ics of ion transport results from a delicate balance of very large interactions. This raises the question of the potential function and the influence of induced polarization, which is usually neglected in current calculations. A second problem arises from the time scales involved. The passage of one ion across a channel takes place on a microsecond time scale and realistic simulations of biological systems, which typically do not exceed a few nanoseconds, are insufficiently short. Straight molecular dynamics still cannot account for the time scales of ion permeation, and specialized simulation methods must be used to investigate these systems. A last difficulty is the translation of the results obtained from a microscopic model into macroscopic observables such as channel conductance and current-voltage relations (IV). How to go effectively from MD to IV curves remains a fundamentally unresolved question.

Future progress in theoretical studies of ion transport will come from efforts to push forward the limits in three directions: improving the potential function, developing appropriate simulation methods, and formulating useful theoretical frameworks for establishing a link between detailed trajectory and macroscopic quantities that are measured experimentally. An essential prerequisite for undertaking meaningful studies based on atomic models is the availability of a high resolution structure. The present work was made possible because the structure of OmpF was determined by x-ray crystallography (Cowan et al., 1992). The very recent determination of the structure of the K channel from *Streptomyces lividans* will provide another very exciting system to investigate ion permeation (Doyle et al., 1998). Meanwhile, it is stimulating to read about this impressive calculation.

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Cells Use the Singular Properties of Different Channels to Produce Unique Electrical Songs

Robert L. Ruff

Departments of Neurology and Neurosciences, Case Western Reserve University, Cleveland, Ohio 44106 USA

A challenge of membrane biophysics is to determine how the gating properties of the ionic channels expressed in a cell contribute to the electrical activity pattern of that cell. Acting as a conductor, the cell chooses which channels are expressed and modifies those channels so that the electrical notes of each class of channels combine to form a unique song. In this issue of *Biophysical Journal*, Richmond et al. (1998) examined how the unique gating properties of cardiac Na^+ channels enable the channels to remain excitable in the setting of repetitive long-duration cardiac action potentials.

We have some understanding of how the gating properties and distribution of Na^+ channels enable different activity patterns in mature innervated skeletal muscle fibers (Ruff, 1996). Fast twitch skeletal muscle fibers fire action potentials at relatively high frequencies but are active briefly. In contrast, slow twitch fibers fire at relatively slow rates and are tonically active (Hennig and Lømo, 1985). Fast twitch fibers have a high density of Na^+ channels. The high channel density reduces the refractory period for action potential generation, which enable fast twitch fibers to fire at a high rate. The resting potentials of fast twitch fibers are close to the operating voltage ranges for fast and slow inactivation. Therefore, action potential activity and membrane depolarization produced by accumulation of extracellular potassium inactivate Na^+ channels in fast twitch fibers and prevent fast twitch fibers from firing continuously. In slow twitch fibers, the resting potential is separated from the operating ranges for fast and slow inactivation by a relatively large margin, which enables slow twitch fibers to fire tonically. The low density of Na^+ channels on slow twitch fibers forces the slow twitch fibers to fire at a slow rate. Consequently, variations in the distribution and gating properties of skeletal muscle Na^+ channels enable fast and slow twitch fibers to have distinctive activity patterns (Ruff, 1996).

Cardiac cells have very different activity patterns compared with skeletal muscle cells. Extremely long-duration cardiac action potentials would inactivate skeletal muscle Na^+ channels. Natural firing rates of cardiac cells are slow enough to permit Na^+ channels to recover from fast inactivation. However, if cardiac cells were populated with skeletal muscle Na^+ channels, the tardy recovery from slow inactivation would prevent cardiac cells from firing at rates $\geq$1 Hz. In skeletal muscle, slow inactivation regulates the popula-

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Address reprint requests to Robert L. Ruff, M.D., Ph.D., Chief, Neurology Service 127(W), Cleveland VAMC, 10701 East Blvd., Cleveland, OH 44106. Tel.: 216-421-3040 or 216-844-5550; Fax: 216-421-3040. E-mail:rlr@cwru.edu.

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tion of excitable Na^+ channels. Disruption of slow inactivation in mutant skeletal muscle Na^+ channels potentiates the ability of the mutant channels to produce depolarization-induced paralysis in disorders such as hyperkalemic periodic paralysis (Hayward et al., 1997). While slow inactivation may act as governor for membrane excitability in skeletal muscle, slow inactivation would prevent the electrical activity pattern characteristic of cardiac cells. Richmond et al. (1998) demonstrate that cardiac cells circumvent the problem presented by the presence of slow inactivation in skeletal muscle Na^+ channels by using a different Na^+ channel. Slow inactivation reduces cardiac Na^+ currents by only 40% in response to prolonged depolarizations. Cardiac Na^+ channels manifest complete fast inactivation. However, the rapid kinetics for recovery from fast inactivation enables the cardiac Na^+ channels to regain excitability in sufficient time to permit cardiac cells to have repetitive long-duration action potentials at 1 $\geq$Hz firing rates.

The unique properties of cardiac Na^+ channels help to explain some electrical patterns observed in immature skeletal muscle fibers and in denervated fibers. Early in development and after denervation, skeletal muscle cells express cardiac Na^+ channels (Trimmer, 1990). Immature and denervated skeletal muscle fibers are depolarized compared with mature innervated muscle fibers. The presence of the cardiac Na^+ channel isoform may enable immature fibers to be electrically excitable. Cardiac Na^+ channels expressed in denervated skeletal muscle fibers probably enable the denervated muscle fibers to be electrically excitable and to manifest spontaneous action potentials called fibrillation potentials. Spontaneous electrical activity in denervated skeletal muscle fibers may be important in slowing the rate of disuse atrophy. The spontaneous electrical activity in denervated fibers could enable the fibers to survive until reinnervation occurs.

By selecting the appropriate Na^+ channels a striated muscle cell can produce the brief staccato song of the fast twitch skeletal muscle cell or the slow persistent song of the cardiac myocyte.

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