amino acid[4,11,15]. Although the details of the interactions between receptor domains remain to be elucidated, these data suggest the fascinating hypothesis that, in contrast to its inhibitory function in spinal tissue, glycine acts in higher brain areas to facilitate allosterically NMDA receptor-mediated excitation.

The domain structure of the NMDA receptor (see figure) is, in many respects, similar to that which has been described for other transmitter-gated ion channels. At both the nicotinic acetylcholine and $GABA_A$ receptors, 'non-competitive' antagonists interact with the receptor complex in an agonist-dependent manner, reflecting, as in the case of PCP or MK-801 at the NMDA receptor, a preference for activated or open states of the ion channel. At the $GABA_A$ receptor, the well-documented ability of benzodiazepines to enhance receptor activity allosterically can be compared with the action of glycine at the NMDA receptor. As well as these common features, the NMDA receptor has evolved a unique form of voltage-dependent gating, involving binding of Mg^{2+} inside the channel. Hence, 'switching on' NMDA receptor mechanisms requires at the minimum: (1) binding of transmitter to its recognition site; and (2) relief of the channel blockade (for example, by local depolarization of the postsynaptic membrane by other excitatory inputs). In addition, receptor function may be subject to rapid up- or down-regulation by changes in the levels of glycine and/or Mg^{2+} in the local extracellular environment.

Now that the basic functional organization of the NMDA receptor is understood, what are the next steps? First, understanding the full physiological implications and intricacies of its regulatory mechanisms requires detailed studies of the interactions between receptor domains and their stoichiometric relationships, the modulation of different affinity states, and the seemingly diverse effects of divalent cations. In view of recent reports that Zn^{2+} non-competitively antagonizes NMDA-evoked responses at a site distinct from that at which Mg^{2+} binds [16,17], one might ask how many more domains of potential significance there are. Second, although the biophysical properties of the NMDA receptor-channel complex can account for its involvement in electrical phenomena such as signal amplification and rhythmic firing, they cannot alone explain its role in prolonged events like long-term potentiation or synaptic reorganization. In this respect, a clue for future studies is that the NMDA receptor channel is permeable to Ca^{2+} (ref. 18), which may activate long-term biochemical changes in the post-synaptic neuron.

The goal of the reductionist approach is to understand function in terms of molecular structure. Such studies are under way for the nicotinic acetylcholine receptor[19] and, given its unique properties, these will undoubtedly be of special interest for the NMDA-receptor complex. The path ahead is certainly long, but the recent work described here is a valuable initial step towards elucidating the molecular basis of some of the most intriguing excitatory and plastic events in the central nervous system. □

1. Fagg, G.E. *et al. Trends pharmac. Sci.* **7**, 357–363 (1986).
2. Cotman, C.W. *et al. Trends Neurosci.* **10**, 263–302 (1987).
3. Watkins, J.C. & Olverman, H.J. *Trends Neurosci.* **10**, 265–272 (1987).
4. Fagg, G.E. & Baud, J., in *Excitatory Amino Acids in Health and Disease* (eds Lodge, D. *et al.*) (Wiley, Chichester, in the press).
5. Nowak, L. *et al. Nature* **307**, 462–465 (1984).
6. Mayer, M.L. & Westbrook, G.L. *Prog. Neurobiol.* **28**, 197–276 (1987).
7. Lodge, D. *et al.* in *Excitatory Amino Acid Transmission* (eds Hicks, T.P. *et al.*) 83–90 (Liss, New York, 1987).
8. Honey, C.R. *et al. Neurosci. Lett.* **61**, 135–139 (1985).
9. Kemp, J.A. *et al. Trends Neurosci.* **10**, 294–298 (1987).
10. MacDonald, J.F. *et al. J. Neurophysiol.* **58**, 251–266 (1987).
11. Johnson, K.M. *et al.* in *Sigma Opioid Phencyclidine-like Compounds as Molecular Probes in Biology* (eds Domino, E.F. & Kamenka, J.M.) (NPP Books, Ann Arbor, in the press.
12. Wong, E.H.F. *et al. J. Neurochem.* (in the press).
13. Johnson, J.W. & Ascher, P. *Nature* **325**, 529–531 (1987).
14. Bowery, N.G. *Nature* **326**, 338 (1987).
15. Reynolds, I.J. *et al. Proc. natn. Acad. Sci. U.S.A.* (in the press).
16. Peters, S. *et al. Science* **236**, 589–593 (1987).
17. Westbrook, G.L. & Mayer, M.L. *Nature* **328**, 640–643 (1987).
18. MacDermott, A.B. *et al. Nature* **321**, 519–522 (1986).
19. Mishina, M. *et al. Nature* **321**, 406–411 (1986).

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John Howard Northrop (1891–1987)

JOHN NORTHROP probably did more than any other individual to establish the view that pure enzymes are indeed proteins. He was not, however, the first to crystallize an enzyme. That honour belonged to J.B. Sumner of Cornell University, who reported the crystallization of urease from jack bean in 1926. Northrop's work, however, was both more extensive and more searchingly critical than Sumner's. Both men had to face widespread scepticism concerning their work: Richard Willstätter in Munich, with his great prestige, had denied the protein nature of enzymes. Most biochemists, particularly in Europe, followed Willstätter, and for years discounted the evidence of Sumner and Northrop.

Northrop, born in Yonkers, New York, did both his undergraduate and graduate work at Columbia University, receiving his PhD in 1915. In 1916 he became an assistant in the laboratory of Jacques Loeb at the Rockefeller Institute in New York. Loeb was a major influence in his development. From the beginning Northrop worked on enzymes; many of his early papers concerned the kinetics of enzyme-catalysed reactions. After Loeb's death in 1924, Northrop arranged to be transferred to the Princeton branch of the Rockefeller Institute. He loved open country, and strongly disliked living in the city.

It was in Princeton that he achieved the crystallization of three major proteolytic enzymes — pepsin in 1930, and trypsin and chymotrypsin a few years later — and provided the most rigorous test then available to demonstrate that they are pure proteins. He well knew that the preparation of a substance in crystalline form is not in itself an adequate criterion of purity; mixed crystals of two or more closely related substances were a common occurrence. Northrop's test for purity involved careful solubility studies in well-defined media, with application of the phase rule of Willard Gibbs. A truly pure protein in such a medium should give a constant solubility, independent of the amount of crystalline phase in equilibrium with the solution. He was able to show, for his preparations, that this was indeed the case. Sumner, in his pioneer work, had not applied such rigorous tests; so on the whole it was Northrop's work that was most influential in gradually convincing the sceptics.

Northrop's associate, Moses Kunitz, shared much of this work, and later continued independently to crystallize other enzymes, notably ribonucleases and deoxyribonucleases. Northrop and Kunitz, together with Roger Herriott, described this research in their book *Crystalline Enzymes*.

In 1938, the trustees of the Rockefeller Institute closed the Princeton branch of the Institute. Most of the Princeton workers moved back to New York or retired. Northrop, however, refused to live in New York and the trustees permitted him to move elsewhere, to a place of his choice, while still remaining a member of the Institute and receiving its support for his work. In 1939 he settled at the University of California at Berkeley, where he became a professor and did extensive work on bacteriophage, his approach being similar to that of his earlier work on enzymes. But he missed the biological significance of the life cycle of bacteriophage, and his findings were eclipsed by the work of molecular biologists.

In 1946, Sumner and Northrop received the Nobel prize in chemistry (together with Wendell Stanley, for his work on viruses). At last the sceptics had been convinced of the validity of Northrop and Sumner's work. This was the chief of the many honours that Northrop received. He retired from Berkeley in 1959, and characteristically chose to live far away from noise and bustle, in the rather remote district of Wickenburg, Arizona, where he died.

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