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COVER False color map of intracellular calcium concentration in a guinea pig cerebellar Purkinje cell at the onset of a wave of complex spike activity. A high calcium concentration is observed in the distal dendritic tree. The map was produced from microfluorometric imaging of the fluorescent calcium indicator fura-2. See page 773. [D. W. Tank and J. A. Connor, Molecular Biophysics Research Department, AT&T Bell Laboratories, Murray Hill, NJ 07974; M. Sugimori and R. R. Llinás, Department of Physiology and Biophysics, New York University School of Medicine, New York, NY 10016]

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Frontiers in Neuroscience

The human brain contains about 10^{12} neurons, many of which have more than 10,000 connections with other neurons. This incredibly sophisticated supercomputer presents an enormous intellectual challenge. Elucidating its function will be of great importance to the understanding of human behavior and the support of mental health. In this issue, assembled with the expertise of Katrina Kelner, eight articles cover selected aspects of modern neurobiology and illustrate the power of new concepts and new experimental tools.

Memory is of course one of the most intriguing areas of study in the brain, and describing the physiological changes in neurons that generate long-term memory is a first step in understanding all subsequent learning processes. Major developments in this area are discussed by Brown and co-workers, who have used the technique of long-term potentiation, that is, a long-lasting change in a neuron as a result of repetitive stimulation. Indications of Hebbian feedback behavior in these stimulated neurons combine modern molecular biology with classical postulates of psychology.

Learning also involves complex motor patterns such as hitting a baseball moving at 150 kilometers per hour. This action requires the training of motor skills so that a rudimentary native ability is converted to a more precise learned ability, as described by Lisberger. Moreover, as discussed by Wise and Desimone, correlation of movements with visual stimuli requires groups of neurons that can select objects and also constantly adjust to the fact that limbs grow, muscle mass changes, and visual experience accumulates.

How neurons make connections to develop the complex wiring diagram of the brain is discussed in three papers. To the dismay of some who may like to think that humans are appreciably more worthy than insects, the development of neuronal interconnections in a grasshopper is not so different from that of so-called higher species. It appears that neurons making distant connections follow predetermined pathways by groping along structural elements that contain molecular signposts in the form of proteins on the surface of cells. They also may use chemical gradients that attract or repel the advancing tip of the neuron, the growth cone. Moreover, these extensions have feedback mechanisms that allow them to withdraw from incorrect surfaces and fasten tightly to the correct ones. Dodd and Jessell focus on vertebrate glycoproteins that provide a guidance system in nonspecific parts of the developing neuron and discuss axon guidance by contact inhibition. Harrelson and Goodman discuss the same subject with emphasis on fasciculation in invertebrates, particularly as mediated by fasciclin II, a member of the immunoglobulin superfamily. These immunoglobulin-like molecules are structurally homologous to guidance molecules in the vertebrate neural system. Finally, Smith discusses the mechanics of cell motility during neuron development and identifies actin polymerization as the force behind the protrusion of the growth cone while the actin-myosin system, fueled by adenosine triphosphate, appears to drive growth cone retraction.

Koob and Bloom discuss the currently prominent issue of drug dependence from the molecular point of view. The drug problem will not be solved solely by elucidating the biochemical mechanisms, but understanding the molecular basis of tolerance and withdrawal will help. Such findings may also help explain why people become addicted to drugs and lead to the development of better procedures for detoxification.

Churchland and Sejnowski consider some aspects of theoretical computer programs that show computation patterns analogous to those of the brain. Some experimenters regard such theoretical programming as too esoteric to be of much practical use in understanding brain function. Nevertheless, there are principles applied in algorithms that are functionally similar to mechanisms in the human brain. In fact, insight into new types of information processing is leading to an entire industry in which the simulation of neuronal activity in an algorithm is being used to attract venture capital. The brain is becoming big business, as well as a big intellectual challenge.

Sometimes intellectual challenges are fascinating but of debatable value such as the design of new weapons or the breaking of secret codes. Understanding the brain is a monumental puzzle, the solution of which can provide great humanitarian advances. This issue presents some beginnings at unraveling that Gordian knot.

—DANIEL E. KOSHLAND, JR.