Modulation and alteration of the elementary calcium release events under normal and pathological conditions

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The aim of our experiments was the investigation of the calcium homeostasis of cultured skeletal muscle myotubes and adult mammalian and amphybian skeletal muscle fibers in the presence of a low affinity heavy metal chelator – TPEN. We were also interested in studying the properties of elementary calcium release events in a chronic heart failure rat animal model.

On C2C12 mouse myotubes in culture, we have shown that low concentrations (20, 50 μM) of TPEN increased the responsivness and the amplitude of Ca^{2+}-transients. In contrast, when applying the drug in higher concentrations (500 μM), it seemed to suppress not only the removal of Ca^{2+} from the myoplasm but also the peak of the depolarization- and agonist-induced Ca^{2+} transients and the underlying Ca^{2+}-flux.

Further experiments carried out on mammalian and amphybian single skeletal muscle fibers were meant to investigate the properties of the building blocks of the global Ca^{2+}-release, namely the elementary calcium release events (ECRE) *spark* and *ember*. On amphybian skeletal muscle fibers we have shown that in the presence of lowered $[Mg^{2+}]_i$, low concentraction of TPEN (50 μM) altered the characteristic parameters of ECRE, increasing the frequency and the full width at half maximum, decreasing the amplitude, but most importantly, evoking travelling *spark*s. These travelling *spark*s (also called *macrospark*s) were never observed in case of mammals or when using slightly increased $[Mg^{2+}]_i$.

Several studies have reported that under pathological conditions, like chronic heart failure, characterized with altered Ca^{2+}-homeostasis properties, the ECREs are showing modified freqvencies. In our hands, confocal microscopy experiments carried out on single skeletal muscle fibers obtained from a CHF animal model, confirmed these observations. The *spark-ember* ratio changed dramatically compared to the control group, along with the number of simultaneously opening channels, which were significanly decreased in the PMI rats.

Taken all this together, we think that our data can contribute to the better understanding of the putative effects of TPEN on the calcium release mechanism, and with this to elucidate certain aspects of Ca^{2+}-homeostasis in skeletal muscle cells under normal and pathological conditions.

Key words: ryanodin receptor, sarcoplasmic reticulum, elementary calcium release events, TPEN, Ca^{2+}-homeostasis
Kulcsszavak: rianodinreceptor, szarkoplazmatikus retikulum, elemi kalciumfelszabadulási események, TPEN, Ca^{2+}-homeosztázis