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CA2+ HEMOSTASIS IN THE SMOOTH MUSCLE CELL

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Abstract. Control of smooth muscle is vital for health. The major route to contraction is a rise in intracellular [Ca^{2+}], determined by the entry and efflux of Ca^{2+} and release and re-uptake into the sarcoplasmic reticulum (SR). We review these processes in myometrium, to better understand excitation-contraction coupling and develop strategies for preventing problematic labours. The main mechanism of elevating [Ca^{2+}] is voltage-gated L-type channels, due to pacemaker activity, which can be modulated by agonists. The rise of [Ca^{2+}] produces Ca-calmodulin and activates MLCK. This phosphorylates myosin and force results. Without Ca^{2+} entry uterine contraction fails. The Na/Ca exchanger (NCX) and plasma membrane Ca-ATPase (PMCA) remove Ca^{2+}, with contributions of 30% and 70% respectively. Studies with PMCA-4 knockout mice show that it contributes to reducing [Ca^{2+}] and relaxation.

Keywords: uterus, SR, signalling, Ca-ATPase

Introduction: The solutions to medical problems that we encounter arise from understanding the nature of the problem and enough of the associated factors to enable the development of therapy. Problems associated with smooth muscle function are no different. Already, significant advances have been made in diagnosis and treatment in this area, e.g. hypertension. However, there are still significant gaps in our knowledge and conditions such as pre-term labour and asthma remain significant clinical problems.

It has long been recognised that a rise in intracellular calcium concentration ($[Ca^{2+}]_i$) is fundamental to smooth muscle contraction. Recent research has focussed on understanding the local and global changes in [Ca^{2+}] that occur as a consequence of stimulation (2). In this brief review we will examine the progress that has been made in understanding these mechanisms in one particular smooth muscle _ the myometrium.

Materials And Methods

What are the mechanisms responsible for the increase in $[Ca^{2+}]_i$ for uterine contraction, and how do these relate to changes in force production? Linking changes in membrane potential to changes in $[Ca^{2+}]_i$ and force is known as "excitation-contraction coupling", or EC coupling. EC coupling starts with a depolarisation of the plasma membrane that is above the activation threshold of voltage-activated dihydropyridine-sensitive L-type Ca^{2+} channels (LTCC) and causes them to open. The open Ca^{2+} channels allow the influx of Ca^{2+} (down its 10,000-fold concentration gradient) that not only contributes to the further explosive depolarisation of the plasmalemma, but also binds to the Ca^{2+} binding protein, calmodulin (see Fig. 1). Calmodulin then forms a complex with and activates myosin light chain kinase (MLCK), which, as its name suggests, phosphorylates the myosin light chain. Myosin continually forms cross bridges with actin, and the cycling of these cross bridges is the molecular mechanism for contraction. Phosphorylation of myosin light chains increases the rate of cross bridge cycling, as the myosin ATPase is stimulated, and hence produces

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contraction. The vast majority of these steps can be regulated and fine tuned, by phosphorylation and dephosphorylation reactions or the binding of further accessory proteins and thus alteration of binding affinity or activity (28; 33).

Results And Discussion

Perhaps the most critical event in the control of uterine contractile activity is the influx of Ca^{2+} from the extracellular space. A large proportion of recent work on smooth muscle contractility has used fluorescent dyes that exhibit a shift in excitation/emission wavelength upon binding Ca^{2+} to measure $[Ca^{2+}]_i$. In this way we have gained insight into the nature of these changes and their relation to the observed changes in force. The application of nifedipine, a specific antagonist to the LTCC, rapidly abolishes contractions (see Fig. 2A, (25)). If the myometrium is exposed to Bay K8644, an agent that increases the open probability of the LTCC channel, an increase in the frequency and strength of contractions is observed (12). Application of controlled membrane potential steps to cells under voltage clamp conditions have demonstrated that the opening of the LTCC is dependent on depolarization (Fig. 2B) _ without the changes in membrane potential, contractions do not occur.

Ca^{2+} is removed from the cell interior by the operation of two proteins that span the plasmalemma: the Ca^{2+}-ATPase (PMCA) and the Na/Ca exchanger (NCX) (14; 24; 34; see also Carafoli, this issue, ref 3a). It is the activity of these proteins that is responsible for the maintenance of the 10,000-fold concentration gradient across the plasmalemma. Differences in the properties of these proteins reveal the characteristics that define them, and are fundamental to their operation; the NCX has a lower affinity for Ca^{2+}, but is a higher capacity system (3), whereas the PMCA extrudes Ca^{2+} at a lower $[Ca^{2+}]_i$ (1). Thus PMCA may be viewed as providing a "fine tuning" of resting $[Ca^{2+}]_i$, and the NCX having a role in the regulation of higher, stimulatory $[Ca^{2+}]_i$.

As its name suggests, the NCX depends upon the transplasmalemmal Na^+ gradient, which is maintained by the Na^+/K^+ ATPase. The NCX relies upon a higher $[Na^+]_o$ than $[Na^+]_i$, and can reverse, i.e. drawing Ca^{2+} into the cell, in the event of a reversed transplasmalemmal Na^+ gradient. Although this is not considered its primary physiological role, such conditions are used experimentally, and NCX mediated Ca^{2+} influx can trigger Ca^{2+} release events from nearby SR (23).

The PMCA extrudes Ca^{2+} at the expense of ATP and counter-transports protons (5; 19). Both the NCX and the PMCA are accompanied by accessory proteins that allow the modulation of each respective protein (22). Experimental elimination of either NCX or PMCA can provide information on their contributions to Ca^{2+} efflux.

Conclusion: There are a multitude of key points for the regulation of uterine function. These points of regulation are of fundamental importance to the function of the uterus, as large changes in contractile behaviour are required to accomplish the demands on the tissue at different gestational states. Numerous studies have clearly demonstrated the change in expression of specific proteins that control the contractility of the myometrium (e.g. BK channel (10), contractile activators (4)). Changes may also be expected in the expression of other proteins associated with the role of the SR, as well as in the Ca^{2+} efflux mechanisms.

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Therefore Ca^{2+} entry, together with SR Ca^{2+} release and efflux will optimise the Ca^{2+} transient profile to the function of the uterus.

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