NMDA receptors in sensory information processing

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During the past year electrophysiological studies, particularly in the visual and somatosensory systems, have begun to uncover the specific roles played by NMDA receptors in the processing of sensory information. Many of the features of NMDA-receptor-mediated sensory responses reflect known properties of the receptor.

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Introduction

The N-methyl-D-aspartate (NMDA) receptor is a unique voltage- and ligand-gated subtype of excitatory amino acid (EAA) receptor whose role in excitotoxicity and synaptic plasticity has been well studied. Recently, it has become increasingly clear, however, that NMDA receptors play a role not only in plastic or pathological situations, but also in normal sensory transmission.

NMDA receptors have several features that distinguish them from other EAA receptors (for reviews, see [1,2]). First, they are highly permeable to Ca^{2+} ions; second, their kinetics lead to a current with a relatively slow timecourse; and third, they are subject to voltage-dependent blockade by Mg^{2+} ions. Although there are several other subtypes of EAA receptor, two of the subtypes that commonly coexist with NMDA receptors in the central nervous system, the kainate and quisqualate receptors, are both blocked by quinoxalinediones and hence are difficult to distinguish pharmacologically [1]. For the purposes of this review, the kainate and quisqualate receptors are collectively referred to as 'non-NMDA' receptors.

NMDA receptors in specific sensory pathways

Do NMDA and non-NMDA receptors subserve different sensory pathways and/or different functional cell types, or are both types of receptor always found together? Both arrangements have been reported, but the most common finding is that NMDA and non-NMDA receptors are activated in tandem. Where only one of the subtypes is present, it is usually the non-NMDA receptor.

Visual system

In the retina, non-NMDA receptors mediate depolarizing responses in both horizontal cells [3•,4•] and bipolar cells [5], while both NMDA and non-NMDA receptors appear to mediate input from bipolar cells to retinal ganglion cells [6].

NMDA and non-NMDA receptors are also present in all three of the central targets of the retina that have been studied, although the roles played by the two receptor subtypes may differ. In the suprachiasmatic nucleus of the hypothalamus, stimulation of either retinal or non-retinal inputs activates both NMDA and non-NMDA receptors [7•].

Recent studies of the lateral geniculate nucleus (LGN) *in vitro* indicate that both ascending retinal input and descending corticofugal inputs depend on both types of receptor (M Esguerra and M Sur: *Soc Neurosci Abstr* 1991, 17:628) [8•,9]. *In vivo* studies of the LGN [10–12,13,14•] indicate that responses of on- and off-centered neurons show a similar degree of dependence on NMDA receptors, as do X and Y cells (cells that show linear and non-linear spatial summation, respectively). Recently, a new classification of LGN neurons, based on temporal rather than spatial response properties, has been proposed [15,16]. 'Lagged' responses have long latencies to visual stimulation, slow increases to peak firing rate, and a more delayed return to baseline firing; 'non-lagged' responses are more rapid in onset and offset, and have an initial transient peak. Whether or not these two types of responses represent different cell classes, or different response modes on the same cells remains controversial [16,17•]. Responses in these two classes do appear to differ in their dependence on NMDA receptors, however. Lagged responses are much more sensitive to blockade of NMDA receptors than are non-lagged responses [11,12,14•].

An *in vitro* study of the optic tectum has found that both NMDA and non-NMDA receptors appear to contribute to retinotectal transmission [18]. However, a recent study of the analogous mammalian structure (the superior colliculus) failed to demonstrate a significant role for NMDA receptors in visual transmission [19•].

In the visual cortex, a large number of studies have demonstrated a dependence of visual- and electrically-evoked responses on NMDA receptors. The precise mag-

Abbreviations

APV—D-2-amino-5-phosphonovalerate; **EAA**—excitatory amino acid; **EPSP**—excitatory postsynaptic potential; **LGN**—lateral geniculate nucleus; **NMDA**—N-methyl-D-aspartate; **VB**—ventrobasal nucleus.

nitude and laminar distribution of NMDA-mediated responses has been a matter of some debate. Intracellular studies *in vitro* have in general revealed a monosynaptic response to afferent stimulation mediated by both receptor subtypes [20]. Patch-clamp studies indicate that both types of receptor are spontaneously activated by an endogenous agonist [21], or by stimulating a single pre-synaptic neuron (P Stern and B Sakmann: *J Physiol* 1991, *Abstract 320P*: 438) and, at least in cultured cortical neurons, most synapses contain both types of receptor [22•]. It has recently been suggested that short-latency monosynaptic inputs from LGN afferents may be mediated solely by non-NMDA receptors, and that NMDA-receptor-mediated responses to white matter stimulation are polysynaptic [23,24•].

In vivo studies have reported different degrees of sensitivity to blockade of NMDA receptors [25–27]. Functionally defined cell classes (e.g: simple, complex) do not appear to differ in their dependence on NMDA receptors, although cells do differ as a function of laminar position in adult cats. Recently it has been reported that NMDA receptors contribute mainly to visual responses in the superficial layers [27], although two prior studies, one *in vivo* [28] and one *in vitro* [20], reported a substantial contribution to responses of deep layer cells.

Somatosensory system

In the spinal cord, primary afferent input to dorsal horn neurons is primarily via non-NMDA receptors [29], although NMDA receptors may play a role in mediating slow potentials evoked in dorsal [30•] and ventral [31] cord following stimulation of thinly myelinated and unmyelinated fibers. *In vivo*, NMDA receptors modulate the responsiveness of spinothalamic neurons [32] and appear to be especially important in transmitting nociceptive information [33•].

In somatosensory thalamus, non-nociceptive mechanoreceptor inputs activate both NMDA and non-NMDA receptors [34,35•], while nociceptive inputs activate only NMDA receptors [36]. It is interesting to note that nociceptive responses in the ventrobasal nucleus of the thalamus are similar in many ways to lagged responses in the LGN. Both appear to depend mainly or entirely on NMDA receptors, increase slowly upon stimulation, and can outlast the stimulus.

NMDA and non-NMDA receptors are both present in the somatosensory cortex (see below), although little has been reported about receptor specificity of individual cell types and pathways.

Bursting

In several systems, activation of NMDA receptors leads to oscillatory bursting behavior which depends on Ca^{2+} [37]. It has recently been proposed that synchronous neuronal oscillations serve as a mechanism for feature-linking within disparate regions of cortex [38•]. In the somatosensory cortex, NMDA activates, and D-2-amino-5-phosphonovalerate (APV) blocks, synchronized bursting of layer 4 and 5 neurons [39]. NMDA-receptor-mediated synchronized bursting is also present in the superficial layers of the visual cortex (R Langdon and M Sur: *Neurosci Abstr* 1990, 16:1218). Under conditions that facilitate NMDA-receptor activation (e.g: in medium containing low Mg^{2+}) synchronized cortical oscillations originate in layer 5 pyramidal neurons [40•].

Temporal integration

The ability of NMDA receptors to integrate over time resides in their slow kinetics and in the fact that channel opening and closing are independent of Mg^{2+} block. This means that at any given time there may be an 'occult conductance,' which may be expressed with subsequent depolarization [2]. Frequency-dependent enhancement of NMDA-receptor-mediated excitatory postsynaptic potentials (EPSPs) has been reported in many *in vitro* systems including the hippocampus [41], mammalian [42] and reptilian cortex [24•], and LGN [9].

In the ventrobasal nucleus (VB) of somatosensory thalamus, single shocks activate only non-NMDA receptors, but trains of shocks activate both types of receptors. Extracellular responses to somatosensory stimulation in VB consist of an early transient response, which does not depend on NMDA receptors, and a later sustained response which does [34]. These studies have led to the view that in general non-NMDA receptor activation is necessary to depolarize the cell sufficiently to relieve Mg^{2+} block of NMDA receptors. More recently, Salt and Eaton [35•] combined the techniques of iontophoresis and intracellular recording *in vivo* and found that brief stimuli do in fact evoke NMDA-dependent EPSPs, but that, as *in vitro*, these EPSPs are slower in time course than the non-NMDA dependent EPSPs. The initial rising phase of the response appeared to depend primarily on non-NMDA receptors, and accounted for most of the initial spikes.

In the LGN, there have been conflicting reports concerning the relative contribution of the different receptor subtypes to transient and sustained responses. For non-lagged cells, which have clear transient components, Sillito *et al.* [10] and Kwon *et al.* [14•] reported no difference in the degree to which early and late response components depended on NMDA receptors, while Hartveit and Heggelund [12] and Funke *et al.* [13] reported a greater dependence of late components on NMDA receptors. In any case, the effect, if present, is clearly much less pronounced than in the VB. The difference between the somatosensory and visual systems probably reflects a difference in the timecourse of sensory stimulation in the two pathways. VB neurons (and even primary somatosensory cortical neurons) can respond quite rapidly even to very brief stimuli. LGN neurons (and visual cortical neurons to an even greater degree) respond with longer latencies and appear to require much longer temporal integration of inputs to respond.

In vitro studies of the LGN [8•,9] and visual cortex [20,21], as well as somatosensory cortex [42], reveal NMDA-receptor-mediated EPSPs that have a slow timecourse, as found in other brain regions. *In vivo* intracellular recordings in the visual cortex reveal barrages of fast EPSPs superimposed on much slower depolarizations in

response to visual stimuli [43]. The pharmacology of these slow events is not yet known.

Voltage-dependence

The most characteristic feature of NMDA-receptor-mediated responses recorded *in vitro* is their voltage-dependence. In the LGN, several studies have demonstrated a voltage-dependence of optic-tract induced EPSPs [8•,9]. A functional consequence of this voltage-dependence has recently been demonstrated (M Esguerra and M Sur: *Soc Neurosci Abstr* 1990, 16:159). In this study corticofugal inputs also activated NMDA receptors on LGN neurons, and stimulation of these inputs produced an NMDA-dependent enhancement of subsequent retinogeniculate transmission within a short time-window. This provided evidence for the suggestion that corticofugal inputs serve to gate or modulate transmission through the LGN [44].

In the cat visual cortex, stimulation of intracortical pathways facilitates EPSPs produced by optic radiation stimulation. Interestingly, however, this facilitatory effect appears to depend on voltage-sensitive Na^+ channels, and not on NMDA receptors [45•].

Recently, two studies in the visual cortex [46] and LGN [47•] have focused on how the voltage-dependence of NMDA receptors may contribute to responses at varying levels of sensory input *in vivo*. In both studies, iontophoretic techniques were used to assess the contribution of NMDA receptors, while features of the visual stimulus were varied in order to alter the amount of excitatory and/or inhibitory synaptic input reaching the cell. Neurons in the LGN and visual cortex increased their firing in response to increasing stimulus contrast, presumably due to a greater excitatory synaptic drive. One might expect, given the voltage-dependence of NMDA receptors, that they might contribute proportionately less during low levels of stimulation and more during higher levels of stimulation. In fact, in both cortex [46] and LGN [47•], the proportion of the visual response mediated by NMDA receptors was the same at all contrasts. This means that during visual stimulation, NMDA receptors act in a graded rather than 'switch-like' fashion. Even a very small amount of sensory input depolarizes cortical or LGN neurons sufficiently to relieve the Mg^{2+}-block of NMDA receptors.

Kwon *et al.* [47•] have studied the effect of changing the balance of visually-evoked inhibition and excitation on the fraction of the response mediated by NMDA receptors in the LGN. LGN neurons respond best to small spots confined to the center of their receptive fields, and respond more poorly as stimulus size is increased. This is due to both a withdrawal of excitation (because of surround inhibition in the retina) and lateral inhibitory circuits in the LGN [48]. Kwon *et al.* found that NMDA receptors accounted for a proportionately larger fraction of the response to small spots, and a smaller fraction of the response to large spots. This suggests that the balance of excitatory and inhibitory input to a cell can regulate the degree to which NMDA receptors participate in the transmission of sensory information.

In the cortex, Fox *et al.* [46] also studied the effects on visual responses of exogenously applied agonists. The non-NMDA agonist kainate excited cortical neurons by a constant amount regardless of the degree of visual stimulation. NMDA, however, had a multiplicative effect; a given dose produced a small excitation at low stimulus contrasts but a large excitation at higher stimulus contrasts. Hence, NMDA receptors appear to regulate the 'gain' of the contrast response of cortical neurons. Fox and Daw [49•] have modeled their results in terms of lumped conductances and known properties of NMDA and non-NMDA receptor-mediated currents, and have been able to reproduce most of the behavior of the neurons they studied. The model suggests the somewhat surprising conclusion that the multiplicative effect of exogenously applied NMDA depends much more on the fact that the receptor has two ligand-binding sites, than on its voltage-dependence. A model with multiple synaptic compartments would seem to be the next step. In any case, taken together the experimental and theoretical results call attention to the fact that NMDA receptors may have a multiplicative effect that is graded rather than switch-like, and which may depend not only on voltage-dependence, but on other properties of the NMDA receptor as well.

Conclusion

NMDA receptors contribute to sensory responses at all levels of the visual and somatosensory pathways, and are most often activated in tandem with non-NMDA receptors. The participation of NMDA receptors in bursting may be due to their permeability to Ca^{2+}. Synchronized bursting responses may be a mechanism for feature-linking, or may reflect state-dependent changes in information processing. NMDA-mediated responses generally require greater temporal integration than do responses mediated by non-NMDA receptors. This makes NMDA receptors particularly well suited for conveying signals that vary only slowly. Examples include lagged responses in the LGN and nociceptive responses in the spinal cord and VB. The voltage-dependence (and perhaps cooperative agonist binding) of NMDA receptors allows them to act as 'amplifiers' within the visual cortex. Their participation is, however, graded rather than 'switch-like.' The voltage-dependence of NMDA receptors also makes them especially sensitive to inhibitory control.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. NICOLL RA, MALENKA RC, KAUER JA: **Functional Comparison of Neurotransmitter Receptor Subtypes in Mammalian Central Nervous System.** *Physiol Rev* 1990, 70:513–565.

2. BEKKERS JM, STEVENS CF: **Computational Implications of NMDA Receptor Channels.** *Cold Spring Harb Symp Quant Biol* 1990, 55:135.

3. • YANG X, WU SM: **Coexistence and Function of Glutamate Receptor Subtypes in the Horizontal Cells of the Tiger Salamander Retina.** *Vis Neurosci* 1991, 7:377–382.

Intracellular responses of horizontal cells in the salamander retina *in vitro* to various glutamate agonists were compared. The results suggest that the light response of horizontal cells is mediated by non-NMDA receptors and that NMDA receptors are not present on these cells.

4. • HANKINS MW, IKEDA H: **Non-NMDA Type Excitatory Amino Acid Receptors Mediate Rod Input to Horizontal Cells in the Isolated Rat Retina.** *Vision Res* 1991, **31**:609–617.

Rod-driven horizontal cells in the isolated rat retina were studied intracellularly during application of glutamate agonists and antagonists. The results support the conclusion that, as in the amphibian retina [3•], horizontal cell responses are mediated by non-NMDA receptors, and NMDA receptors do not contribute.

5. MILLER RF, SLAUGHTER MM: **Excitatory Amino-Acid Receptors of the Retina: Diversity of Subtypes and Conductance Mechanisms.** *Trends Neurosci* 1986, 9:211–218.

6. MITTMAN S, TAYLOR WR, COPENHAGEN DR: **Concomitant Activation of Two Types of Glutamate Receptor Mediates Excitation of Salamander Retinal Ganglion Cells.** *J Physiol* 1990, **428**:175–197.

7. • KIM YI, DUDEK FE: **Intracellular Electrophysiological Study of Suprachiasmatic Nucleus Neurons in Rodents: Excitatory Synaptic Mechanisms.** *J Physiol* 1991, 444:269–287.

An *in vitro* slice preparation was used to demonstrate that retinal inputs activate both NMDA and non-NMDA receptors. As in other systems the NMDA component is voltage-dependent and slow in time course.

8. • ESGUERRA M, KWON YH, SUR M: **Retinogeniculate EPSPs Recorded Intracellularly in the Ferret Lateral Geniculate Nucleus In Vitro: Role of NMDA Receptors.** *Vis Neurosci* 1992, **8**:545–555.

Blockade of NMDA receptors shortened the time course and reduced the amplitude of optic-tract evoked EPSPs. As in other systems, the NMDA-dependent component increased with depolarization. An important result of this study was that NMDA receptors appeared to contribute substantially even to early (< 10 ms) components of the EPSP.

9. SCHARFMAN HE, LU SM, GUIDO W, ADAMS PR, SHERMAN SM: **N-Methyl-D-Aspartate Receptors Contribute to Excitatory Postsynaptic Potentials of Cat Lateral Geniculate Neurons Recorded in Thalamic Slices.** *Proc Natl Acad Sci USA* 1990, **87**:4548–4552.

10. SILLITO AM, MURPHY PC, SALT TE, MOODY CI: **Dependence of Retinogeniculate Transmission in Cat on NMDA Receptors.** *J Neurophysiol* 1990, **63**:347–355.

11. HEGGELUND P, HARTVEIT E: **Neurotransmitter Receptors Mediating Excitatory Input to Cells in the Cat Lateral Geniculate Nucleus. I. Lagged Cells.** *J Neurophysiol* 1990, 63:1347–1360.

12. HARTVEIT E, HEGGELUND P: **Neurotransmitter Receptors Mediating Excitatory Input to Cells in the Cat Lateral Geniculate Nucleus. II. Nonlagged Cells.** *J Neurophysiol* 1990, 63:1361–1372.

13. FUNKE K, EYSEL UT, FITZGIBBON T: **Retinogeniculate Transmission by NMDA and Non-NMDA Receptors in the Cat.** *Brain Res* 1991, **547**:229–238.

14. • KWON YH, ESGUERRA M, SUR M: **NMDA and Non-NMDA Receptors Mediate Visual Responses of Neurons in the Cat's Lateral Geniculate Nucleus.** *J Neurophysiol* 1991, 66:414–428.

NMDA and non-NMDA agonists and antagonists were applied to LGN neurons recorded *in vivo*. Both receptor subtypes were found to contribute to visual responses. No differences were found between on and off or between X and Y type cells, but lagged responses were more dependent on NMDA receptors than were non-lagged responses.

15. MASTRONARDE DN: **Two Classes of Single-Input X-Cells in Cat Lateral Geniculate Nucleus. I. Receptive-Field Properties and Classification of Cells.** *J Neurophysiol* 1987, 57:357–379.

16. HUMPHREY AL, WELLER RE: **Structural Correlates of Functionally Distinct Groups of X-Cells in the Lateral Geniculate Nucleus of the Cat.** *J Comp Neurol* 1988, **268**:448–468.

17. • MCCORMICK DA: **Functional Properties of a Slowly Inactivating Potassium Current in Guinea Pig Dorsal Lateral Geniculate Relay Neurons.** *J Neurophysiol* 1991, 66:1176–1189.

A rapidly activating and slowly inactivating K^+ current was studied under current- and voltage-clamp *in vitro*. This current could account for some of the properties of lagged responses observed *in vivo*.

18. VAN DEUSEN EB, MEYER RL: **Pharmacologic Evidence for NMDA, APB and Kainate/Quisqualate Retinotectal Transmission in the Isolated Whole Tectum of Goldfish.** *Brain Res* 1990, **536**:86–96.

19. • ROBERTS WA, SEATON SA, SALT TE: **Excitatory Amino Acid Receptors Mediate Synaptic Responses to Visual Stimuli in Superior Colliculus Neurones of the Rat.** *Neurosci Lett* 1991, **129**:161–164.

NMDA and non-NMDA receptor agonists and antagonists were applied iontophoretically to neurons in the rat superior colliculus. Neurons were excited by both types of agonist. Visual responses were depressed by antagonism of non-NMDA receptors, but were affected by antagonism of NMDA receptors in only 2 out of 16 cases.

20. JONES KA, BAUGHMAN RW: **NMDA- and Non-NMDA-Receptor Components of Excitatory Synaptic Potentials Recorded from Cells in Layer V of Rat Visual Cortex.** *J Neurosci* 1988, 8:3522–3534.

21. LO TURCO JJ, MODY I, KRIEGSTEIN AR: **Differential Activation of Glutamate Receptors by Spontaneously Released Transmitter in Slices of Neocortex.** *Neurosci Lett* 1990, **114**:265–271.

22. • JONES KA, BAUGHMAN RW: **Both NMDA and Non-NMDA Subtypes of Glutamate Receptors are Concentrated at Synapses on Cerebral Cortical Neurons in Culture.** *Neuron* 1991, 7:593–603.

Whole cell currents were recorded from visual cortical neurons in culture in response to focal application of glutamate in the presence of NMDA or non-NMDA receptor antagonists. Responses mediated by the two receptor subtypes colocalized to 'hot-spots,' which also corresponded to the location of synapses as indicated by immunohistochemical staining for synaptic vesicles.

23. NISHIGORI A, TSUMOTO T, KIMURA F: **Contribution of Quisqualate/Kainate and NMDA Receptors to Excitatory Synaptic Transmission in the Rat's Visual Cortex.** *Vis Neurosci* 1990, 5:591–604.

24. • LARSON-PRIOR LJ, ULINSKI PS, SLATER NT: **Excitatory Amino Acid Receptor-Mediated Transmission in Geniculocortical and Intracortical Pathways within Visual Cortex.** *J Neurophysiol* 1991, 66:293–306.

Intracellular recordings were made from an *in vitro* preparation of turtle visual cortex. Electrical stimulation of the geniculocortical pathway produced EPSPs that were mediated by non-NMDA receptors, while stimulation within the cortex produced compound EPSPs that contained three components: an early component mediated by an unknown receptor, a second component mediated by non-NMDA receptors, and a late component mediated by NMDA receptors. The late component showed potentiation during repetitive stimulation.

25. MILLER KD, CHAPMAN B, STRYKER MP: **Visual Responses in Adult Cat Visual Cortex Depend on N-Methyl-D-Aspartate Receptors.** *Proc Natl Acad Sci USA* 1989, **86**:5183–5187.

26. KLEINSCHMIDT A, BEAR MF, SINGER W: **Blockade of 'NMDA' Receptors Disrupts Experience-Dependent Plasticity of Kitten Striate Cortex.** *Science* 1987, **238**:355–358.

27. FOX K, SATO H, DAW N: **The Location and Function of NMDA Receptors in Cat and Kitten Visual Cortex.** *J Neurosci* 1989, 9:2443–2454.

28. HAGIHARA H, TSUMOTO T, SATO H, HATA Y: **Actions of Excitatory Amino Acid Antagonists on Geniculo-Cortical Transmission in the Cat's Visual Cortex.** *Exp Brain Res* 1988, 69:407–416.

29. SCHNEIDER SP, PERL ER: **Comparison of Primary Afferent and Glutamate Excitation of Neurons in the Mammalian Spinal Dorsal Horn.** *J Neurosci* 1988, 8:2062.

30. • GERBER G, CERNE R, RANDI M: **Participation of Excitatory Amino Acid Receptors in the Slow Excitatory Synaptic Transmission in Rat Spinal Dorsal Horn.** *Brain Res* 1991, **561**:236–251.

Repetitive stimulation of primary afferents evoked a two-phase slow depolarization in dorsal horn neurons in an *in vitro* slice. The results suggest that the early component requires activation of both NMDA and non-NMDA receptors, while the late component does not.

31. THOMPSON SWN, KING AE, WOOLF CJ: **Activity-Dependent Changes in Rat Ventral Horn Neurons In Vitro; Summation of Prolonged Afferent Evoked Postsynaptic Depolarizations Produce a D-2-Amino-5-Phosphovaleric Acid Sensitive Windup.** *Eur J Neurosci* 1990, 2:638–649.

32. DOUGHERTY PM, WILLIS WD: **Modification of the Responses of Primate Spinothalamic Neurons to Mechanical Stimulation by Excitatory Amino Acids and an N-Methyl-D-Aspartate Antagonist.** *Brain Res* 1991, **542**:15–22.

33. • SCHAIBLE H, GRUBB BD, NEUGEVAUER V, OPPMANN N: **The Effects of NMDA Antagonists on Neuronal Activity in Cat Spinal Cord Evoked by Acute Inflammation in the Knee Joint.** *Eur J Neurosci* 1991, 3:981–991.

NMDA antagonists were applied while recording mechanical responses of spinal neurons receiving input from an acutely inflamed knee joint. The results demonstrated enhanced responses that were in part mediated by NMDA receptors.

34. SALT TE: **Excitatory Amino Acid Receptors and Synaptic Transmission in the Rat Ventrobasal Thalamus.** *J Physiol* 1987, **391**:499–510.

35. • SALT TE, EATON SA: **Sensory Excitatory Postsynaptic Potentials Mediated by NMDA and non-NMDA Receptors in the Thalamus *In Vivo*.** *Eur J Neurosci* 1991, 3:296–300.

A technical tour-de-force in which composite electrodes were used for simultaneous extracellular iontophoresis of glutamate antagonists and intracellular recording in the rat somatosensory thalamus *in vivo*. The results indicate that brief stimuli activate both NMDA and non-NMDA receptors, but that the earliest action potentials in the response are dependent primarily on non-NMDA receptors. This finding is important as it demonstrates that NMDA receptors may be activated without a prior activation of non-NMDA receptors.

36. EATON SA, SALT TE: **Thalamic NMDA Receptors and Nociceptive Sensory Synaptic Transmission.** *Neurosci Lett* 1990, **110**:297–302.

37. GRILLNER S, WALLEN P, DALE N, BRODIN L, BUCHANAN J, HILL R: **Transmitters, Membrane Properties and Network Circuitry in the Control of Locomotion in Lamprey.** *Trends Neurosci* 1987, **10**:34–41.

38. • GRAY CM, ENGEL AK, KÖNIG P, SINGER W: **Synchronization of Oscillatory Neuronal Responses in Cat Striate Cortex: Temporal Properties.** *Vis Neurosci* 1992, **8**:337–347.

The latest in a series of studies of 40–60 Hz oscillations in the visual cortex. This study focuses on the time course of synchronized oscillations in local field potentials recorded at two widely separated (> 5 mm) sites in cat primary visual cortex. An important finding is that episodes of synchrony are brief—most last 100–200 ms.

39. FOX K, ARMSTRONG-JAMES M: **The Role of the Anterior Intralaminar Nuclei and N-Methyl-D-Aspartate Receptors in the Generation of Spontaneous Bursts in Rat Neocortical Neurones.** *Exp Brain Res* 1986, **63**:505–518.

40. • SILVA LR, AMITAI Y, CONNORS BW: **Intrinsic Oscillations of Neocortex Generated by Layer 5 Pyramidal Neurons.** *Science* 1991, **251**:432–435.

Synchronized 5–10 Hz oscillations resembling those seen *in vivo* [39] were recorded in an *in vitro* neocortical slice preparation. The bursts originated in layer 5 neurons, occurred when NMDA receptors were facilitated by lowering the Mg^{2+} concentration, and were abolished when NMDA receptors were blocked. The bursts appeared to depend on both Ca^{2+} and Na^{+} conductances.

41. HERRON CE, LESTER RAJ, COAN EJ, COLLINGRIDGE GL: **Frequency-Dependent Involvement of NMDA Receptors in the Hippocampus: a Novel Synaptic Mechanism.** *Nature* 1986, **322**:265–268.

42. THOMPSON AM: **A Magnesium-Sensitive Post-Synaptic Potential in Rat Cerebral Cortex Resembles Neuronal Responses to N-Methyl-D-Aspartate.** *J Physiol* 1986, **370**:531–549.

43. FERSTER D: **Orientation Selectivity of Synaptic Potentials in Neurons of Cat Primary Visual Cortex.** *J Neurosci* 1986, 6:1284–1301.

44. SHERMAN SM, KOCH C: **The Control of Retinogeniculate Transmission in the Mammalian Lateral Geniculate Nucleus.** *Exp Brain Res* 1986, **63**:1–20.

45. • HIRSCH JA, GILBERT CD: **Synaptic Physiology of Horizontal Connections in the Cat's Visual Cortex.** *J Neurosci* 1991, **11**:1800–1809.

An *in vitro* slice preparation was used to study intracellular responses of layer 2/3 neurons to electrical stimulation. Stimulation within the same layer, but displaced laterally 1–3 mm, revealed a small EPSP at rest, which grew several hundred-fold with depolarization. This voltage-dependence was not blocked by APV, but was blocked by internal blockade of Na^{+} channels.

46. FOX K, SATO H, DAW N: **The Effect of Varying Stimulus Intensity on NMDA-Receptor Activity in Cat Visual Cortex.** *J Neurophysiol* 1990, **64**:1413–1428.

47. • KWON YH, NELSON SB, TOTH LJ, SUR M: **Effect of Stimulus Contrast and Size on NMDA Receptor Activity in the Cat Lateral Geniculate Nucleus.** *J Neurophysiol* 1992, in press.

Extracellular responses of LGN neurons to visual stimuli of varying contrast and size were studied during iontophoretic application of glutamate antagonists. The NMDA-receptor mediated portion of the response was a constant fraction regardless of contrast, but was diminished by larger stimuli which engaged inhibitory surround mechanisms. The results suggest that NMDA-receptor activation in the LGN is particularly sensitive to inhibitory control.

48. SILLITO AM, KEMP JA: **The Influence of GABAergic Inhibitory Processes on the Receptive Field Structure of X and Y Cells in the Cat Dorsal Lateral Geniculate Nucleus (dLGN).** *Brain Res* 1983, **277**:63–77.

49. • FOX K, DAW N: **A Model for the Action of NMDA Receptors in the Visual Cortex.** *Neural Computation* 1992, 4:59–83.

The paper describes a two compartment, steady state conductance-based model of cortical pyramidal cells which attempts to account for the effects of NMDA and non-NMDA receptor activation and antagonism observed in a prior study [46]. An intriguing result is that the non-linear increase in the NMDA response with increasing stimulation results not only from its voltage-dependence, but also from the fact that the receptor needs to bind two molecules of agonist before it is activated.

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