Nmda receptor pathways as drug targets in cns therapeutics

1. Introduction:

Glutamate is the king of excitatory neurotransmission in the central nervous system (SNC) and acts on receptors located at the presynaptic terminal and in the postsynaptic membrane at synapses in the brain and spinal cord (Ghasemi and Schachter, 2011). Although glutamate was known to have central nervous system effects for more than 75 years, it was not until 1984 that it was truly acknowledged as fulfilling the criteria of a neurotransmitter. (Niciu et al., 2012). Glutamate receptors are divided into two broad categorizations: ionotropic and metabotropic receptors. Ionotropic glutamate receptors are ion channels that flux cations (Ca2+, Na+) and open the channels in response to agonist binding. On the other hand, metabotropic receptors activate or inhibit second messenger systems via interactions with cognate G-proteins. (Niciu et al., 2012). Ionotropic glutamate receptors can be subdivided into three large families: AMPA receptors (AMPARs), kainate receptors and NMDA receptors (NMDARs). Since three decades ago, the discovery NMDARs have kept fascinating neuroscientists while their dysfunctions are also involved in various neurological and psychiatric disorders, including stroke, pathological pain, neurodegenerative diseases and schizophrenia. (Paoletti et al., 2013) Fortunately, the NMDA receptor complex is composed with modulatory sites, and the late 1970s and 1980s saw the development of agonists, antagonists and modulators acting at different binding sites. In the last decade, the molecular biology of the NMDA receptors has been defined, and now it is known that these receptors are formed of an NR1 subunit in combination with one or more NR2 or less commonly an NR3 subunit. (Kemp and McKernan, 2002).

2. Molecular mechanisms

NMDA receptors are named after their selective agonist N-methyl-D-aspartate. The receptors are multisubunit complexes associating NR1, NR2 and, more rarely, NR3 subunits. NR2 and NR3 subunits exist as four and two subtypes, respectively (NR2A-D and NR3A-B). NR1 exists as seven subtypes (NR1a–g) (Mony et al., 2009) The receptors are heterotetramers comprising a combination of NR1, NR2A-D and NR3A-B subunits. The main agonists are glutamate and NMDA, with their binding site on NR2 subunits, while the binding site for the co-agonists D-serine and glycine is located on NR1 and NR3 subunits and the T most common composition of NMDA receptors includes two NR1 and two NR2 subunits, or two NR1, one NR2 and one NR3 subunits (Dzamba et al., 2013). A common structure for glutamate receptors contains an extracellular amino-terminal domain (ATD) for various modulatory functions, extracellular S1S2 domains for agonist binding, an ion channel domain with four transmembrane segments (M1–4) for gating and ion permeation, and a carboxy-terminal domain for communicating with intracellular milieu Fig 1 (Majdi and Chen, 2009).

Pharmacological regulation of the NMDAR depends on effects on unique combinations of subunit-specific binding sites. Once glycine coagonist attaches to its site, the glutamate can activate the ion channel and the Na+ and Ca2+ rush in. The Mg2+ blocks channel pore and the blockade is relieved by cellular depolarization, which has implications for synaptic plasticity, especially long-term potentiation (LTP). (Ghasemi and Schachter, 2011) Most compounds that act at NMDA receptors interact with one of 4 drug binding sites on the NMDA receptor complex, the glutamate or glycine

binding sites, the ion channel pore, or a binding site on the regulatory NTD. The first compounds identified were agonists and antagonists of the glutamate like D-α-aminoadipic acid and D-2-amino-5phosphonopentanoic acid (D-AP5) then glycine competitive antagonists like 7-chloro-5-iodokynurenic acid and partial agonists were identified. It was also soon recognized that some dissociative anesthetics (e. g. ketamine and phencyclidine) were NMDA receptor blockers and the widely used inhibitor MK-801 was shown to be a potent NMDA receptor channel blocker Fig 2 (Monaghan et al., 2012). Another important aspect of NMDA receptor pharmacology is modulation by posttranslational modifications, such as phosphorylation of the intracellular C-terminal of NR2 subunits. NMDA receptor-mediated calcium increases activate many downstream targets like protein kinase C (PKC) and the Modulation by protein kinase C (PKC) depends on NMDA receptor subunit composition; NR2A- and NR2B-containing receptors are potentiated by PKC activation, whereas NR2Cand NR2D containing receptors are unaffected or inhibited by PKC. PKC phosphorylates the NR1 subunit at serine 890 (S890) in the C1 cassette. The potentiatory effects of PKC are not dependent on phosphorylation of NR1, but inhibitory effects are blocked by mutation of S890 or removal of the C1 domain. The NMDA receptor function is also modulated by MAGUK protein family which controls the NMDA receptor localization, the binding to the scaffolding proteins plays a major role in the control of downstream signals resulting from receptor activation. It thought that synaptic NMDA receptors are retained at the synapse by an attachment to PSD-95 through a PDZ interaction with the NR2 subunits.(Gardoni and Di Luca, 2006)

3. Therapeutics

A high number of central nervous system disease states in which neuronal cell death is associated to glutamate induced excitotoxicity could be treated by blocking NMDA receptors such as neurological disorders including ischemia, epilepsy, brain trauma, dementia, and neurodegenerative disorders. ï‚· Ischemia : it has been shown that loss of calcium homeostasis may be an important mechanism of ischemic brain damage. Ischemia also resulted in a decrease in the size of protein complexes containing PSD-95. In addition, transient cerebral ischemia increases tyrosine phosphorylation of NMDA receptor subunits NR2A and NR2B. Recent studies suggested to treat stroke transducing neurons with peptides able to disrupt the interaction of NMDA receptor NR2B subunits with the postsynaptic density protein PSD-95. This procedure dissociated NMDA receptors from downstream neurotoxic signaling without blocking synaptic activity or calcium influx and protected cultured neurons from excitotoxicity. .(Gardoni and Di Luca, 2006). Many NR1/NR2B antagonists, including ifenprodil, eliprodil and the selective and potent congeners, Ro 25, 6981 and CP-101, 606, offer promise in preclinical models of ischaemia (Chazot, 2004) ï‚· Epilepsy: Recent work has suggested that hyper-phosphorylation of NR2B may results in hypersensitivity to the endogenous transmitter, and induction of neuronal hyperexcitability and epilepsy. Furthermore, kainic acid-induced alters tyrosine phosphorylation of NR2A and NR2B receptors. Interestingly, the high affinity NR2B compound, Ro 63-1908 was shown to be active versus acoustic-induced convulsions and NMDA-induced seizures at 4. 5 mg/kg ip and 2. 31 mg/kg iv, respectively and no adverse cardiovascular, motor deficits or other CNS sideeffects were

observed at these active. (Chazot, 2004). ï‚· Huntington’s disease: The normal huntingtin binds to PSD-95 scaffold protein which inhibit the NMDA receptor Overexpression of the normal huntingtin N terminus significantly attenuates neuronal toxicity induced by both NMDA receptors and the mutated huntingtin. This suggests that PSD-95 is a mediator of neuronal toxicity induced by NMDA receptors and mutated huntingtin. In addition, in a transgenic model of Huntington disease. Other studies show that expression of mutant htt (but not wild-type htt) in combination with NR1/NR2B increases cell death compared to transfection of only NMDA receptor subunits, suggesting a role for NR1/NR2B NMDA receptors in cell death mediated by mutant htt . As NR2B antagonists block most of the NMDA receptor mediated currents in neuronal models of Huntington, the selective localization of NR2B in the striatum may also play a role in the efficacy of NR2B antagonists against cell death in models of Huntington.(Gardoni and Di Luca, 2006). ï‚· Alzheimer’s disease : In animal models, NR2B subunit expression decreases with age, which correlates well withreduced Long Term Potentiation (LTP) and inferior cognitive performance. The NR1/NR2B subtype decreases, in comparison to other subtypes, in the frontal cortex of aged humans while overexpression of the forebrain NR2B subunit in transgenic mice has been shown to have profound beneficial effects upon cognitive performance. Such information suggests that controlled potentiation of the NR2B may offer a novel strategy for treating cognitive disabilities. (Chazot, 2004). ï‚· Parkinson’s disease: At the molecular level, alterations of NMDA receptor subunits localization in striatum have been described in Dopamine-denervated rats as well as in L-DOPA-treated dyskinetic monkeys. In particular, NR2B subcellular redistribution from synaptic to extrasynaptic

sites represents the key element in the complex modifications of the glutamatergic synapse in L-DOPA-induced dyskinesia. On the other hand, recent studies in primates suggested that upregulation of NR2A abundance in synaptosomal membranesmay be an important player in L-DOPA induced dyskinesias. And recently, two studies described results on the effects of NR2B selective NMDA receptor antagonist CP-101, 606 on L-DOPA induced dyskinesia in two different models of experimental parkinsonism.(Gardoni and Di Luca, 2006). ï‚· Psychosis : Studies have suggested that the NR2B has role in psychotic disorders, including schizophrenia and bipolar disorder. The mRNA encoding the NR2B subunit and NR1/NR2B-type binding sites have been shown to be selectively increased in hippocampal and cortical regions, Recent work has identified a novel T200G variant located in the NR2B promoter, which endows dysfunction of the NR2B subunit. The frequency of this variant was significantly up-regulated in a schizophrenia group compared to a control group. The possible link between these observations is yet to be investigated. (Chazot, 2004). ï‚· Pain: Studies suggest that the NR2B subunit plays distinct roles in acute and chronic pain states, recently NR2B antagonists were developped, including Ro 25, 6981, CP -101, 606, PD 174494 and PD 196860, are effective in a range of animal chronic pain models with a wide separation between anti-hyperalgesic and side-effect doses . . (Chazot, 2004).

4. References

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