Our serendipitous encounter with CICR

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In 1967, Dr. Tanaka and I were working on the effect of caffeine on SR in skinned fibers. In the presence of 50 μM EGTA, 0.2 mM caffeine induced a large transient contraction in the skinned fiber after a long latent period. To our surprise, similar contractions spontaneously recurred at intervals of minutes. The falling phase of the transient contraction must have been caused by removal of Ca^{2+} from the fiber space due to diffusion and binding to EGTA. Ca^{2+} would have then been taken up again by the SR with its strong Ca^{2+} pump forming the basis of the repeated contraction. However, a question remained. The peak tension of the repeated contractions was close to the maximum tension of the same fiber, which indicated that Ca^{2+} was released along the entire length of the fiber. In the first contraction the whole fiber was exposed to caffeine simultaneously. However, after many minutes Ca^{2+} release would still occur again along the entire length of the fiber. This suggested propagation of the release of Ca^{2+} through the entire length of the fiber. We believed that some consequence of Ca^{2+} release must induce further Ca^{2+} release to form a positive feedback loop. All the results of contraction, mechanical stress or increases in the concentration of ADP or Pi could not induce Ca^{2+} release. As a result, we finally found out that Ca^{2+} itself can induce further release of Ca^{2+}.