Abstract

L-glutamate, the major excitatory neurotransmitter of the central nervous system (CNS), plays a vital role in the normal functions of brain. Glutamate receptors can be divided into ionotropic Glutamate receptors (iGluRs), metabotropic Glutamate receptors (mGluRs). The iGluRs are ligand-gated ion channels with three major classes that are named based on the specific activation of three agonists: N-methyl-D-aspartic acid (NMDA), (S)-2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)-propionic acid (AMPA) and Kainate (KA). NMDA receptors are composed of GluN1, GluN2A-D, and/or GluN3A/B subunits. Tremendous work has been done to develop subtype selective ligands over the past decades. However, it’s still elusive to find subtype selective compounds due to the high sequence homology within different subtypes.

In this PhD dissertation, based on the reported crystal structure of NMDA receptor, a large number of (R)-3-acylamino-2-aminopropanoic acid analogues targeting the glycine binding site of the GluN1 NMDA receptor subunit were designed and synthesized. Pharmacological profiles of these compounds were determined using two-electrode voltage-clamp (TEVC) electrophysiology at the different NMDA receptors subtypes. The compounds displayed different potency, efficacy and selectivity among NMDA receptor subtypes. Compound 3.4.2.7a displays low nano-molar subtype-selective potency at GluN1/2C (EC<sub>50</sub> = 6.3 nM) and 3.4.3.4a possesses incredibly 896% of subtype-selective efficacy at GluN1/2C compared to glycine. 4.15b displays higher potency at GluN1/2C than leading compound AICP (EC<sub>50</sub> = 1.48 nM). Furthermore, the detailed structure activity relationships (SARs) provide plentiful information for further NMDA subtype ligands development and the promising compounds identified could be used as pharmacological tools for elucidation of NMDA receptors function and drugs for treatment of the psychiatric disorders.