

# The function of the nmda receptor in hypoxic-ischemic encephalopathy

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## Introduction

The clinical definition of hypoxic-ischemic encephalopathy (HIE) is “ asphyxia of the umbilical blood supply to the human fetus occurring at 36 gestational weeks or later” ( [Millar et al., 2017](#) ). This is one of the most common causes of long-term neuronal impairment in children ( [Perlman, 1997](#), [2006](#); [Maxwell et al., 2020](#) ). Studies have shown that the incidence rate of HIE for full-term newborns with more than 36 weeks gestational age is 3/1, 000 ( [Knox et al., 2013](#); [Hagberg et al., 2015](#) ), and this is approximately 7/1, 000 for premature fetus within the gestational age of 33–35 weeks ( [Chalak et al., 2012](#) ). When the gestational age is less than 32 weeks, the rate significantly increases ( [Oskoui et al., 2013](#) ). In 2013, Oskoui et al. reported an incident rate of 62/1, 000 for 28–31 weeks fetuses and more than 146/1, 000 for less than 28 week fetuses ( [Oskoui et al., 2013](#) ).

Perinatal hypoxic-ischemic injury is characterized by high incidence and high mortality. It can cause permanent injury to the newborn and even endanger life. The newborns who survive usually suffer from various neurological disabilities, including developmental delay, cerebral palsy, epilepsy, visual impairment, and learning disabilities ( [Li et al., 2017](#); [Koehler et al., 2018](#) ). In developed countries, the incidence of hypoxic-ischemic brain damage per thousand neonates is approximately 1. 5 cases ( [Glass, 2018](#) ), while in developing countries, the incidence increases to 26 cases per thousand neonates ( [Li et al., 2017](#) ).

## **Pathological Process of Neonatal Hypoxic-Ischemic Encephalopathy**

The pathological process of neonatal HIE includes energy failure, oxidative stress, inflammation, and excitotoxicity. Together, these mechanisms lead to neuronal apoptosis, swelling, and necrosis. Under normal physiological conditions, the human brain has a high demand for oxygen and glucose, which are used to produce adenosine triphosphate (ATP) ( [Rocha-Ferreira and Hristova, 2016](#) ). In early HIE, due to the reduced supply of oxygen and blood flow, brain tissue turns to depend on anaerobic respiration for ATP, which will result in the depletion of ATP and decreased level of oxidative phosphorylation, followed by a series of abnormal cellular activities, such as severe metabolic acidosis induced by lactic acid accumulation. This was primary energy failure that occurred within 6 h after HIE ( [Juil and Ferriero, 2014](#) ). The destruction of cell homeostasis can lead to the imbalance of  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ , and water, as well as excitatory neurotransmitter release, resulting in “ excitatory oxidative cascade reaction” ( [Juil and Ferriero, 2014](#) ). Then secondary energy failure occurs after 6 h, resulting in mitochondrial dysfunction and failure of energy metabolism in mitochondria. This would continue to cause excitotoxicity, oxidative stress, and inflammation and aggravate the brain tissue damage ( [Yang and Lai, 2011](#) ; [Rocha-Ferreira and Hristova, 2015](#) ). These serious reactions promote the initial inflammatory reaction ( [Juil and Ferriero, 2014](#) ) and further cause secondary neuronal damage, which may last for several days, followed by the anti-inflammatory stage and repair stage ( [Juil and Ferriero, 2014](#) ; [Rocha-Ferreira and Hristova, 2015](#) ). Furthermore, studies have shown the activation of glia

cells, including the microglia, astrocytes, and oligodendrocytes in neonatal hypoxic-ischemic brain damage, activates immune response and results in the release of a large number of proinflammatory cytokines that promote neuronal apoptosis ( [Li et al., 2017](#) ; [Mamun et al., 2020](#) ).

There are some differences between neonatal and adult hypoxic ischemia. For example, in early development, the N-methyl -D -aspartate (NMDA) receptor-mediated selective vulnerability increased ( [Huang and Castillo, 2008](#) ). Compared with adults, the developing brain is high in plasticity and also more susceptible to external stimuli ( [Rocha-Ferreira and Hristova, 2016](#) ). For example, it is shown that HIP3 (suffered to HI injury at postnatal day 3) rat tolerates better than HIP11 (suffered to HI injury at postnatal day 11) rat because of its more resilient metabolism ( [Odorczyk et al., 2020](#) ), but the sustained changes of brain metabolism may in turn influence the long-term cognitive development ( [Azevedo et al., 2020](#) ). Furthermore, although the immature brain can exhibit a certain resistance when it is subjected to hypoxia alone ( [Johnston et al., 2001](#) ), the coexistence of hypoxia and ischemia could reduce the resistance of neonatal brain, exaggerate neuronal excitability, and thereby cause neurons to more likely be damaged, and the injury would develop for several days ( [Johnston et al., 2001](#) ). In addition, the immature brain can endure long-term energy consumption due to its low energy demand. However, when the exhaustion of energy reaches a threshold, this would eventually activate the excitatory pathways and aggravate the damage ( [Rocha-Ferreira and Hristova, 2016](#) ). Moreover, it is recently reported that HIE could also impact brain development by interfering with the maturation of several types of cells in the central

nervous system. For example, the maturation of oligodendrocytes is impaired after HIE and therefore causes abnormal myelination ( [Ziemka-Nalecz et al., 2018](#) ; [Baldassarro et al., 2020](#) ; [Janowska et al., 2020](#) ).

Another study found that HIE impairs GABAergic development in hippocampus which might be the cause of HIE-induced long-term memory deficiency ( [Chavez-Valdez et al., 2020](#) ).

## **The NMDA Receptor Is Involved in Neonatal Hypoxic-Ischemic Encephalopathy**

Glutamate mediates most of the excitatory transmissions in the central nervous system. There are three types of ionergic glutamate receptors in the mammalian brain: NMDA receptor, AMPA receptor, and KA receptor ( [Yang and Lai, 2011](#) ). The NMDA receptor has high affinity for glutamate ( [Rosenberg and Aizenman, 1989](#) ; [Rosenberg et al., 1992](#) ; [Káradóttir et al., 2005](#) ). Therefore, it plays an important role in glutamate-mediated excitotoxicity ( [Rosenberg and Aizenman, 1989](#) ; [Rosenberg et al., 1992](#) ; [Lynch and Guttman, 2002](#) ; [Káradóttir et al., 2005](#) ; [Makarewicz et al., 2014](#) ) and is also involved in many physiological processes ( [Forrest et al., 1994](#) ).

The physiological activity of the NMDA receptor is essential for normal neurological function, including synaptic plasticity, cognition, learning, and memory formation. However, the excessive release of glutamate under pathological conditions leads to the over-activation of NMDA receptors, resulting in excessive Ca<sup>2+</sup> influx that activates downstream death signaling pathways and finally leads to cell necrosis or apoptosis, which is known as excitotoxicity ( [Szydłowska and Tymianski, 2010](#) ; [Lai et al., 2011](#) ; [Zhou et al., 2013](#) ; [Wu et al., 2017](#) ; [Wu and Tymianski, 2018](#) ). NMDA receptors exist

in neurons and glial cells of newborns ( [Jantzie et al., 2015](#) ) and are composed of four different subunits, including the structural subunit GluN1 and the regulatory subunits GluN2 and GluN3 ( [Traynelis et al., 2010](#) ; [Paoletti et al., 2013](#) ). GluN1 knockout in mice is lethal in the perinatal period, indicating its important role in development and survival ( [Zhou et al., 2013](#) ). GluN2 subunits are regulatory subunits, which determine the biophysical and pharmacological properties of different NMDA receptor subtypes and affect the assembly, downstream signaling, transport, and synaptic targeting of NMDA receptors ( [Lau and Zukin, 2007](#) ). GluN2 subunits have four different types, namely, GluN2A, GluN2B, GluN2C, and GluN2D. Among these, GluN2A and GluN2B are the major subunits expressed in frontal cortex and hippocampus ( [Monyer et al., 1994](#) ). At the early stage of development, the GluN2B-containing NMDA receptor is dominant, and the expression of the GluN2A-containing NMDA receptor gradually increases in the later stage of development and eventually outnumbers the GluN2B-containing NMDA receptor ( [Knox et al., 2013](#) ). Studies have shown that neonatal hypoxic-ischemic injury is correlated to NMDA receptor-mediated excitotoxicity ( [Johnston et al., 2002](#) ; [Wu et al., 2017](#) ). Furthermore, it has also been proven that after 6 h of hypoxia ischemia, the expression of GluN2A significantly decreases, while the expression of GluN2B exhibits an opposite trend, which reaches a maximum at 24 h after hypoxic ischemia ( [Lai et al., 2016](#) ). This suggests that GluN2A and GluN2B might play different roles in neonatal HIE.

## **The Role of the GluN2B-Containing NMDA Receptor in Hypoxic Ischemic Injury**

Membrane-associated guanylate kinase (MAGUK) is a neuronal scaffold protein that interacts with GluN2A and GluN2B ( [Niethammer et al., 1996](#) ). The two MAGUK family members, postsynaptic density protein 95 (PSD95) and synapse-associated protein 102 (SAP102), were found to interact with GluN2A and GluN2B in adult brains ( [Lim et al., 2002](#) ). In neonatal neurons, the GluN2B/SAP102 complex is dominant, while the GluN2A/PSD95 complex gradually increases during development ( [van Zundert et al., 2004](#) ). In the early stage after HIE, the interaction between GluN2B and MAGUK decreases ( [Shao et al., 2017](#) ; [Lu et al., 2018](#) ), while PSD95 subsequently increases its binding with GluN2B ( [Shao et al., 2017](#) ).

Neonatal hypoxia ischemia can rapidly activate the phosphorylation network of GluN2B and regulate the function of the NMDA receptor by recruiting new proteins, including Src family kinase (SFK), protein kinase C (PKC), calmodulin kinase (CaMKII), and other kinases, to the postsynaptic dense region (PSD) ( [Shao et al., 2017](#) ). SFK plays the role of the molecular center in NMDA receptors coupled signaling cascade ( [Jiang et al., 2008](#) ). After neonatal hypoxic-ischemic injury, SFK is activated in the PSD area ( [Jiang et al., 2011](#) ) and interacts with the GluN2B subunits ( [Knox et al., 2013](#) ). Fyn as a member of SFK mainly mediates tyrosine phosphorylation at three sites of GluN2B, including tyrosine (Y) 1472, Y1336, and Y1252 ( [Nakazawa et al., 2001](#) ). It has been shown that after neonatal HIE, the phosphorylation of Y1472 would increase ( [Knox et al., 2014](#) ). Furthermore, the overexpression of Fyn enhances the phosphorylation of GluN2B in neonatal HIE ( [Jiang et al.,](#)

[2008](#)) and exaggerates the neuronal damage, suggesting the pro-death role of SFK in GluN2B-mediated neuronal death. It has also been reported that in early stage of HIE, the phosphorylation of DAPK1 and the P85 subunit of PI3K ([Lu et al., 2018](#)) increases. These kinases are known to phosphorylate GluN2B and amplify its downstream pro-death signals ([Takagi et al., 2003](#); [Tu et al., 2010](#)). Hence, they might also play similar roles in HIE. Although most researches have indicated the pro-death role of GluN2B in HIE, there is also evidence that GluN2B could protect neurons against apoptosis during development ([Martel et al., 2009](#); [Lai et al., 2016](#)). Since the GluN2B-containing NMDA receptor is the dominant subtype in early development, it remains to be determined whether GluN2B plays dual roles in HIE.

### **The Role of the GluN2A-Containing NMDA Receptor in Hypoxic Ischemic Injury**

The expression of GluN2A in neonatal brain is relatively low in neonatal brains, and it was found that the expression of GluN2A further decreases after neonatal HIE ([Lai et al., 2016](#)). It has been suggested that excessive GluN2A phosphorylation in neonates increases the NMDA receptor-mediated excitotoxicity and affects normal brain function ([Gurd et al., 2002](#)).

Therefore, the downregulation of GluN2A after 6 h of hypoxia ischemia injury might play a protective role ([Lai et al., 2016](#)). As mentioned above, after HIE, the SFK is activated and recruited into PSD ([Shao et al., 2017](#)). In addition to binding with GluN2B, they also interact with GluN2A ([Gurd et al., 2002](#); [Jiang et al., 2011](#)). However, although tyrosine phosphorylation of GluN2A was detected in adult rats ([Hardingham, 2009](#)), no change was detected in neonatal rats ([Takagi et al., 2002](#)). Another possible



explanation is that HIE inhibits the developmental switch of subtypes of the NMDA receptor from the GluN2B dominant to GluN2A dominant, and this might cause long-term cognitive impairment. Overall, despite the extensive studies of GluN2A in adult hypoxic ischemia, its role in neonatal HIE is not clear at present and requires further investigation.

### **The NMDA Receptor Subtype Hypothesis and Neonatal Hypoxic-Ischemic Encephalopathy**

Activation of NMDA receptor can induce neuronal survival or death during central hypoxia ischemia injury, and there are different hypotheses about the mechanism of this dual function of the NMDA receptor. The most famous hypotheses include location hypothesis and subtype hypothesis ( [Wu and Tymianski, 2018](#) ).

The location hypothesis suggests that the synaptic NMDA receptors are coupled to pro-survival signaling pathways, while the extrasynaptic NMDA receptors triggers neuronal death ( [Wu and Tymianski, 2018](#) ). For example, during ischemia, synaptic NMDA receptors activate the phosphoinositide 3 kinase (PI3K)-protein kinase B (PKB, also known as Akt) pathway and extracellular signal-regulated kinase (ERK)-cAMP response element-binding protein(CREB) pathway ( [Hetman and Kharebava, 2006](#) ; [Zhang et al., 2007](#) ; [Hardingham, 2009](#) ; [Zhou et al., 2013](#) ) and exerts protective function. When synaptic NMDA receptor is opened, PI3K is phosphorylated and activated by calmodulin ( [Joyal et al., 1997](#) ) and further phosphorylates Akt ( [Impey et al., 2002](#) ), followed by a series of downstream survival cascades. In addition, synaptic NMDA receptors can also induce survival gene expression through activating Ras-ERK pathway and phosphorylating CREB ( [Wu et al., 2001](#) ;

[Hardingham et al., 2002](#) ; [Impey et al., 2002](#) ; [Hardingham, 2009](#) ). In contrast to the synaptic NMDA receptor's role in protection, the extrasynaptic NMDA receptor is coupled to the death signaling pathway. The activation of extrasynaptic NMDA receptors deactivates the CREB pathway ( [Hardingham et al., 2002](#) ; [Vanhoutte and Bading, 2003](#) ; [Lai et al., 2011](#) ), and at the same time, it also phosphorylates ERK pathway to prevent CREB activation, promote the expression of death-promoting genes, and cause neuronal death ( [Vanhoutte and Bading, 2003](#) ; [Hardingham, 2009](#) ).

Compared to adult neurons, a mature spine structure is rare in neonate brain. Therefore, it remains unclear whether the location hypothesis of NMDA receptor also stands in HIE. Another possibility is that binding with different signaling cascades that are designated to be synaptic and extrasynaptic in mature neuron determines the role of GluN2A and GluN2B in HIE.

The subtype hypothesis suggests that different NMDA receptor subtypes mediate different downstream signaling molecules and play different roles in ischemia ( [Lai et al., 2011](#) ; [Wu et al., 2017](#) ). In adult brains, the GluN2B-containing NMDA receptor is enriched outside the synapses and coupled to pro-death signaling cascade, while the GluN2A-containing NMDA receptor is mainly expressed in the synapse and mediates neuroprotection and neuronal survival ( [Liu et al., 2007](#) ; [Chen et al., 2008](#) ). The roles of different NMDA receptor subtypes in hypoxia ischemia have been extensively studied, but a consensus is still not reached. Studies have shown that the activation of GluN2B-containing NMDA receptors is more lethal than GluN2A-containing NMDA receptors ( [Liu et al., 2007](#) ; [Choo et al., 2012](#) ; [Zhou et al., 2013](#) ; [Sun et al., 2015](#) ). This suggests that GluN2B is the main hub of NMDA receptor-

mediated excitotoxicity and plays a leading role in inducing cell death ( [Wu et al., 2017](#) ). However, some other researches show an opposite role of the GluN2B-containing NMDA receptor ( [Soriano et al., 2008](#) ; [Martel et al., 2009](#) ).

Researches on the roles of GluN2B in neonatal HIE are relatively abundant than GluN2A, which is perhaps due to its high expression. The existing studies indicated that GluN2B might have both pro-death and protective roles in HIE. Although the activation of the pro-death signaling network coupled to GluN2B is activated early after HIE ( [Jiang et al., 2008](#) ; [Knox et al., 2014](#) ; [Lu et al., 2018](#) ), it has been proven that the GluN2B-containing NMDA receptors may also promote neurogenesis in the subventricular zone ( [Lai et al., 2016](#) ). Compared to GluN2B, the role of GluN2A is even more unclear. The expression of GluN2A is extremely low in early development and is further decreased after HIE ( [Lai et al., 2016](#) ), which makes it difficult to contribute much in mediating protection in neonate brain. However, because the developmental switch of GluN2A and GluN2B is required for the normal cognition, the lasting low level of GluN2A may interfere with the normal development of numerous neuronal functions.

Overall, since the expression pattern of GluN2A and GluN2B of newborn is quite different from that of adult, it is possible that their role in neonatal HIE may be different from adults.

## **NMDA Receptors Participate in Glia-Mediated Neuronal Damage and Protection**

Under normal physiological conditions, microglia in neonatal brain are more active than in adults ( [Li et al., 2017](#) ), these participate in synaptic pruning and neurogenesis ( [Matcovitch-Natan et al., 2016](#) ). The activation of microglia can be detected after HIE ( [Hagberg et al., 2015](#) ; [Zhao et al., 2016](#) ), along with increase of glutamate, reactive oxygen species (ROS), and nitric oxide (NO), which cause oxidative damage and promote secondary energy failure ( [Jellema et al., 2013](#) ; [Kaur et al., 2013](#) ). Astrocytes play an important role in maintaining the integrity of the blood-brain barrier and are responsible for glutamate transport ( [Anderson and Swanson, 2000](#) ). They regulate the homeostasis of extracellular ions, such as sodium and calcium ions ( [Lian and Stringer, 2004](#) ; [Li et al., 2017](#) ). In addition, activated astrocytes secrete various chemokines to attract immune cells to migrate to the injured area and further aggravate hypoxic-ischemic brain damage ( [Miller et al., 2005](#) ; [Koh et al., 2015](#) ; [Zhao et al., 2016](#) ). In adult ischemic brain, astrocytes play roles in both pro-inflammation and anti-inflammation ( [Dong and Benveniste, 2001](#) ). However, the function of astrocytes in neonatal HIE remains unclear. It has been speculated that in neonatal HIE, astrocytes may function to attenuate inflammation ( [Li et al., 2017](#) ). The activation of glutamate receptors in oligodendrocytes leads to massive calcium influx and accumulation in mitochondria, contributing to the production of oxygen free radicals and caspase family-mediated cell death ( [Sánchez-Gómez et al., 2003](#) ; [Matute et al., 2006](#) ). There is evidence that oligodendrocytes and its precursor cells express NMDA receptors that comprise GluN1 and GluN2A, GluN2B, GluN2C, or GluN3A, in which the most

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abundant were GluN2C- and GluN3A-containing NMDA receptors ( [Káradóttir et al., 2005](#) ; [Koodziejczyk et al., 2009](#) ). It was also shown that the NMDA receptor participates in the myelination of oligodendrocytes in neonatal rats ( [Káradóttir et al., 2005](#) ), and during ischemia, the activation of NMDA receptors results in the Ca<sup>2+</sup>-dependent detachment and disintegration of oligodendroglial processes ( [Káradóttir et al., 2005](#) ; [Salter and Fern, 2005](#) ), which might contribute to developmental delay caused by HIE.

## **Treatment of Neonatal Hypoxic-Ischemic Encephalopathy**

At present, there are few ways to effectively treat neonatal hypoxic-ischemic injury. Among these, hypothermia is the most widely used ( [Wassink et al., 2019](#) ). Hypothermia can intervene some critical steps in the excitatory oxidative cascade. It can reduce energy failure and protect the blood-brain barrier and thereby reduce the glutamate release and nitric oxide production and alleviate neuronal death ( [Thoresen et al., 1995](#) ; [Kim et al., 2011](#) ; [Wassink et al., 2014](#) ; [Sun et al., 2019](#) ). And it is recently reported that HIE can also upregulate the expression and releasing of erythropoietin (EPO) in astrocyte to inhibit neuronal apoptosis ( [Toriuchi et al., 2020](#) ). In addition, hypothermia can also improve the survival of hypoxic-ischemic injury and benefit the development of the nervous system in moderate and severe HIE ( [Tagin et al., 2012](#) ). In the clinic, hypothermia is the standard treatment for hypoxic ischemic injury in neonates. After the birth of the child, the body temperature is reduced to 33. 5°C immediately for 72 h. However, excessively low temperatures or long durations may lead to more severe damage ( [Martinello et al., 2017](#) ). Although hypothermia can provide some protection against hypoxic ischemic injury, improve neurocognition, and

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reduce mortality ( [Jacobs et al., 2011](#) ; [Tagin et al., 2012](#) ), statistics show that merely one sixth of the patients benefit from this treatment ( [Dixon et al., 2015](#) ). Thus, in order to provide a complete neuroprotective effect, other adjuvant therapies are required ( [Adstamongkonkul and Hess, 2017](#) ).

Drugs such as melatonin, edaravone, erythropoietin (EPO), and growth factor have also been used for the treatment of hypoxic ischemic injury ( [Hua et al., 2017](#) ; [Zhou et al., 2020](#) ). Melatonin has antioxidant, anti-inflammatory, and anti-apoptotic effects ( [Alonso-Alconada et al., 2013](#) ). In animal models, melatonin combined with hypothermia therapy has protective effect, which shows a good prospect as an adjuvant therapy ( [Merchant et al., 2013](#) ; [Shea and Palanisamy, 2015](#) ; [Cardinali, 2019](#) ). However, further research is needed on the dosage and dosing time window ( [Dixon et al., 2015](#) ).

Edaravone is an antioxidant that can remove hydroxyl radicals, peroxy radicals, and superoxide free radicals. It can reduce blood-brain barrier dysfunction and reduce infarct size ( [Lapchak, 2010](#) ). A clinical study revealed that edaravone can improve memory and learning ability after several days of hypoxic-ischemic injury ( [Lee et al., 2007](#) ). EPO can resist cell apoptosis, reduce excitotoxicity, and promote the repair after injury by regulating neuronal differentiation. In addition, EPO can also promote post-damage repair by regulating the differentiation of neurons ( [Lee et al., 2007](#) ; [Zhu et al., 2009](#) ; [Wu et al., 2012](#) ). However, although clinical trial studies have shown that EPO combined with hypothermia therapy is safe and effective ( [Hua et al., 2017](#) ; [Nonomura et al., 2019](#) ), a recent study revealed that the therapeutic function of EPO may overlap with hypothermia, since

these two treatments share intracellular signaling cascades ( [Wassink et al., 2020](#) ).

Since NMDA receptor-mediated excitotoxicity is the main cause of HIE pathological damage, inhibiting NMDA receptors to reduce excitotoxicity has also been considered a potential treatment for HIE. At present, studies have explored the therapeutic effects of magnesium, noble gas xenon, and a variety of NMDA receptor antagonists in HIE.

Magnesium sulfate can exert neuroprotective effects by inhibiting the activation of excitatory neurotransmitters (such as glutamate) of NMDA receptors, but the effects of magnesium on perinatal hypoxic-ischemic injury are not very uniform. Prenatal administration of magnesium sulfate has been shown to have neuroprotective effects on premature newborns ( [Doyle et al., 2007](#) ; [Juul and Ferriero, 2014](#) ; [Cho et al., 2015](#) ; [Solevåg et al., 2019](#) ).

However, in the hypoxic-ischemic piglet and neonate rat model, magnesium sulfate failed to effectively reduce severe tissue damage ( [Penrice et al., 1997](#) ; [Zhu et al., 2004](#) ). In addition, the use of magnesium sulfate did not improve the neuron loss in the fetal sheep model with umbilical cord occlusion ( [Groenendaal et al., 2002](#) ). Although the combined treatment of hypothermia and MgSO<sub>4</sub> has a certain effect in reducing the risk of death and improving short-term adverse consequences, it appears to be only effective for some children ( [Galinsky et al., 2014](#) ). Hence, further evaluations are needed to determine whether this is effective for the long-term survival and neurodevelopment of children ( [Rahman et al., 2015](#) ; [Nonomura et al., 2019](#) ).

The noble gas xenon is shown to have neuroprotective effects in hypoxic-ischemic models through inhibiting NMDA receptors by competing for the binding of glycine in many *in vitro* and *in vivo* animal models ( [Hobbs et al., 2008](#) ; [Zhuang et al., 2010](#) ; [Faulkner et al., 2011](#) ; [Zhao et al., 2013](#) ; [Juul and Ferriero, 2014](#) ; [Alam et al., 2017](#) ; [Rüegger et al., 2018](#) ; [Koziakova et al., 2019](#) ). Xenon can also be used as an adjuvant with hypothermia therapy to treat neonatal HIE and has been proven to be effective in reducing brain injury and improving long-term recovery ( [Ma et al., 2005](#) ; [Chakkarapani et al., 2010](#) ; [Amer and Oorschot, 2018](#) ). However, at present, there is not enough evidence to support xenon as a conventional clinical adjuvant neuroprotective agent ( [Rüegger et al., 2017](#) ; [Amer and Oorschot, 2018](#) ). Hence, further studies are required to optimize its application for human neonatal hypoxia ischemia.

Recent studies have shown that the non-competitive NMDA receptor antagonist memantine has neuroprotective effects on hypoxic-ischemic brain injury *in vivo* ( [Landucci et al., 2018](#) ), but the damage or protection of memantine is correlated to the dose. Melissa [Trotman et al. \(2015\)](#) reported that low-dose memantine treatment can significantly reduce infarct volume and improve behavioral prognosis, while higher doses of memantine can significantly aggravate injury. The study conducted by [Solevåg et al. \(2019\)](#) revealed that memantine combined with low temperature can produce greater neuroprotective effects ( [Liu et al., 2020](#) ). There is still controversy on the effect of another non-competitive antagonist, MK801. Most studies have considered that in neonatal hypoxic-ischemic injury, MK801 alone or in combination with hypothermia can exert a neuroprotective effect, and its



effect is enhanced when applied together with hypothermia ( [McDonald et al., 1987](#) ; [Olney et al., 1989](#) ; [Ikonomidou et al., 1999](#) ; [Alkan et al., 2001](#) ; [Gerriets et al., 2003](#) ). However, another study revealed that although MK801 can reduce necrotic cell death, it can activate caspase-3 in cortical GABAergic interneurons, thereby aggravating the apoptosis ( [Desfeux et al., 2010](#) ). In addition, studies have shown that MK801 may cause other side effects, including inhibiting the spontaneous activity of mice, seizure, or increase mortality ( [Ikonomidou et al., 1999](#) ; [Liu et al., 2020](#) ), suggesting that MK801 may have a dual effect or that its effect is correlated to the type of neuron.

In addition, a variety of inhibitors of NMDA receptors have been shown to have protective effects in adult hypoxic ischemia. For example, ifenprodil and Tat-NR2B9c have neuroprotective effects in adult ischemic brain injury ( [Cui et al., 2007](#) ; [Chen et al., 2008](#) ; [Sun et al., 2008](#) ; [Amico-Ruvio et al., 2012](#) ; [Bhatt et al., 2013](#) ). Among these, ifenprodil can reduce ischemic cell death and enhance the neuroprotection induced by preconditioning ( [Chen et al., 2008](#) ), Tat-NR2B9c interferes with the interaction between NMDA receptors and PSD95 to protect neurons against excitotoxicity and reduce ischemic damage ( [Cui et al., 2007](#) ; [Bach et al., 2012](#) ; [Liu et al., 2020](#) ). However, it remains unclear whether these antagonists also play a protective role in neonatal ischemic brain injury, because the role of NMDA receptors and their intracellular signaling are different between neonates and adults.

Importantly, it was found that the application of NMDA receptor antagonist in neonates may cause abnormal neurodegeneration ( [Ikonomidou et al., 1999](#) ;

[Olney et al., 2002](#) ; [Jevtovic-Todorovic et al., 2003](#) ; [Nikizad et al., 2007](#) ), because the activation of the NMDA receptor is required for the normal development of the brain ( [Adesnik et al., 2008](#) ). Therefore, the safety and long-term effect of applying NMDA receptor antagonist for HIE treatment requires further evaluation. Furthermore, present protective agents in adult ischemia based on NMDA receptor, ifenprodil and Tat-NR2B9c, exert their protective function through inhibiting the GluN2B-containing NMDA receptor, which is the major type of NMDA receptor in neonate brains ( [Sheng et al., 1994](#) ; [Cull-Candy et al., 2001](#) ; [Liu et al., 2004](#) ). Therefore, normal function of NMDA receptors may be more substantially inhibited by these two agents in neonates than in adults. More comprehensive studies are needed to address this issue.

## Conclusion

Hypoxic ischemic injury in newborns is correlated to NMDA receptor-mediated excitotoxicity. After HIE, the over-activation of NMDA receptor leads to excessive  $\text{Ca}^{2+}$  influx and results in cell damage ( [Monyer et al., 1994](#) ). Compared with adults, neonatal brains are more susceptible to excitotoxic damage ( [Gurd et al., 2002](#) ), while the main mechanism may be the overexcitability of NMDA receptors ( [Monyer et al., 1994](#) ). The study of hypoxia ischemia in adult rodents revealed that GluN2A may mediate the survival effect through the ERK-CREB pathway ( [Terasaki et al., 2010](#) ), while GluN2B may play a lethal role through the GluN2B-PSD95-nNOS pathway ( [Wu et al., 2017](#) ). However, for neonates, since the expression of GluN2A and GluN2B is different from that of adults, the role of different NMDA receptors in mediating survival and lethal signaling pathways may be different. Recent <https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

studies have indicated that GluN2B-containing NMDA receptors may exaggerate damage but promote neurogenesis in the subventricular zone of neonatal rats ( [Nakazawa et al., 2001](#) ; [Jiang et al., 2008](#) ; [Lai et al., 2016](#) ).

Therefore, regarding the important role of NMDA receptor in neuronal development, as well as the difference between NMDA receptor subtype expression, trafficking, and function between neonate and adult brains, further studies are needed to fully investigate the specific mechanism of NMDA receptors in neonatal hypoxic-ischemic injury and develop new drugs, ways, and methods to treat neonatal hypoxic ischemia.

### **Author Contributions**

XMZ: conceptualization. XMZ and XTZ: writing—original draft preparation.

KZP, XTZ, and XMZ: writing—review and editing. XMZ: funding acquisition.

All authors contributed to the article and approved the submitted version.

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### **Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

Adesnik, H., Li, G., During, M. J., Pleasure, S. J., and Nicoll, R. A. (2008). NMDA receptors inhibit synapse unsilencing during brain development. *Proc. Natl. Acad. Sci. U. S. A.* 105, 5597–5602. doi: 10.1073/pnas.0800946105

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Adstamongkonkul, D., and Hess, D. C. (2017). Ischemic conditioning and neonatal hypoxic ischemic encephalopathy: a literature review. *Cond. Med.* 1, 9–16.

[Google Scholar](#)

Alam, A., Chun Suen, K., Hana, Z., Sanders, R. D., Maze, M., and Ma, D. (2017). Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon. *Neurotoxicol. Teratol.* 60, 102–116. doi: 10.1016/j.ntt.2017.01.001

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Alkan, T., Kahveci, N., Buyukuysal, L., Korfali, E., and Ozluk, K. (2001). Neuroprotective effects of MK 801 and hypothermia used alone and in combination in hypoxic-ischemic brain injury in neonatal rats. *Arch. Physiol. Biochem.* 109, 135–144. doi: 10.1076/apab.109.2.135.4271

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Alonso-Alconada, D., Álvarez, A., Arteaga, O., Martínez-Ibargüen, A., and Hilario, E. (2013). Neuroprotective effect of melatonin: a novel therapy

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

against perinatal hypoxia-ischemia. *Int. J. Mol. Sci.* 14, 9379–9395. doi: 10.3390/ijms14059379

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Amer, A. R., and Oorschot, D. E. (2018). Xenon combined with hypothermia in perinatal hypoxic-ischemic encephalopathy: a noble gas, a noble mission. *Pediatr. Neurol.* 84, 5–10. doi: 10.1016/j.pediatrneurol.2018.02.009

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Amico-Ruvio, S. A., Paganelli, M. A., Myers, J. M., and Popescu, G. K. (2012). Ifenprodil effects on GluN2B-containing glutamate receptors. *Mol. Pharmacol.* 82, 1074–1081. doi: 10.1124/mol.112.078998

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Anderson, C. M., and Swanson, R. A. (2000). Astrocyte glutamate transport: review of properties, regulation, and physiological functions. *Glia* 32, 1–14.

[Google Scholar](#)

Azevedo, P. N., Zanirati, G., Venturin, G. T., Schu, G. G., Durán-Carabali, L. E., Odorcyk, F. K., et al. (2020). Long-term changes in metabolic brain network drive memory impairments in rats following neonatal hypoxia-ischemia. *Neurobiol. Learn. Mem.* 171: 107207. doi: 10.1016/j.nlm.2020.107207

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Bach, A., Clausen, B. H., Møller, M., Vestergaard, B., Chi, C. N., Round, A., et al. (2012). A high-affinity, dimeric inhibitor of PSD-95 bivalently interacts with PDZ1-2 and protects against ischemic brain damage. *Proc. Natl. Acad. Sci. U. S. A.* 109, 3317–3322. doi: 10. 1073/pnas. 1113761109

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Baldassarro, V. A., Marchesini, A., Giardino, L., and Calzà, L. (2020). Differential effects of glucose deprivation on the survival of fetal versus adult neural stem cells-derived oligodendrocyte precursor cells. *Glia.* 68, 898–917. doi: 10. 1002/glia. 23750

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Bhatt, J. M., Prakash, A., Suryavanshi, P. S., and Dravid, S. M. (2013). Effect of ifenprodil on GluN1/GluN2B N-Methyl-D-aspartate receptor gating. *Mol. Pharmacol.* 83, 9–21. doi: 10. 1124/mol. 112. 080952

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cardinali, D. P. (2019). An assessment of melatonin's therapeutic value in the hypoxic-ischemic encephalopathy of the newborn. *Front. Synapt. Neurosci.* 11: 34. doi: 10. 3389/fnsyn. 2019. 00034

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Chakkarapani, E., Dingley, J., Liu, X., Hoque, N., Aquilina, K., Porter, H., et al. (2010). Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. *Ann. Neurol.* 68, 330–341. doi: 10. 1002/ana. 22016

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Chalak, L. F., Rollins, N., Morriss, M. C., Brion, L. P., Heyne, R., and Sánchez, P. J. (2012). Perinatal acidosis and hypoxic-ischemic encephalopathy in preterm infants of 33 to 35 weeks' gestation. *J. Pediatr.* 160, 388–394. doi: 10.1016/j.jpeds.2011.09.001

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Chavez-Valdez, R., Lechner, C., Emerson, P., Northington, F. J., and Martin, L. J. (2020). Accumulation of PSA-NCAM marks nascent neurodegeneration in the dorsal hippocampus after neonatal hypoxic-ischemic brain injury in mice. *J. Cereb. Blood Flow Metab.* 2020: 271678X20942707. doi: 10.1177/0271678X20942707

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Chen, M., Lu, T. J., Chen, X. J., Zhou, Y., Chen, Q., Feng, X. Y., et al. (2008). Differential roles of NMDA receptor subtypes in ischemic neuronal cell death and ischemic tolerance. *Stroke* 39, 3042–3048. doi: 10.1161/STROKEAHA.108.521898

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cho, G. J., Hong, H. R., Hong, S. C., Oh, M. J., and Kim, H. J. (2015). The neuroprotective effect of magnesium sulfate in preterm fetal mice. *J. Perinat. Med.* 43, 537–543. doi: 10.1515/jpm-2014-0176

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

Choo, A. M., Geddes-Klein, D. M., Hockenberry, A., Scarsella, D., Mesfin, M. N., Singh, P., et al. (2012). NR2A and NR2B subunits differentially mediate MAP kinase signaling and mitochondrial morphology following excitotoxic insult. *Neurochem. Int.* 60, 506–516. doi: 10. 1016/j. neuint. 2012. 02. 007

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cui, H., Hayashi, A., Sun, H. S., Belmares, M. P., Cobey, C., Phan, T., et al. (2007). PDZ protein interactions underlying NMDA receptor-mediated excitotoxicity and neuroprotection by PSD-95 inhibitors. *J. Neurosci.* 27, 9901–9915. doi: 10. 1523/JNEUROSCI. 1464-07. 2007

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Cull-Candy, S., Brickley, S., and Farrant, M. (2001). NMDA receptor subunits: Diversity, development and disease. *Curr. Opin. Neurobiol.* 11, 327–335. doi: 10. 1016/S0959-4388(00)00215-4

[CrossRef Full Text](#) | [Google Scholar](#)

Desfeux, A., El Ghazi, F., Jégou, S., Legros, H., Marret, S., Laudénbach, V., et al. (2010). Dual effect of glutamate on GABAergic interneuron survival during cerebral cortex development in mice neonates. *Cereb. Cortex* 20, 1092–1108. doi: 10. 1093/cercor/bhp181

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)



Dixon, B. J., Reis, C., Ho, W. M., Tang, J., and Zhang, J. H. (2015). Neuroprotective strategies after neonatal hypoxic ischemic encephalopathy. *Int. J. Mol. Sci.* 16, 22368–22401. doi: 10. 3390/ijms160922368

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Dong, Y., and Benveniste, E. N. (2001). Immune function of astrocytes. *Glia* 36, 180–190. doi: 10. 1002/glia. 1107

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Doyle, L. W., Crowther, C. A., Middleton, P., and Marret, S. (2007). Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst. Rev.* 21: CD004661. doi: 10. 1002/14651858

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Faulkner, S., Bainbridge, A., Kato, T., Chandrasekaran, M., Kapetanakis, A. B., Hristova, M., et al. (2011). Xenon augmented hypothermia reduces early lactate/N-acetylaspartate and cell death in perinatal asphyxia. *Ann. Neurol.* 70, 133–150. doi: 10. 1002/ana. 22387

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Forrest, D., Yuzaki, M., Soares, H. D., Ng, L., Luk, D. C., Sheng, M., et al. (1994). Targeted disruption of NMDA receptor 1 gene abolishes NMDA response and results in neonatal death. *Neuron* 13, 325–338. doi: 10. 1016/0896-6273(94)90350-6

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

[CrossRef Full Text](#) | [Google Scholar](#)

Galinsky, R., Bennet, L., Groenendaal, F., Lear, C. A., Tan, S., Van Bel, F., et al. (2014). Magnesium is not consistently neuroprotective for perinatal hypoxia-ischemia in term-equivalent models in preclinical studies: a systematic review. *Dev. Neurosci.* 36, 73–82. doi: 10.1159/000362206

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Gerriets, T., Stolz, E., Walberer, M., Kaps, M., Bachmann, G., and Fisher, M. (2003). Neuroprotective effects of MK-801 in different rat stroke models for permanent middle cerebral artery occlusion adverse: Effects of hypothalamic damage and strategies for its avoidance. *Stroke* 34, 2234–2239. doi: 10.1161/01.STR.0000087171.34637.A9

[CrossRef Full Text](#) | [Google Scholar](#)

Glass, H. C. (2018). Hypoxic-ischemic encephalopathy and other neonatal encephalopathies. *Contin. Lifelong Learn. Neurol.* 24, 57–71. doi: 10.1212/CON.0000000000000557

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Groenendaal, F., Rademaker, C. M., Toet, M. C., and de Vries, L. S. (2002). Effects of magnesium sulphate on amplitude-integrated continuous EEG in asphyxiated term neonates. *Acta Paediatr. Int. J. Paediatr.* 91, 1073–1077. doi: 10.1080/080352502760311575

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

Gurd, J. W., Bissoon, N., Beesley, P. W., Nakazawa, T., Yamamoto, T., and Vannucci, S. J. (2002). Differential effects of hypoxia-ischemia on subunit expression and tyrosine phosphorylation of the NMDA receptor in 7- and 21-day-old rats. *J. Neurochem.* 82, 848–856. doi: 10. 1046/j. 1471-4159. 2002. 01026. x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hagberg, H., Mallard, C., Ferriero, D. M., Vannucci, S. J., Levison, S. W., Vexler, Z. S., et al. (2015). The role of inflammation in perinatal brain injury. *Nat. Rev. Neurol.* 11, 192–208. doi: 10. 1038/nrneurol. 2015. 13

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hardingham, G. E. (2009). Coupling of the NMDA receptor to neuroprotective and neurodestructive events. *Biochem. Soc. Trans.* 37(Pt 6), 1147–1160. doi: 10. 1042/BST0371147

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hardingham, G. E., Fukunaga, Y., and Bading, H. (2002). Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nat. Neurosci.* 5, 405–441. doi: 10. 1038/nn835

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hetman, M., and Kharebava, G. (2006). Survival Signaling Pathways Activated by NMDA Receptors. *Curr. Top. Med. Chem.* 6, 787–799. doi: 10. 2174/156802606777057553

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hobbs, C., Thoresen, M., Tucker, A., Aquilina, K., Chakkarapani, E., and Dingley, J. (2008). Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. *Stroke* 39, 1307–1313. doi: 10.1161/STROKEAHA.107.499822

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Hua, C., Ju, W. N., Jin, H., Sun, X., and Zhao, G. (2017). Molecular chaperones and hypoxic-ischemic encephalopathy. *Neural Regen. Res.* 12, 153–160. doi: 10.4103/1673-5374.199008

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Huang, B. Y., and Castillo, M. (2008). Hypoxic-Ischemic brain injury: Imaging findings from birth to adulthood. *Radiographics* 28, 417–439. doi: 10.1148/rg.282075066

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Ikonomidou, C., Bosch, F., Miksa, M., Bittigau, P., Vöckler, J., Dikranian, K., et al. (1999). Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* 283, 70–74. doi: 10.1126/science.283.5398.70

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Impey, S., Fong, A. L., Wang, Y., Cardinaux, J. R., Fass, D. M., Obrietan, K., et al. (2002). Phosphorylation of CBP mediates transcriptional activation by neural activity and CaM kinase IV. *Neuron* 34, 235–244. doi: 10.1016/S0896-6273(02)00654-2

[CrossRef Full Text](#) | [Google Scholar](#)

Jacobs, S. E., Morley, C. J., Inder, T. E., Stewart, M. J., Smith, K. R., McNamara, P. J., et al. (2011). Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Arch. Pediatr. Adolesc. Med.* 165, 692–700. doi: 10.1001/archpediatrics.2011.43

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Janowska, J., Gargas, J., Ziemka-Nalecz, M., Zalewska, T., and Sypecka, J. (2020). Oligodendrocyte response to pathophysiological conditions triggered by episode of perinatal hypoxia-ischemia: role of IGF-1 secretion by glial cells. *Mol. Neurobiol.* 57, 4250–4268. doi: 10.1007/s12035-020-02015-z

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Jantzie, L. L., Talos, D. M., Jackson, M. C., Park, H. K., Graham, D. A., Lechpammer, M., et al. (2015). Developmental expression of N-methyl-D-aspartate (NMDA) receptor subunits in human white and gray matter: Potential mechanism of increased vulnerability in the immature brain. *Cereb. Cortex* 25, 4250–4268. doi: 10.1093/cercor/bht246

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

Jellema, R. K., Lima Passos, V., Zwanenburg, A., Ophelders, D. R. M. G., De Munter, S., Vanderlocht, J., et al. (2013). Cerebral inflammation and mobilization of the peripheral immune system following global hypoxia-ischemia in preterm sheep. *J. Neuroinflamm.* 10: 13. doi: 10.1186/1742-2094-10-13

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Jevtovic-Todorovic, V., Hartman, R. E., Izumi, Y., Benshoff, N. D., Dikranian, K., Zorumski, C. F., et al. (2003). Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J. Neurosci.* 23, 867–882. doi: 10.1523/jneurosci.23-03-00876.2003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Jiang, X., Knox, R., Pathipati, P., and Ferriero, D. (2011). Developmental localization of NMDA receptors, Src and MAP kinases in mouse brain. *Neurosci. Lett.* 503, 215–219. doi: 10.1016/j.neulet.2011.08.039

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Jiang, X., Mu, D., Biran, V., Faustino, J., Chang, S., Rincón, C. M., et al. (2008). Activated Src kinases interact with the N-methyl-D-aspartate receptor after neonatal brain ischemia. *Ann. Neurol.* 63, 632–641. doi: 10.1002/ana.21365

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Johnston, M. V., Nakajima, W., and Hagberg, H. (2002). Mechanisms of hypoxic neurodegeneration in the developing brain. *Neuroscientist* 8, 212–220. doi: 10.1177/1073858402008003007

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Johnston, M. V., Trescher, W. H., Ishida, A., Nakajima, W., and Zipursky, A. (2001). Neurobiology of hypoxic-ischemic injury in the developing brain. *Pediatr. Res.* 49, 735–741. doi: 10.1203/00006450-200106000-00003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Joyal, J. L., Burks, D. J., Pons, S., Matter, W. F., Vlahos, C. J., White, M. F., et al. (1997). Calmodulin activates phosphatidylinositol 3-kinase. *J. Biol. Chem.* 272, 28183–28186. doi: 10.1074/jbc.272.45.28183

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Juul, S. E., and Ferriero, D. M. (2014). Pharmacologic neuroprotective strategies in neonatal brain injury. *Clin. Perinatol.* 41, 119–131. doi: 10.1016/j.clp.2013.09.004

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Káradóttir, R., Cavelier, P., Bergersen, L. H., and Attwell, D. (2005). NMDA receptors are expressed in oligodendrocytes and activated in ischaemia. *Nature* 438, 1162–1166. doi: 10.1038/nature04302

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Kaur, C., Rathnasamy, G., and Ling, E. A. (2013). Roles of activated microglia in hypoxia induced neuroinflammation in the developing brain and the retina. *J. Neuroimmune Pharmacol.* 8, 66–78. doi: 10. 1007/s11481-012-9347-2

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Kim, J. Y., Kim, N., Yenari, M. A., and Chang, W. (2011). Mild hypothermia suppresses calcium-sensing receptor (CaSR) induction following forebrain ischemia while increasing GABA-B receptor 1 (GABA-B-R1) Expression. *Transl. Stroke Res.* 2, 195–201. doi: 10. 1007/s12975-011-0082-4

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Knox, R., Brennan-Minnella, A. M., Lu, F., Yang, D., Nakazawa, T., Yamamoto, T., et al. (2014). NR2B phosphorylation at tyrosine 1472 contributes to brain injury in a rodent model of neonatal hypoxia-ischemia. *Stroke* 45, 3040–3047. doi: 10. 1161/STROKEAHA. 114. 006170

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Knox, R., Zhao, C., Miguel-Perez, D., Wang, S., Yuan, J., Ferriero, D., et al. (2013). Enhanced NMDA receptor tyrosine phosphorylation and increased brain injury following neonatal hypoxia-ischemia in mice with neuronal Fyn overexpression. *Neurobiol. Dis.* 51, 113–119. doi: 10. 1016/j. nbd. 2012. 10. 024

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)



Koehler, R. C., Yang, Z. J., Lee, J. K., and Martin, L. J. (2018). Perinatal hypoxic-ischemic brain injury in large animal models: relevance to human neonatal encephalopathy. *J. Cereb. Blood Flow Metab.* 38, 2092–2111. doi: 10.1177/0271678X18797328

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Koh, H. S., Chang, C. Y., Jeon, S. B., Yoon, H. J., Ahn, Y. H., Kim, H. S., et al. (2015). The HIF-1/gial TIM-3 axis controls inflammation-associated brain damage under hypoxia. *Nat. Commun.* 6: 6340. doi: 10.1038/ncomms7340

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Koodziejczyk, K., Hamilton, N. B., Wade, A., Kradtir, R., and Attwell, D. (2009). The effect of N-acetyl-aspartyl-glutamate and N-acetyl-aspartate on white matter oligodendrocytes. *Brain* 132(Pt 6), 1496–1508. doi: 10.1093/brain/awp087

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Koziakova, M., Harris, K., Edge, C. J., Franks, N. P., White, I. L., and Dickinson, R. (2019). Noble gas neuroprotection: xenon and argon protect against hypoxic-ischaemic injury in rat hippocampus in vitro via distinct mechanisms. *Br. J. Anaesth.* 123, 601–609. doi: 10.1016/j.bja.2019.07.010

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lai, Q., Hu, P., Li, Q., Li, X., Yuan, R., Tang, X., et al. (2016). NMDA receptors promote neurogenesis in the neonatal rat subventricular zone following

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

hypoxic-ischemic injury. *Mol. Med. Rep.* 13, 206–212. doi: 10. 3892/mmr. 2015. 4501

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lai, T. W., Shyu, W. C., and Wang, Y. T. (2011). Stroke intervention pathways: NMDA receptors and beyond. *Trends Mol. Med.* 17, 266–275. doi: 10. 1016/j. molmed. 2010. 12. 008

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Landucci, E., Filippi, L., Gerace, E., Catarzi, S., Guerrini, R., and Pellegrini-Giampietro, D. E. (2018). Neuroprotective effects of topiramate and memantine in combination with hypothermia in hypoxic-ischemic brain injury in vitro and in vivo. *Neurosci. Lett.* 668, 103–107. doi: 10. 1016/j. neulet. 2018. 01. 023

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lapchak, P. A. (2010). A critical assessment of edaravone acute ischemic stroke efficacy trials: Is edaravone an effective neuroprotective therapy? *Expert Opin. Pharmacother.* 11, 1753–1763. doi: 10. 1517/14656566. 2010. 493558

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lau, C. G., and Zukin, R. S. (2007). NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nat. Rev. Neurosci.* 8, 413–426. doi: 10. 1038/nrn2153

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lee, M. Y., Kuan, Y. H., Chen, H. Y., Chen, T. Y., Chen, S. T., Huang, C. C., et al. (2007). Intravenous administration of melatonin reduces the intracerebral cellular inflammatory response following transient focal cerebral ischemia in rats. *J. Pineal Res.* 42, 297–309. doi: 10. 1111/j. 1600-079X. 2007. 00420. x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Li, B., Concepcion, K., Meng, X., and Zhang, L. (2017). Brain-immune interactions in perinatal hypoxic-ischemic brain injury. *Prog. Neurobiol.* 159, 50–68. doi: 10. 1016/j. pneurobio. 2017. 10. 006

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lian, X. Y., and Stringer, J. L. (2004). Astrocytes contribute to regulation of extracellular calcium and potassium in the rat cerebral cortex during spreading depression. *Brain Res.* 1012, 177–184. doi: 10. 1016/j. brainres. 2004. 04. 011

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lim, I. A., Hall, D. D., and Hell, J. W. (2002). Selectivity and promiscuity of the first and second PDZ domains of PSD-95 and synapse-associated protein 102. *J. Biol. Chem.* 277, 21697–21711. doi: 10. 1074/jbc. M112339200

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Liu, C. W., Liao, K. H., Tseng, H., Wu, C. M., Chen, H. Y., and Lai, T. W. (2020). Hypothermia but not NMDA receptor antagonism protects against stroke  
<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

induced by distal middle cerebral arterial occlusion in mice. *PLoS One* 15: e0229499. doi: 10.1371/journal.pone.0229499

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Liu, X. B., Murray, K. D., and Jones, E. G. (2004). Switching of NMDA receptor 2A and 2B subunits at thalamic and cortical synapses during early postnatal development. *J. Neurosci.* 24, 8885–8895. doi: 10.1523/JNEUROSCI.2476-04.2004

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Liu, Y., Wong, T. P., Aarts, M., Rooyakkers, A., Liu, L., Lai, T. W., et al. (2007). NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both in vitro and in vivo. *J. Neurosci.* 27, 2846–2857. doi: 10.1523/JNEUROSCI.0116-07.2007

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lu, F., Shao, G., Wang, Y., Guan, S., Burlingame, A. L., Liu, X., et al. (2018). Hypoxia-ischemia modifies postsynaptic GluN2B-containing NMDA receptor complexes in the neonatal mouse brain. *Exp. Neurol.* 299(Pt A), 65–74. doi: 10.1016/j.expneurol.2017.10.005

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Lynch, D. R., and Guttman, R. P. (2002). Excitotoxicity: perspectives based on N-methyl-D-aspartate receptor subtypes. *J. Pharmacol. Exp. Ther.* 300, 717–723. doi: 10.1124/jpet.300.3.717

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Ma, D., Hossain, M., Chow, A., Arshad, M., Battson, R. M., Sanders, R. D., et al. (2005). Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Ann. Neurol.* 58, 182–193. doi: 10. 1002/ana. 20547

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Makarewicz, D., Sulejczak, D., Duszczak, M., Małek, M., Słomka, M., and Lazarewicz, J. W. (2014). Delayed preconditioning with NMDA receptor antagonists in a rat model of perinatal asphyxia. *Folia Neuropathol.* 52, 270–284. doi: 10. 5114/fn. 2014. 45568

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Mamun, A. A., Yu, H., Sharmeen, R., McCullough, L. D., and Liu, F. (2020). IRF5 signaling in phagocytes is detrimental to neonatal hypoxic ischemic encephalopathy. *Transl. Stroke. Res.* doi: 10. 1007/s12975-020-00832-x [Epub ahead of print].

[CrossRef Full Text](#) | [PubMed Abstract](#) | [Google Scholar](#)

Martel, M. A., Wyllie, D. J. A., and Hardingham, G. E. (2009). In developing hippocampal neurons, NR2B-containing N-methyl-d-aspartate receptors (NMDARs) can mediate signaling to neuronal survival and synaptic potentiation, as well as neuronal death. *Neuroscience* 158, 334–343. doi: 10. 1016/j. neuroscience. 2008. 01. 080

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

Martinello, K., Hart, A. R., Yap, S., Mitra, S., and Robertson, N. J. (2017). Management and investigation of neonatal encephalopathy: 2017 update. *Arch. Dis. Child. Fetal Neonatal Edn.* 102, F346–F358. doi: 10.1136/archdischild-2015-309639

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Matcovitch-Natan, O., Winter, D. R., Giladi, A., Aguilar, S. V., Spinrad, A., Sarrazin, S., et al. (2016). Microglia development follows a stepwise program to regulate brain homeostasis. *Science* 353: aad8670. doi: 10.1126/science.aad8670

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Matute, C., Domercq, M., and Sánchez-Gómez, M. V. (2006). Glutamate-mediated glial injury: mechanisms and clinical importance. *Glia* 53, 212–224. doi: 10.1002/glia.20275

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Maxwell, J. R., Zimmerman, A. J., Pavlik, N., Newville, J. C., Carlin, K., Robinson, S., et al. (2020). Neonatal hypoxic-ischemic encephalopathy yields permanent deficits in learning acquisition: a preclinical touchscreen assessment. *Front. Pediatr.* 8: 289. doi: 10.3389/fped.2020.00289

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

McDonald, J. W., Silverstein, F. S., and Johnston, M. V. (1987). MK-801 protects the neonatal brain from hypoxic-ischemic damage. *Eur. J. Pharmacol.* 140, 359–361. doi: 10. 1016/0014-2999(87)90295-0

[CrossRef Full Text](#) | [Google Scholar](#)

Merchant, N. M., Azzopardi, D. V., Hawwa, A. F., Mcelnay, J. C., Middleton, B., Arendt, J., et al. (2013). Pharmacokinetics of melatonin in preterm infants. *Br. J. Clin. Pharmacol.* 76, 725–733. doi: 10. 1111/bcp. 12092

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Millar, L. J., Shi, L., Hoerder-Suabedissen, A., and Molnár, Z. (2017). Neonatal hypoxia ischaemia: mechanisms, models, and therapeutic challenges. *Front. Cell Neurosci.* 11: 78. doi: 10. 3389/fncel. 2017. 00078

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Miller, J. T., Bartley, J. H., Wimborne, H. J. C., Walker, A. L., Hess, D. C., Hill, W. D., et al. (2005). The neuroblast and angioblast chemotaxic factor SDF-1 (CXCL12) expression is briefly up regulated by reactive astrocytes in brain following neonatal hypoxic-ischemic injury. *BMC Neurosci.* 6: 63. doi: 10. 1186/1471-2202-6-63

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Monyer, H., Burnashev, N., Laurie, D. J., Sakmann, B., and Seeburg, P. H. (1994). Developmental and regional expression in the rat brain and

functional properties of four NMDA receptors. *Neuron* 12, 529–540. doi: 10.1016/0896-6273(94)90210-0

[CrossRef Full Text](#) | [Google Scholar](#)

Nakazawa, T., Komai, S., Tezuka, T., Hisatsune, C., Umemori, H., Semba, K., et al. (2001). Characterization of Fyn-mediated tyrosine phosphorylation sites on GluR $\epsilon$ 2 (NR2B) subunit of the N-methyl-D-aspartate receptor. *J. Biol. Chem.* 276, 693–699. doi: 10.1074/jbc.M008085200

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Niethammer, M., Kim, E., and Sheng, M. (1996). Interaction between the C terminus of NMDA receptor subunits and multiple members of the PSD-95 family of membrane-associated guanylate kinases. *J. Neurosci.* 16, 2157–2163. doi: 10.1523/jneurosci.16-07-02157.1996

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Nikizad, H., Yon, J. H., Carter, L. B., and Jevtovic-Todorovic, V. (2007). Early exposure to general anesthesia causes significant neuronal deletion in the developing rat brain. *Ann. N. Y. Acad. Sci.* 1122, 69–82. doi: 10.1196/annals.1403.005

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Nonomura, M., Harada, S., Asada, Y., Matsumura, H., Iwami, H., Tanaka, Y., et al. (2019). Combination therapy with erythropoietin, magnesium sulfate and hypothermia for hypoxic-ischemic encephalopathy: An open-label pilot

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>



study to assess the safety and feasibility 11 medical and health sciences  
1117 public health and health services. *BMC Pediatr.* 19: 13. doi: 10.  
1186/s12887-018-1389-z

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Odorcyk, F. K., Duran-Carabali, L. E., Rocha, D. S., Sanches, E. F., Martini, A.  
P., Venturin, G. T., et al. (2020). Differential glucose and beta-  
hydroxybutyrate metabolism confers an intrinsic neuroprotection to the  
immature brain in a rat model of neonatal hypoxia ischemia. *Exp. Neurol.*  
330: 113317. doi: 10.1016/j.expneurol.2020.113317

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Olney, J. W., Ikonomidou, C., Mosinger, J. L., and Friedrich, G. (1989). MK-801  
prevents hypobaric-ischemic neuronal degeneration in infant rat brain. *J.*  
*Neurosci.* 9, 1701–1704. doi: 10.1523/jneurosci.09-05-01701.1989

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Olney, J. W., Wozniak, D. F., Jevtovic-Todorovic, V., Farber, N. B., Bittigau, P.,  
and Ikonomidou, C. (2002). Drug-induced apoptotic neurodegeneration in the  
developing brain. *Brain Pathol.* 12, 488–498. doi: 10.1111/j.1750-3639.  
2002.tb00467.x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Oskoui, M., Coutinho, F., Dykeman, J., Jetté, N., and Pringsheim, T. (2013). An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. *Dev. Med. Child Neurol.* 55, 509–519. doi: 10. 1111/dmcn. 12080

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Paoletti, P., Bellone, C., and Zhou, Q. (2013). NMDA receptor subunit diversity: Impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci.* 14, 383–400. doi: 10. 1038/nrn3504

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Penrice, J., Amess, P. N., Punwani, S., Wylezinska, M., Tyszczuk, L., D'Souza, P., et al. (1997). Magnesium sulfate after transient hypoxia-ischemia fails to prevent delayed cerebral energy failure in the newborn piglet. *Pediatr. Res.* 41, 443–447. doi: 10. 1203/00006450-199703000-00024

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Perlman, J. M. (1997). Intrapartum hypoxic-ischemic cerebral injury and cerebral palsy: Medicolegal issues. *Pediatrics* 99, 851–859. doi: 10. 1542/peds. 99. 6. 851

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Perlman, J. M. (2006). Summary proceedings from the neurology group on hypoxic-ischemic encephalopathy. *Pediatrics* 117(3 Pt 2), S28–S33. doi: 10. 1542/peds. 2005-0620E

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

Rahman, S., Siham, A., Tuzun, H., Rahmani, A., Rahman, M., Rijims, M., et al. (2015). Multicenter randomized controlled trial of therapeutic hypothermia plus magnesium sulfate versus therapeutic hypothermia plus placebo in the management of term and near-term infants with hypoxic ischemic encephalopathy (The Mag Cool study): a pilot study. *J. Clin. Neonatol.* 4, 158-163. doi: 10. 4103/2249-4847. 159863

[CrossRef Full Text](#) | [Google Scholar](#)

Rocha-Ferreira, E., and Hristova, M. (2015). Antimicrobial peptides and complement in neonatal hypoxia-ischemia induced brain damage. *Front. Immunol.* 6: 56. doi: 10. 3389/fimmu. 2015. 00056

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Rocha-Ferreira, E., and Hristova, M. (2016). Plasticity in the neonatal brain following hypoxic-ischaemic injury. *Neural Plast.* 2016: 4901014. doi: 10. 1155/2016/4901014

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Rosenberg, P. A., and Aizenman, E. (1989). Hundred-fold increase in neuronal vulnerability to glutamate toxicity in astrocyte-poor cultures of rat cerebral cortex. *Neurosci. Lett.* 103, 162-168. doi: 10. 1016/0304-3940(89)90569-7

[CrossRef Full Text](#) | [Google Scholar](#)

Rosenberg, P. A., Amin, S., and Leitner, M. (1992). Glutamate uptake disguises neurotoxic potency of glutamate agonists in cerebral cortex in dissociated cell culture. *J. Neurosci.* 12, 56–61. doi: 10.1523/jneurosci.12-01-00056.1992

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Rüegger, C. M., Davis, P. G., and Cheong, J. L. (2017). Xenon as an adjuvant to therapeutic hypothermia in near term and term newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst. Rev.* 8: CD012753. doi: 10.1002/14651858

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Rüegger, C. M., Davis, P. G., and Cheong, J. L. (2018). Xenon as an adjuvant to therapeutic hypothermia in near-term and term newborns with hypoxic-ischaemic encephalopathy. *Cochrane Database Syst. Rev.* 8: CD012753.

[Google Scholar](#)

Salter, M. G., and Fern, R. (2005). NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. *Nature* 438, 1167–1171. doi: 10.1038/nature04301

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sánchez-Gómez, M. V., Alberdi, E., Ibarretxe, G., Torre, I., and Matute, C. (2003). Caspase-dependent and caspase-independent oligodendrocyte death

mediated by AMPA and kainate receptors. *J. Neurosci.* 23, 9519–9528. doi: 10.1523/jneurosci.23-29-09519.2003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Shao, G., Wang, Y., Guan, S., Burlingame, A. L., Lu, F., Knox, R., et al. (2017). Proteomic analysis of mouse cortex postsynaptic density following neonatal brain hypoxia-ischemia. *Dev. Neurosci.* 39, 66–81. doi: 10.1159/000456030

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Shea, K. L., and Palanisamy, A. (2015). What can you do to protect the newborn brain? *Curr. Opin. Anaesthesiol.* 28, 261–266. doi: 10.1097/ACO.000000000000184

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sheng, M., Cummings, J., Roldan, L. A., Jan, Y. N., and Jan, L. Y. (1994). Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. *Nature* 368, 144–147. doi: 10.1038/368144a0

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Solevåg, A. L., Schmölzer, G. M., and Cheung, P. Y. (2019). Novel interventions to reduce oxidative-stress related brain injury in neonatal asphyxia. *Free Radic. Biol. Med.* 142, 113–122. doi: 10.1016/j.freeradbiomed.2019.04.028

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Soriano, F. X., Martel, M. A., Papadia, S., Vaslin, A., Baxter, P., Rickman, C., et al. (2008). Specific targeting of pro-death NMDA receptor signals with differing reliance on the NR2B PDZ ligand. *J. Neurosci.* 28, 10696–10710. doi: 10.1523/JNEUROSCI.1207-08.2008

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sun, H. S., Doucette, T. A., Liu, Y., Fang, Y., Teves, L., Aarts, M., et al. (2008). Effectiveness of PSD95 inhibitors in permanent and transient focal ischemia in the rat. *Stroke* 39, 2544–2553. doi: 10.1161/STROKEAHA.107.506048

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sun, Y., Zhang, L., Chen, Y., Zhan, L., and Gao, Z. (2015). Therapeutic targets for cerebral ischemia based on the signaling pathways of the GluN2B C terminus. *Stroke* 46, 2347–2353. doi: 10.1161/STROKEAHA.115.009314

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Sun, Y. J., Zhang, Z. Y., Fan, B., and Li, G. Y. (2019). Neuroprotection by therapeutic hypothermia. *Front. Neurosci.* 13: 584. doi: 10.3389/fnins.2019.00586

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Szydlowska, K., and Tymianski, M. (2010). Calcium, ischemia and excitotoxicity. *Cell Calcium* 47, 122–129. doi: 10.1016/j.ceca.2010.01.003

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Tagin, M. A., Woolcott, C. G., Vincer, M. J., Whyte, R. K., and Stinson, D. A. (2012). Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch. Pediatr. Adolesc. Med.* 166, 558–566. doi: 10.1001/archpediatrics.2011.1772

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Takagi, N., Sasakawa, K., Besshoh, S., Miyake-Takagi, K., and Takeo, S. (2003). Transient ischemia enhances tyrosine phosphorylation and binding of the NMDA receptor to the Src homology 2 domain of phosphatidylinositol 3-kinase in the rat hippocampus. *J. Neurochem.* 84, 67–76. doi: 10.1046/j.1471-4159.2003.01500.x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Takagi, N., Shinno, K., Teves, L., Bissoon, N., Wallace, M. C., and Gurd, J. W. (2002). Transient ischemia differentially increases tyrosine phosphorylation of NMDA receptor subunits 2A and 2B. *J. Neurochem.* 69, 1060–1065. doi: 10.1046/j.1471-4159.1997.69031060.x

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Terasaki, Y., Sasaki, T., Yagita, Y., Okazaki, S., Sugiyama, Y., Oyama, N., et al. (2010). Activation of NR2A receptors induces ischemic tolerance through CREB signaling. *J. Cereb. Blood Flow Metab.* 30, 1441–1449. doi: 10.1038/jcbfm.2010.18

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Thoresen, M., Penrice, J., Lorek, A., Cady, E. B., Wylezinska, M., Kirkbride, V., et al. (1995). Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr. Res.* 37, 667–670. doi: 10. 1203/00006450-199505000-00019

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Toriuchi, K., Kakita, H., Tamura, T., Takeshita, S., Yamada, Y., and Aoyama, M. (2020). Prolonged astrocyte-derived erythropoietin expression attenuates neuronal damage under hypothermic conditions. *J. Neuroinflamm.* 17: 141. doi: 10. 1186/s12974-020-01831-3

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., et al. (2010). Glutamate receptor ion channels: Structure, regulation, and function. *Pharmacol. Rev.* 62, 405–496. doi: 10. 1124/pr. 109. 002451

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Trotman, M., Vermehren, P., Gibson, C. L., and Fern, R. (2015). The dichotomy of memantine treatment for ischemic stroke: dose-dependent protective and detrimental effects. *J. Cereb. Blood Flow Metab.* 35, 230–239. doi: 10. 1038/jcbfm. 2014. 188

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)



Tu, W., Xu, X., Peng, L., Zhong, X., Zhang, W., Soundarapandian, M. M., et al. (2010). DAPK1 interaction with NMDA receptor NR2B subunits mediates brain damage in stroke. *Cell* 140, 222–234. doi: 10.1016/j.cell.2009.12.055

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

van Zundert, B., Yoshii, A., and Constantine-Paton, M. (2004). Receptor compartmentalization and trafficking at glutamate synapses: a developmental proposal. *Trends Neurosci.* 27, 428–437. doi: 10.1016/j.tins.2004.05.010

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Vanhoutte, P., and Bading, H. (2003). Opposing roles of synaptic and extrasynaptic NMDA receptors in neuronal calcium signalling and BDNF gene regulation. *Curr. Opin. Neurobiol.* 13, 366–371. doi: 10.1016/S0959-4388(03)00073-4

[CrossRef Full Text](#) | [Google Scholar](#)

Wassink, G., Davidson, J. O., Dhillon, S. K., Zhou, K., Bennet, L., Thoresen, M., et al. (2019). Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. *Curr. Neurol. Neurosci. Rep.* 19: 2. doi: 10.1007/s11910-019-0916-0

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wassink, G., Davidson, J. O., Fraser, M., Yuill, C. A., Bennet, L., and Gunn, A. J. (2020). Non-additive effects of adjunct erythropoietin therapy with

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

therapeutic hypothermia after global cerebral ischaemia in near-term fetal sheep. *J. Physiol.* 598, 999–1015. doi: 10. 1113/JP279131

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wassink, G., Gunn, E. R., Drury, P. P., Bennet, L., and Gunn, A. J. (2014). The mechanisms and treatment of asphyxial encephalopathy. *Front. Neurosci.* 8: 40. doi: 10. 3389/fnins. 2014. 00040

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wu, G. Y., Deisseroth, K., and Tsien, R. W. (2001). Activity-dependent CREB phosphorylation: Convergence of a fast, sensitive calmodulin kinase pathway and a slow, less sensitive mitogen-activated protein kinase pathway. *Proc. Natl. Acad. Sci. U. S. A.* 98, 2808–2813. doi: 10. 1073/pnas. 051634198

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wu, Q. J., and Tymianski, M. (2018). Targeting nmda receptors in stroke: new hope in neuroprotection. *Mol. Brain.* 11: 15. doi: 10. 1186/s13041-018-0357-8

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wu, Y., Chen, C., Yang, Q., Jiao, M., and Qiu, S. (2017). Endocytosis of GluN2B-containing NMDA receptor mediates NMDA-induced excitotoxicity. *Mol. Pain* 13: 1744806917701921. doi: 10. 1177/1744806917701921

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Wu, Y. W., Bauer, L. A., Ballard, R. A., Ferriero, D. M., Glidden, D. V., Mayock, D. E., et al. (2012). Erythropoietin for neuroprotection in neonatal encephalopathy: Safety and pharmacokinetics. *Pediatrics* 130, 683–691. doi: 10.1542/peds.2012-0498

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Yang, S. N., and Lai, M. C. (2011). Perinatal hypoxic-ischemic encephalopathy. *J. Biomed. Biotechnol.* 2011: 609813. doi: 10.1155/2011/609813

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhang, S. J., Steijaert, M. N., Lau, D., Schütz, G., Delucinge-Vivier, C., Descombes, P., et al. (2007). Decoding NMDA receptor signaling: identification of genomic programs specifying neuronal survival and death. *Neuron* 53, 549–562. doi: 10.1016/j.neuron.2007.01.025

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhao, H., Mitchell, S., Ciechanowicz, S., Savage, S., Wang, T., and Ji, X. (2013). Argon combined with hypothermia protects against hypoxia-ischaemia-induced brain damage in rat neonates. *Br. J. Anaesth.* 125, 180–192. doi: 10.1093/bja/aes490

[CrossRef Full Text](#) | [Google Scholar](#)

Zhao, M., Zhu, P., Fujino, M., Zhuang, J., Guo, H., Sheikh, I., et al. (2016). Oxidative stress in hypoxic-ischemic encephalopathy: molecular mechanisms

<https://assignbuster.com/the-function-of-the-nmda-receptor-in-hypoxic-ischemic-encephalopathy/>

and therapeutic strategies. *Int. J. Mol. Sci.* 17: 2078. doi: 10.3390/ijms17122078

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhou, K. Q., Davidson, J. O., Bennet, L., and Gunn, A. J. (2020). Combination treatments with therapeutic hypothermia for hypoxic-ischemic neuroprotection. *Dev. Med. Child Neurol.* 62, 1131–1137. doi: 10.1111/dmcn. 14610

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhou, X., Ding, Q., Chen, Z., Yun, H., and Wang, H. (2013). Involvement of the GluN2A and GluN2B subunits in synaptic and extrasynaptic N-methyl-D-aspartate receptor function and neuronal excitotoxicity. *J. Biol. Chem.* 288, 24151–24159. doi: 10.1074/jbc. M113. 482000

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhu, C., Kang, W., Xu, F., Cheng, X., Zhang, Z., Jia, L., et al. (2009). Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. *Pediatrics* 124, e218–e226. doi: 10.1542/peds.2008-3553

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhu, H. D., Martin, R., Meloni, B., Oltvolgyi, C., Moore, S., Majda, B., et al. (2004). Magnesium sulfate fails to reduce infarct volume following transient

focal cerebral ischemia in rats. *Neurosci. Res.* 49, 347–353. doi: 10. 1016/j. neurores. 2004. 04. 001

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)

Zhuang, L., Yang, T., Vizcaychipi, M. P., Yu, B., and Ma, D. (2010). Argon provides neuroprotection against ischemia/hypoxia induced brain damage in rat neonates. *Intensive Care Med.* 7, 25640–25651. doi: 10. 1007/s00134-010-2001-7

[CrossRef Full Text](#) | [Google Scholar](#)

Ziemka-Nalecz, M., Janowska, J., Strojek, L., Jaworska, J., Zalewska, T., Frontczak-Baniewicz, M., et al. (2018). Impact of neonatal hypoxia-ischaemia on oligodendrocyte survival, maturation and myelinating potential. *J. Cell. Mol. Med.* 22, 207–222. doi: 10. 1111/jcmm. 13309

[PubMed Abstract](#) | [CrossRef Full Text](#) | [Google Scholar](#)