Magnesium/Calcium Competition at Excitable Membranes

Bill Belzer Panni Fry

Despite his contemporaries' dissension, M.L. Heilbrunn pioneered the idea that calcium mediates certain cell functions, particularly muscle contraction (Heilbrunn 1940; Heilbrunn & Wiercinski 1947). Heilbrunn's vision was eventually validated, expanded, and now stands as a fundamental of modern cellular physiology. The cation is a mediator of numerous processes, including enzyme function, cellular signal transduction, neurotransmitter release, cell movement, and ion channel alterations (e.g. see Alberts et al. 1994; Baer et al. 1996). Cellular calcium action is variously examined in modern physiology courses.

Calcium's role in muscle contraction and synaptic transmission is a focus in allied health physiology courses. If we introduce the simple fact that magnesium competes with calcium for entry into cells, and examine functional consequences of their competition, we can sharpen our students' clinical insight and awareness of calcium physiology.

Calcium enters cells through fairly selective calcium pores. Magnesium's similarities to calcium permit it to also enter through those same pores. During the brief moment that a calcium channel opens, fewer calcium ions will get into a cell if higher numbers of magnesium ions are competing to flow through the same pores. Conversely, lowered ambient magnesium increases calcium's competitive entry. Let's consider some consequences of altering intracellular calcium supply by magnesium concentration changes.

Bill Belzer is Professor of Biology at Clarion University—Venango Campus, Oil City, PA 16301. **Panni Fry** is a Biology Teacher at Oil City Area High School, Oil City, PA 16301.

Smooth Muscle Cells

The calcium needed to trigger contractile events inside a smooth muscle cell is derived from extracellular calcium that diffuses into the cell when calcium pores open. (Striated muscle cells, in contrast, use calcium from internal stores.) Hypermagnesemia (elevated ambient magnesium) will competitively decrease the amount of calcium that enters smooth muscle cells, and hence the cells' contractile capacity. Decreased contraction by smooth muscle cells in blood vessel walls manifests as vasodilation (which can lower blood pressure). Conversely, hypomagnesemia allows excessive amounts of calcium to enter smooth muscle cells. The resulting excessive contraction of vascular smooth muscle can cause vasoconstriction, elevated blood pressure, and restricted blood flow (ischemia) to organs. In fact, hypomagnesemia has produced critical ischemic episodes by spasms of vessels supplying the heart, brain, and developing fetus (Turlapaty & Altura 1980; Altura et al. 1983).

Infusions of magnesium, or more selective calcium-channel-blocking drugs like nefidipine, are exploited clinically to dilate constricted vessels. Nefidipine is now a routine therapeutic for coronary ischemia (Porth 1994), while magnesium infusion has long been the standard to reverse vasospasms that accompany eclampsia (Goodman & Gilman 1975).

Synaptic Transmission

Magnesium infusion has also long been a standard treatment for counteracting excessive neural activity (Goodman & Gilman 1975). In this case, the relevant therapeutic magnesium/calcium competition is at the synapse (Pritchard 1979).

When a nerve impulse (action potential) reaches the end of the neuron's axon, transmitter molecules must be released if the neuron is to stimulate its target (e.g. a muscle or another nerve cell). The released transmitters traverse the small synaptic space between axon terminus and target cell, to chemically communicate the neuron's message to that cell. Events inside the axon terminal that cause this crucial release of transmitter molecules are triggered by the entry of calcium ions through pores which momentarily open when an action potential arrives at the axon ending (Baer et al. 1996).

Therapeutic elevation of magnesium competitively reduces the calcium that enters axon terminals, and thereby reduces the capacity of neurons to release transmitters when they fire. Hyperactive neurons are consequently less able to affect postsynaptic target cells, and a patient's convulsions and muscle spasms can be allayed.

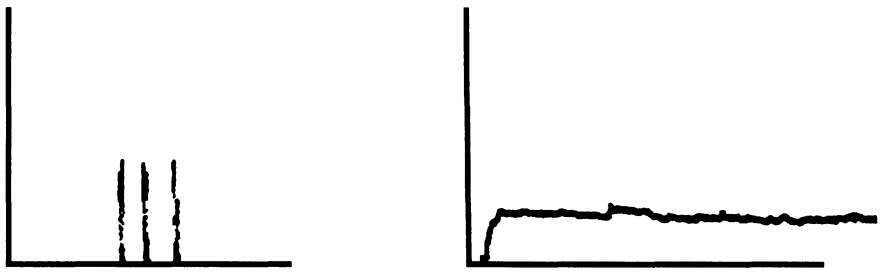
Student Awareness

During clinical visits, many of our allied health students witness these therapeutic uses of magnesium and other calcium-entry-inhibitors, with scant, if any, recognition of the underlying calcium physiology. Barber & Grinnel (1976) provide a laboratory exercise for increasing student awareness of calcium's role in neurotransmitter release. They employ a frog sciatic nerve with attached muscle to demonstrate that reducing transmitter release by soaking the tissue in magnesium-enriched saline reduces the nerve's ability to trigger its muscle's contractions. Although the laboratory is valuable, it's too time and equipment intensive for many introductory courses. Some of the exercise's impact can be gained, however, by student interpretation of its data, provided as a classroom overhead or take-home handout.

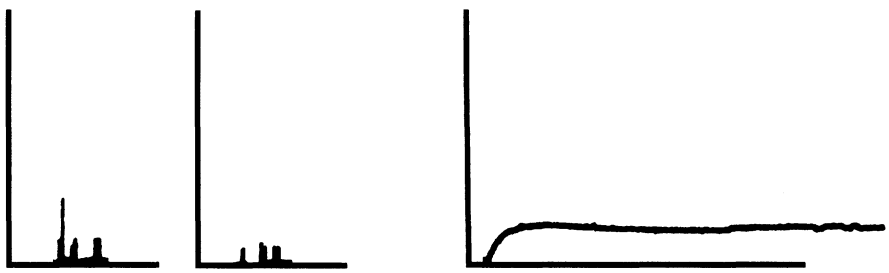
Transparency Master
Twitch and Tonic Contractions of Frog Muscle

TWITCH
(25V stimuli)

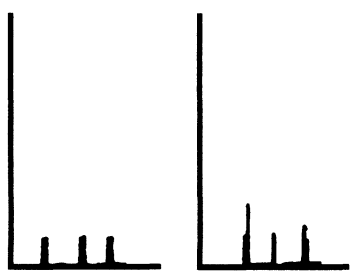
TONIC
(0.2% ACh)



BALANCED RINGER



Mg-ENRICHED RINGER



BALANCED RINGER

The transparency master accompanying this article presents recordings from the exercise.

Interpreting the Transparency Master

For the first three minutes of the exercise, the muscle-nerve preparation was soaking in balanced physiological frog saline.

Trace A on the transparency master records the base-line contraction twitches of the muscle in response to three consecutive 25V stimuli given to its attached sciatic nerve at the start of the exercise. Acetylcholine (ACh) is the transmitter released by the nerve endings onto the muscle to induce the twitches. Thus, for reference, a baseline tonic contraction by the muscle, in response to two drops of 0.2% ACh applied directly to the muscle at one minute into the exercise, is recorded in Trace B.

At three minutes, the balanced saline, soaking the nerve-muscle preparation, was replaced with a magnesium-rich saline.

The magnitude of the muscle's response to standard 25V stimulations of its attached sciatic nerve at time marks 18 and 33 minutes (i.e. after having soaked in magnesium-enriched saline for 15 and 30 minutes) is seen in Traces C and D (respectively).

Compare Traces A, C and D of the Transparency Master. Notice that uniform stimulations of the nerve achieve smaller and smaller muscle twitches the longer that the nerve/muscle preparation soaks in magnesium-rich saline. As more magnesium penetrates the tissue, calcium's competitive entry at axon terminals, when nerve impulses arrive, progressively diminishes. Consequently, the neurons can release fewer transmitter (ACh) molecules with each nerve impulse, and thus can stimulate the muscle less.

At 35 minutes, just before the magnesium-rich saline was removed and the muscle-nerve preparation returned to balanced saline, the tonic response (Trace E) of the muscle to 0.25% ACh, dripped directly onto it, is retested. Compare Trace E with Trace B and notice that, while the capacity of nerve stimulation to induce muscle contraction had diminished dramatically during prolonged exposure to magnesium, the muscle retained its capacity to respond to directly applied transmitter. Its declining response to nerve stimulation was largely due to the nerve's diminishing transmitter release.

The muscle's response to standard 25V stimulations of its attached nerve seen in Traces F and G, at 57 and 67 minutes into the exercise (i.e. at 20 and 30 minutes, respectively, following the muscle/nerve preparation's return to balanced saline). Observe that the nerve's capacity to stimulate the muscle is improving. After the magnesium-rich Ringer was removed and replaced by a balanced Ringer, at 37 minutes into the exercise, magnesium began leaching out of the tissue. The resulting decline in competition from magnesium ions increasingly allowed calcium to again enter axon terminals to trigger ACh-release with each nerve impulse. The recovering capacity to release ACh returns a nerve's ability to stimulate muscle response to each nerve impulse.

With clinical applications for magnesium, and more specific calcium-channel-blocking drugs, proliferating rapidly for the treatment of hypertension, congestive heart failure, cardiac arrhythmias, atherosclerosis, etc. (e.g. see reviews by McLean 1994; Altura & Altura 1995), it is increasingly important for our allied health majors to be aware of calcium's roles in cellular function. Having students engage in interpreting data such as those presented here can nurture that awareness.

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