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REGULATION OF TREKS BY LIPIDS

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40 YEARS ON: MECHANISMS OF Ca REGULATION OF TONE IN RAT AND HUMAN VASCULATURE

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In just over 4 decades since the level of free Ca^{2+} bathing the myofilaments was found to be a determinant of smooth muscle tone, we have learnt an incredible amount as to how this ion regulates contractility. In particular in the last decade, important information on the spatiotemporal dynamics of Ca^{2+} signalling has come to light. Our own work is concerned with understanding (i) how the Ca2+ dynamics in smooth muscle cells of pressurised resistance arteries of animals and humans regulates lumen diameter and (ii) how this is related to the structure of the sarcoplasmic reticulum (SR). It is now generally accepted that tonic tone maintenance of pressurised animal arteries (rat mesentery e.g.) upon agonist stimulation occurs by asynchronous activation of medial smooth muscle cells. The changes take the form of waves of Ca^{2+} originating in a focal point, probably as a result of the modulation of many shorter duration Ca^{2+} spark events, into a globalised Ca^{2+} increase that propagates tens of microns throughout the rest of the cell. Electron microscopic examination of these blood vessels reveals a peripheral SR localisation often intertwined with membrane invaginations (caveolae) that links with a central SR coursing through much of the cell. Disruption of the SR-caveolae links (with the cholesterol-depeleting cyclodextrin or the phosphatase inhibitor calyculin A) alters the dynamics of Ca^{2+} sparks, waves and lumen diameter thus supporting the notion that the SR ultrastructural arrangement is crucial for regulation of vessel diameter. Of great interest for our understanding of human vascular (patho)physiology is whether a similar SR structure-function relationship exists in human resistance arteries yet, thus far, little is known of the spatiotemporal dynamics of Ca^{2+} signalling in healthy human vessels. Therefore, we have begun to examine the SR ultrastructure in adult omental or uterine pressurised arteries obtained from pregnant women at the time of Caesarean section. We have found a similar appearance of smooth muscle peripheral-central SR to that in rat mesenteric arteries indicating a structural basis, at least in principle, for similar Ca^{2+} dynamic processes in rat and human vessels. This is not, however, so apparent in arteries of a fetal origin (placenta) indicating that SR Ca^{2+} homeostasis in developing human vessels may differ to that of mature adult arteries. Rather than the next 4 decades, we look forward to many groups efforts adding to this information in the next 4 years and establishing the basic tenets of Ca^{2+} dynamics in smooth muscle cells of human arteries.