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# EXCITATORY AMINO ACID RELATED AGENTS
## Symposium in Print

### Foreword

Research into excitatory amino acids is now well into its third decade of life. Despite this longevity, it has really been the last decade of research which has taken this field from relative obscurity to a position of preeminence in the neuroscience community. Along this rapidly accelerating evolutionary path, several milestones are clearly evident. The first of these has been the availability of new and selective receptor antagonists particularly of the N-methyl-D-aspartate (NMDA) receptor. Using these tools, the second key observation in this field was made. This was the realization that glutamic and aspartic acids may play a central role in mediating the neuronal cell death which follows a stroke. The possibility of developing an effective therapy for such a devastating and, as yet untreatable condition, galvanized both academic and industrial laboratories to enter this field in strength. The significant success of this combined effort is self evident and it is hoped that this Symposium-in-Print will provide the reader with a snap shot of progress in this key area of neuroscience research.

Early in the evolution of this field, it was realized that glutamic and perhaps aspartic acid mediated their effects through the activation of several dissimilar receptor subtypes. These receptors, named for the prototypic agent or natural products which activated them (Figure 1), were initially suggested to activate an integral ion channel and were accordingly designated as ionotropic receptors. However, more recently, it has been established that the ionotropic ligand, quisqualic acid also activated a G-protein-linked receptor which has since been named the metabotropic or *1S,3R*-ACPD receptor after its prototypic ligand *trans*-1-amino cyclopentane-1,3-dicarboxylic acid. The original ionotropic QUIS receptor has since been renamed for the more selective ligand γ-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA).

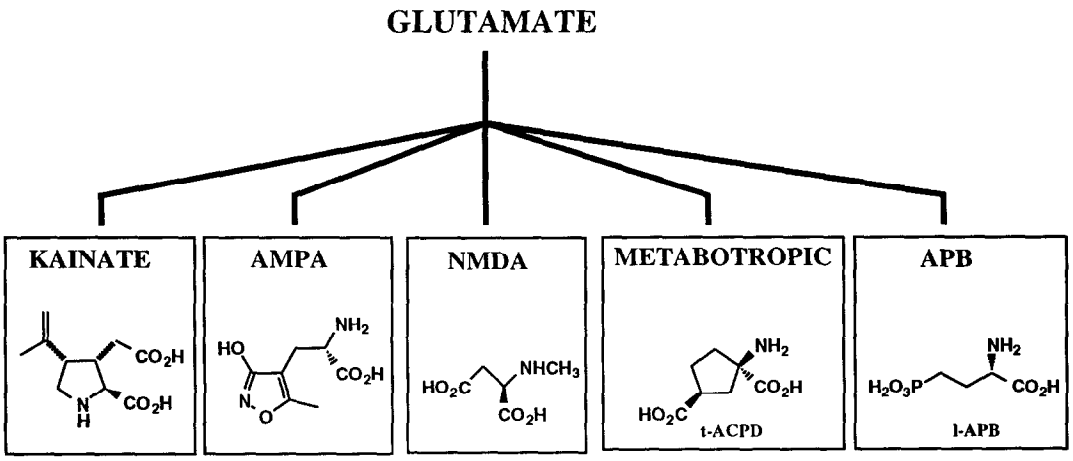


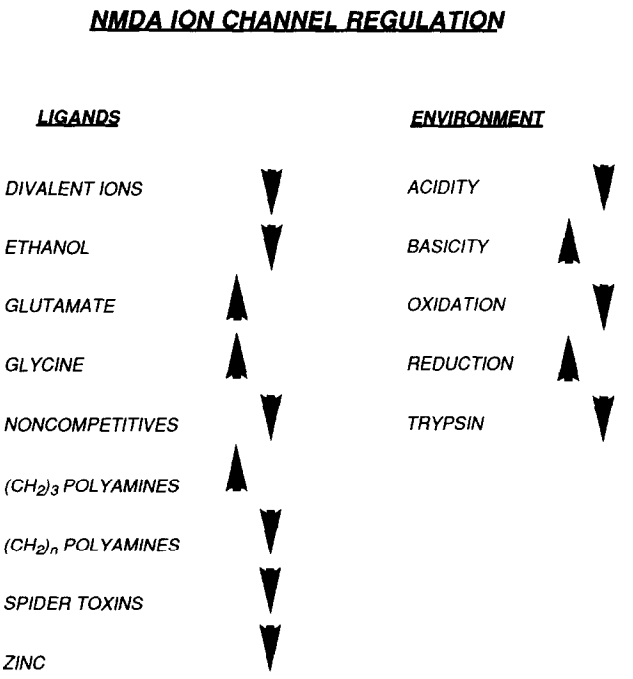

Figure I

As with many other areas of neuroscience research, the application of molecular biology has both clarified and at the same time added complexity to our understanding of EAA receptor classification, structure and function. Past confusion over the unity or dissimilarities of AMPA and KA receptors has, in large measure, been resolved with the identification of a extensive family of homologous protein subunits and binding proteins. These proteins have been expressed in Xenopus oocytes in the form of homomeric or heteromeric complexes which, upon ligand binding, vary significantly in their ionic permeability and gating characteristics. In a similar manner, the existence of a family of phosphoinositol and *c*-AMP activating G-protein-linked glutamate receptors is also emerging. The cloning and expression of dissimilar NMDA receptor protein subunits has been reported recently. In the first of these reports[1], a protein subunit of 105,000 Da has been identified, which, when expressed in oocytes, responds to the application of ligands in a manner qualitatively similar to the native receptor. Surprisingly, the distribution of its *m*RNA is much wider than that established for the NMDA receptor. Using probes based on this initial protein sequence, a series of similar sized receptor subunits have been reported[2,3]. Interestingly, these proteins show in several instances limited sequence homology to the initially reported NMDA receptor subunit. Using a more biochemical approach, a significantly smaller NMDA protein subunit has also been isolated from rat brain following solubilization and affinity chromatography[4]. Subsequent cloning and sequencing afforded a protein showing no sequence homology to any other known receptor. However, for this protein, its *m*RNA does show an overlapping distribution with the native NMDA receptor.

It is perhaps ironic that despite an extensive literature describing both an *in vitro* and *in vivo* neuroprotective action for various NMDA antagonists, their relevance as therapeutic agents for stroke, once the key driving force for the development of the EAA field, is now mired in controversy and confusion[5,6]. Although several NMDA antagonists are reported to be in early clinical development *vide infra*, the search for new and effective antiischemic agents free from serious side effects has most recently been extended to include the AMPA receptor and its selective antagonist, NBQX. Here robust and reproducible efficacy in several models of global ischemia has been demonstrated[7,8]. Given the almost ubiquitous distribution of EAA receptors, it should not be surprising that other promising applications for EAA antagonists should also have emerged. Perhaps the most significant of these being analgesics for the treatment of chronic pain, new treatments for Parkinson's Disease[9,10], drug addiction and most recently, new antagonists for chemotherapy-induced emesis[11].

Due perhaps to its critical role in certain forms of memory, the NMDA receptor is stimulated, antagonized and influenced by an unprecedented range of substances (Figure II)[11,9]. Not surprisingly, this diversity of modulatory sites has provided a wealth of opportunities for targeted drug discovery. Indeed, many of the reports which appear in this Symposium-in-Print detail studies directed towards the discovery of potent and selective NMDA antagonists. Such compounds might act directly at the glutamate or glycine recognition sites or indirectly at the noncompetitive or channel blocking site (Figure III).

Figure II



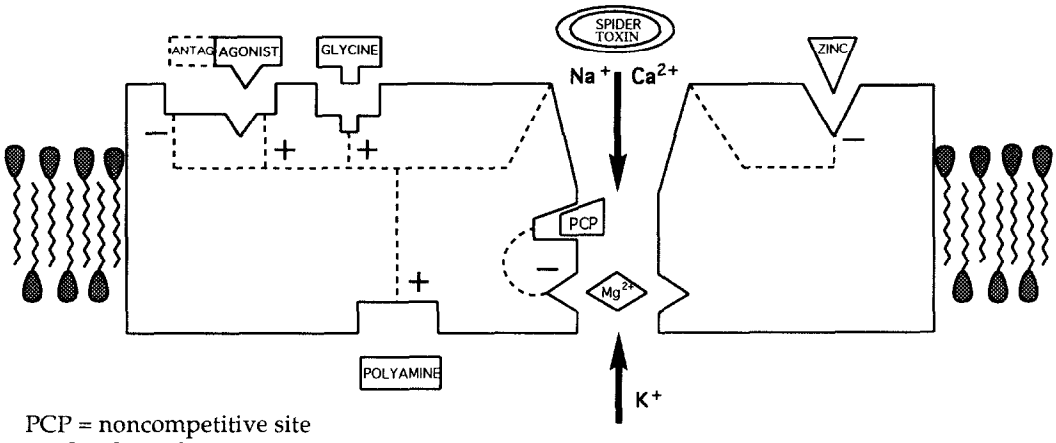

▲ represents an enhancement of receptor activation.

▼ represents an inhibition of receptor activation.

The AMPA/KA receptors have yet to provide an equal diversity of modulatory sites. However, the appreciation of its broad therapeutic potential has catalyzed recent interest in this receptor. To date, most research on the AMPA/KA receptor has focused on elaborating the quinoxalinedione-based antagonists typified by CNQX and NBQX, although, in a more recent report, a benzodiazepine like functional antagonist of receptor activation has been described[8]. This recent disclosure is further elaborated in this Symposium-in-Print. In another example of AMPA receptor modulation, aniracetam, a prototypic member of the pyrrolidinone class of nootropic agents clearly reduces AMPA receptor desensitization, thereby providing a possible explanation for its memory enhancing properties. Although no potent and selective antagonists for the metabotropic receptor have been reported, the diversity of ligands recognized by other G-protein receptors suggest that this will also be a very fruitful and exciting area for future research.

**Figure III**

## NMDA RECEPTOR - LIGAND INTERACTIONS




PCP = noncompetitive site
AGONIST = glutamate site

As with any new mechanistic approach, the confirmation of therapeutic promise and determination of true side effect liability can only be determined by clinical evaluation. To date, only three EAA antagonists, ketamine, dextromethorphan and memantine are currently approved for human use. Two of these compounds, ketamine and dextromethorphan, whose neuropsychological side effects were recognized early in their development, were marketed long before their true mechanism of action was appreciated. Of these three rather weak noncompetitive NMDA antagonists however, only dextromethorphan and memantine are now under clinical investigation for the treatment of stroke. The majority of EAA antagonists currently in clinical study belong to the competitive NMDA antagonist class (Table 1). However, SL 820715, a reported polyamine antagonist and remacemide, a glycine derivative of a rather weak noncompetitive NMDA antagonist are both reported to have progressed into late stage clinical evaluation. Of the new wave of strychnine-insensitive glycine antagonists L-687414 and L-689560 are still under preclinical evaluation. Finally from the AMPA antagonist area, NBQX and a compound selected from the GYKI 52466 series are reported to have progressed to early clinical evaluation.

It is clear from the evolving pharmacology of excitatory amino acid agonists and antagonists that even after three decades of research we are still a long way from appreciating the full potential of this fascinating area. The confirmation of clinical efficacy with minimal side effect liability is eagerly awaited. Following such a demonstration, this field will, no doubt, undergo a further surge in activity.

**Graham Johnson (1992)**
**Bristol-Myers Squibb**

## Table 1*

| Compound | Company | Target | Clinical Phase |
|---|---|---|---|
| **Competitive NMDA Antagonists** | | | |
| CGS 19755 | Ciba-Geigy | Stroke | II |
| CGP-37849 | Ciba-Geigy | Epilepsy | I |
| LY-235959 | Eli Lilly | Neurodegenerative Disorders | Preclinical |
| SDZ-EAA-494 | Sandoz | Epilepsy | I |
| MDL-100453 | Marion Merrel Dow | Stroke | Preclinical |
| **Noncompetitive NMDA Antagonists** | | | |
| CNS-1102 | Cambridge Neuroscience | Stroke/Traumatic Brain Injury | Preclinical |
| CNS-1505 | Cambridge Neuroscience | Stroke/Traumatic Brain Injury | Preclinical |
| Memantine | Merz | Stroke | Launched |
| Remacemide/ FPL-12495 | Fisons | Stroke/Epilepsy | II |
| Dextromethorphan | Hoffman LaRoche | Stroke | II |
| **Glycine Antagonists** | | | |
| L-687414 | Merck | Stroke/Epilepsy | Preclinical |
| L-689560 | Merck | Stroke/Epilepsy | Preclinical |
| ACPC | NIH/Res. Triangle | Epilepsy | Preclinical |
| Felbamate | Carter Wallace | Epilepsy | Pre-registration |
| **AMPA Antagonists** | | | |
| NBQX | Novo Nordisk/ Schering AG | Stroke | I |
| **Polyamine Antagonist** | | | |
| SL-820715 | Synthelabo | Stroke | II |

** Data incorporated in this table was derived from Pharmaprojects and confirmed wherever possible by personal communication*

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