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Calcium Sparks in Arterial Smooth Muscle Cells Regulate Vascular Tone.

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It is named Ca^{2+} sparks a local, rapid and transient Ca^{2+} release from sarcoplasmic reticulum (SR) by the opening of ryanodine-sensitive (RyR) channels. RyR channels localized in SR are found in all muscle cell types (cardiac, skeletal, smooth) and many other cell types, including those from mammals, birds, amphibians, reptiles, fish, insects, crustaceans, and molluscs. Three molecularly distinct subtypes of RyR channels (RyR1, RyR2, RyR3) have been identified. RyR1 is found primarily in skeletal muscle, whereas RyR2 and RyR3 are predominantly found in cardiac tissue and brain, respectively. RyR channels from smooth muscle are activated by micromolar cytoplasmic Ca^{2+}, by caffeine and are inhibited by Mg^{2+} and ruthenium red.

Ca^{2+} sparks in smooth muscle cells were first described in myocytes from rat cerebral arteries (1), subsequently Ca^{2+} sparks have been measured in smooth muscle cells from coronary arteries, mesenteric artery, rat portal vein, guinea pig and porcine trachea, guinea pig vas deferens and toad stomach. The properties of Ca^{2+} sparks appear to be similar in these different smooth muscle preparations. In arterial smooth muscle, a Ca^{2+} spark is due to the simultaneous activation of a cluster of RyR Channels, it has a rise time of ~20 ms and a spatial spread of 2.4 mM. Ca^{2+} sparks occur most frequently close to the cell membrane with a frequency of about 1/sec/cell at physiological membrane potentials (-60 to -40 μV). In smooth muscle cells SR is very close to the plasma membrane, and the close spatial localization suggests a special communication between the RyR channels and the sarcolemmal ion channel large-conductance Ca^{2+}-sensitive K^+ channels (BK_{Ca}) (fig.1)

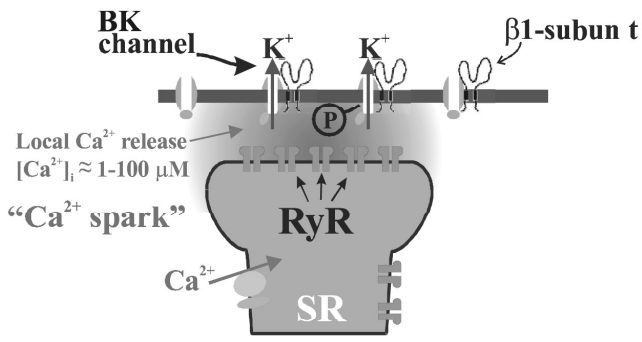

Fig. 1 - Spatial relation between the RyR channels and the sarcolemmal Ca^{2+}-sensitive K^+ channels (BK_{Ca}) in smooth muscle cells.

BK_{Ca} channels require micromolar Ca^{2+} for significant levels of activity under physiological conditions. A single Ca^{2+} spark is capable of producing a very high (10-100 μM) subsarcolemmal increase in $[Ca^{2+}]$, by its high local $[Ca^{2+}]$ elevation has the potential to induce a spontaneous transient outward currents through BK_{Ca} channels (referred to as "spontaneous transient outward currents" or STOCs). A single Ca^{2+} spark through activation of BK_{Ca} channels increase strongly cell membrane potential, hyperpolarization [up to 20 mV in an isolated cerebral artery myocyte, (2)] which closes voltage-dependent Ca^{2+} channels and leads to smooth muscle relaxation (fig. 2.)

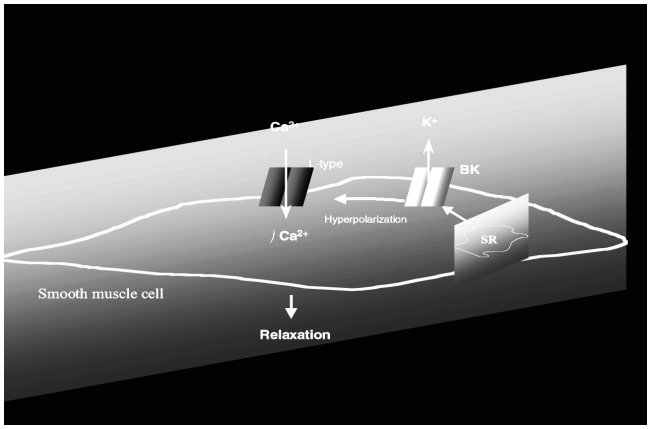

Fig. 2 - Ca^{2+} sparks by BK channels and their control of global Ca^{2+} through voltage-depend calcium channel (L-type) induce smooth mucle cell relaxation.

The triumvirate of dihydropyridine-sensitive voltage-dependent Ca^{2+} channels, RyR channels, and BK_{Ca} channels act as a functional unit to regulate vascular tone by controlling the levels of smooth muscle cells $[Ca^{2+}]_i$ (3). Nitric oxide, a potent endogenous vasodilator activates guanylyl cyclase, leading to increased production of cGMP and stimulation of cGMP-dependent protein kinase (PKG) (4). PKG has been shown to activate BK_{Ca} channels through direct phosphorylation effects on the channel protein (5) and through elevation of Ca^{2+} spark frequency (6). An increase in Ca^{2+} spark frequency following elevation of cGMP may be due to phosphorylation of RyR channels, or of phospholamban. Phospholamban, when phosphorylated by PKG, dissociates from the SR Ca^{2+}-ATPase, which leads to increased Ca^{2+} pumping and an elevated SR Ca^{2+} load, which increases Ca^{2+} spark frequency (7) and STOC frequency and amplitude with a

final smooth muscle relaxation effect.
Furthermore, also for Sodium nitroprusside (SNP) a donor of NO esogenous was shown increasing, by two- to threefold, frequency of Ca^{2+} sparks release in myocytes isolated from cerebral arteries of rats (8).
In conclusion the discovery of local Ca^{2+} transient, Ca^{2+} spark, suggest a new mechanism in the regulation of spatially homogeneous cytoplasmic Ca^{2+} as intracellular signal. Further, modulation of Ca^{2+} spark frequency and amplitude by smooth muscle relaxants appears to regulate smooth muscle membrane potential and hence vascular tone, in a negative feedback manner, through activation of BK_{Ca} channels.

References

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Sunto in Italiano

Nel 1995, per la prima volta, nelle cellule muscolare liscie delle arterie cerebrali isolate da ratto è stato osservato un rapido ed intenso rilascio di calcio dal reticolo sarcoplasmatico (SR). Tale rilascio, detto "Ca^{2+} spark", è generato dall' apertura contemporanea dei canali ionici sensitivi alla rianodina da cui il nome "ryanodine-sensitive (RyR) channels".
Nelle cellule muscolari liscie il SR si trova immediatamente sotto la membrana plasmatica cellulare, tale particolare organizzazione strutturale permette una diretta interazione dei RyR con i canali per il potassio sensitivi al Ca^{2+} (BK_{Ca2+}), di cui la membrana plasmatica delle cellule muscolare liscie è ricca. Un evento di Ca^{2+} spark aumenta la concentrazione locale di Ca^{2+} a valori dell'ordine dei μM sufficiente per attivare BK_{Ca2+} (fig.1). L' attivazione dei BK_{Ca2+} comporta fuoriuscita di ioni K^+ ed iperpolarizzazione che inibisce il canale voltagggio dipendente per il Ca^{2+} (V_{Ca2+}) con conseguente rilascio della cellula muscolare (fig.2). Quindi nella cellulare muscolare liscia i canali: RyR, BK_{Ca2+} and V_{Ca2+} costituiscono una unita' funzionale nella regolazione della contrazione muscolare.
Precedenti studi hanno dimostrato che l'ossido nitrico (NO), sia endogeno che esogeno, aumenta la frequenza del Ca^{2+} spark, questo puo' rappresentare una via alternativa alla diretta fosforilazione del BK_{Ca2+} mediante PKG nella regolazione del Tono vascolare.