

Glutamate Neurotransmission: Characteristics of NMDA Receptors in the Mammalian Brain

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Introduction

L-Glutamic acid – glutamate – is the most prevalent excitatory neurotransmitter in the vertebrate nervous system (1-3). In addition to subserving rapid synaptic transmission, this amino acid can induce prolonged changes in neuronal excitability such as long-term potentiation (LTP) and depression (LTD) (2,4-7). Glutamate-induced excitation of neurons is believed to be crucial in the early development of the brain (8,9). *In vivo*, the glutamate receptors (GluRs) influence synapse formation in the visual pathways in the brain (10-12) and cause the elongation of neuritic processes (13). In primary cultures, they enhance the survival of granule cells of the cerebellum (14). Activation of Ca²⁺ influx seems to be a key event in GluR-initiated neuronal responses.

GluR activation leads to Ca²⁺ entry into neurons that in turn leads to the stimulation of calmodulin-dependent kinase II and the tyrosine kinases (15,16). Stimulation of these kinases likely activates signal transduction cascades that lead to altered transcriptional regulation (17,18). The GluRs indirectly induce synthesis of the immediate early genes *c-fos* and *NFG1-A*, and the induction of these genes is related to the changes in the central nervous system (CNS) during early development and in the adult (19).

Excessive activation of glutamatergic pathways, and of their associated receptors, leads to a number of neuropathologies (20-22). This process may be responsible for the initiation of neuronal damage in the mammalian brain under a variety of insults (e.g., ischemia) and chronic neurodegenerative disease (e.g., Alzheimer's disease). Therefore, important investigations now target the role of the GluRs in CNS function over the lifespan of an organism in hopes for possible therapeutic intervention in devastating neurological diseases.

Glutamate Receptor Classification

The neuronal GluRs, based on pharmacological and physiological properties, are classified in Table 1. Two general categories of GluR are evident, the "ionotropic" or ion channel-forming receptors and the "metabotropic" receptors, which are linked to phospholipase C activation and adenylyl cyclase inhibition. The ionotropic receptors

can be divided further into two subpopulations, those that respond to *N*-methyl-D-aspartate (NMDA) and those that respond to kainic acid (KA) or α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). NMDA, KA and AMPA are analogs of glutamate that exhibit different sensitivities and receptor binding affinities to GluR. This classification scheme is based on the sensitivity of the receptors to NMDA, KA and AMPA that function as activators of the respective receptor types (23).

Cloning of cDNAs for GluR and Molecular Classification of the Ionotropic Receptors

The cDNAs for the three major classes of the ionotropic GluR were identified by functional expression cloning from a rat brain cDNA library (24-26). Heterologous expression of the cDNA-encoded proteins in frog oocytes, injected with cRNA, led to the identification of the KA/AMPA and the NMDA receptor-ion channel genes, GluR1 and NMDAR1, and the metabotropic receptor gene mGluR1. The initial cDNA clones, each from a major class of GluR, were used to identify several homologous genes for each class of receptors, including genes for orphan receptors. The size range of the predicted GluR proteins, 94-163kDa based upon the cDNAs, is considerably larger than the sizes of other neurotransmitter receptors including the ion channel-forming receptors and G-protein coupled receptors.

Besides the cDNAs cloned by heterologous expression in frog oocytes, the cDNAs for three additional CNS proteins, with characteristics akin to those of the GluRs, have been cloned since the biochemical isolation and characterization of the cognate proteins (27-30). These include a KA-binding protein (KBP) from amphibian and chick brain, and a glutamate-binding (GBP) and a glycine/thienylcyclohexyl-piperidine-binding protein (Gly/TCP-BP) from rat brain. The estimated sizes for these three proteins, ranging between 47 and 70kDa when isolated from brain, differ from those of the GluRs. The sizes based on the predicted structure of the cDNA-encoded proteins are in the range of 52-57kDa.

Physiological Importance of the NMDA Receptors in CNS

The NMDA receptor (NMDAR) is involved in processes related to memory formation and in neuropathological states that result from physical and physiological insults to the brain. Fortunately, the greatest success in identifying antagonists for the GluRs came from antagonists designed for the NMDAR. The NMDAR antagonists fall into four categories based on function: the competitive antagonists; the allosteric modulators; the modulatory site antagonists (polyamines); and the ion channel inhibitors.

The NMDARs are inhibited tonically by extracellular Mg²⁺ and require relief from the Mg²⁺ blockade for activation. The rapid activation of the KA/AMPA receptors by glutamate, and subsequent depolarization of

Table 1. Classification of Glutamate Receptor Subtypes Found in the Mammalian Central Nervous System.

| Receptor Classes | Ionotropic | | | Metabotropic |
|-----------------------------|--|---|---|---|
| Receptor Subtype | NMDA | AMPA | KA | Quisqualate, L-AP4 |
| Selective Agonists | NMDA | AMPA | KA | 1s3rACPD, L-AP4 |
| Functional Characteristics | Activation of channels for Na ⁺ , K ⁺ and Ca ²⁺ ; Slow excitation | Activation of channels for Na ⁺ and K ⁺ ; Fast excitation | Activation of channels for Na ⁺ and K ⁺ ; Fast excitation | Activation of PLC; Inhibition of adenylyl cyclases |
| Non-selective Agonists | Ibotenate, L-HCA, Quinolinate | Quisqualate, KA, Domoate, Willardine | Domoate, Acromelic acids A & B | ACPD, Quisqualate, L-serine-O-phosphate, Ibotenate, CCG |
| Allosteric Modulators | Glycine, D-serine, Spermine | Benzothiazides | Concanavalin A | |
| Competitive Antagonists | 2-AP5, 2-AP7, CPP, CPP-ene, CGP39653, CGS19755 | CNQX, NBQX, DNQX | GAMS, γ -D-glutamyl-glycine | Phenylglycine analogs (3HPG, 4CPG, 4C3HPG, MCPG) |
| Modulatory Site Antagonists | 5,7-diCl-Kyn, HA-966, CNQX | 2, 3-Benzodiazepines (GYKI52466) | | |
| Ion Channel Inhibitors | PCP, MK-801, Ketamine | JST, Barbiturates | | |

Abbreviations used: ACPD, 1-aminocyclopentane-1,3-dicarboxylate; L-AP4, L-2-amino-4-phosphonobutanoic acid; 2-AP5, D-2-amino-5-phosphonopentanoic acid; 2-AP7, D-2-amino-7-phosphonoheptanoic acid; CCG, 2-carboxycyclopropylglycine; CGP39653, (\pm)-(*E*)-2-amino-4-propyl-5-phosphonopentanoic acid; CGS19755, [[[\pm]-2-carboxypiperidin-4-yl]methyl]-phosphonic acid; 4C3HPG, (*S*)-4-carboxy-3-hydroxy-phenylglycine; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; 4CPG, (*S*)-4-carboxy-phenylglycine; CPP, [3-[[\pm]-carboxypiperazin-4-yl]prop-1-yl]-phosphonic acid; CPP-ene, [3-[[\pm]-2-carboxypiperazin-4-yl]-propen-1-yl]-phosphonic acid; 5,7-di-Cl-Kyn, 5,7-dichlorokynurenic acid; DNQX, 6,7-dinitroquinoxaline-2,3-dione; GAMS, γ -D-glutamylamino-methylsulfonate; HA-966, 3-amino-1-hydroxy-2-pyrrolidone; 3HPG, (*S*)-3-hydroxy-phenylglycine; JST, Joro spider toxin; MCPG, (+)- α -methyl-4-carboxy-phenylglycine; MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5,10-imine; NBQX, 2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo-(*F*)-quinoxaline; PLC, phospholipase C.

the membrane, diminishes the voltage-dependent Mg²⁺ inhibition and allows for activation of NMDAR. This increases the permeability of the neuronal membrane to Na⁺, K⁺ and Ca²⁺, and initiates a cascade of events outlined in Figure 1. The neurotoxic processes that follow excessive glutamate release and activation of the NMDARs are due primarily to excessive Ca²⁺ influx (31-33). This increases the activity of the calmodulin-activated form of nitric oxide synthase (NOS) and phospholipase A₂ (34,35) leading to the generation of intracellular nitric oxide radicals and superoxide anions, both of which are involved in neuronal degeneration (36-38). Thus, neuronal degeneration through free radical formation is considered a plausible mechanism for NMDA-induced cell damage.

However, the cascade of events that leads to cell death has not yet been fully delineated, nor has an explanation been advanced for the relative resistance of neurons exhibiting high levels of NOS, such as the granule cells of the cerebellum, to episodes of ischemia or anoxia in the brain. It is conceivable that some forms of NMDARs may be involved more directly in glutamate-induced neuronal degeneration than others. This differential association of specific types of NMDARs and neurodegeneration may mimic that seen with some neurotrophin receptors. It is known, for example, that for nerve growth factor (NGF) and other neurotrophins, the activation of the tyrosine kinase receptors, TrkA, TrkB and TrkC, mediates trophic effects on neurons,

whereas stimulation of the p75^{NTR} receptors leads to programmed cell death (39). NMDARs probably exist in different molecular forms, and one form may be involved more directly in the neurotoxicity induced by glutamate.

Evidence for Multiple Forms of NMDAR in Brain

The variable distribution of the NMDAR receptors in brain was demonstrated using four radiolabeled agents selective for either the agonist, the competitive antagonist, the co-activator or the noncompetitive antagonist recognition sites (40). Several disparities were observed in the density of sites labeled by each of these ligands in various brain regions. NMDA-sensitive agonist sites had a substantially different distribution in brain from the sites labeled by a competitive antagonist. This suggests that a heterogeneity of NMDARs exists in the mammalian brain, possibly due to complexes formed by different combinations of the R1 and R2A-R2D subunits (41).

Structure of an NMDA Receptor by Cloning of the Cognate cDNA

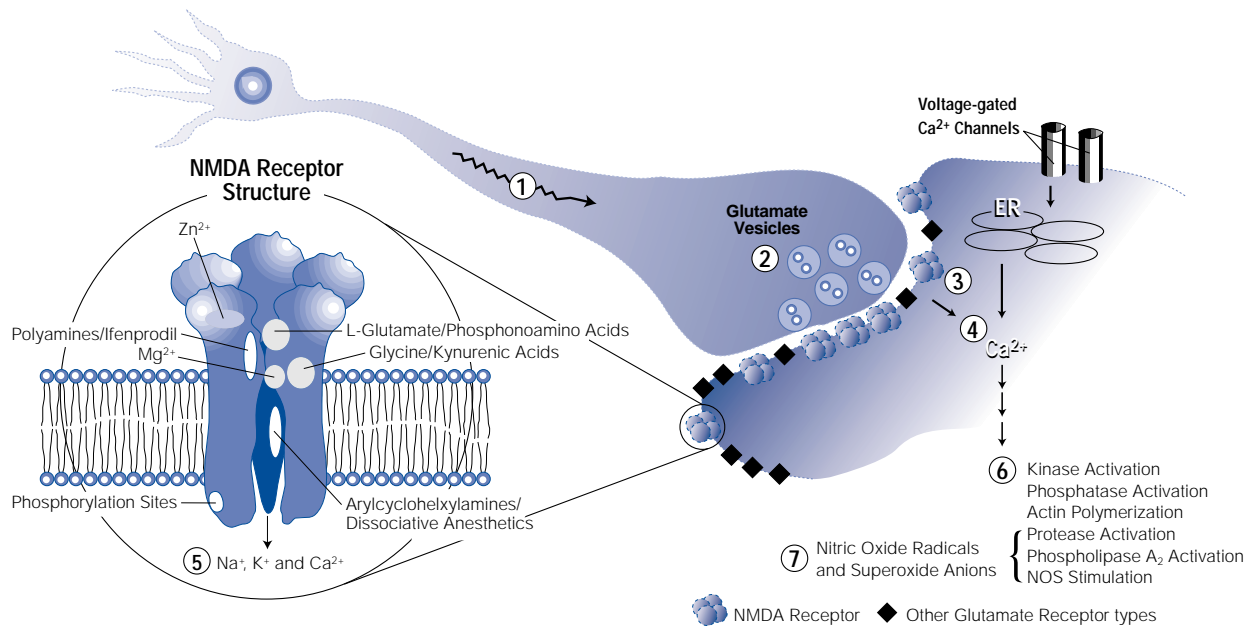
Moriyoshi *et al.* (26) identified the cDNA for NMDAR1 by functional expression cloning. In their study, NMDAR1 transcripts were injected into frog oocytes and functional NMDARs were formed. The cDNAs for the NMDAR isoforms 2A, 2B, 2C and 2D were cloned shortly thereafter (42-44). Formation of functional

NMDAR depends on the co-expression of NMDAR1 and R2, which leads to the formation of ion channels with conductances very similar to those of NMDAR in neurons. Each NMDAR1/R2 heterodimer exhibits a different degree of sensitivity to co-agonist, competitive antagonist, and ion channel inhibitors (43-45). In addition, localization of the NMDAR proteins in synaptic regions may be determined by carboxy termini of both subunits; the NMDAR2B subunit contains a carboxy terminus that enhances binding of the post-synaptic membrane protein PSD-95 (46,47).

NMDAR1 is the key subunit in the formation of the receptor complex. In its absence, no NMDA-activated ion channels are formed. Diminution of the expression of this subunit partially suppresses the neuronal damage produced by excessive glutamate release during ischemic episodes *in vivo* and exposure of neurons to NMDA *in vitro* (48). Eight variants of NMDAR1, due to alternative mRNA splicing, have been identified; clones NMDAR1a-h, which have distinct sensitivities to agonists, antagonists, Zn^{2+} and the polyamines (49-51). Thus, a wide array of receptor complexes with differing affinities for ligands may be expressed in neurons through the various combinations of the NMDAR1 splice variants and the NMDAR2 isoforms. Since each of the NMDAR2 subunits shows a unique pattern of expression in rodent brain, their differential expression may

cause the observed differences in the binding selectivity of agonists and antagonists to NMDARs expressed in these regions (40).

Neuronal toxicity may be dictated by the subunit makeup of the NMDARs. Recent studies indicate that kidney cell death occurs after transfection with the R1 and R2 subunits of NMDA, but not when transfected with the GluR-1 and GluR-2 proteins (52). Toxicity is greatest with R1/2A heterodimer, is less with R1/2B heterodimer, and is not apparent with R1/2C heterodimer. Caution should be applied, however, as expression in frog oocytes and kidney cells may not be the most appropriate environment for examining neuronal manifestations of toxicity. Proteins native to these cells may determine substantially the activity of the receptor-ion channels. For example, expression of NMDAR1 in frog oocytes leads to the formation of homomeric ion channels that are activated by glutamate and NMDA, but its expression in rodent epithelial cells (e.g., CHO) or human embryonic kidney cells (e.g., HEK 293) does not lead to functional ion channels or expression of binding sites for glutamate and the competitive antagonists of NMDAR (52,53). Thus, although the combination of the multiple isoforms and splice variants of the NMDAR proteins may account for most differences in ligand binding and sensitivities to glutamate and NMDA in specific brain regions, one cannot exclude the possibility that a related



▲ Figure 1.

Schematic diagram illustrating the cascade of events following postsynaptic glutamate binding in a mammalian neuron, and the structure of the NMDA receptor. The major sequence of events are numbered 1 through 7. **1)** An impulse is conducted along the presynaptic axon. **2)** vesicles fuse with the membrane and release glutamate into the synaptic space, **3)** glutamate binds KA/AMPA receptor complexes in the dendritic membrane, **4)** depolarization of the membrane releases the tonic Mg^{2+} -induced inhibition of NMDA ion-channels and **5)** Na^+ , K^+ and Ca^{2+} influx occurs through the NMDA ion-channels. **6)** These membrane changes trigger a multitude of effects listed under the Ca^{2+} influx. **7)** Excessive release of glutamate and activation of NMDA receptors, due to the increased levels of intracellular Ca^{2+} , can lead to production of nitric oxide radicals and superoxide anions. The NMDA receptor structure blow-up schematic shows the sites that can regulate the function of the receptor in neurons.

family of expressed NMDAR proteins in neurons may account for some of these observations.

NMDAR-Like Complex of Proteins in Synaptic Membranes

An NMDAR-like complex with ligand binding characteristics of NMDAR has been purified from brain synaptic membranes (54,55). The complex consists of GBP, a CPP-binding protein, a Gly/TCP-BP and a 36kDa protein of unknown ligand binding capability. The NMDAR-like complex contains no NMDAR1 protein nor does it have KA/AMPA binding sites (55,56). Furthermore, the cDNAs for the subunits with known protein binding capabilities reveal no significant homology to any previously cloned GluRs, glutamate transporters or glutamate-metabolizing enzymes (29,30).


The exact role of the NMDA-like complex in neuronal function has yet to be defined completely. Reconstitution of partially purified preparations of the subunits of the complex leads to the appearance of both glutamate and NMDA-activated cation fluxes and activated ion channels with conductances similar to those described for native NMDARs (57,58). The developmental expression of the GBP in cultured hippocampal neurons and cerebellar granule cells correlates with the developmental appearance of sensitivity of the neuron to NMDA-induced cytotoxicity and NMDA-activated ion channels (59-61). In addition, two antibodies raised against the GBP subunit, as well as antisense oligonucleotides designed on the basis of the GBP cDNA sequence, block glutamate and NMDA-induced Ca^{2+} influx and neurotoxicity in hippocampal neurons (59,62) and cerebellar granule cells (61,63). These results indicate that this NMDAR-like complex of proteins, especially the GBP subunit, may play an important role in modulating glutamate-induced neurotoxicity in the mammalian brain.

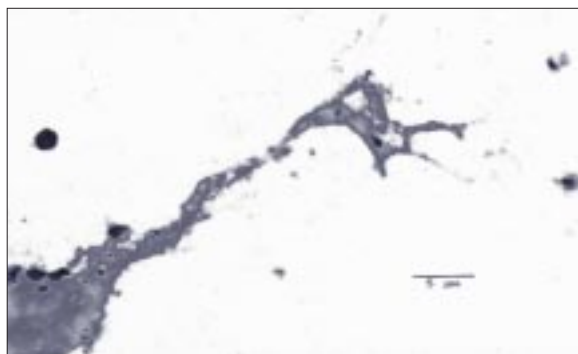
The GBP as a Marker of a Different Form of an NMDA-Sensitive Receptor in Brain

GBP localizes to the postsynaptic membranes (59,61,64,65). Labeling by anti-GBP antibodies was seen also along the dendrites and around the neuronal cell bodies in brain sections and in primary neuronal cultures, but was not seen in the axons of these cells (data not shown). In developing neurons, GBP immunoreactivity extends to the growth cone region as evident in Figure 2. Antibodies raised to the CPP-binding protein and the Gly/TCP-BP of this complex labeled the same populations of neurons in the hippocampus, olfactory tubercle, cerebral cortex and cerebellum as those labeled by anti-GBP antibodies. Please see panels B and C of the Inside Cover Figure. Parallel analysis of the expression of the GBP and the NMDAR1 in rat brain by *in situ* hybridization revealed that both protein mRNAs are expressed in most regions of the brain in a nearly identical fashion, but that the NMDAR1 mRNA expression is generally higher

than that of GBP (66). It is interesting to note that both protein mRNAs are highly expressed in the hippocampus, dentate gyrus and cerebellar granule cell layer. The GBP mRNA was present only in neurons (59,64), and not in glial cells (66), in brain sections and in culture.

Conclusion

The discovery of the multiple roles of the neurotransmitter glutamate in synaptic transmission, brain development, acquisition and storage of new information, and even the initiation of neurotoxic events, is one of the remarkable achievements in the neurosciences over the past two decades. The NMDARs are crucial nodal points in many of the events seen in physiological and pharmacological processes in neurons. The data indicate that many neurons in the CNS express two types of receptors, heterodimers of NMDAR1/R2 and the NMDR-like complex, with distinct functions in glutamate signaling. Even though both types of complexes may be ligand-gated ion-channel receptors, substantial evidence from other Ca^{2+} -conducting channel complexes suggests that the different microenvironments in neurons may determine the intracellular signals generated by the entry of Ca^{2+} (67). This hypothesis is best exemplified by the differences in the signal transduction cascades initiated by Ca^{2+} entering through the NMDARs as compared with those initiated by Ca^{2+} influx through voltage-gated calcium channels (68). By using specific immunochemical and oligonucleotide probes for the various proteins that form the diverse receptor complexes in neuronal cells, it should be possible to gather valuable information about the structure and function of all the GluR and NMDAR complexes in the mammalian nervous system. 



▲ Figure 2.

Distribution of the glutamate binding protein (GBP) in a neuritic process and growth cone of a single granule cell from the cerebellum. Neurons were grown in culture for 18 hours (216X magnification). Immunoreactivity to GBP was detected by reacting rabbit polyclonal antibodies to the protein followed by fluorescein-labeled anti-rabbit antibodies in dark blue. The primary and secondary antibody dilutions were 1:1,000. Light blue indicates immunolabeling of *Gap43* using secondary antibodies (1:1,000 dilution) derivatized with Texas Red.

(Figure kindly provided by Y. Xia, R. Ragan and E. Michaelis.)

References

1. Fonnum, F. (1984) *J. Neurochem.* **42**, 1.
2. Cotman, C.W. and Iversen, L.L. (1987) *Trends Neurosci.* **10**, 263.
3. Cotman, C.W. *et al.* (1987) *Trends Neurosci.* **10**, 273.
4. Collingridge, G.L. (1985) *Trends Pharmacol. Sci.* **6**, 407.
5. Kimura, F. *et al.* (1989) *J. Physiol. (Lond.)* **414**, 125.
6. Ito, M., Sakurai, M. and Tongroach, P. (1982) *J. Physiol. (Lond.)* **324**, 113.
7. Kano, M. and Kato, M. (1987) *Nature* **325**, 276.
8. Komuro, H. and Rakic, P. (1993) *Science* **260**, 95.
9. LoTurco, J.J. *et al.* (1995) *Neuron* **15**, 1287.
10. Bear, M.F. *et al.* (1990) *J. Neurosci.* **10**, 909.
11. Cline, H.T. and Constatine-Paton, M. (1989) *Neuron* **3**, 413.
12. Hahm, J.O., Langdon, R.B. and Sur, M. (1991) *Nature* **351**, 568.
13. Brewer, G.J. and Cotman, C.W. (1989) *Neurosci. Lett.* **99**, 268.
14. Balazs, R., Jorgensen, O.S. and Hack, N. (1988) *Neurosci.* **27**, 437.
15. Fukunaga, K. and Soderling, T.R. (1990) *Mol. Cell. Neurosci.* **1**, 1.
16. Bading, H. and Greenberg, M.E. (1991) *Science* **253**, 912.
17. Kaltschmidt, C., Kaltschmidt, B. and Baeuerle, P.A. (1995) *Proc. Natl. Acad. Sci. USA* **92**, 9618.
18. Bulleit, R.F., Cui, H. and Lin X. (1994) *J. Neurosci.* **14**, 1584.
19. Lerea, L.S., Carlson, N.G. and McNamara, J.O. (1995) *Mol. Pharmacol.* **47**, 1119.
20. Choi, D.W. (1987) *J. Neurosci.* **7**, 369.
21. Greenamyre, J.T. and Porter, R.H.P. (1994) *Neurology* **44** (Suppl. 8), S7.
22. Meldrum, B.S. (1994) *Neurology* **44** (Suppl. 8), S14.
23. Watkins, J.C., Krogsgaard-Larsen, P. and Honoré, T. (1990) *Trends Pharmacol. Sci.* **11**, 25.
24. Hollmann, M. *et al.* (1989) *Nature* **342**, 643.
25. Masu, M. *et al.* (1991) *Nature* **349**, 760.
26. Moriyoshi, K. *et al.* (1991) *Nature* **354**, 31.
27. Wada, K. *et al.* (1989) *Nature* **342**, 684.
28. Gregor, P. *et al.* (1989) *Nature* **342**, 689.
29. Kumar, K.N. *et al.* (1991) *J. Biol. Chem.* **266**, 14947.
30. Kumar, K.N. *et al.* (1995) *Biochem. Biophys. Res. Commun.* **216**, 390.
31. MacDermott, A.B. *et al.* (1986) *Nature* **341**, 519.
32. Murphy, D.E. *et al.* (1987) *J. Pharmacol. Exp. Ther.* **240**, 778.
33. Mody, I. and McDonald, J.F. (1995) *Trends Pharm. Sci.* **16**, 356.
34. Dawson, V.L. *et al.* (1991) *Proc. Natl. Acad. Sci. USA* **88**, 6368.
35. Dumuis, A. *et al.* (1988) *Nature* **336**, 68.
36. Lafon-Cazal, M. *et al.* (1993) *Nature* **364**, 535.
37. Lipton, S.A. *et al.* (1993) *Nature* **364**, 626.
38. Bonfoco, E. *et al.* (1995) *Proc. Natl. Acad. Sci. USA* **92**, 7162.
39. Carter, B.D. *et al.* (1996) *Science* **272**, 542.
40. Monaghan, D.T. *et al.* (1988) *Proc. Natl. Acad. Sci. USA* **85**, 9836.
41. Marti, T. *et al.* (1993) *Proc. Natl. Acad. Sci. USA* **90**, 8434.
42. Maguro, H. *et al.* (1992) *Nature* **357**, 70.
43. Katsuwada, T. *et al.* (1992) *Nature* **358**, 36.
44. Monyer, H. *et al.* (1992) *Science* **258**, 1217.
45. Ishii, T. *et al.* (1993) *J. Biol. Chem.* **268**, 2836.
46. Kornau, H-C. *et al.* (1995) *Science* **269**, 1737.
47. Ehlers, M.D. *et al.* (1995) *Science* **269**, 1734.
48. Wahlestedt, C. *et al.* (1993) *Nature* **363**, 260.
49. Durand, G. M. *et al.* (1992) *Proc. Natl. Acad. Sci. USA* **89**, 9359.
50. Nakanishi, N., Axel, R. and Shneider, N.A. (1992) *Proc. Natl. Acad. Sci. USA* **89**, 8552.
51. Hollmann, M. *et al.* (1993) *Neuron* **10**, 943.
52. Aneqawa, N.J. *et al.* (1995) *J. Neurochem.* **64**, 2004.
53. Boeckman, F.A. and Aizenman, E. (1994) *Neurosci. Lett.* **173**, 189.
54. Ikin, A.F., Kloog, Y. and Sokolovsky, M. (1990) *Biochemistry* **29**, 2290.
55. Kumar, K. *et al.* (1994) *J. Biol. Chem.* **269**, 27384.
56. Babcock, K.A. *et al.* (1996) *Neurochem. Intl.*, in press.
57. Ly, A.M. and Michaelis, E.K. (1991) *Biochemistry* **30**, 4307.
58. Aistrup, G. *et al.* (1994) *Neurosci. Abstr.* **20**, 310.
59. Mattson, M., Wang, H. and Michaelis, E.K. (1991) *Brain Res.* **565**, 94.
60. Balazs, R. *et al.* (1992) *Neurosci. Lett.* **137**, 109.
61. Xia, Y. *et al.* (1995) *Neurochem. Res.* **20**, 617.
62. Mattson, M. *et al.* (1993) *J. Neurosci.* **13**, 4575.
63. Hoffman, P.L. *et al.* (1996) *Mol. Brain Res.*, in press.
64. Eaton, M.J. *et al.* (1990) *J. Biol. Chem.* **265**, 16195.
65. Wang, H., Kumar, N.K. and Michaelis, E.K. (1992) *Neuroscience* **46**, 793.
66. Sato, K. *et al.* (1994) *Neurosci.* **64**, 459.
67. Lerea, L.S., Butler, L.S. and McNamara, J.O. (1992) *J. Neurosci.* **12**, 2973.
68. Ghosh, A. and Greenberg, M.E. (1995) *Science* **268**, 239.

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