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LETTER

Zinc Modulation of Cardiac Ryanodine Receptor Gating: Alternate Interpretation of the Interplay between Zinc and Calcium

Woodier *et al.* (1) report that the cardiac type 2 ryanodine receptor channel (RyR2) shows two modes (sites) of regulation by zinc. When calcium is activating the channel, zinc increases channel P_o around 100 pM (high affinity), whereas in the absence of calcium, zinc must reach 100 nM (low affinity) before channel P_o is increased (compare Fig. 1 with Fig. 4, model in Fig.10). We would like to offer an alternate interpretation of these data. In order to achieve nominally 0 free calcium, 1 mM BAPTA (2,2′-(ethylenedioxy)dianiline-*N*,*N*,*N*′,*N*′-tetraacetic acid) was added. We believe the primary reason that higher zinc (100 nM) must be added to modulate RyR2 gating in 0 free calcium is that zinc is chelated by BAPTA as well. It is not possible to use BAPTA to selectively chelate calcium without similarly affecting free zinc concentrations because Zn^{2+} binds to BAPTA (K_d = 7.9 nM) with greater affinity than Ca^{2+} (K_d = 110 nM) (2–4). Using these values, one can estimate free zinc concentrations under the conditions given in Fig. 4 (with the addition of 1 mM BAPTA). With 1 nM zinc added, the free zinc concentration will be ~0.1 fM, and with 100 μM zinc added, the free zinc concentration will be ~1 nM. It is noteworthy that 1 nM free zinc is approximately the same concentration range that modulates gating with calcium present (Fig. 1). Thus, the simplest interpretation of these data is that RyR2 has a single high affinity (1 nM) zinc binding site that functions to both modulate calcium-activated gating and activate channel opening when calcium is absent.

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