Letters to the Editor

Slow Na^+ Channel Inactivation Must Be Disrupted to Evoke Prolonged Depolarization-Induced Paralysis

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In the July, 1993, issue of *Biophysical Journal*, Drs. Cannon, Brown, and Corey developed a theoretical model that explored the conditions under which partial disruption of Na^+ channel inactivation in a portion of skeletal muscle Na^+ channels could result in myotonic behavior and depolarization-induced paralysis of mammalian skeletal muscle as is seen in patients who have hyperkalemic periodic paralysis with myotonia (Cannon et al., 1993). The model that Cannon, Brown and Corey used only considered fast inactivation of Na^+ channels. My contention is that although blocking fast inactivation in a fraction of Na^+ channels can produce myotonic behavior and depolarization-induced paralysis, the flaccid, electrically silent paralysis will last for only a few minutes unless slow inactivation is also compromised in the abnormal Na^+ channels. The paralytic attacks in patients with hyperkalemic periodic paralysis and myotonia manifest as a flaccid, electrically silent paralysis that usually lasts for several hours (Ruff and Gordon, 1986). Slow, as well as fast, inactivation needs to be disrupted in a small fraction of Na^+ channels in order to produce a small persistent inward current that depolarizes the membrane and produces depolarization-induced membrane inexcitability that persists for several hours as is seen in patients with hyperkalemic periodic paralysis (Lehmann-Horn et al., 1987). Because slow inactivation was not considered in the model, the model acted as if slow inactivation was inoperative for all of the channels, including those channels in which fast inactivation did not function. If only fast inactivation is disrupted in a fraction of Na^+ channels, the membrane will depolarize for only a few minutes because the abnormal Na^+ channels will stop conducting current due to slow inactivation.

Na^+ channels in rat (Ruff et al., 1987; Simoncini and Stühmer, 1987) and human (Ruff and Whittlesey, 1992; Ruff and Whittlesey, 1993) skeletal muscle manifest both fast and slow inactivation. Slow inactivation operates at more negative potentials than fast inactivation, so that the distribution of channels between the closed and slow inactivated state regulates the number of excitable Na^+ channels as a function of the membrane potential (Ruben et al., 1992; Ruff et al., 1987; Ruff and Whittlesey, 1992; Ruff and Whittlesey, 1993). Interestingly, slow inactivation develops about five-fold faster in human skeletal muscle compared to rat skeletal muscle (Ruff and Whittlesey, 1993). Therefore, slow inactivation would terminate depolarization-induced paralysis more rapidly in human than in rat skeletal muscle.

I appreciate the complexity of the model that Cannon, Brown and Corey used and that the addition of slow inactivation to that model might have made it excessively cumbersome (Cannon et al., 1993). However, I believe that the potential role of slow inactivation in regulating skeletal muscle membrane excitability must be recognized in order to develop a model that accurately depicts the duration of the electrically silent flaccid paralysis in patients with hyperkalemic periodic paralysis.

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