

NMDA Receptors and Disease+C464

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Introduction

N-Methyl-D-aspartate (NMDA) receptors are a major subtype of ionotropic excitatory glutamate receptors that mediate synaptic transmission at the vast majority of excitatory synapses in the central nervous system. Functional NMDA receptors are heterotetrameric complexes of NR1, NR2A–NR2D, and NR3A and NR3B subunits. The subunit compositions of the receptors affect both their functional properties and subcellular distributions. Like other types of ionotropic glutamate receptors, NMDA receptors are ion channels that allow major monovalent cations such as sodium and potassium to cross the plasma membrane, either into or out of the neuron, depending on the chemical and electrical gradients of these ions at a given time. However, NMDA receptors possess several unique properties that distinguish them from other ionotropic glutamate receptors. In addition to monovalent cations, NMDA receptors are also highly permeable to the divalent cation Ca^{2+} , which has numerous important intracellular functions. (Note: the only other type of glutamate receptor that exhibits similar Ca^{2+} permeability is the GluR2 subunit-lacking α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, which represents a minor proportion of AMPA receptors in the brain.) The permeability of NMDA receptors to Ca^{2+} places them in a unique position to control the initiation of a lengthy list of Ca^{2+} -dependent cellular events. NMDA receptors also have two unique requirements that control their activation. Unlike other glutamate receptors, NMDA receptors require co-agonists such as glycine to bind to specific sites at the same time as glutamate binds, in order to be activated. Additionally, under resting conditions, magnesium ions block the channel pore of NMDA receptors. In order for the magnesium block to be removed, the membrane must be depolarized, which enables NMDA receptors to function as a detector for the coincidental presynaptic release of glutamate and postsynaptic depolarization, a process critical for computation of neuronal signals and for the establishment of certain forms of activity-dependent synaptic plasticity. These unique properties place NMDA receptors in a position to regulate various neuronal functions, ranging from synaptic plasticity at a single synapse to complex cognitive functions

such as learning and memory. However, abnormal activation of NMDA receptors may also result in cellular dysfunction and contribute to the symptoms of many disorders of the nervous system. Therefore, the contribution of NMDA receptor abnormalities to the pathogenesis of several disorders will be discussed in the following sections, with a particular focus on progress made in the last decade.

Potential Mechanisms Underlying the Roles of NMDA Receptors in Brain Dysfunction

Excitotoxicity: A Common Mechanism by which NMDA Receptors Contribute to the Pathogenesis of Neurodegenerative Disorders

Excitotoxicity refers to the overactivation of glutamate receptors as a result of increased release and/or decreased uptake of excitatory amino acid transmitters, primarily glutamate. During pathological conditions such as those experienced during ischemia, excessive release of glutamate overactivates glutamate receptors, resulting in a massive influx of sodium ions, chloride ions, and water, which cause neurons to swell and may ultimately lead to rapid neuronal loss from necrosis. Because of the high calcium permeability of NMDA receptors, their overactivation is also accompanied by an accumulation of excessive amounts of intracellular calcium, which initiates other intracellular cascades, leading to slow (delayed) apoptotic neuronal loss. The mechanisms through which excessive calcium influx leads to apoptosis are complex and not fully understood. Accumulating evidence has implicated several intracellular molecules and signaling pathways, including mitochondrial dysfunction, reactive oxygen species production, activation of catabolic enzymes which degrade proteins, nucleic acids, and other cellular components. While the detailed mechanisms through which overactivation of NMDA receptors lead to excitotoxicity may differ between disorders, a large body of evidence implicates NMDA receptor-mediated excitotoxicity as a common mechanism mediating the pathogenesis of many neurodegenerative disorders, ranging from acute events such as stroke and brain trauma to chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Evidence for the involvement of NMDA receptor-mediated excitotoxicity in the pathogenesis of central nervous neurodegenerative disorders will be discussed in later sections using stroke and Alzheimer's disease as examples of acute and chronic neuronal degeneration, respectively.

Altered NMDA Receptor-Mediated Synaptic Plasticity May Contribute to the Pathophysiology of Brain Disorders with Abnormal Synaptic Function

Synaptic plasticity refers to the ability of synapses to change their strength. Such plastic changes in synaptic efficacy are fundamental for both neuronal development and normal brain functions. Because of the unique features of high calcium permeability and the voltage-dependent blockade by extracellular magnesium, NMDA receptors are essential for mediating many forms of synaptic plasticity in the brain throughout development. The best characterized forms of NMDA receptor-mediated synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD) of AMPA receptor-mediated synaptic transmission at CA3–CA1 synapses in the hippocampus. LTP and LTD are prominent cellular models of certain forms of learning and memory. Not surprisingly, alterations in LTP and LTD are correlated with cognitive impairments in rodent models of brain disorders such as Alzheimer's disease and fragile X syndrome. In addition, accumulating evidence supports the hypothesis that abnormal NMDA receptor function and synaptic plasticity are involved in the pathogenesis of brain dysfunctions in a number of neurological and neuropsychiatric disorders not characterized by evidence of cell death or gross structural damage to the brain. In these disorders, it is hypothesized that relatively subtle functional and structural alterations in synaptic connections between neurons in affected brain regions may underlie some of the symptoms. Examples of such brain disorders include pain, addiction, and schizophrenia. In the following sections there is a discussion of research on these disorders that has demonstrated the pathological effects of abnormal synaptic plasticity and has provided insight into a number of therapeutic strategies for reversing these abnormalities.

Examples of Disorders Hypothesized to Occur as a Result of NMDA Receptor Dysfunction

Stroke

Stroke is a sudden loss of blood supply to part of the brain that occurs when a blood vessel either bursts or is blocked. Neurons in the affected area are severely injured or die as a result of the interrupted supply of oxygen and nutrients from the blood. The specific consequences of a stroke depend on a number of factors, including the duration of blood loss and the specific brain area affected. Different cellular processes underlie neuronal injury following stroke, but particularly strong evidence suggests that excitotoxicity is the primary cause of neuronal death following

stroke. For example, in both *in vitro* and *in vivo* experimental models, levels of extracellular glutamate are rapidly elevated after stroke to concentrations that produce massive increases in intracellular calcium. The levels of intracellular calcium reach concentrations sufficient to cause excitotoxic necrotic and apoptotic neuronal loss. Most importantly, administration of NMDA receptor antagonists before or immediately after stroke onset is effective in reducing the neuronal damage in various preclinical animal models.

Significant evidence thus supports the critical involvement of NMDA receptor-mediated excitotoxicity in mediating stroke-related neuronal loss and NMDA receptors as an important target for stroke therapy. As a result, numerous pharmaceutical companies have spent considerable resources in an attempt to design effective NMDA receptor antagonists for treatment of stroke. However, the effectiveness of NMDA receptor antagonists in clinical trials for stroke and traumatic brain injuries has been low. A number of factors, including undesirable side effects at therapeutically effective doses, an inability to administer the drugs within their neuroprotective windows, and heterogeneity in the patient population, likely underlie these disappointing results.

Importantly, recent advancements in understanding the detailed molecular mechanisms of NMDA receptor-mediated excitotoxicity may aid in developing novel NMDA receptor-based neuroprotective therapeutics that would reduce neurotoxicity without causing significant side effects. For example, one potential challenge in using NMDA receptor antagonists for stroke therapy is to avoid inhibiting the normal functions of NMDA receptor signaling, which are essential for neuronal survival. One promising approach to avoid completely block NMDA receptors is to use low-affinity NMDA receptor antagonists such as memantine to treat stroke. Memantine is a low-affinity, open-channel blocker of NMDA receptors. Due to its relatively low affinity, memantine only blocks significant numbers of NMDA receptors when they are highly overactivated, such as during stroke. Therefore, memantine has minimal effects on NMDA receptors in areas unaffected by the stroke, thereby reducing the side effects typical of potent NMDA receptor antagonists. Another promising therapeutic approach for stroke is to specifically target the cell death signaling pathways downstream of NMDA receptors without blocking normal functioning of the receptors. For example, one of these pathways is initiated by the association of NR2B subunit-containing NMDA receptors with the scaffolding protein PSD95. Recent experiments using preclinical models of stroke have shown that administration of a synthetic peptide that disrupts the association of the C-terminal tail

of NR2B subunits with PSD95 substantially reduces ischemia-induced damage without noticeable side effects. Given their promise in preclinical models of stroke, both low-affinity NMDA receptor antagonists and interference peptides are currently being tested in clinical trials for use in human patients suffering from stroke.

Alzheimer's Disease

Alzheimer's disease (AD) is the main cause of dementia in the elderly. Pathologically, AD is characterized by cortical atrophy, the presence of amyloid plaques and neurofibrillary tangles, and the granulovacuolar degeneration of neurons in vulnerable brain areas such as the neocortex and the hippocampus. While the mechanisms underlying AD neuropathology are not well understood, emerging evidence suggests that altered NMDA receptor function and enhanced NMDA receptor-mediated excitotoxicity may contribute to both pathological and functional abnormalities of AD. For example, amyloid plaques are primarily composed of the amyloid beta peptide ($A\beta$ peptide). Recent studies have shown that the $A\beta$ peptide enhances NMDA-receptor-mediated neurotoxicity by either potentiating NMDA receptor function or increasing available glutamate by inhibiting glutamate transport.

The $A\beta$ peptide also has significant effects on NMDA receptor-mediated synaptic plasticity in the hippocampus and may be a cellular substrate for dementia in AD. Application of the $A\beta$ peptide inhibits hippocampal LTP in both *in vitro* and *in vivo* preparations. LTP is also greatly reduced in transgenic AD animal models expressing high levels of $A\beta$ peptide. Interestingly, the $A\beta$ peptide may not affect or even potentiate LTD in the hippocampus. Since LTP and LTD may be mediated by distinct subpopulations of NMDA receptors, the differential effects of the $A\beta$ peptide on LTP and LTD may result from subunit-specific actions on NMDA receptors. Future studies of the effects of $A\beta$ peptide on NR2A- and NR2B-containing NMDA receptors are required to test this hypothesis. Whether the effects of the $A\beta$ peptide on LTP and LTD contribute to the neurodegeneration in AD remains unclear. However, a recent study provides compelling evidence that the enhanced LTD caused by the $A\beta$ peptide may mediate the spine and neuronal loss typically observed in AD. The importance of altered NMDA receptor signaling and synaptic plasticity for the neuropathology and cognitive dysfunction in AD is further supported by the beneficial effect of treatment of AD patients with memantine at various stages of dementia. These results also provide strong support for using NMDA receptor modulators/antagonists as part of the treatment of AD.

Pain

Pain is an unpleasant sensation associated with actual or potential tissue damage in the body. While normal pain responses are adaptive, pathological pain disorders are common and debilitating for many people. Pain disorders are caused by a number of conditions, including chronic inflammation or aberrant activity in peripheral nerves and nervous tissue (neuropathic pain). Neuropathic pain may be caused by either increased pain responses toward noxious stimuli (hyperalgesia) or decreased pain threshold to the point that normally nonnoxious stimuli such as touch or gentle pressure produce pain (allodynia). These pathological alterations are produced by hyperresponsiveness of nociceptive afferents sending sensory information to the dorsal horn of the spinal cord. After synapsing in the dorsal horn, this information is transmitted to the brain. Importantly, these pain pathways can be experimentally sensitized by repetitive stimulation of pain afferents, an effect that is mediated primarily by glutamate. Sensitization of glutamatergic transmission after noxious stimuli has also been reported in the cingulate cortex, an important forebrain region for nociception. Given the importance of the NMDA receptor in glutamatergic transmission and plasticity, it has become a research target for understanding the mechanism of central pain sensitization.

Using preclinical models, the involvement of NMDA receptors in the induction and expression of pain-induced sensitization in the spinal cord is supported by a number of findings. For example, direct administration of NMDA receptor antagonists on dorsal horn neurons abolishes the postsynaptic hyperexcitability caused by repetitive stimulation of primary pain afferents. Additionally, the intrathecal application of either NMDA receptor agonists or allosteric modulators such as D-serine induces hyperalgesia. NMDA receptor antagonists are also clinically effective in reducing hyperalgesia in patients with chronic pain.

Although NMDA receptors are important for central sensitization to pain, little is known about the mechanisms of how NMDA receptor activation contributes to causing hyperexcitability of dorsal horn neurons. However, a number of possibilities exist. For example, central sensitization may alter glutamate receptor function. Consistent with this possibility, the expression levels and kinetics of NMDA and AMPA receptors in the dorsal horn are altered in an animal model of inflammatory pain. Intriguingly, levels of AMPA receptor expression are increased in neuropathic pain, and this increase parallels the time course of hyperalgesia, suggesting an important role of increased AMPA receptor expression in the hyperexcitability of dorsal horn neurons. Given that potentiated AMPA

receptor function is also the underlying mechanism of hippocampal LTP, these enhancements of AMPA receptor function in sensitized dorsal horn neurons may be the result of an NMDA receptor-mediated mechanism similar to LTP. It is noteworthy that NMDA receptor-mediated LTP is readily induced in dorsal horn neurons by high-frequency stimulation of the primary nociceptive afferents. The recent discovery of 'silent synapses' in dorsal horn neurons also supports a potential role of LTP-like synaptic plasticity in the formation of central pain sensitization. Silent synapses are glutamatergic synapses that contain NMDA but not AMPA receptors; therefore, they are not activated during low levels of synaptic activity. Evidence suggests that during LTP, silent synapses are converted into functional synapses by recruiting AMPA receptors into the postsynaptic membrane. Recent experiments have shown that silent synapses can be activated in dorsal horn neurons, suggesting that recruitment of AMPA receptors could be a potential mechanism underlying central pain sensitization.

Available evidence also suggests that NR2B subunit-containing NMDA receptors may mediate the central sensitization of pain perception. The expression of NR2B subunits is enriched in dorsal horn neurons compared to other NR2 subunits. Additionally, specific antagonists of NR2B-containing NMDA receptors are effective analgesic agents for neuropathic pain. Finally, inflammation causes an increase in NR2B-containing NMDA receptors in the anterior cingulate cortex, while overexpression of NR2B subunits in the anterior cingulate cortex facilitates hyperalgesia caused by inflammation. Taken together, these findings highlight the importance of NR2B-containing NMDA receptors as therapeutic targets for chronic pain.

Drug Addiction

Drug addiction is a brain disorder that may be caused by maladaptive alterations in synaptic networks involving the mesocorticolimbic dopamine system. The mesocorticolimbic system consists of dopaminergic neurons which project from the ventral tegmental area (VTA) in the midbrain to forebrain areas such as the nucleus accumbens (NAc), amygdala, hippocampus, and prefrontal cortex. Alterations of dopaminergic inputs from the VTA to NAc and other forebrain regions have been investigated extensively in an effort to determine their potential role in addictive behavior. Both the VTA and NAc also receive glutamatergic inputs that undergo long-lasting modifications in response to commonly abused drugs such as cocaine and amphetamine. Accumulating evidence supports the hypothesis that the formation of addictive behavior involves plastic changes of glutamatergic inputs to various areas of the mesocorticolimbic system. Not surprisingly, there is strong

evidence for the role of NMDA receptors in these plastic changes. For example, a single exposure to cocaine readily induces NMDA receptor-mediated LTP of glutamatergic inputs to the VTA (VTA-LTP). Biochemical experiments suggest that this VTA-LTP results from an increase in AMPA/NMDA receptor ratio on the postsynaptic membranes of VTA neurons. In addition, repetitive drug exposure reduces the induction threshold of VTA-LTP. However, a causal role for altered VTA synaptic plasticity in drug addiction remains to be established, partially due to a lack of specific inhibitors that interfere with the expression of LTP without affecting the normal function of NMDA receptors and downstream signaling pathways.

In addition to the plastic changes observed in the VTA, repeated administration of psychostimulants to rats enables LTD of glutamatergic inputs to the NAc (NAc-LTD), an effect which requires activation of NMDA receptors. Similar to hippocampal CA1 LTD, the expression of NAc-LTD is also mediated by the removal of synaptic AMPA receptors through GluR2 subunit-dependent clathrin-mediated endocytosis. Importantly, when a short synthetic peptide derived from the carboxyl tail region of GluR2 that blocks clathrin-mediated endocytosis was delivered into the NAc neurons, it blocked the formation of NAc LTD and the expression of amphetamine-induced behavioral sensitization. (Note: behavioral sensitization is a common behavioral model used to model some aspects of drug addiction.) Given that the peptide did not affect normal AMPA or NMDA receptor function, basal synaptic transmission, or LTP, these results provide strong evidence that NAc-LTD underlies the expression of amphetamine sensitization. These findings from the VTA and NAc provide strong evidence that abnormal NMDA receptor function and glutamatergic synaptic plasticity are involved in the pathogenesis of certain drug addiction-related behaviors. Targeting these processes may provide a new avenue for developing novel drug addiction treatments.

Schizophrenia

Schizophrenia is a severe psychiatric disorder that affects approximately 1% of the population. The neurobiological causes of schizophrenia remain largely unknown but are likely related to relatively subtle structural abnormalities in various limbic areas and an imbalance of various neurotransmitters in the brain. The positive symptoms of schizophrenia, which include hallucinations and paranoia, are at least partially caused by dopamine hyperactivity, as they are reduced by dopamine antagonists (typical antipsychotics) and exaggerated by dopamine agonists. However, the cognitive and negative symptoms of schizophrenia, which are particularly debilitating, are generally resistant

to treatment with typical antipsychotic drugs. This suggests that other neurotransmitter systems may be abnormal in schizophrenia. Indeed, strong evidence suggests that alterations in the glutamatergic system exist in schizophrenia. For example, a number of psychotomimetic drugs, such as the NMDA receptor antagonists phencyclidine and ketamine, induce schizophrenic-like psychosis in normal people as well as exaggerate some of the symptoms of patients with schizophrenia. Interestingly, the effects of NMDA receptor antagonists more closely resemble those of schizophrenia than the primarily positive symptoms induced by dopamine agonists such as amphetamine. These findings suggest that hypofunction of NMDA receptors contribute to a variety of schizophrenia symptoms.

Several lines of emerging evidence support the NMDA receptor hypofunction hypothesis of schizophrenia: (1) biochemical analyses of the brains of patients with schizophrenia demonstrate abnormal distribution and expression levels of NMDA receptors in some studies, (2) various genetic approaches to disrupting NMDA receptor function are sufficient to model some of the symptoms of schizophrenia in mice, and (3) augmenting NMDA receptor function with positive modulators of the glycine binding site has displayed subtle but promising antipsychotic effects.

The complexity of schizophrenia makes determining the exact role of NMDA hypofunction in the disorder difficult. Since NMDA receptors are important for mediating the basal activity of inhibitory interneurons in cortical and limbic regions known to be involved in schizophrenia, NMDA receptor hypofunction may disrupt normal processing in these areas by decreasing inhibitory synaptic drive. Additionally, NMDA receptors have significant neurotrophic roles during early development. Current theories suggest that the etiology of schizophrenia has a strong developmental component that is likely caused by a combination of genetic and environmental effects. Therefore, early alterations in NMDA receptors could interact with other genetic or environmental effects and contribute to the development of the disorder.

Concluding Remarks

Evidence from both preclinical and clinical studies demonstrates the importance of NMDA receptor dysfunction in numerous acute and chronic neurological and psychiatric disorders. Although the detailed cellular signaling pathways likely vary between the disorders, excitotoxicity and abnormal modification of synaptic transmission are two primary mechanisms by which NMDA receptor dysfunction is involved in these disorders. Unfortunately, the results of clinical trials testing generalized NMDA receptor-based modulators

and antagonists for the treatment of these disorders have achieved limited success at the present time. Ongoing research aimed at delineating the downstream signaling pathways mediated by specific subpopulations of NMDA receptors provides a rich avenue for the development of new NMDA receptor-based treatments with greater therapeutic benefits and fewer side effects. The use of low-affinity NMDA antagonists like memantine for reducing NMDA receptor-mediated excitotoxicity highlights the importance of developing NMDA receptor-based therapies with different pharmacological profiles for treating brain disorders. The success of this strategy could be further enhanced by better understanding the subunit-specific mechanisms involved in individual disorders. In addition to directly targeting the NMDA receptor, a second promising strategy is to develop novel drugs that specifically target signaling molecules downstream of NMDA receptor activation, as exemplified by the recent success in ameliorating ischemic damage by disrupting the interaction between NR2B subunits of the NMDA receptor and PSD95. Given the rapid pace of research in the area of NMDA receptor function, significant advancements in treating these disorders are likely in the near future.

See also: Alzheimer's Disease: An Overview; Excitotoxicity in Neurodegenerative Disease; Long-Term Depression (LTD): Metabotropic Glutamate Receptor (mGluR) and NMDAR-Dependent Forms; Long-Term Potentiation (LTP): NMDA Receptor Role; NMDA Receptors and Development; NMDA Receptors, Cell Biology and Trafficking; NMDA Receptor Function and Physiological Modulation.

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