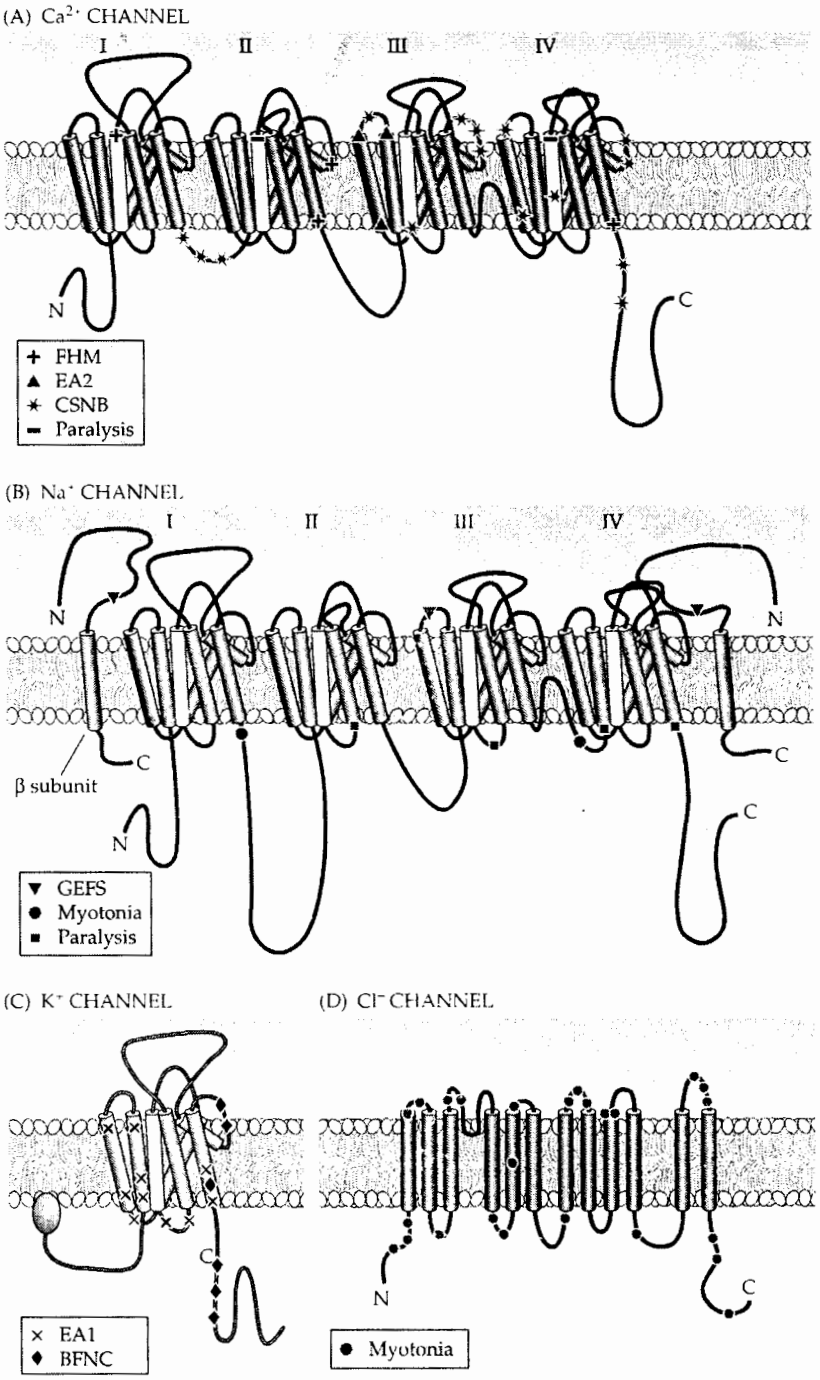
Box D

Diseases Caused by Altered Ion Channels

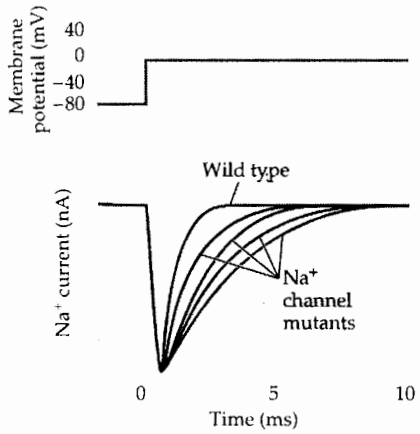
Several genetic diseases, collectively called *channelopathies*, result from small but critical alterations in ion channel genes. The best-characterized of these diseases are those that affect skeletal muscle cells. In these disorders, alterations in ion channel proteins produce either myotonia (muscle stiffness due to excessive electrical excitability) or paralysis (due to insufficient muscle excitability). Other disorders arise from ion channel defects in heart, kidney, and the inner ear.

Channelopathies associated with ion channels localized in brain are much more difficult to study. Nonetheless, voltage-gated Ca^{2+} channels have recently been implicated in a range of neurological diseases. These include episodic ataxia, spinocerebellar degeneration, night blindness, and migraine headaches. *Familial hemiplegic migraine* (FHM) is characterized by migraine attacks that typically last one to three days. During such episodes, patients experience severe headaches and vomiting. Several mutations in a human Ca^{2+} channel have been identified in families with FHM, each having different clinical symptoms. For example, a mutation in the pore-forming region of the channel produces hemiplegic migraine with progressive cerebellar ataxia, whereas other mutations cause only the usual FHM symptoms. How these altered Ca^{2+} channel properties lead to migraine attacks is not known.

Episodic ataxia type 2 (EA2) is a neurological disorder in which affected individuals suffer recurrent attacks of abnormal limb movements and severe ataxia. These problems are sometimes accompa-



Genetic mutations in (A) Ca^{2+} channels, (B) Na^+ channels, (C) K^+ channels, and (D) Cl^- channels that result in diseases. Red regions indicate the sites of these mutations; the red circles indicate mutations. (After Lehmann-Horn and Jurkat-Kott, 1999.)



Mutations in Na^+ channels slow the rate of inactivation of Na^+ currents. (After Barchi, 1995.)

nied by vertigo, nausea, and headache. Usually, attacks are precipitated by emotional stress, exercise, or alcohol and last for a few hours. The mutations in EA2 cause Ca^{2+} channels to be truncated at various sites, which may cause the clinical manifestations of the disease by preventing the normal assembly of Ca^{2+} channels in the membrane.

X-linked *congenital stationary night blindness* (CSNB) is a recessive retinal disorder that causes night blindness, decreased visual acuity, myopia, nystagmus, and strabismus. Complete CSNB causes retinal rod photoreceptors to be nonfunctional. Incomplete CSNB causes subnormal (but measurable) functioning of both rod and cone photoreceptors. Like EA2, the incomplete type of CSNB is caused by mutations producing truncated Ca^{2+} channels. Abnormal retinal function may arise from decreased Ca^{2+} currents and neurotransmitter release from photoreceptors (see Chapter 11).

A defect in brain Na^+ channels causes *generalized epilepsy with febrile seizures* (GEFS) that begins in infancy and usually continues through early puberty. This defect has been mapped to two mutations: one on chromosome 2 that encodes an α subunit for a voltage-gated Na^+ channel, and the other on chromosome 19 that encodes a Na^+ channel β subunit. These mutations cause a slowing of Na^+ channel inactivation (see figure above), which may explain the neuronal hyperexcitability underlying GEFS.

Another type of seizure, *benign familial neonatal convulsion* (BFNC), is due to K^+ channel mutations. This disease is characterized by frequent brief seizures commencing within the first week of life and disappearing spontaneously within a few months. The mutation has been mapped to at least two voltage-gated K^+ channel genes. A reduction in K^+ current flow through the mutated channels probably accounts for the hyperexcitability associated with this defect. A related disease, episodic ataxia type 1 (EA1), has been linked to a defect in another type of voltage-gated K^+ channel. EA1 is characterized by brief episodes of ataxia. Mutant channels inhibit the function of other, non-mutant K^+ channels and may produce clinical symptoms by impairing action potential repolarization. Mutations in the K^+ channels of cardiac muscle are responsible for the irregular heartbeat of patients with long Q-T syndrome. Numerous genetic disorders affect the voltage-gated channels of skeletal muscle and are responsible for a host of muscle diseases that either cause muscle weakness (*paralysis*) or muscle contraction (*myotonia*).

References

BARCHI, R. L. (1995) Molecular pathology of the skeletal muscle sodium channel. Ann. Rev. Physiol. 57: 355–385.

BERKOVIC, S. F. AND I. E. SCHEFFER (1997) Epilepsies with single gene inheritance. Brain Develop. 19 :13–28.

COOPER, E. C. AND L. Y. JAN (1999) Ion channel genes and human neurological disease: Recent progress, prospects, and challenges. Proc. Natl. Acad. Sci. USA 96: 4759–4766.

DAVIES, N. P. AND M. G. HANNA (1999) Neurological channelopathies: Diagnosis and therapy in the new millennium. Ann. Med. 31: 406–420.

JEN, J. (1999) Calcium channelopathies in the central nervous system. Curr. Op. Neurobiol. 9: 274–280.

LEHMANN-HORN, F. AND K. JURKAT-ROTT (1999) Voltage-gated ion channels and hereditary disease. Physiol. Rev. 79: 1317–1372.

OPHOFF, R. A., G. M. TERWINDT, R. R. FRANTS AND M. D. FERRARI (1998) P/Q-type Ca^{2+} channel defects in migraine, ataxia and epilepsy. Trends Pharm. Sci. 19: 121–127.

In short, ion channels are integral membrane proteins with characteristic features that allow them to assemble into multimolecular aggregates. Collectively, these structures allow channels to conduct ions, sense the transmembrane potential, to inactivate, and to bind to various neurotoxins. A combination of physiological, molecular biological and crystallographic studies has begun to provide a detailed physical picture of K^+ channels. This work has now provided considerable insight into how ions are conducted from one side of the plasma membrane to the other, how a channel can be selectively permeable to a single type of ion, how they are able to sense changes in membrane voltage, and how they gate the opening of their pores. It is likely that other types of ion channels will be similar in their functional architecture. Finally, this sort of work has illuminated how mutations in ion channel genes can lead to a variety of neurological disorders (Box D).