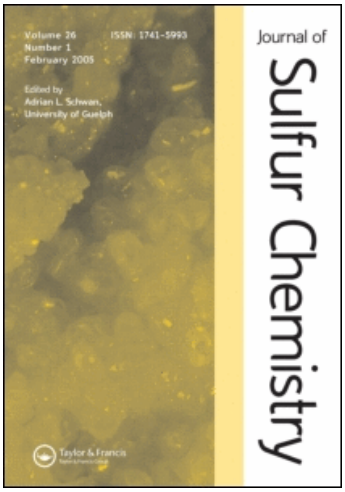

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A review of: "Excitatory Amino Acid Receptors, Design of Agonists and Antagonists"

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BOOK REVIEWS

P. Krogsgaard-Larsen and J. J. Hansen (Eds.), *Excitatory Amino Acid Receptors, Design of Agonists and Antagonists*, Ellis Horwood Limited, Chichester, 1992, ISBN 0-13-296716-2, 382 pp., US $ 135.00.

This book contains the following chapters:

1. *Excitatory amino acids, excitotoxicity and neurodegenerative disorders* by D. Sauer and G. F. Fagg.
2. *Excitatory amino acid receptors: multiplicity and ligand selectivity of receptor subtypes* by P. Krogsgaard-Larsen, U. Madsen, B. Ebert, and J. J. Hansen.
3. *Isolation and structural characterization of excitatory amino acids in mammalian neurons in slice preparations* by G. Johnson.
4. *Electrophysiological techniques for the study of excitatory amino acid receptors* by J. D. C. Lambert and M. Andreasen.
5. *Receptor autoradiography of excitatory amino acid receptors: basic and clinical aspects* by S. Y. Sakurai and A. B. Young.
6. *NMDA receptors: heterogeneity and agonism* by D. J. Kyle, R. J. Patch, E. W. Karbon, and J. W. Ferkany.
7. *Sulphur-containing excitatory amino acids* by R. Griffiths, S. P. Butcher, and H. J. Olverman.
8. *Competitive NMDA receptor antagonists* by P. J. Ornstein and V. J. Klimkowski.
9. *Ligands for NMDA receptor modulatory sites* by D. Lodge.
10. *AMPA receptor agonists: structural, conformational and stereochemical aspects* by J. J. Hansen, F. S. Jørgensen, T. M. Lund, B. Nielsen, A. Reinhardt, I. Breum, L. Brehm, and P. Krogsgaard-Larsen.
11. *Quinoxalinediones as AMPA receptor antagonists: mechanism and structure-activity studies* by P. Jacobsen, L. Naerum, F. E. Nielsen, and T. Honoré.
12. *Kainic acid receptor agonists* by H. Shinozaki.
13. *Polyamine toxins as excitatory amino acid receptor ligands* by N. Kawai.
14. *L-AP4 receptor ligands* by J. F. Koerner and R. L. Johnson.
15. *The quisqualate metabotropic receptor coupled to phospholipase C (Qp)* by J. Bockaert, O. Manzoni, M. Sebben, J.-P. Pin, A. Dumuis, L. Fagni, and F. Sladeczek.
16. *Therapeutic opportunities in modulators of excitatory amino acid-mediated neurotransmission* by J. Drejer.

Five different glutamate receptors (NMDA, AMPA, kainate, L-AP4 and the metabotropic glutamate receptor) have so far been distinguished. Much progress has been achieved in the mid- and especially the late eighties, and this book provides a thorough review of the present knowledge of these systems.

Subjects spanning the full range from the molecular knowledge of receptor assemblies to the biochemical and pharmacological characterization of agonists and antagonists leading to valuable therapeutic clues are covered adequately in this book.

The authors are typically active researchers who have made substantial contributions to the impressive progress in this area, and the literature appears to be covered through 1991, i.e. the book is up to date.

The book is liberally provided with colored and black-and-white illustrations which, with the exception of a rather unprofessional illustration in Chapter 5 (p. 105) and a very crowded illustration in Chapter 10 (p. 229), are of excellent quality.

A good overview of excitatory amino acid pharmacology is presented in Chapter 2.

Sulfur-containing excitatory amino acids (Chapter 7):

This is, of course, the most interesting for the readers of this journal (the outdated spelling of sulfur notwithstanding) where compounds like L-cysteic acid, L-cysteine, L-cysteinesulfinic acid, L-homocysteic acid, L-homocysteine, L-homocysteinesulfinic acid, homohypotaurine, homotaurine, L-methionine, L-serine *O*-sulfate, β-sulfinopyruvic acid, *S*-sulfo-L-cysteine, and taurine are examined with regard to their biosynthetic interrelationships and possible roles as neurotransmitters. While L-cysteinesulfinic acid, L-cysteic acid, L-homocysteinesulfinic acid, and L-homocysteic acid do possess some of the required attributes (presence in brain tissue, active transport, affinity to and agonist action on NMDA and non-NMDA receptors, etc.) the authors conclude that their role as CNS transmitters and/or modulators of excitatory amino acid neurotransmission has not yet been demonstrated beyond doubt.

Non-NMDA receptors (Chapters 10, 11, 12, 14, and 15):

Among this group the AMPA receptor (Chapters 10 and 11) is at present the best described. The receptor is named after the selective agonist (R,S)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA). The most selective AMPA receptor antagonist known is the quinoxaline derivative NBQX (6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3-dione).

A number of agonists based on the kainic acid structure have been developed for the kainate receptor (Chapter 12). No selective antagonists are known.

The metabotropic glutamate receptor (Chapter 15) is, as apparent from its name, not linked to an ion channel, but activates the inositol phosphate secondary messenger system, and pharmacological evidence seems to indicate that several metabotropic glutamate receptors exist. *trans*-1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD) is the only well-known selective agonist [2S,3S,4S-

(carboxycyclopropyl)glycine has also been proposed to be a selective agonist]. L-AP3 (L-2-amino-3-phosphonopropanoic acid) is known to be an antagonist, although with partial agonist properties.

The L-AP4 (2-amino-4-phosphonobutanoic acid), a very close analog of glutamate, has shown to selectively activate a subset of glutamate receptors, now named the L-AP4 receptor (Chapter 14). No selective antagonists are known.

Much evidence points in the direction of a presynaptic role for this receptor as mediator of a negative feedback mechanism. The L-AP4 receptor could therefore be a target of future therapeutic efforts.

Methods for the study of excitatory amino acid receptors (Chapter 3, 4, and 5):

The isolation and characterization of excitatory amino acid receptors is treated in Chapter 3. Molecular information such as e.g. disulfide bridges, glycosylation, intracellular domains, phosphorylation, cloning, sequencing and determination of the size of excitatory amino acid receptors is covered.

Chapter 4 treats electrophysiological techniques for the study of excitatory amino acid evoked potentials. Accounts of studies of autoradiographic binding both in animal brain slice preparations and in human post mortem material from e.g. Alzheimer and Huntington patients can be found in Chapter 5.

Therapeutic prospects (Chapters 1 and 16):

L-Glutamate is generally accepted to be the major excitatory neurotransmitter in the CNS and the primary endogenous acidic amino acid toxin responsible for a number of neurodegenerative disorders.

Structurally analogous neuroexcitants found in the brain include L-aspartate, L-homocysteate, L-cysteinesulfinate, and the tryptophan metabolite quinolinate.

Increased release and a decrease in energy dependent reuptake of glutamate during anoxia (as a consequence of e.g. stroke, head injury, cardiac arrest, or subarachnoid hemorrhage) causes a sustained increase in the intracellular free calcium ion concentration leading ultimately to neurodegeneration. Such neurodegeneration could also be implicated in a number of other disease states.

Hyperactivity of the excitatory neurotransmission may therefore be involved in the **pathogenesis** of Alzheimer's disease, Huntington's disease, AIDS-related dementia, and the neuronal death accompanying the status epilepticus. Involvement of NMDA receptor stimulation has also been demonstrated in a number of animal epilepsy models, and a misbalance between excitatory glutamatic and inhibitory GABA'ergic input has been observed in Parkinson patients. In the case of Huntington's disease and AIDS-related dementia some increase in the endogenous excitatory substance quinolinic acid has been demonstrated.

Hypoactivity, on the other hand, could be involved in schizophrenia and learning or memory deficits.

Hyperactivity could hopefully be modulated therapeutically by glutamate receptor antagonists, whereas diseases stemming from hypoactivity might be ameliorated with glutamate receptor agonists or potentiators of the glutamatic response.

The NMDA antagonist AP-5 has been shown to be antiischemic and anticonvulsive, to block pain, to be anxiolytic and muscle relaxing and to block spreading depression (migraine). None of the known competitive NMDA antagonists (including AP-5) is, however, under clinical development due to the fact that they all are polar substances (containing phosphonate and/or tetrazole groups) which are almost fully ionized at physiological pH with poor penetration of the blood brain barrier, low bioavailabilities, and short half-lives as the consequence.

Sulfur analogs would be more lipophilic and could be a possible solution to this problem.

Chronic treatment with NMDA antagonists may, however, be unsatisfactory due to their psychotomimetic effects known e.g. from PCP (also known as "angel dust"). A chronic change of the NMDA stimulatory input might instead be achieved with compounds acting at the modulatory sites (glycine and polyamine sites) which are devoid of psychotomimetic effects. Competitive NMDA antagonists might, on the other hand, be of benefit in conditions such as stroke. Investigations aiming at the solution of the abovementioned polarity problems appear definitely worthwhile.

Therapeutic modulation of the negative feedback from the L-AP4 receptor would also appear to be a promising approach.

Conclusions

We consider this book as a fine collection of excellent reviews aptly covering all relevant aspects of the contemporary knowledge of excitatory amino acid receptors. However, one notices a certain lack of editorial efforts which could have ensured less overlap between individual chapters as well as the exclusion of outdated statements (such as Chapter 1's to the effect that the secondary messenger system for the L-AP4 system is unknown while Chapter 14 routinely presents exactly this system).

This book contains very useful tabulations of binding assay conditions as well as of the potency and specificity of agonists/antagonists, and extensive SAR considerations. This condensed, but highly readable, information is invaluable for every scientist working in the area and, obviously, this book is a must for both experts as well as newcomers in this rapidly expanding research area.

This rapid development is sustained by a constant flow of key discoveries such as the recent finding [A. Frandsen and A. Schousboe, *Proc. Natl. Acad. Sci. USA* **89**, 2590 (1992)] that stimulation of the different glutamate receptors brings about the ensuing increase in the intracellular free calcium ion concentration by different mechanisms (influx vs. intracellular mobilisation).

While the price of this book might appear high on a per page basis the book is certainly a bargain based on the value of its contents.

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N. S. Simpkins, *Sulphones in Organic Synthesis*, Tetrahedron Organic Chemistry Series Volume 10, Pergamon Press, Oxford, New York, Seoul, Tokyo, 1993, hardcover edition ISBN 0 08 040283 6, £ 55.00/US $99.00, flexicover edition ISBN 0 08 040284 4, £ 30.00/US $54.00, xi + 381 pp.

This book contains an introductory chapter as well as chapters on the preparation of sulfones, on sulfonyl carbanions, on additions to unsaturated sulfones, on rearrangements of sulfones, on cycloaddition chemistry of unsaturated sulfones, on carbon-carbon double bond formation by sulfone elimination, on cyclic sulfones, and on desulfonylations. Unfortunately, the author has not honored the official change of British spelling from sulphur to sulfur as of January 1, 1992 which detracts from the book's otherwise highly contemporary flavor.

Its well over 1038 references cover mainly the 1970–1991 period and include a token 1992 reference. The uniform computer drawn and highly legible structural formulas and the lucid language make for pleasant and stimulating reading, there are no obvious misprints. The material is well organized and caters both to the casual browser and to the busy synthetic chemist searching for clues to some tricky problem.

Professor Simpkins' congenial and well-balanced book is a welcome and timely addition to the standard reference material in the Houben-Weyl and Patai series etc. and should not be missing in any personal or departmental reference library wherever synthetic organic or sulfone chemistry is practised. It could also form the basis of a graduate course in synthetic organic chemistry since it covers a wide range of reactions and preaches the synthetic gospel without the cumbersome lingo which often obscures modern synthetic lore.

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