[S1-4] [4/17/2003(Thur) 15:50-16:25/Grand Hall]

Development of New NMDA Receptor Agonists/Antagonists

No-Sang Park

CNS Laboratory, Korea Research Institute of Chemical Technology,
P.O. Box 107, Yusong, Taejon, 305-600, Korea

Excitatory amino acid (EAA) receptor, particularly NMDA receptor, are now known to be one of major transmitter receptors involved in synaptic excitation. Excessive release of EAA neurotransmitter, glutamate, is an important causative factor in the neurodegenerative processes and can cause neuronal damage and cell death. This excitotoxicity has been shown to be Ca^{++} dependent. Following neuronal trauma a large Ca^{++} influx into the neuron through gated ion channel, such as glutamate receptors, initiates a cascade of biochemical events that disrupt normal cellular processes and can feedback to accelerate the release of glutamate and excitotoxicity. A great deal of evidence has been accumulated that it plays a key role in neurodegeneration and stroke related brain cell death. Thus, NMDA antagonists are proposed to have a number of clinical indications including ischemia and epilepsy. They may also be useful in the prevention of chronic neurodegenerative disorders such as Alzheimer's disease, Huntington's disease and Parkinsonism (G. Johnson, Annu. Rep. Med. Chem. 24, 41 (1989); G. Johnson and C. F. Bigge, ibid. 26, 11, (1991) and Werling et al., J. Pharmacol. Exp. Ther. 255, 40, (1990).

Recent successes in identifying orally active glycine receptor antagonists have reported several classes of 4-hydroxyquinolin-2(1H)-one derivatives (McOuaid, L. A., et al., J. Med. Chem. 35, 3423 (1992); Leeson, P. D., et al. J. Med. Chem. 36, 3386, (1993); Kulagowski, J. J., et al., J. Med. Chem. 37, 1402 (1994); Cai, S. X., et al., J. Med. Chem. 39, 4682, (1996); and 39, 3248 (1996); EP 489,458; EP 459,561; EP 685,466 A1; WO 94/20470; WO 93/10783, EP 685,466A1 and EP 481,676 A1), indole-2-carboxylic acid derivatives (Rowley, M., et al. BioMed. Chem. Lett. 2, 1627 (1992); Louvert, P., et al., J. Med. Chem. 28, 71 (1993); EP 512,817 A1; GB 2, 266,091B) as well as quinoxalinone derivatives (Keana, J. F., et al., J. Med. Chem. 38, 4367 (1995), Nagata, R., et al., J. Med. Chem. 37, 3956 (1994); EP 609,371B1) as

selective noncompetitive antagonists of NMDA receptors possessing potent in vivo activity. Those have been appeared in literatures and are generally declaimed as therapeutically useful agents to prevent or treat neurodegenerative disorders, convulsion and schizophrenia.

Despite intensive investigations about NMDA receptor for the past few decades, the physiological function and the nature of interaction between NMDA receptor and its ligands are of considerable interest but still remains to be fully resolved. In addition, although much work has been done in the field of development of NMDA receptor agonists and antagonists as new drugs to treat neurodegenerative disorders, there are nearly few significant progress in marketed drugs. In most cases in vivo activity is poor.

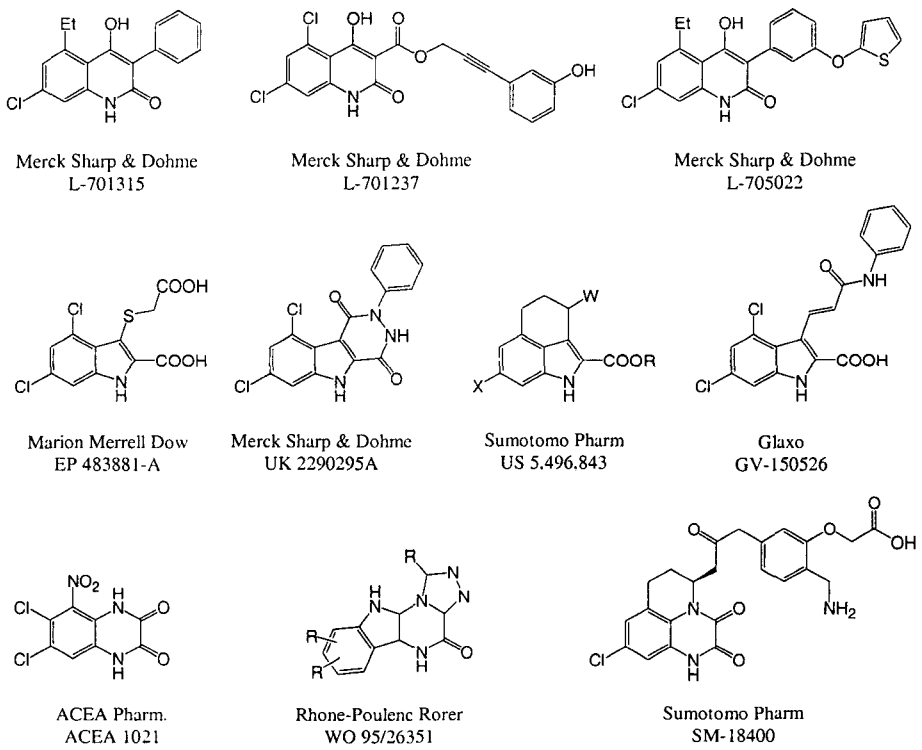

Figure 1. Antagonists at the NMDA receptor glycine modulatory site

Under these circumstances, newly designed NMDA receptor ligands are of major interest not only as experimental tools for investigating fundamental central nervous mechanisms but also as potential drugs for CNS disorder. The development of agonists and antagonists for

NMDA receptor will proceed in the three distinct phases: (1) elucidation of the general structural features underlying NMDA receptor agonist actions; (2) extension of knowledge of agonist structure-activity relationship (SAR) and concomitant recognition of a range of selective antagonists, allowing differentiation of NMDA receptor from other excitatory amino acid receptors (Quisqualate, Kainate etc.); (3) futher development of new NMDA receptor antagonists for use as basic phamacological tools and as new centrally acting drugs such as antipsychotic, anti-ischemic, anticonvulsant, and neuroprotective agents. For pursuiting the goal of third phase, we have developed several potential modulators and also explored the preliminary pharmacological investigation with potential therapeutical candidates during the span of this research.