Review

Targeting N-methyl-D-aspartate Receptors in Neurodegenerative Diseases

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Review

Targeting N-methyl-D-aspartate Receptors in Neurodegenerative Diseases

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Abstract: N-methyl-D-aspartate receptors (NMDARs) are the main class of ionotropic receptor for the excitatory neurotransmitter glutamate. It plays a crucial role in the permeability of Ca^{2+} ions and excitatory neurotransmission in the brain. Being heteromeric receptors, they are composed of several subunits, including two obligatory GluN1 subunits (eight splice variants) and regulatory GluN2 (GluN2A~D) and/or GluN3 (GluN3A~B) subunits. Widely distributed in the brain, they regulate other neurotransmission systems and are therefore involved in essential functions such as synaptic transmission, learning and memory, plasticity, excitotoxicity. The present review will discuss the physiopathological impacts of NMDAR and particularly GluN2A and GluN2B subunits in cognitive processes and neurodegenerative diseases (Alzheimer's disease, Huntington's disease, Parkinson's disease). The pharmacology of different NMDAR antagonists and their potentialities will be presented. In particular, a focus will be given on fluoroethylnormemantine (FENM), an investigational drug with very promising developments as a tomography radiotracer for NMDARs, an anxiolytic in post-traumatic stress disorder and a neuroprotective agent in Alzheimer's disease.

Keywords: N-methyl-D-aspartate receptor; Alzheimer's disease; post-traumatic stress disorder; Fluoroethylnormemantine (FENM)

1. Introduction

Neurotransmission within the central nervous system (CNS) is essentially based on two main neuronal systems that coordinate their excitatory and inhibitory inputs to establish and maintain a constant excitation/inhibition ratio. Glutamate is the most important excitatory neurotransmitter from the CNS, with 50-70% utilization by synapses [1]. Glutamate binds to two types of receptors, namely metabotropic glutamate receptors (mGluRs) which belongs to the G protein-coupled receptor (RCPG) superfamily and ionotropic glutamate receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), N-methyl-D-aspartate receptor (NMDAR), and kainate receptor. These receptors are present in the entire CNS, with greater density at the cortical and hippocampal level [2,3] and are involved in different neurodevelopmental processes, cognitive functions, learning, memory and synaptic plasticity [4–6]. All these receptors are localized in the synaptic and/or extra-synaptic membranes [7], depending on the neuronal maturation stage and receptor function, and with complex inter-relations. The extra-synaptic NMDARs in immature hippocampal neurons represent 75% of NMDARs and are still expressed during adulthood, while, during development, there is an increase in synaptic NMDARs [8,9].

In the CNS, NMDARs are distributed ubiquitously and play a critical role in the synaptic plasticity and learning and memory processes. The glutamate binding leads to an increase in intracellular calcium (Ca^{2+}) inside the neurons which acts as a second messenger to modify synapse necessary for neurotransmission and brain plasticity [10]. Current flow through NMDAR channels is largely blocked by external Mg^{2+} ions at resting membrane potentials, but can be relieved by depolarization [11]. The receptors are modulated also by different molecules including the co-

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agonists glycine and D-serine, which bind to a specific site on NMDAR [12]. It is now accepted that the induction of long-term potentiation (LTP) and long-term depression (LTD), in the CAl layer of the hippocampus, is highly dependent on NMDAR activation, permeable to Ca^{2+} at the postsynaptic synapse [13,14]. NMDAR is a voltage-dependent channel and at resting potential, it is blocked by Mg^{2+}. Astrocytes reuptake about 90% of the glutamate released in the synaptic cleft, through sodium dependent glutamate transporters, named excitatory amino acid transporters (EAATs), and approximately 20% of the synaptic glutamate released fixed on the post-synaptic glutamate receptors, while the rest reached extra-synaptic receptors [15]. Through these transporters, glutamate is metabolized and recycled by glutamine synthetase, which generates glutamine, and redistributed to the pre-synapse to recycle as a neurotransmitter.

In Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), post-traumatic-stress-disorder (PTSD), epilepsy or schizophrenia, NMDARs pathological activation is a main mediator of neuronal injury or dysfunction [16–19]. In neurodegenerative conditions, an excess of glutamate release resulting from synaptic alterations massively increases intracellular Ca^{2+} influx. The normal blockade by Mg^{2+} of the ionophore is removed and abnormally enhanced NMDAR activity. Since the calcium permeability is relatively high, extra-synaptic NMDA receptors are preferentially targeted in these conditions and lead to neuronal excitotoxicity [20].

In the present review, we will describe why and how NMDARs are presently still considered as a potential target for therapeutical treatments, particularly in AD, HD, PD, or PTSD, discussing the therapeutic use of memantine and ketamine as treatments. Finally, we propose a novel drug, fluoroethylnormemantine (FENM) that shows several benefits over memantine in AD models and over ketamine in PTSD models. FENM particularly illustrated that NMDAR dysfunction could still represent an essential target for innovative drugs in neurodegenerative diseases.

2. Physiology of NMDA receptors

2.1. Structure, composition, localization

The NMDAR is a transmembrane protein supercomplex with four domains. The extracellular amino-terminal domain (ATD) the extracellular ligand binding domain (LBD), the transmembrane domain (TMD), and the intracellular carboxyl C-terminal domain (CTD) [21]. Structurally, functional NMDARs are heterotetramers (≈ 1.5 KDa) composed of two glycine or D-serine binding GluN1 subunits, two glutamate binding GluN2 subunits, e.g. A, B, C or D, and a glycine binding GluN3 subunit (Figure 1) [22,23]. The difference between each subunit, it's the length of the GluN CTD region [24]. Non-competitive binding sites are localized within the ion channel pore. First, Mg^{2+} exerts a voltage-dependent blockade of the ion flux, dependent on an asparagine residue in second transmembrane segment. Depolarization results in Mg^{2+} ion removal and influx of Ca^{2+}. Second, phencycline (PCP) and PCP-like drugs bind within the pore and exert an uncompetitive antagonism of NMDAR. The PCP site is most accessible when the receptor is in an activated state [25–27]. Other antagonists binding to this PCP site include derivatives such as thienylcyclidine or ketamine, by also chemically unrelated molecules like dizocilpine or memantine. Third, Zn^{2+} inhibits NMDARs current by a high affinity binding site in GluN2A [28], inducing a reduction of channel open probability. The NMDAR subunits are encoded by seven genes. The GluN1 subunit is encoded by a unique gene, GRIN1, but has eight distinct isoforms (a-h, with different splice variants of one single gene). The two GluN1 association with two out of four GRIN2 genes encodes GluN2 subunits are specific on spatiotemporal expression in the brain [21]. And the last is GluN3A/B is encoded by two GRIN3 genes. Compelling evidence indicates that diheteromers and triheteteromers coexist within a single cell or even at a single synapse, adding to the functional diversity of the postsynaptic response [29]. In the adult brain, there is a predominant expression of diheteromeric GluN1/GluN2A or GluN1/GluN2B receptors in hippocampus and cortex. Moreover, triheteromeric GluN1/GluN2A/GluN2B receptors represent, in the hippocampus and cortex, between 15% and 50% of the total receptor population [30–33]. The distribution is also localization-specific, and there is a predominance of GluN2A subunits in NMDAR at the post-synapse vs. GluN2B subunits at the extra-

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synaptic membrane [23]. However, NMDARs are mobile on the plasma membrane and GluN2B containing receptors can move through lateral diffusion between synaptic and extra-synaptic spaces.

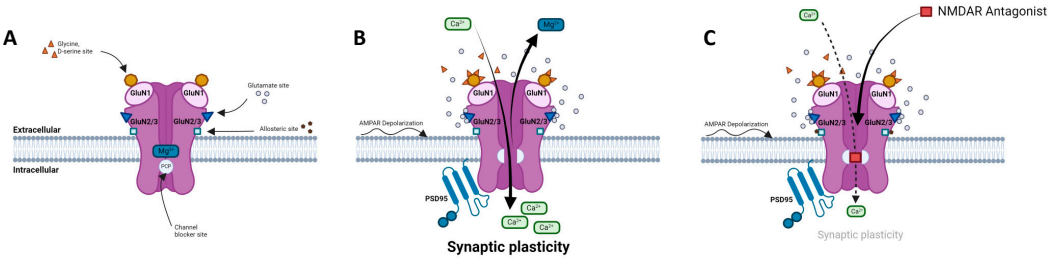

Figure 1. N-methyl-D-aspartate (NMDA) receptor and its ligand binding sites. (A) NMDAR to the resting potential blocks by Mg^{2+} with its ligand binding sites. (B) Activation of NMDAR by AMPAR depolarization and binding of both glutamate and glycine/D-serine. This activation results in the opening of the channel and allows voltage-dependent flow of Mg^{2+} out of the NMDAR and entrance of massive Ca^{2+} into the cell inducing activation of PSD95 and synaptic plasticity. (C) NMDAR antagonist binds PCP site and partially blocks the influx of Ca^{2+} thus preventing neuronal membrane depolarization. This preventing further propagation of the neuronal signal, neurotransmitter release and downstream signaling mechanisms.

In the cortex and the hippocampus, GluN2A and GluN2B are the most expressed subunits. Although there is a 70% identical sequence of GluN2A and GluN2B, these subunits play different roles in the physiological or pathological processes [34,35]. GluN3A and GluN3B show a more heterogeneous expression, inducing smaller NMDA currents with reduced calcium permeability in the post-synapse. These subunits therefore act in a dominant-negative manner to block receptor activity. GluN3A is localized in dendritic spines of glutamatergic neurons and influence synaptic stability, receptor assembly and the functional activity in the neuron [36,37]. In particular, GluN1/GluN3A NMDARs are functionally expressed in native neurons, at least in the juvenile brain, and are mediated the excitatory effect of glycine [38]. NMDARs with GluN2C/2D subunits display lower sensitivity to Mg^{2+} ions and slower deactivation kinetics compared with GluN2A/2B containing NMDARs. The expression of GluN2C/2D has been reported in adult cerebral cortices and more precisely GluN2D subunits were reported to play roles in synaptic transmission of hippocampal neurons [39].

The cellular distribution of NMDARs is also of importance and, in the physiological concept of "tripartite synapse" (Figure 2), based on direct communication between neurons, pre-synaptic terminal, and postsynaptic spine, and peri-synaptic astrocytes, NMDARs are expressed in all cell types with specific roles and impact on the synapse efficiency [40]. NMDARs were also described in oligodendrocytes, which play a major regulatory role on glucose transport and axonal metabolism [41,42]. The existence of functional glial NMDARs shows specificities, notably with an activation at negative membrane potential and differ from most of neuronal NMDARs not only by a weaker Mg^{2+} block but also by lower calcium permeability. Transcripts for all seven NMDAR subunits have been found in cultured human and rat astrocytes. The permeability of calcium in cortical astrocytes is about 3-4 times lower than in neurons [43]. Astrocytic NMDARs also play an active role in storage, processing of information and neuronal plasticity [44] and astrocytic activation in-creased calcium release pair to post-synaptic depolarization induced LTP [45–47]. Moreover, microglia express functional NMDARs in the murine and human CNS system. A microglia treatment with NMDAR antagonist prevented NMDA-induced microglial proliferation and reduced morphological activation and the release of pro-inflammatory cytokines [48].

2.2. NMDARs in the glutamatergic synapse

Glutamate, synthetized from glutamine and sequestered within synaptic vesicles, is released from the pre-synapse into the synaptic cleft and binds to NMDAR in the post-synapse (Figure 1).

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Only 10% of glutamate present in the synaptic cleft (~1.1 mM) reach glutamate receptors within approximately 1.2 msec. 90% is reuptake by the EAAT-1 transporters in astrocytes and transform back into glutamine by glutamine synthase. Glutamine can be released into the synaptic space by the sodium-coupled neutral amino acid transporter (SNAT3/5). SNAT1/2 transporters on pre-synaptic neurons uptake glutamine and predominantly regulate neuronal glutamine uptake [49,50]. In response to the glutamate synaptic release, NMDARs are activated over hundreds of msec, and activation is maintained long after all glutamate has been removed from the synaptic cleft. In response to glutamate release, AMPARs induced a depolarization in the post-synapse and allowed Na^+, K^+ and mainly Ca^{2+} flows through the NMDAR pore. At negative membrane potentials, or near to the resting membrane potential, Mg^{2+} although reach the NMDAR pore and prevent ion fluxes, but at the positive membrane potentials, Mg^{2+} is released with the depolarization of NMDAR, allowing an importantly permeability for all ions with a large outward current. Activation of NMDARs lasts thereafter much longer than AMPARs closing rapidly within a few msec. Activation of synaptic NMDARs and large increases in $[Ca^{2+}]_i$ are required for the induction of LTP, whereas internalization of synaptic NMDARs, activation of extrasynaptic NMDARs and lower increases in $[Ca^{2+}]_i$ are necessary for the induction of LTD. LTP induction promotes recruitment of AMPARs and growth of dendritic spines, whereas LTD induces spine shrinkage and synaptic loss.

When penetrating the post-synaptic cell, Ca^{2+} binds to calmodulin and activates calcium moduling kinase II (CaMKII) which leads to its autophosphorylation at Thr^{286} [51]. CaMKII is a highly abundant kinase in postsynaptic density, which phosphorylates AMPAR in GluA1 subunit. This phenomenon allows to increase the conductance of AMPAR which bind to postsynaptic density protein 95 (PSD-95), a pivotal scaffolding protein in excitatory neurons also bound to NMDAR and leads to the trans-location of internalized AMPAR to the post-synapse [52,53]. PSD-95 regulates NMDAR activity and in turn neuronal maturation, synapse stabilization, clustering of postsynapse and plasticity [54–56]. At the same time, the increase in intracellular Ca^{2+} activates other kinases such as Ras-Raf, which activates mitogen-activated protein kinases (MAPK family: Map3K, Map2K) that consequently activate extracellular signal-regulated protein kinase 1/2 (ERK1/2). The phosphorylation of ERK1/2 in the nucleus, generates the phosphorylation of cAMP response element binding protein (CREB) principal at Ser^{133}, allowing gene transcription. This pathway is predominantly involved in antioxidant defense, neuroprotection, memory processes, and hippocampal LTP. However, intracellular Ca^{2+} also activates other second messenger pathways such as adenylate cyclase or guanylate cyclase, leading to increases of 3',5'-adenosine monophosphate and/or 3',5'-guanosine monophosphate (cAMP and/or cGMP). Induction of cAMP and/or cGMP activated protein kinase A (PKA), PKG or PKB (AKT). Activations of PKA or AKT, by phosphorylation on Thr^{197} or Thr^{308}, respectively, also contribute to CREB phosphorylation on Ser^{133}. CREB phosphorylation consequently promotes cellular plasticity by regulating the expression of mRNA levels of CREB targets genes such as c-fos or Nr4a1 different proteins, like tissue-type plasminogen activator (tPA) or brain-derived neurotrophic factor (BDNF). These proteins play indeed a major role in LTP, memory processes and anxiety-related behaviors. tPA, a serine protein, facilitates the conversion of pro-BDNF to mature BDNF a major regulator of brain plasticity [57,58].

Signal diminution or weakening of network connection is also important in the brain. To ensure circuit remodeling, encoding or even erasure of memory, LTD processes make it possible to maintain synaptic efficiency. If in the pre-synapse in the brain, the activity of glutamate released is weak, whereas there is a modest depolarization in the AMPAR and NMDAR post-synapse. The consequence is that there is a weak calcium influx through the NMDAR and activation of PP2B or PP1 phosphatases, and mitochondrial caspase-3. ultimately, it could lead to apoptosis by a mechanism that involves in the dephosphorylation of AMPAR. This phenomenon leads to endocytosis of AMPAR, a degradation by lysosome and long-term depression [59–61]. Electrophysiology, LTD could be induced using, for example, a repetition of activation of the presynaptic synapse at low frequencies, without post-synapse activation. In physiological conditions, with neurons at their resting membrane potential and sub-maximal Mg^{2+} block of NMDAR, calcium

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influx could induce in response to low frequency synaptic stimulation [61,62]. In rodent models, a stimulation at 1 Hz for 15 min is typically used to induce LTD acutely in hippocampal slices [63].

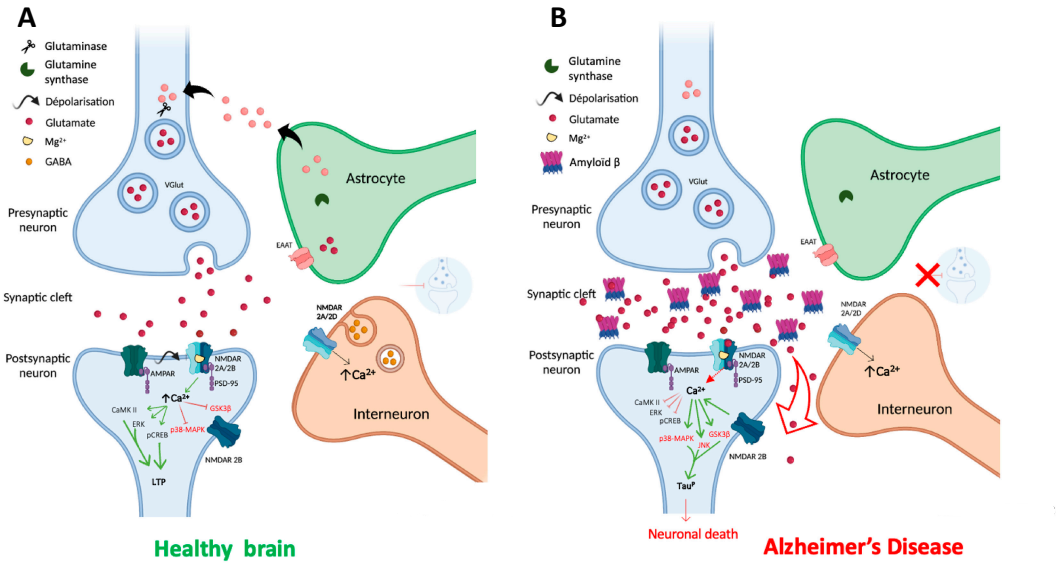

Figure 2. The tripartite synapse comprising pre- and post-synaptic glutamatergic neurons, astrocyte and interneuron in (A) a healthy brain and (B) AD patient brain. Glutamatergic excitotoxicity is induced by accumulation of amyloid ß aggregates in the synaptic cleft, interacting with post-synaptic NMDARs and astrocytic EAATs, leading to synaptic loss and impaired physiological and behavioral responses.

2.3. Regulation of NMDAR activity

Data suggests that NMDARs can be internalized quickly after physiological triggers [64,65] or that a switch in the NMDAR subunit com-position can happen during early development of neurons [22,66,67]. For instance, in the cortex GluN2B are more expressed than GluN2A in early postnatal brain and there is a shift during the development, and therefore a progressive increase in GluN2A/GluN2B ratio. This switch could be driven by sensory experience during the brain development [68] and is related to an increase in GluN2A mRNA levels, which are driven by an activation of NMDAR.

In basal conditions, AMPARs (GluA1/2) and NMDARs (GluN2A/2B) are expressed at the post-synapse with the scaffold PSD-95. An important regulation is achieved by the trafficking of NMDARs and AMPARs in synapses during LTP. In the presence of intra-cellular Ca^{2+}, AMPARs are immobilized in post-synapse in a CaMKII-dependent manner and anchored by PSD-95. For NMDARs, GluN2A is tightly anchored at the synapse as it allows an entry of Ca^{2+} in the developing hippocampus [69], allowing activation of postsynaptic kinase cascades while GluN2B is more diffusible in immature neuron, allowing to diffuse and/or redistribute more intracellular actors such as CaMKII or casein kinase 2 [70–72]. Ca^{2+} increase allows the induction of LTP and concentration of AMPARs in post-synapse. This phenomenon is very important during the initial phase of synaptic potentiation and for the recycling by exocytosis of receptors to the synapse. Moreover, AMPARs diffuse lat-erally in the cell surface when it is not bound to PSD-95. The phosphorylation of the γ2 TARP of PSD-95 auxiliary subunit can separate in C-terminal PSD-95 PDZ domains and allows the diffuse on cell membrane [73–76]. Some studies highlighted that AMPARs trafficking did not impact NMDAR-mediated LTP, but the reverse is true. It suggested that the expression of NMDAR at the post-synapse could be due to the exocytosis of NMDARs, induced by the phosphorylation of SAP97 by CaMKII at Ser^{39} in the endoplasmic retic-ulum [53,77–79]. Thus, this complex drives GluN2A to the post-synapse compartment in the developing hippocampus.

The regulation of NMDARs is also directed by the phosphorylation of its subunits. For example, it was shown that the GluN1 subunit is phosphorylated by PKC on two residues, Ser^{890} and Ser^{896}.

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The Ser^{890} phosphorylation disrupted the clustering of the GluN1 subunit while the Ser^{896} phosphorylation did not affect clustering. Interestingly, the phosphorylation of Ser^{896} by PKA appeared necessary to increase NMDAR surface expression at the postsynapse [80,81]. The regulation of the intracellular trafficking of GluN1 is also directed by Ser^{896} and Ser^{897} hyperphosphorylation in the endoplasmic reticulum and Golgi apparatus [82]. Among other NMDAR subunits, GluN2A can be phosphorylated on 3 tyrosines, Tyr^{1325}, Tyr^{1292}, and Try^{1387}, resulting in a potentiation of NMDAR currents in the synapse [83]. The phosphorylation of Ser^{1048} of GluN2A regulated the surface expression of GluN1/GluN2A and the current of NMDAR. It was shown that the dual specificity tyrosine phosphorylation-regulated kinase 1 (DYRK1A)-dependent phosphorylation of GluN2A at Ser^{1048} blocked GuN1/GluN2A internalization that allowed to express more GluN1/GluN2A receptors at the surface. This phosphorylation resulted in potentiation of NMDAR currents [84]. For GluN2B, the phosphorylation of Ser^{1303} affected the synapse distribution and activation [85]. GluN2B bears also 3 tyrosines as phosphorylation sites: Tyr^{1252}, Tyr^{1326}, and Tyr^{1472}. These residues are phosphorylated by Fyn, a kinase expressed in the post-synapse. The phosphorylation of Tyr^{1472} is notably controlled by striatal enriched tyrosine phosphatase, which belongs to a family of protein tyrosine phosphatases in glutamatergic synapse. The action of these phosphatases is to increase endocytosis of NMDAR at the post-synapse. Conversely, the phosphorylation of Tyr^{1472} stabilizes NMDAR at the post-synapse while phosphorylation of Ser^{1480} induced a destabilization of NMDAR and involved a decrease of NMDAR expression [86,87]. Numerous studies showed that the phosphorylation of GluN2A or GluN2B subunit reflected NMDAR activity [88,89].

2.4. NMDARs modulators

NMDAR activity can be modulated by small molecules acting through different mechanisms (Table 1). Among competitive NMDAR agonists, the highly selective prototype drug is D-AP5. D-AP5 inhibits excitatory response and blocks plasticity (LTP) in GluN2A subunit-containing NMDAR in rodents, thus having an impact on learning at the behavioral level [92]. Phencyclidine is a dissociative anesthetic with strong addictive properties. PCP induces psychotic and dissociative schizophrenia-like symptoms resulting from the impairment of NMDAR neurotransmission in vivo [93,94]. Its derivative, ketamine also acts as an uncompetitive NMDAR antagonist and is still used as an anesthesic. Ketamine applied in post-synapse induces an inhibition of excitatory pyramidal neuron in extra-synaptic GluN2B subunit. When applied in pre-synapse, the drug induced an inhibition of GluN2D subunit in interneurons and provoked a disinhibition of glutamate release in post-synapse. At the same time, it induced an up-regulation of hippocampal AMPARs (GluA1/GluA2). This phenomenon has a consequence on plasticity and sustains its rapid antidepressant efficacy [95,96]. Among other uncompetitive antagonists acting at the PCP site, dizocilpine (or (+)-MK-801 maleate) is a nanomolar affinity anticonvulsant but amnestic and ataxic drug [97].

Table 1. Listing of the reference NMDAR modulators.

Compounds	*Modulator*	*Selectivity*	*Action*	*References*
D-AP5	*Hight selective competitive antagonist*	*GluN2A*	*Inhibits excitatory response. Impacts behavioural learning, blocks plasticity (LTP).*	[90–92]
Riluzole	*Competitive antagonist*	*GluN1/GluN2B*	*Indirect block of NMDAR. Protect from motor deficit*	[98–100]
Phencyclidine	*Selective uncompetitive antagonist*	*GluN2B/D (PCP site)*	*Induces psychotic and dissociative schizophrenia-like symptoms. Impairs NMDAR neurotransmission in vivo.*	[93]
Ketamine	*Uncompetitive antagonist*	*GluN2B/D (PCP site)*	*Applied in post-synapse : inhibits excitatory pyramidal neuron in extra-synaptic GluN2B. Applied in pre-synapse: inhibits GluN2D in interneuron (induces disinhibition of*	[95,101]

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			glutamate release in post-synapse). Up-regulates hippocampal AMPARs (GluA1/GluA2). antidepressant.	
Dizocilpine	*Uncompetitive antagonist*	*GluN2B/D (PCP site)*	*Anticonvulsant, antidepressant. Induces memory impairments.*	[97,102]
Ifenprodil	*Uncompetitive antagonist*	*GluN1/GluN2B*	*Blocks GluN2B (140-fold preference for NR2B over NR2A subunits). Induces an inhibition of GluN2R receptor currents. anti-Parkinsonian effect.*	[103–105]
Memantine	*Uncompetitive antagonist*	*GluN1/GluN2B*	*Blocks GluN2B extra-synaptic and induces glutamatergic excitotoxicity. Used for moderate-to-severe AD.*	[106,107]
Amantadine	*Uncompetitive antagonist*	*GluN1/GluN2B*	*Blocks GluN1/GluN2B by accelerating channel closure during channel block. Used as antiparkinsonian drug*	[108]
Dextrometorphan	*Uncompetitive antagonist*	*GluN2A*	*Blocks GluN2A subunit. Prevent neuronal damage and modulates pain sensation*	[109–113]

Ifenprodil is an uncompetitive antagonist binding specifically on GluN2B (140x preference for GluN2B *vs.* GluN2A). It was shown that 150 nM of ifenprodil induced 75% inhibition of GluN2B receptor currents in human embryonic kidney (HEK-293) cells [114]. Another blocker on GluN2B subunit receptor, memantine, it was shown that memantine improves cognitive functions and enhance be-havioral disturbance alone as monotherapy or combination with donepezil to moderate at severe form of AD [115]. Amantadine, a demethylated analogue of memantine, was initially assumed to result from effects on dopaminergic systems, before later discovered that it blocks the NMDAR ion channel. The remarkably fast unblocking kinetics of amantadine in comparison of memantine allow it to unblock during the brief depolarization of an action potential at least partly, a characteristic that may decrease deleterious clinical effects [108]. Dextromethorphan is a non-competitive NMAR antagonist which has properties similar to ketamine and phencyclidine. This NMDA receptor antagonism is believed to result in a decreased reuptake of catecholamines. Dextromethorphan also inhibits the reuptake of serotonin [116]. These properties make dextromethorphan have a high abuse and misuse potential. Although the role of dextromethorphan as an NMDAR antagonist appears attractive, its clinical use in the treatment of pain in cancer patients led to controversial results [112,113]. Riluzole has neuroprotective, anticonvulsant, anxiolytic and anesthetic properties. These actions are dominated by its effects on glutamate transmission which are predominately mediated by NMDAR. It decreased glutamatergic transmission probably via inhibition of PKC that regulated presynaptic NMDAR having a facilitatory effect on glutamate release [100]. The anti-cataleptic potential of the drug is the most important finding and is implicate beneficial effects in the treatment of muscle rigidity [117]. Finally, antagonists of the GluN2C and GluN2D subunits also exist, making it possible to determine their localization in the brain, particularly in astrocytes but also in neurons [38].

3. The impact of NMDARs in neurodegenerative diseases

3.1. Alzheimer's disease

According to World Health Organization, there are currently more than 55 million peoples with dementia in worldwide. Every year, 10 million of new cases are detected. This dementia result from different injuries and pathology in the brain. More 60-70% of the total cases are people who were affected by AD. It is an aging-related neurodegenerative disorder characterized by slow deterioration of cognitive functions, such as autonomy, declarative memory, and recognition memory. AD is a progressive disorder, asymptomatic in its early stage but with symptoms evolving from mild cognitive impairment to severe dementia. Histopathologically, AD is characterized by extracellular

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accumulation of aggregated amyloid-β (Aβ) proteins in the hippocampus and cortex and intraneuronal fibrillary tangles composed of hyperphosphorylated tau protein. Brain neuroinflammation is also massive and typified by a reactive gliosis (microgliosis and astrogliosis), oxidative stress, loss of synapses and neurons in layers III/IV of the neocortex, hippocampus, and cortex [118–121]. Pathologically elevated oligomeric Aβ may indirectly cause a partial block of NMDARs and shift the activation of NMDAR-dependent signaling cascades toward pathways involved in the induction of LTD and synaptic loss. The consequence is a progressive cognitive decline, due to a deficient cholinergic transmission and excitotoxicity in glutamatergic synapses. Indeed, in the AD brain and human cortical neurons, excitatory synapses containing the GluN2B subunit of the NMDARs appear to be the main sites of Aβ oligomers accumulation inducing a high level of glutamate in the synaptic cleft (Figure 2). Moreover, oligomeric Aβ block glutamate recapture by the EAATs in astrocytes and activate mGluR in the post-synapse [122], resulting in oxidative stress and apoptosis. The mGluR over-activation led to AMPARs internalization, desensitization of NMDARs and an en-docytosis of GluN2B in post-synapse resulting in LTP alteration and increased LTD, and, finally, more neuroinflammation [123–125]. In the extra-synapse region, the binding of glutamate to ionotropic glutamatergic receptors, with a GluN2B subunit, generates a massive extra-synaptic Ca^{2+} entry and activates deleterious signaling pathways involving MAPK, GSK-3β, or JNK. Activations of these pathways result in an increase in apoptosis and hyperphosphorylation of the tau protein [21,126]. Moreover, Aβ deposits increase the Src kinase Fyn, which phosphorylates GluN2B in Try^{1472}. This GluN2B phosphorylation increases the subunit association with its scaffold PSD-95 and causes a disruption of synaptic plasticity and LTP in the brain leading to death of glutamatergic neuron [86,127]. The massive entry of Ca^{2+} also concours to inhibit signaling pathways beneficial to LTP, involving CAMKII, calcineurin, pCREB, and ERK, to reduce cellular survival factors, including BNDF and CREB, contributing to LTP/LTD alterations [128]. The activation of extra-synaptic NMDARs leads to an increase in the production of Aβ [129]. In post-mortem AD human brain, the levels of GluN1, GluN2A, and GluN2B were reported to be de-creased in the hippocampus and entorhinal cortex [130–134]. GluN2C or GluN2D mRNA level did not change in AD patient brain [133]. Clinical trials showed that a significant efficacy for memantine over placebo in moderate to severe forms of AD with an improvement of cognitive functions and activities of daily living [135,136]. Memantine is well tolerated by the patient but shows side effects like dizziness, headache, or constipations [137]. The drug was approved by FDA in 2003.

3.2. Huntington's disease

In the world, the prevalence of Huntington's disease (HD) is approximately 5 cases per 100,000 individuals [138]. HD is an autosomal dominant neurodegenerative disorder characterized by the presence of motor symptoms due to the brain atrophy, degeneration of striatal neurons (caudate nucleus and putamen) and cerebral cortex with specific loss of efferent medium spiny neurons [139]. Patients are affected around 35-50 years of age and the symptoms include movement disorders, dementia, cognitive impairment and behavioral or psychiatric manifestations [140]. HD is caused by a pathological expansion of cytosine-adenine-guanine (CAG) repeats, between 10 to 35, in the exon 1 of the huntingtin gene, on chromosome 4p16.3. This gene encodes the huntingtin (Htt) protein that shows, in HD, an elongation of polyQ, gener-ating mutant huntingtin (mHtt) [141]. There is a strong correlation between length of the polyQ repeats and the age of the disease onset [142]. Htt protein is necessary for the formation of cortical and striatal excitatory synapses, embryonic shaping of the nervous system, protein trafficking, post-synaptic signaling, vesicle transport, transcription factor regulation and regulation of cell death [143,144]. Htt is localized in the cytoplasm and associated with vesicle membranes by the scaffold PSD95 [145]. The mHtt aggregates in the brain in the nucleus and cytoplasm and this accumulation results in alterations of gene transcription, neurotransmitter metabolism, and alterations of BDNF and its TrkB receptor expressions and distributions. Post-mortem studies showed a loss of striatal NMDARs in early symptomatic and pre-symptomatic stages of the disease [146,147]. In the R6/2 transgenic mouse model of HD, the expression of GluN2A and GluN2B, but not GluN1, decreased in the striatal region [148,149]. In YAC128 mice, no change in NR1,

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NR2A, or NR2B in the striatum of mice with symptoms was reported but a decrease in phosphorylation of NR1 at Ser^{897}, previously reported to decrease NMDAR current [150].

The pathological context resulted in an imbalance between glutamate and dopamine in the striatum with an increase in dopamine in the post-synapse and an alteration of glutamate reuptake by the glial glutamate transporter in corticostriatal synapses. GLT mRNA was reduced in rodent models in HD in relation with motor dysfunction [151]. Glutamatergic alterations therefore included: (i) an accumulation of glutamate in the synaptic cleft, (ii) a decrease of post-synaptic NMDARs, and (iii) an increase of GluN2B extra-synaptic expression in striatal spiny neurons that could be responsible for cell death when GluN2A is decreased [152,153]. Glutamatergic NMDAR neurotransmission promotes the expression of an-ti-apoptotic factor Bcl-2, antioxidant, and of the pro-survival trophic factor BDNF. In HD condition, BDNF release and TrkB activation are decreased in the post-synapse, together with increases in pro-apoptotic factor Bax, pro-death genes such as FOXO or FBS, dysregulation of mitochondrial calcium and CREB-inactivating dephosphorylation signals [154,155]. mHtt indeed contributed to suppress CREB gene by sequestering its coactivator CBP [156]. Current therapy developments focus on gene therapies and antisense oligos. Alternatively, symptomatic treatments rely on neuroleptics, dopaminergic inhibitors, such as tetrabenazine, and antidepressants adapted to reduce motor and psychiatric signs, and sleep disorders [157].

3.3. Parkinson's disease

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder after AD and represents a large health burden to society. Approximately 1% of the population over 60 years of age is affected. PD is a progressive neurodegenerative disorder resulting from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the accumulation of intracytoplasmic inclusions, known as Lewy bodies [158]. A series of alterations in the circuitry of basal ganglia nuclei leads to severe motor control impairments such as tremor, muscular rigidity, and bradykinesia [159]. Pharmacological approaches to PD predominantly target the dopaminergic system, with dopamine replacement by its precursor, L-3,4-dihydroxyphenylalanine (L-Dopa) [160]. However, a prolonged treatment leads to the development of motor complications, known as L-Dopa-induced dyskinesia, involving choreic movements, dystonia, and ballism [161].

NMDARs largely regulated by dopaminergic afferents are very abundant in the basal ganglia and control the release of the neurotransmitters γ-aminobutyric acid (GABA) and acetylcholine [162]. NMDAR antagonists could be used to decrease L-Dopa dosage and diminish any potential oxidative damage as oxidative products of dopaminergic neurons play a role in cell death [163]. In addition, expression and activity of glutamate receptors are also affected during L-Dopa-induced dyskinesia [164]. NMDAR antagonists, such as dextromethorphan, have been reported to suppress dyskinesia in PD patients. Adverse effects at high doses limit however this treatment strategy [165]. Alternatively, amantadine, a non-selective NMDAR antagonist approved by FDA in 2003, remains an interesting therapeutic option in the management of L-Dopa-induced dyskinesias [166]. Amantadine was associated with an increased lifespan in patients with PD, suggesting that it may have neuroprotective properties [167]. Memantine has also been tested in PD patients with a moderate success, as it did not appear to share the anti-dyskinetic activity of amantadine [168]. A second generation of adamantane-based drugs are being designed in the hope of improving its clinical efficacy [169].

4. Fluoroethylnormemantine (FENM): a new generation NMDAR uncompetitive antagonist

4.1. ^{18}F-FENM as a PET NMDAR radiotracer

Memantine and several derivatives have been fluorinated with a positon-emitting isotope ^{18}F and tested as radiotracers of positron emission tomography (PET) for the in vivo labeling of NMDARs [170–172]. ^{18}F-memantine was homogeneously distributed in the cortex and basal ganglia regions, as well as the cerebellum. However, the observed pattern of ^{18}F-memantine uptake in the whole brain

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was not consistent with autoradiographic studies performed on postmortem human brain using ^{3}H-thienylcyclidine [173] and did not reflect the regional NMDAR distribution [170–172]. Moreover, the radioligand binding was also partly displaced by haloperidol, suggesting some binding at sigma-1 receptors. Therefore, the radiotracer did not appear suitable for the PET imaging of the NMDA receptors. Among derivatives, ^{18}F-fluoroethylnormemantine (^{18}F-FENM) showed an excellent selectivity and specificity for NMDAR in preclinical models *in vivo* In particular, ^{18}F-FENM injected intravenously has been shown to effectively cross the blood brain barrier and to bind to the grey matter, cerebellar cortex and central grey nuclei [174,175]. Its specific distribution matched the one of NMDAR GluN1 mandatory subunit, and a low non-specific binding level was seen after pre-injection with ketamine at anesthetic doses. Moreover, FENM competed in vitro with ^{3}H-thienylcyclidine in rat brain membranes with a Ki of 3.5 μM [174,175]. As observed for memantine, FENM is poorly metabolized *in vivo* with good stability in plasma and plasma protein binding, but with a low effective dosimetric dose as compared to other PET radiotracers [175]. Moreover, the tracer was used recently in a rat preclinical model of excitotoxicity [176]. *In vivo* brain lesions were performed using stereotaxic quinolinic acid injections in the left motor area of Sprague Dawley rats. PET detected a significant increase in ^{18}F-FENM uptake 24 and 72 h after excitotoxic lesions compared to the control group. So, although FENM showed only a moderate affinity for the NMDAR PCP site, the tracer appeared suitable to track activation of NMDARs in neurological diseases.

4.2. FENM as an anxiolytic agent in PTSD

NMDAR antagonists have shown efficacy against a variety of neuropsychiatric disorders. Ketamine is widely known for its rapid-acting long-lasting antidepressant effect and its efficacy in treatment-resistant depression [101,177,178]. Ketamine also prevented stress-induced behavioral despair and, when administered prior to stress, attenuated learned fear [179–181]. Available PTSD treatments, including medications and therapy, effectively treat only a fraction of people who try them for adequate dose and duration. This indicates a need to develop treatments targeting durable remission of PTSD. Agencies (FDA and EMA) have approved only two pharmacotherapies for PTSD, the selective serotonin reuptake inhibitors paroxetine and sertraline [182,183]. FENM therefore appeared as a putative alternative and preclinical studies examined its efficacy in rodent models of PTSD, compared to the reference NMDAR antagonists ketamine and memantine [184,185]. FENM or memantine were administered in rats submitted to a battery of behavioral assays, including paired-pulse inhibition, open field, light dark test, forced swim test, and cued fear conditioning [184]. When administered at a variety of timepoints prior to both cued fear conditioning and extinction training, FENM exerted long-lasting reductions in fear behavior in a dose-specific manner. FENM was also effective in attenuating learned fear when administered acutely prior to fear conditioning, indicating that it may also be leveraged as a resilience-enhancing prophylactic. Importantly, FENM did not alter sensorimotor gating during paired-pulse inhibition or locomotion in the open field acutely after injection. These results are in direct contrast with data obtained using memantine, as the drug significantly reduced startle response and locomotion 30 min after injection. This data suggests that FENM is devoid of non-specific side effects [184]. In a PTSD model, the drug was tested as a prophylactic or antidepressant against stress-induced maladaptive behavior, contextual fear conditioning in mice, and compared to ketamine [185]. Given after stress, FENM decreased behavioral despair and reduced perseverative behavior. When administered after re-exposure, FENM facilitated extinction learning. As a prophylactic, FENM attenuated learned fear and decreased stress-induced behavioral despair [185]. Interestingly, ketamine but not FENM increased expression of c-fos in CA3 ventral hippocampal area while both ketamine and FENM attenuated large-amplitude AMPA receptor-mediated bursts in the same area suggesting at least some common neurobiological mechanism [185]. These data outlined the potentialities of FENM as a NMDAR antagonism-acting anxiolytic drug and seeded a future development in PTSD.

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4.3. FENM as a neuroprotective agent in AD

FENM was examined, in comparison with memantine, as a neuroprotectant in AD models. Two models were used in parallel, a pharmacological model induced in mice by intracerebroventricular injection of pre-aggregated/oligomeric amyloid-β$_{25-35}$ (Aβ$_{25-35}$) peptide [186,187] and the APP$_{swe}$/PSEN1$^{\partial E9}$ transgenic line [[188,189]; *Carles et al., submitted*]. Both memantine and FENM showed symptomatic anti-amnesic effects at a low mg/kg dose-range, in Aβ$_{25-35}$-treated mice submitted, one week after the peptide injection, to a battery of behavioral tests: spontaneous alternation, passive avoidance, object recognition, place learning in the water-maze, and topographic memory in the Hamlet. Interestingly, FENM was not amnesic when tested alone at a high dose, 10 mg/kg, contrarily to memantine. When drugs were injected in the same low mg/kg dose-range but once-a-day during one week, they prevented Aβ$_{25-35}$-induced memory deficits, oxidative stress (lipid peroxidation, cytochrome c release), inflammation (IL-6, TNFα increases; GFAP and Iba1 immunoreactivity in the hippocampus and cortex), and apoptosis and cell loss (Bax/Bcl-2 ratio; cell loss in the hippocampus CA1 area) [187]. FENM effects, notably on neuroinflammation, were more robust than observed with memantine. A second study examined FENM efficacy when the drug was subcutaneously infused using an osmotic minipump during one week after the Aβ$_{25–35}$ injection in mice. Deficits in spontaneous alternation and object recognition were prevented by infused FENM [*Carles et al., submitted*]. Similar effects were observed with daily intraperitoneal FENM or memantine treatments. Animals infused at 0.1 mg/kg/day showed prevention of Aβ$_{25–35}$-induced neuroinflammation, oxidative stress and apoptosis. Aβ$_{25–35}$ provoked, in hippocampal homogenates or synaptosomes, a decrease in PSD95 level, an increase in GluN2A subunit of the NMDAR with a decreased phosphorylation level, and no change in GluN2B but an increase in its phosphorylation. The FENM infusion attenuated Aβ$_{25–35}$-induced alteration in PSD95, GluN2A and P-GluN2B levels but not P-GluN2A, showing a direct regulation of NMDAR in AD mice. GluN2D levels were unchanged whatever the treatment. In 10-month-old APP$_{swe}$/PSEN1$^{\partial E9}$ and wildtype control mice, FENM was administered for four weeks, either by daily intraperitoneal injections at 0.3 mg/kg or chronic subcutaneous infusion at 0.1 mg/kg/day using osmotic minipump. Animals were then examined for spatial working memory, neuroinflammation, apoptosis, amyloid load markers, and synaptic LTP in hippocampal slices [*Carles et al., submitted*]. Both infused and repeated intraperitoneal FENM treatments attenuated the behavioral deficits, microglial activation, resulting increases in cytokines TNFα and IL-6, and increase in Bax levels in the mouse hippocampus. Both soluble and insoluble Aβ$_{1-40}$ and soluble Aβ$_{1-42}$ cortical levels were attenuated by the treatments. Alteration of long-term potentiation maintenance in the dentate gyrus of APP$_{swe}$/PSEN1$^{\partial E9}$ mice was also improved by the treatments. These data confirmed that a post-symptomatic treatment with FENM allowed a significant prevention of AD pathology in a transgenic mouse model. Moreover, under a pre-symptomic long-term treatment, 1-5 mg/kg/day in drinking water for 9 months starting at the age of 3-month-old, APP$_{swe}$/PSEN1$^{\partial E9}$ mice showed a prevention of the memory deficits in the same battery of behavioral tests, spontaneous alternation, passive avoidance, object recognition, and place learning in the water-maze. *Post-mortem*, the FENM treatment decreased neuroinflammation (GFAP and Iba1 immunoreactivity) in the hippocampus, and insoluble Aβ$_{1-40}$ Aβ$_{1-42}$ levels. This decrease of amyloid load was associated to a decrease of amyloid plaques in hippocampus [*unpublished data*].

Recombinant NMDARs were expressed in a canonical electrophysiological model [*unpublished data*]. A dose-response curve of inhibition of currents elicited by application of agonists by FENM was performed, with memantine as a benchmark and internal control, and in presence of physiologically relevant level of magnesium and at resting potential of -60 mV, the IC$_{50}$ values of FENM on the different NMDAR subtypes were: 168 μM for GluN1/GluN2A, 127.3 μM for GluN1/GluN2B, 13.9 μM for GluN1/GluN2C, and 11.5 μM for GluN1/GluN2D receptors. FENM therefore appeared a direct NMDAR antagonist, with a significant subtype selectivity for GluN2C and GluN2D subunit-containing receptors. The potentialities as a neuroprotective and anxiolytic NMDAR antagonist of FENM could be link to this selectivity. Further studies will be essential to clearly identify how its mode of action at NMDAR is translated into its neuroprotective action, and to determine whether biochemical or regional specifications sustain its pharmacological profile.

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5. Conclusions

NMDARs generated tremendous research efforts in neuropharmacology since the mid 80's, not only for their prominent role in the balance between excitation and inhibition in the brain, their role in major physiological responses, such as neurological, cognitive and motor functions, but also due to their direct responsibilities in numerous pathological conditions. Among them, neurodegenerative pathologies are due or amplified by a chronic excitotoxic status and involve specific alterations, as observed with Aβ affecting the excitatory synapse in AD. NMDAR antagonists, and mainly uncompetitive antagonists targeting the PCP site within the ionophore, have led to major clinical breakthroughs, including memantine in AD, ketamine in anesthesia or major depression, amantadine in PD. Novel drugs are still in development and we particularly develop FENM, a memantine derivative that present superior neuroprotective activity in AD, as compared to memantine, and anxiolytic properties in PTSD, as compared with ketamine. The drug is expected to enter clinical trials for the second semester of 2024.

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Abbreviations

ABD agonist binding domain
AD Alzheimer's disease
AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Aβ amyloid-β
BDNF brain-derived neurotrophic factor
CaMKII calcium moduling kinase II
cAMP 3′,5′-adenosine monophosphate
cGMP 3′,5′-guanosine monophosphate
CNS central nervous system
CREB cAMP response element binding protein
CTD carboxyl C-terminal domain
DYRK1A dual specificity tyrosine-phosphorylation-regulated kinase 1
EAAT excitatory amino acid transporter
ERK1/2 extracellular signal-regulated protein kinase 1/2
FENMfluoroethylnormemantine
GABAγ-aminobutyric acid
HD Huntington's disease
HEK-293 human embryonic kidney 293 cells
L-Dopa L-3,4-dihydroxyphenylalanine
LTD long-term depression
LTP long-term potentiation
MAPK mitogen-activated protein kinases
NMDAR N-methyl-D-aspartate receptor
PCP phencycline
PD Parkinson's disease

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PET positron emission tomography
PKA protein kinase A
PSD-95 postsynaptic density protein 95
PTSD post-traumatic-stress-disorder
RCPG G protein-coupled receptor
SANT sodium-coupled neutral amino acid transporter
tPA tissue-type plasminogen activator

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