Errata

Original Document: "Mechanisms of Asynchronous Ca^{2+} Oscillations and Their Role in (Mal)function of Vascular Smooth Muscle"

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Pages 2-3 – Replace with the following:

1.1.1 Endothelium

"The vascular endothelium consists of a continuous monolayer of cells, lining the luminal surface of the entire vascular system, which provides a structural and metabolic barrier between the blood and the underlying tissues. Endothelial cells are induced to migrate during the process of new capillary blood formation and during repair of the endothelial lining which result from injury of large vessels. Moreover, the endothelium plays a central role in the regulation of the vascular tone (Furchgott and Zawadzki, 1980)" (Haefliger *et al.*, 2004, p. 345), releasing a variety of vasoactive mediators, including prostaglandins, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF) to regulate smooth muscle contractility and thus vascular smooth muscle tone (Ramsey *et al.*, 1995; Boutouyrie *et al.*, 1997; Wilkinson *et al.*, 2002; Vanhoutte, 2004).

"Within vessels, the endothelial and the smooth muscle cells are separated by connective tissue and the internal elastic membrane. However, these two cell types also establish close contacts with each other, via myo-endothelial bridges that cross fenestration of the internal elastic lamina (Emerson and Segal, 2000; Sandow and Hill, 2000)" (Haefliger *et al.*, 2004, p. 347).

Page 8, First full paragraph – Replace with the following:

The transient receptor potential (TRP) proteins have also been suggested as components of SOCs. "A number of mammalian homologues of TRP have been found and are classified into three major subfamilies closely related to TRP" (Salido *et al.*, 2004, p. 224) (transient receptor potential canonical, TRPC; transient receptor potential vanilloid, TRPV; transient receptor potential melastatin, TRPM), two subfamilies that are more distantly related to TRP (transient receptor potential polycystic, TRPP; transient receptor potential mucolipin, TRPML), and a less related no mechanoreceptor potential C (TRPN) group that is "expressed in flies and worms (Montell *et al.*, 2002)" (Salido *et al.*, 2004, p. 224). TRP channels are mostly nonselective for monovalent and divalent cations ($P_{Ca}/P_{Na} \leq 10$), with exceptions including TRPM4 and TRPM5, which shows a great selectivity for monovalent cations, and the Ca^{2+}-selective TRPV5 and TRPV6. As with Orai proteins, TRP channels lack voltage sensitivity (Venkatachalam and Montell, 2007).

Page 10, Sentence beginning with "Gating by DAG of several NSCCs…" – Replace with the following:

"Gating by DAG of several NSCCs has been subsequently described, including TRPC3/6/7 channel proteins expressed in cell lines (Hofmann *et al.*, 1999; Inoue *et al.*, 2001; Estacion *et al.*, 2004; Shi *et al.*, 2004) and it has been shown that TRPC6 and TRPC3 proteins are components of native ROCs in portal vein and cerebral artery myocytes (Inoue *et al.*, 2001; Reading *et al.*, 2005)" (Albert and Large, 2006, p. 46).

Pages 10-11, Last paragraph – Replace with the following:

"One functional characteristic distinguishing these two subgroups is the ability of diacylglycerol (DAG) to activate TRPC3/6/7 channels but not the TRPC1/4/5 channels" (Wang *et al.*, 2008, p. 1127) (Hoffman *et al.*, 1999; Venkatachalam *et al.*, 2003; Freichel *et al.*, 2004; Dietrich *et al.*, 2005a; Dietrich *et al.*, 2005b; Parekh and Putney Jr., 2005). DAG appears to have an important dual role in TRPC channels; in addition to rapidly activating TRPC3 channel directly, DAG also mediates a slower PKC-mediated deactivation of the TRPC3 channel (Venkatachalam *et al.*, 2003; Estacion *et al.*, 2006). This bimodal regulation may form the basis of a spectrum of regulatory phenotypes of expressed TRPC channels.

Pages 14-15, Last paragraph – Replace with the following:

"Storage of Ca^{2+} in cellular organelles also provides important physiological regulation and the potential for release of Ca^{2+} during physiological signaling. The main storage compartment is the SR, and this organelle has a major role in maintaining low $[Ca^{2+}]_i$" (Sanders, 2001, p. 1441). "The SR is surrounded by a membrane that is not freely permeable to Ca^{2+}" (Sanders, 2001, p. 1442), and on which SERCA pumps sit. SERCA actively sequesters cytosolic Ca^{2+} into the SR (Sanders, 2001) and maintains a 10,000-fold concentration gradient between the SR lumen and the cytosol. Three genes encode for SERCA, and "smooth muscle mainly expresses the SERCA2b isoform (>70%), with the SERCA2a and SERCA3 isoforms forming the remainder of the SERCA population (Lytton *et al.*, 1989; Wuytack *et al.*, 1989; Eggermont *et al.*, 1990; Amrani *et al.*, 1995; Trepakova *et al.*, 2000; Wu *et al.*, 2001)" (Laporte *et al.*, 2004, p. 449). All SERCAs encode a cytoplasmic region that contains the catalytic site and a transmembrane domain that forms a channel-like structure allowing Ca^{2+} translocation across the membrane

(Engelender and De Meis, 1996; Zhang *et al.*, 1998). Phospholamban is a small protein that negatively regulates SERCA; upon phosphorylation via PKC or cGMP-dependent protein kinase (PKG) (Raeymaekers *et al.*, 1990), this inhibition is relieved and SERCA is activated, thereby pumping Ca^{2+} into the SR.

Page 15, Sentence beginning with "After Ca^{2+} is pumped…" in first full paragraph – Replace with the following:

"After Ca^{2+} is pumped into the SR, it is buffered by proteins, such as calreticulin and calsequestrin. These proteins can bind large amounts of Ca^{2+}" (Sanders, 2001, p. 1442) (Milner *et al.*, 1992; Raeymaekers *et al.*, 1993).

Page 16, First full paragraph – Replace with the following:

Two other pathways to extrude Ca^{2+} from smooth muscle cells are the PMCA and the Na^+/Ca^{2+} exchanger (NCX), the latter of which is also regulated by the Na^+/K^+ pump (Na^+/K^+-ATPase) (Blaustein and Lederer, 1999). The PMCA "uses energy from ATP to pump Ca^{2+} up the steep electrochemical gradient from cytosol to extracellular space. This pump is thought to be electron neutral because the Ca^{2+} pumped to the extracellular space is exchanged for two protons" (Sanders, 2001, p. 1443). Therefore, "Ca^{2+} extrusion results in uptake of H^+, and this has to be compensated for by transporters such as Na^+/H^+ exchange" (Sanders, 2001, p. 1443) (Lucchesi and Berk, 1995).

Page 20, Sentence beginning with "Ca^{2+} regulates nearly all…" in last paragraph – Replace with the following:

"Ca^{2+} regulates nearly all fast processes in the body, including contraction, chemotaxis, secretion, and synaptic transmission, and several slower processes, including fertilization, proliferation, learning, memory and apoptosis" (Poburko *et al.*, 2004a, p. 8).

Page 22, First full paragraph – Replace with the following:

This second type of interaction occurs in nanodomains, which are formed at the sites where Ca^{2+} enters the cytoplasm at either the cell surface or at the internal stores, and are defined by the ultrastructural architecture of the cell, such as the close (nanometre-ranged) spatial association of the PM, SR and mitochondria (Poburko *et al.*, 2008; Fameli *et al.*, 2009). "The resulting microstructural arrangements of the apposing membranes create diffusional barriers defining different types of junctional spaces within the cytoplasm" (Lee *et al.*, 2002, p. H1571). "The diffusional limitations of these junctional spaces allow for accumulation of ions such as Na^{+} and Ca^{2+} in concentrations greatly exceeding that in the bulk cytoplasm" (Lee *et al.*, 2002, p. H1571-1572) (Rizzuto and Pozzan, 2006; van Breemen *et al.*, 2006). "These cytoplasmic nanodomains have important functional implications. For example, Ca^{2+}-sensitive ion channels selective for K^{+}, Cl^{-}, and Ca^{2+} and Ca^{2+}-sensitive enzymes, such as PKC and PLC, which are located in membranes bordering the restricted space between the PM and the superficial SR, can be regulated separately from the myofilaments occupying the bulk of the cytoplasm" (Lee *et al.*, 2002, p. H1572) (Berridge, 2006; Edwards and Pallone, 2007).

Page 23, Sentence beginning with "The SR can be classified…" – Replace with the following:

"The SR has been classified according to its location as superficial or deep," (Lee *et al.*, 2002, p. H1572) and electron microscopy shows that the superficial SR forms a flattened pedestal as it approaches the PM, at which point "it creates a narrow space that extends on average in two dimensions for about 300–400 nm and has a depth of about 15–20 nm" (Lee *et al.*, 2002, p. H1572-1573).

Page 23, Sentence beginning with "The narrow cytoplasmic space…" – Replace with the following:

"The narrow cytoplasmic space between the junctional SR and PM is referred to as the PM-SR junctional space and is thought to present an imperfect barrier to diffusion of small molecules and ions, in particular, Ca^{2+} and Na^{+}" (Lee *et al.*, 2002, p. H1573).

Page 23, First sentence in 2nd paragraph – Replace with the following:

"The structures responsible for this spacing have not yet been identified, although in some instances 'feet' similar to those seen in triadic junctions in skeletal muscle have been reported (Somlyo, 1985), and proteins called 'junctophillins' have been isolated from the diads of cardiac muscle (Takeshima *et al.*, 2000)" (Lee *et al.*, 2002, p. H1573).

Page 27, First full paragraph – Replace with the following:

"The PM-SR junction complexes are likely the sites for interactions among NSCC, NCX, and SERCA during SR refilling and are thus crucial for the occurrence of the recurring Ca^{2+} waves" (Lee *et al.*, 2002, p. H1577). This theory is supported by the observation that "the low Na^{+}-

affinity Na-K-ATPase isoforms α_2 and α_3 have been localized to the junctional PM (Juhaszova and Blaustein, 1997), which would promote elevated junctional [Na^+] and reversal of the NCX" (Lee *et al.*, 2002, p. H1577) (Arnon *et al.*, 2000b). Finally, separation of the superficial SR from the PM with calyculin-A results in the abolishment of Ca^{2+} waves (Lee *et al.*, 2005). This may disrupt SR refilling from Ca^{2+} coming from the PM, because as the junction separates the SERCA molecules are not able to capture as many Ca^{2+} molecules (Fameli *et al.*, 2007).

Page 33, Sentence beginning with "Fibrillin assemblies (microfibrils)…" in the first paragraph – Replace with the following:

"Fibrillin assemblies (microfibrils) serve two key physiological functions: the function of a structural support that imparts tissue integrity and the function of a regulator of signaling events that instruct cellular performance (Ramirez *et al.*, 2004; Hubmacher *et al.*, 2006)" (Ramirez and Dietz, 2009, p. 14677).

References (not originally listed in the dissertation)**:**

Albert AP, Large WA (2006). Signal transduction pathways and gating mechanisms of native TRP-like cation channels in vascular myocytes. *J Physiol* **570:** 45-51.

Laporte R, Hui A, Laher I (2004). Pharmacological modulation of sarcoplasmic reticulum function in smooth muscle. *Pharmacol Rev* **56:** 439-513.

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