

## EDITORIAL VIEWS

Is the current system ideal? Certainly not. Recent reports have claimed that IRB are seriously overworked and subject to many undesirable outside influences that could weaken research reviews.<sup>8,9</sup> Is the current system a suitable first step toward expanding the availability of life-saving therapy? Perhaps. Only in time will this question be answered. Until any further refinements to the system are instituted, anesthesiologists must be aware of the current regulations and work within them to design ethically appropriate emergency trials. Only then will there be sufficient progress toward the future in answering the important questions about emergency research.

**Kent S. Pearson, M.D.**

Associate Professor  
Department of Anesthesia  
Chair  
Institutional Review Board  
University of Iowa  
College of Medicine  
University of Iowa Hospitals and Clinics  
Iowa City, Iowa  
kent-pearson@uiowa.edu

Anesthesiology  
1998; 89:1049-51

© 1998 American Society of Anesthesiologists, Inc.  
Lippincott Williams & Wilkins

## AMPA/Kainate Receptor Antagonists as Novel Analgesic Agents

THE pharmacology of amino acid neurotransmission has brought new understanding for the mechanisms of action of drugs used in anesthesia. A number of agents used by anesthesiologists facilitate  $\gamma$ -aminobutyric acid-mediated inhibitory neurotransmission<sup>1</sup>; molecular research techniques continue to define these mechanisms.<sup>2</sup> Potentially equally important, but less accessible, to anesthesiologists are drugs inhibiting excitatory

## References

1. Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W, Tomaselli GF, Dorman T, Campbell K, Lipsett P, Brews MJ: Beta-adrenergic blockade accelerates conversion of post-operative tachyarrhythmias. *ANESTHESIOLOGY* 1998; 89:1052-9
2. "The Nuremberg Code," *The Ethics of Research Involving Human Subjects*. Edited by Vanderpool HY. Frederick, University Publishing Group, 1996, pp 431-2
3. Federal policy for the protection of human subjects; Notices and rules. *Federal Register* 1991; 56:28003-23
4. Protection of human subjects; Informed consent. *Federal Register* 1996; 61:51498-533
5. Manwick C: Assessment of exception to informed consent (*Medical News and Perspectives*). *JAMA* 1997; 278:1392-3
6. Campbell PW: Debate swirls around new rules for informed consent in trauma research. *The Chronicle of Higher Education* October 24, 1997; A30.
7. Dula A: Bearing the brunt of the new regulation: Minority populations. *Hastings Center Report* January-February; 1997:11-12
8. Marshall K: Review Boards: A system "in jeopardy?" *Science* 1998; 280:1830-1
9. Brown JG: Institutional Review Boards: A time for reform. Washington, DC: Department of Health and Human Services, Office of the Inspector General; 1998. Publication OE I-01-97-00193

This Editorial View accompanies the following article: Sang CN, Hostetter MP, Gracely RH, Chappell AS, Schoepp DD, Lee G, Whitcup S, Caruso R, Max MB: AMPA/kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans. *ANESTHESIOLOGY* 1998; 89:1060-7.

Accepted for publication June 2, 1998.

Key words: Allodynia; excitatory amino acids; hyperalgesia; pain.

amino acid (EAA) neurotransmission by glutamate and aspartate. In this issue of *ANESTHESIOLOGY*, the study by Sang *et al.*<sup>3</sup> presents evidence agreeing with mediation of experimentally induced human hyperalgesia by action at one class of EAA receptors not previously evaluated in humans.

The EAA receptors in the central nervous system convey information through ionotropic, cation-selective, ligand-gated ion channels (ionotropic glutamate receptors) and G protein-coupled metabotropic receptors. Ionotropic EAA receptors can be divided into N-methyl-D-aspartate (NMDA) receptors and non-NMDA receptors. Basic research suggests that new drugs acting at either ionotropic or metabotropic glutamate receptors may have clinical usefulness for various pathophysiologic conditions.

The NMDA receptors are largely permeable to calcium, use glycine as a coagonist, are enhanced by polyamines, have a voltage-dependent magnesium block, and demon-

strate use-dependent, open-channel blockade by non-competitive antagonists. The NMDA receptor antagonists have been emphasized in anesthesiology in part as a result of ketamine, a noncompetitive NMDA receptor antagonist, available clinically since the late 1950s. Other drugs, such as dextrorphan, affect NMDA receptors but are not particularly effective or available in suitable dosage forms.

Because of the emphasis on NMDA receptor antagonists in pain, hyperalgesia and cerebral protection in the anesthesia literature, the pharmacology of non-NMDA EAA receptors, and preclinical research in this area are less familiar. The non-NMDA EAA receptors are ligand-gated ion channels that are not only permeable to sodium, but some receptors are more selective for calcium. Non-NMDA receptors are ubiquitous and mediate fast excitatory neurotransmission in the mammalian central nervous system and therefore should be relevant targets for the development of therapeutic agents (as has been the case for drugs affecting  $\gamma$ -aminobutyric acid transmission). These receptors are referred to as the non-NMDA class because of the lack of specific agonists and antagonists available to influence this receptor system. Non-NMDA receptors can be activated by the synthetic EAAs kainate or  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and these agonists have been used to name these two receptor subclasses based on relative potency. Most antagonists to this receptor system block AMPA and kainate receptors, although early animal studies suggest more selective drugs soon may be available.<sup>4</sup>

The non-NMDA receptor system is further refined by ligand-binding experiments using recombinant receptors that indicate that four genes encode AMPA receptor subunits and five encode the kainate receptor subunits. Glutamate receptor (GluR) subunits 1, 2, 3, and 4 have properties similar to those of AMPA receptors; the GluRs 5, 6, 7, and the kainate 1 and 2 assemble into receptors of the kainate-preferring type; other subtypes may yet be identified. Thus far, the physiologic role of AMPA preferring receptors appears to be better understood.

Preclinical studies in animal models suggest that non-NMDA ionotropic glutamate receptors may be important in cerebral ischemia, learning and memory, neurodegenerative disease, seizures, and pain.<sup>5</sup> In this study by Sang *et al.*,<sup>3</sup> the effect of LY293558, a non-NMDA (AMPA/kainate) receptor antagonist, on capsaicin-evoked hyperalgesia-exaggerated responses to painful stimuli and allodynia-exaggerated responses to nonpainful stimuli were studied in human volunteers. As shown in this report

and by others,<sup>6,7</sup> the physiology of brief painful stimuli and the pathophysiology of persistent enhanced responsiveness after injury are different. This altered central processing in persistent pain states appears to be key to the understanding and treatment of acute postoperative pain and chronic pain states. Basic research and human psychophysical testing have characterized the enhanced pain state created by capsaicin injection,<sup>6,7</sup> the model used in the study by Sang *et al.*<sup>3</sup> Particular features of this model include large afferent fiber (A- $\beta$ )-evoked allodynia (pain responses caused by stroking with a brush), which is in part characteristic of some neuropathic pain conditions. In addition, pinprick hyperalgesia, which may be important for enhanced responses to high-threshold stimuli in persistent clinical pain states, was studied.

As might be expected when modifying a ubiquitous neurotransmitter, side effects after intravenous administration of LY293558 occurred, prompting the investigators to identify a maximum tolerated dose. A high but tolerable dose of this LY293558 had little effect on brief nociceptive stimuli to electrical and heat pain, indicating that this drug potentially permits normal nociception, an important protective mechanism. A reduction in pain intensity to capsaicin injection and decreases in the areas of allodynia and pinprick hyperalgesia occurred after LY293558 administration. Therefore, this drug, in part, prevented the sensitization processes thought to be important for development of persistent pain in humans. The most remarkable side effect observed with this non-NMDA receptor antagonist was visual impairment, which after further study showed that no permanent deficit occurred.

Drugs such as LY293558 may be acting at non-NMDA receptors at several sites along pain transmission pathways to modify the sensitization processes in persistent pain states. Peripheral AMPA and kainate receptors<sup>8</sup> have been identified on nociceptive nerve terminals; thus a peripherally acting non-NMDA receptor antagonist may be useful. Non-NMDA receptor antagonists also powerfully suppress nociception and hyperalgesia when administered spinally,<sup>9</sup> a potential route of administration of particular interest to anesthesiologists. Certainly, systemic administration of a drug such as LY293558 may also modify pain transmission at supraspinal sites. Sang *et al.*<sup>3</sup> hypothesize that the antihyperalgesic and antiallodynic effects of LY293558 may occur through antagonism at a particular glutamate receptor subtype, GluR 5, present on cells in dorsal root ganglia. This is a reminder of the importance of these nine GluR subtypes and the likelihood that specific drugs acting at these receptor

## EDITORIAL VIEWS

subtype may be powerful suppressants of pain and exaggerated pain states with perhaps fewer side effects than LY293558. The development of antagonists to GluRs 1-7 and kainate receptors 1 and 2 with *in vivo* specificity for these subunits is lacking.

As the search continues for new analgesic drugs with improved effectiveness, limited side effects, and enhanced cost benefit, the clinical study by Sang *et al.*<sup>3</sup> indicates that non-NMDA ionotropic EAA receptor antagonists should be considered.

**Timothy J. Brennan, Ph.D., M.D.**  
Associate Professor  
Department of Anesthesia  
University of Iowa College of Medicine  
Iowa City, Iowa  
tim-brennan@uiowa.edu

## References

1. Tanelian DL, Kosek P, Mody I, MacIver MB: The role of the GABA<sub>A</sub> receptor/chloride channel complex in anesthesia. *ANESTHESIOLOGY* 1993; 78(4):757-76
2. Mihic SJ, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Greenblatt EP, Harris RA, Harrison NL: Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors (see comments). *Nature* 1997; 389(6649):385-9
3. Sang CN, Hostetter MP, Gracely RH, Chappell AS, Schoepp DD, Lee G, Whitcup S, Caruso R, Max MB: AMPA/kainate Antagonist LY293558 Reduces Capsaicin-evoked Hyperalgesia but Not Pain in Normal Skin in Humans. *ANESTHESIOLOGY* 1998; 89:1060-7
4. Fletcher EJ, Lodge D: New developments in the molecular pharmacology of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate and kainate receptors. *Pharmacol Ther* 1996; 70(1):65-89
5. Bettler B, Mulle C: Review: Neurotransmitter receptors. II. AMPA and kainate receptors. *Neuropharmacology* 1995; 34(2):123-39
6. Torebjork HE, Lundberg LE, LaMotte RH: Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol* 1992; 448:765-80
7. LaMotte RH, Lundberg LE, Torebjork HE: Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *J Physiol* 1992; 448:749-64
8. Carlton SM, Hargrett GL, Coggeshall RE: Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. *Neurosci Lett* 1995; 197(1):25-8
9. Dougherty PM, Palecek J, Paleckova V, Sorkin LS, Willis WD: The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *J Neurosci* 1992; 12(8):3025-41