal cell excitability (SAH et al., 1989). A very similar tonic action has been reported in vestibular neurons (KNOPFEL, 1987).

The **entry of Ca2+ through the NMDA channel is likely to be responsible for several** of the long- lasting effects that appear to depend on NMDA receptors, including **excitatory amino acid- mediated toxicity** and LTP **(long- term potentiation**). Both of these phenomena appear to **depend specifically on the entry of Ca2+ into the neuron through NMDA receptors.**

Glutamate has been implicated in neuronal death in response to a variety of insults to the nervous systém, including anoxia, hypoglycemia, and seizure (ROTHMAN, 1984; ROTHMAN and OLNEY, 1986). Exposure of tissue slices or cultured neurons to NMDA, glutamate, quisqualate, or kainate results in similar patterns of cytotoxicity. Although an early component of cytotoxicity appears to result from osmotic shock resulting from Na+ and Cl- entry, a later, invariably lethal, component of cytotoxicity does not occur in zero Ca2+

medium and can be prevented by APV, zinc, or ketamine (CHOI, 1987; CHOI et al., 1988; KOH and CHOI, 1988).

These findings suggest that an important part of excitatory amino acid toxicity results from activation of NMDA receptors and, **in particular, from entry of Ca2+ through NMDA channels**. In further support of this are experiments using cultured cells, suggesting that Ca2+ entry through voltage- gated channels is not significantly involved in cytotoxicity (KUDO and OGURA, 1986; MURPHY et al., 1987).

Interestingly, especially from a clinical perspective, addition of NMDA antagonists after the initial exposure to glutamate also significantly reduces toxic effects (CHOI et al., 1988). These results suggest that a major cause of damage may involve a **mechanism that allows glutamate to remain pathologically elevated for long periods**, perhaps an impaired reuptake system or continuous leakage from damaged cells. Such a mechanism would help to explain the relative unimportance of voltage – gated channels , since in the presence of unusually elevated glutamate, NMDA channels would remain tonically activated without necessarily opening voltage- gated channels.

The unique properties of the NMDA receptor are also utilized during the induction of LTP, a long- lasting enhancement of synaptic transmission observed in hippocampus after a brief high- frequency stimulation of an afferent input (BLISS and LOMO, 1988). As a model of learning and memory, **long- term potentiation** (LTP) has been extensively studied , not only because of its long duration but also because of its associative properties (BLISS and LOMO, 1988; NICOLL et al., 1988 ; WIGSTROM and GUSTAFSSON, 1988). It has become clear that it is the NMDA receptor that acts as the associative switch for the initiation of LTP, turning on only when postsynaptic depolarization is paired temporally with the synaptic release of glutamate (GUSTAFSSON et al., 1987; KELSO et al., 1986 ;WIGSTROM et al., 1986).

Thus ordinary low- frequency synaptic transmission **does not provide sufficient depolarization to relieve the Mg2+ block** , and depolarization alone is also insufficient to induce LTP, since the NMDA receptors see no agonist. The long- lasting NMDA component of the EPSP is likely to contribute to the strong cumulative depolarization at the synapse when afferent terminals fire repetitively (COLLINGRIDGE et al., 1983).

The combination of synaptically released glutamate with depolarization results in Ca2+ entry through the NMDA channel, and several lines of evidence **indicate that postsynaptic Ca2+ is necessary to trigger LTP** (DUNWIDDIE and LYNCH, 1979; LYNCH et al., 1983; MALENKA et al., 1988).

On the basis of the injection of inhibitors into the postsynaptic cell, it is thought that both calmodulin (MALENKA et al., 1989) and kinase activity (MALINOW et al., 1989) are required for LTP. The induction of **long- term potentiation** (LTP) can be blocked either competitively ba blocking the NMDA receptor with APV (COLLINGRIDGE et al., 1983) or by blocking Ca2+ entry through the NMDA channel. **Thus both the Mg2+ blockade of the NMDA channel and the selective permeability to Ca2+ of this excitatory amino acid receptor channel are responsible for critical aspects of the LTP induction process.**

These literature sources were obtained (mostly) from „**Health Sciences Library“** (http://www.hsc.wvu.edu/library/#using) in Morgantown (1991).