P phosphorylation and palmitoylation, and degradation [56, 57].

Literature, Play

p { margin-bottom: 0.

25cm; line-height: 120%; }FunctionalDomains of NMDAR SubunitsNMDARshave a 400- to 450-amino-acid-long amino-terminal domain (ATD). This domain plays a role in the control of pharmacological andkinetic properties38. The GluN2B ATD has a clamshell-like structureand is composed of two R1 and R2 domains 41.

The inhibitory Zn 2+binding takesplace in the ATDs of GluN2A and GluN2B41. Ligand-BindingDomain (LBD)Theendogenous ligands of the NMDAR are glutamate, glycine or D-serine42. Glutamate binds to the GluN2 subunit and glycine or d-serinebinds to the GluN1 and GluN3 subunits.

Thus, both of the GluN1andGluN2 subunits are required for NMDAR to be functional. The LBD ofGluR is formed by two extracellular structures of amino acidsreferred to as S1 and S2 48. S1 locates on the extracellularamino-terminal side near M1 and S2 located on the extracellular sidebetween M3 and M4. The LBD structures show a clamshell-likeconformation. The heterodimeric structure of the LBD complex composedof NMDAR with GluN1 and GluN2 reinforces the view that tetramericNMDAR is a dimer of heterodimers. Channel Forming DomainTheactivation of NMDAR requires the binding of two ligands (the agonistglutamate binds to GluN2 subunit and the coagonist glycine/d-serinebinds to GluN1 subunit) and release from extracellular Mg 2+ blockingin channel pore. The positive charge of Mg 2+ is the basis of Mg 2+blocking of NMDAR by the electronic force to the negative charge of aneuron under the physiological membrane potential of about ? 70 mV. Thus, NMDAR is a voltage-dependent and ligand-gated ion channel.

Agonist binding and channel gating involve three sequential steps:(1) agonist binding, (2) conformational change, such as the clamshell closure of LBD, and (3) conformational change of ion channelpore to open. The second hydrophobic region(M2) is involved in theformation of channel pore. In M2, NMDAR subunits have the criticalamino acid residue aspargine (N) determining Mg 2+ blocking and Ca 2+permeability 52, 53. The topology of NMDAR subunits has threetransmembrane helices (M1, M3, and M4) and one loop (M2) structure. The M2 loop lines the inner cavity of the ion channel pore. CytoplasmicCarboxyl-Terminal Domain (CTD)TheNMDAR subunit GluN1 has four distinct carboxyl-termini derived fromalternative splicing and the GluN2 subunit has long carboxyl-terminalregion. The CTD of NMDAR affects membrane targeting, stabilization, modification by phosphorylation and palmitoylation, and degradation56, 57. The CTD of NMDAR also provides interaction sites for manyintracellular proteins important for signal transduction and synapticformation, and is involved in the formation of NMDAR complexes24.

The crystal structure of intact heterotetrameric NMDARs has beenreported 58, 59. The crystal structure of NMDAR revealed theintimate association between ATDs and LBDs and the ATD-LBDinteraction is fundamental to the capability of ligand binding at ATDfor the propagation of conformational change and affects channelactivity.