Symposium Report

Kv7 and Kv11 channels in myometrial regulation

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New Findings

- **What is the topic of this review?**
  The topic of this review is how ion channels contribute to the physiology of the uterus, with particular focus on novel potassium channels.
- **What advances does it highlight?**
  Two families of potassium channels, encoded by *KCNQ* and *KCNH* genes, have been identified as important players in the control of myometrial contraction and may represent interesting novel therapeutic targets.

Ion channels play a key role in defining myometrial contractility. Modulation of ion channel populations is proposed to underpin gestational changes in uterine contractility associated with the transition from uterine quiescence to active labour. Of the myriad ion channels present in the uterus, this article will focus upon potassium channels encoded by the *KCNQ* genes and ether-à-go-go-related (*ERG*) genes. Voltage-gated potassium channels encoded by *KCNQ* and *ERG* (termed Kv7 and Kv11, respectively) are accepted as major determinants of neuronal excitability and the duration of the cardiac action potential. However, there is now growing appreciation that these ion channels have a major functional impact in vascular and non-vascular smooth muscle. Moreover, Kv7 channels may be potential therapeutic targets for the treatment of preterm labour.

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Introduction

The uterus is an incredibly complex organ that displays considerable physiological plasticity, cellular remodelling and robustness during pregnancy. However, perturbations of the precise orchestrations that regulate the contractile state of the uterus can have negative consequences for the mother and fetus. Early activation of contractility that, for example, results in spontaneous preterm birth can be associated with a high risk of neonatal morbidity and mortality, as well as lifelong ill health and socio-economic consequences. Conversely, delayed delivery or dysfunctional labour due to weak or poorly co-ordinated contractions can lead to fetal hypoxia, clinical intervention and a greater risk of postpartum haemorrhage.

If there are to be improvements in clinical management and development of novel therapeutic strategies for complicated pregnancies then a better understanding of the mechanisms that determine normal and pathophysiological uterine contractility is essential. There are many factors that dictate gestational changes in uterine contractility, such as alterations in the steroid hormone environment, inflammation and uterine stretch that is exerted by the growing feto-placental unit. The impact of these stimuli is a fine tuning of the mechanisms controlling uterine smooth muscle contractility at the cellular level, including gap junctions, G-protein-coupled receptors, calcium regulatory proteins and contractile filament interactions, but ultimately, all converge upon a background electrical rhythm generated by the activity

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Experimental Physiology

of ion channels, much like a good concerto relies on the precise contributions from individual instruments in an orchestra. Understanding the contribution of these individual instruments to the uterine symphony is very much a work in progress, but recent studies have identified *KCNQ* and *KCNH*-encoded K^+ channels as new and functionally powerful elements that hold promise as major regulatory mechanisms and potential therapeutic targets for the treatment of intrapartum complications.

The purpose of this article is to provide a brief overview of this field of research, with particular focus on two new pieces of the puzzle rather than a comprehensive summary of the many factors implicated in uterine physiology. The reader is recommended to consult a number of more comprehensive reviews for more depth in specific areas (e.g. Taggart & Tribe, 2007; Wray, 2007).

Inherent excitability

Uterine smooth muscle exhibits spontaneous contractility that can be augmented by receptor agonists, such as oxytocin (Wray, 2007). Spontaneous contractions are intimately related to the generation of slow waves, upon which action potentials are superimposed (Casteels & Kuriyama, 1965; Kuriyama & Suzuki, 1976; Bengtsson *et al.* 1984; Parkington *et al.* 1999). As gestation proceeds towards labour, the resting membrane potential of the uterine smooth muscle becomes progressively more depolarized (Kuriyama & Suzuki, 1976; Bengtsson *et al.* 1984; Parkington *et al.* 1999), and this is associated with an increase in the force and frequency of spontaneous contractions. The initiator of the spontaneous activity, however, remains to be identified unequivocally. In the gastrointestinal tract, peristalsis is driven by multibranched, non-contractile cells that express the c-kit receptor (termed interstitial cells of Cajal or ICC). Similar ICC-like cells have been observed in rodent and human myometrial tissue (Ciontea *et al.* 2005; Duquette *et al.* 2005; Allix *et al.* 2008). Moreover, pharmacological blockade of the c-kit receptor with imantanib or deletion of this gene does affect the frequency of contractions in the myometrium of mice. However, the effects are subtle, and imantanib has negligible effect in human myometrium, suggesting that the impact of ICC-like cells is not as clearly defined in the uterus as it is in the gastrointestinal tract. Irrespective of the genesis of the spontaneous contractility, the operation of specific ion channels maintains contractile activity, and elucidation of the nature of the respective depolarizing (excitatory) and hyperpolarizing (inhibitory) channels remains a key challenge for uterine physiologists.

Excitatory pathways

In its simplest form, contraction of myometrium, like that of all smooth muscle, is mediated by a rise in $[Ca^{2+}]$ leading to activation of myosin light chain kinase, and the subsequent phosphorylation of myosin light chain at serine 19 allows actin–myosin interaction (see Wray, 2007; Taggart & Tribe, 2007). The rise in $[Ca^{2+}]_i$ is mediated by an interplay between increased Ca^{2+} influx through plasmalemmal channels, Ca^{2+} release from the sarcoplasmic reticulum and Ca^{2+} sequestration processes. However, the major precipitatory mechanism is the opening of L-type voltage-dependent Ca^{2+} channels (VDCCs), as evidenced by the marked effect of dihydropyridines, such as nifedipine, on myometrial contraction (Sperelakis *et al.* 1992; Wray, 2007). There is evidence that T-type VDCCs may also have some role in maintaining spontaneous contractile activity (Taggart & Tribe, 2007). In addition to VDCCs, voltage-gated sodium channels have been recorded from isolated myometrial smooth muscle (Sperelakis *et al.* 1992; Seda *et al.* 2007), and the density of these currents increases in late pregnancy. However, little is known about the molecular nature of the sodium channels and how they contribute to functional activity.

Membrane potential is key

If the influx of Ca^{2+} through VDCCs is a major determinant of myometrial contractility then logically the influence of membrane potential is central to this mechanism (see Tong *et al.* 2011 for a computational model). An important question, therefore, is what are the principal mechanisms that propel the membrane potential towards voltages that enhance VDCC open probability and, conversely, which specific ion channels ensure repolarization to more negative membrane potential and closure of VDCCs? In most smooth muscle cells, Ca^{2+}-activated Cl^- channels (CACCs) provide the major depolarizing impetus, because smooth muscle cells actively accumulate Cl^- ions (Chipperfield & Harper, 2000). As a consequence, the activation of CACCs leads to Cl^- ion efflux sufficient to produce membrane depolarization (Leblanc *et al.* 2005) and, subsequently, to further activation of VDCCs. In relationship to uterine smooth muscle, Cl^- currents due to CACC activation have been recorded in rat myometrial cells, and inhibitors of this channel, such as niflumic acid, attenuate myometrial contractility (Jones *et al.* 2004), although these agents are known to have pluripotent effects (Greenwood & Leblanc, 2007). Preliminary data also show that transcripts for *TMEM16A* (Caputo *et al.* 2008; Schroeder *et al.* 2008; Yang *et al.* 2008), the putative molecular correlate of CACCs, are present in mouse and human myometrium (AJ Davis, RM Tribe & IA Greenwood, unpublished observations) as well as in vascular smooth muscle cells (Davis *et al.* 2010). It is worth noting that in the gastrointestinal tract, *TMEM16A* is expressed by the ICCs, not the smooth muscle cells (Hwang *et al.* 2009). A second mechanism to produce

membrane depolarization is to activate non-selective cation channels, and various members of the *ORAI*/*STIM* and *TRP* gene family that encode for proteins associated with store-operated and receptor-operated calcium entry (see Wang *et al.* 2008 for overview) are present in rodent and human myometrium (Dalrymple *et al.* 2002; Yang *et al.* 2002; Babich *et al.* 2004). Non-selective cation channels also have a degree of inherent Ca^{2+} permeability that can potentially contribute to the general rise in $[Ca^{2+}]$ and contraction.

Potassium channels: nature's brakes

Co-ordinated contraction of the myometrium relies on hyperpolarizing influences to limit the extent of membrane depolarization (see Fig. 1) and subsequent contraction. Consequently, potassium channels define the magnitude, duration and periodicity of uterine electrical events. Myometrium expresses a number of genes encoding for different potassium channels, including calcium-activated (BK_{Ca}; Anwer *et al.* 1993; Pérez *et al.* 1993), SK_{Ca} (Brown *et al.* 2007; Pierce *et al.* 2008), acid-sensitive twin-pore channel TREK-1 (Bai *et al.* 2005; Buxton *et al.* 2010), inwardly rectifying ROMK1 (Lundgren *et al.* 1997) and various voltage-dependent K^+ channels, especially members of the Kv4 family (Song *et al.* 2001; Smith *et al.* 2007; Greenwood *et al.* 2009). In terms of functional impact, inhibitors of BK_{Ca}, such as paxilline or iberiotoxin, or blockers of SK_{Ca}, such as apamin, have negligible effect on rodent or human myometrial contractility (Aaronson *et al.* 2006; Brown *et al.* 2007; Smith *et al.* 2007; Noble *et al.* 2010). In comparison, the non-selective Kv inhibitor, 4-aminopyridine, enhances contractility (Aaronson *et al.* 2006; Smith *et al.* 2007), and the Kv4.2/4.3 blocker, phrixotoxin-2, induces contractions in non-pregnant, but not pregnant, rat myometrium (Smith *et al.* 2007). Set against this background, two novel types of Kv channel encoded by members of the *KCNQ* and *KCNH* gene families have been identified that appear to act as key regulators of uterine contractility and offer new therapeutic targets.

KCNQ- and *ERG*-encoded potassium channels

Ether-à-go-go-related genes or *ERG*s (*ERG1*, *2* and *3*) are members of the *KCNH* gene family. All genes encode for voltage-dependent K^+ channels (Kv11.1–11.3) that assemble as a tetramer to generate a Kv channel with unique voltage-dependent properties due to an over-riding c-type inactivation (Smith *et al.* 1996). *ERG1* (*KCNH2*) exists mainly as two splice variants (*ERG1a* and *1b*; London *et al.* 1997) and is expressed predominantly in cardiac myocytes, where it contributes to the late repolarizing phase of the cardiac action potentials; mutations to the underlying gene underpin a major component of hereditary arrhythmias. *ERG2* and *ERG3* are located in neurones and contribute to the suppression of membrane excitability (Selyanko *et al.* 1999). The *KCNQ* gene family contains five members

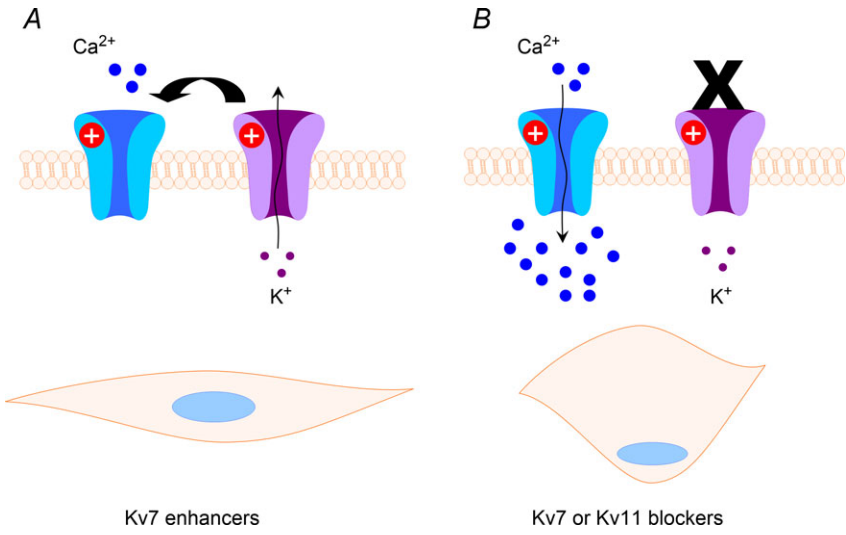

Figure 1. Schematic representation of the functional role of potassium channels in uterine smooth muscle contraction
Left-hand panel shows that open K^+ channels result in membrane hyperpolarization that indirectly limits the opening of voltage-dependent calcium channels shown in blue. This results in a less contracted smooth muscle. In the right-hand panel, the potassium channels are non-functional due to blockade, loss-of-function mutations or trafficking defects. This leads to membrane depolariziation, and the open probability of the calcium channels increases. The concomitant influx of calcium contributes to smooth muscle contraction.

(*KCNQ1–5*), and each gene encodes a Kv channel (Kv7.1–7.5, respectively) with low activation threshold ($V_{0.5} \approx -35$ mV) and minimal inactivation (Haitin & Attali, 2008). Kv7 channels also exist as tetramers, with Kv7.1 assembling homomerically. Kv7 activity is modulated by local phosphoinositide levels (Hernandez *et al.* 2008; Haitin & Attali, 2008), calmodulin and association with auxiliary proteins encoded by the *KCNE* gene family (McCrossan & Abbott, 2004). *KCNQ* genes have a well-defined pattern of expression, with *KCNQ1* located predominantly in the heart as well as the inner ear; *KCNQ2*, *3* and *5* are mainly neuronal where they comprise the so-called M-channel in neurones (Brown & Adams, 1980; Selyanko *et al.* 2002); and *KCNQ4* is restricted to the inner ear and auditory nerves (Kharkovets *et al.* 2000). Mutations to *KCNQ* genes underlie hereditary arrhythmias (*KCNQ1*), epilepsy (*KCNQ2*/*3*) and deafness (*KCNQ4*).

KCNQ- and *ERG*-encoded potassium channels and smooth muscle

The impact of *ERG*- and *KCNQ*-encoded K^+ channels on cardiac and neuronal physiology was established over 10 years ago. However, both gene families have been ascribed new roles of late through their identification as key players in the regulation of smooth muscle activity.

Expression of *KCNQ* in smooth muscle was first identified in rat stomach by Ohya *et al.* (2002*a*). Since then, *KCNQ* transcripts have been identified in mouse, rat and human blood vessels (e.g. Ohya *et al.* 2003; Yeung *et al.* 2007; Makie *et al.* 2008; Ng *et al.* 2011), as well as in the gastrointestinal tract, urinary tract and airways (see Jepps *et al.* 2013 for comprehensive overview). *KCNQ* channel blockers, such as linopirdine or XE991, evoke contractions in the quiescent smooth muscles, such as arteries, or enhance spontaneous contractility (e.g. Yeung & Greenwood, 2005, Jepps *et al.* 2009, Rode *et al.* 2010; Ipavec *et al.* 2011; Anderson *et al.* 2013). Serendipitously, there are also activators of *KCNQ*-encoded channels, such as the novel anticonvulsant retigabine, that relax smooth muscles (see Jepps *et al.* 2013).

Expression of *ERG* has been determined in the gastrointestinal tract (Akbarali *et al.* 1999; Ohya *et al.* 2002*a*; Farrelley *et al.* 2003; Parr *et al.* 2003), mouse portal vein (Ohya *et al.* 2002*b*) and bovine epididymis (Mewe *et al.* 2008), where the smooth muscles exhibit phasic contractions. In these tissues, *ERG* channel blockers, such as dofetilide or E4031, augment spontaneous contractions tremendously and often cause individual events to fuse into a tonic contraction.

In terms of the myometrium, all *KCNQ* isoforms are expressed in non-pregnant mice, with *KCNQ1* being dominant, and the transcript level for all isoforms remains stable throughout the oestrus cycle (McCallum *et al.* 2009). In pregnant mice, the expression of all *KCNQ* genes drops dramatically at early stages of gestation but recovers to robust levels by late stages (McCallum *et al.* 2011), suggesting that their main role is to regulate contractility at the end of pregnancy rather than to induce quiescence in early pregnancy. Transcripts for all *KCNQ* genes except for *KCNQ5* have also been detected in myometrium from women undergoing Caesarean section at term (McCallum *et al.* 2011). Of the three *ERG* genes, only *ERG1* is expressed in mouse (Greenwood *et al.* 2009) and human myometrium (R. M. Tribe & I. A. Greenwood, unpublished observations). In the BALB/c mouse myometrium, both splice variants of *ERG1* were detected, with the longer C-terminal 'a' isoform dominant (Greenwood *et al.* 2009), and the expression of this gene did not vary throughout mouse gestation or following parturition (Greenwood *et al.* 2009). All members of the *KCNE* gene family whose expression products alter the membrane insertion capabilities and biophysical properties of *KCNQ*- and *ERG*-encoded channels (McCrossan & Abbott, 2004) are also expressed in virgin and pregnant mouse myometrium (Greenwood *et al.* 2009; McCallum *et al.* 2009). Moreover, transcripts for *KCNE2* and *KCNE4* increased markedly in mouse myometrium throughout pregnancy (Greenwood *et al.* 2009; McCallum *et al.* 2009), an observation that was mirrored at the protein level (Greenwood *et al.* 2009).

A functional role for both *KCNQ*- and *ERG*-encoded K^+ channels has been determined in isometric tension and single-cell electrophysiological studies. Linopirdine and XE991 are specific inhibitors of all KCNQ channel isoforms that increase contractile activity in either non-pregnant or pregnant mouse myometrium, mainly through an increase in the frequency of contractions (McCallum *et al.* 2009, 2011). These agents have similar effects on term non-labouring samples of human myometrium (McCallum *et al.* 2011). In line with a working hypothesis that increased K^+ channel activity limits membrane depolarization and suppresses voltage-dependent Ca^{2+} influx, the *KCNQ*-encoded K^+ channel activators, flupirtine and retigabine, produce rapid inhibition of spontaneous and oxytocin-driven contractility in mouse and human myometrium (McCallum *et al.* 2009, 2011). This tocolytic activity is more marked in myometrium from late pregnant mice compared with early pregnant mice (McCallum *et al.* 2011).

Specific blockers of *ERG*-encoded channels, such as dofetilide or E4031, have a more striking effect on spontaneous contractility of mouse myometrium than *KCNQ* channel blockers (mean integral of tension increases by ∼300%, in comparison to ∼50% seen with XE991) that is usually manifest as an increase in the amplitude and duration of individual contractions (Greenwood *et al.* 2009). Inhibitors of *ERG*-encoded

channels also have a dramatic effect on oxytocin-mediated contractions in mouse myometrium, with tissues often generating sustained contractions of considerable magnitude (Greenwood *et al.* 2009). Activators of *ERG*-encoded K^+ channels (NS1643 or PD118057) also attenuate contractions in mouse uterus. However, in contrast to KCNQ channel modulators, the effects of channel blockers and activators is lost in the final stages of mouse pregnancy (Greenwood *et al.* 2009). This is associated with an inability to record dofetilide-sensitive K^+ currents in isolated myometrial smooth muscle cells that are present in cells from non-pregnant animals (Greenwood *et al.* 2009). Modulators of *ERG* channels become effective again in tissues harvested only 3 h after delivery (Greenwood *et al.* 2009). Currently, the effects of *ERG* inhibitors in human myometrial tissues have only been studied in samples obtained from non-labouring woman at term (end of pregnancy), so it is not yet confirmed whether a similar molecular mechanism exists in humans. However, this redundancy in the functional impact of *ERG*-encoded channels in late mouse pregnancy represents a potential pivot point in the switch from a quiescent system to an excitable system able to generate considerable rhythmic contraction in order to facilitate fetal delivery.

Conclusion

The uterus remains an enigma. Despite much research, there is still much to ascertain with regard to the mechanisms that drive the switch from quiescence to contractile activity preceding labour, and little is known about the stimulus for induction of preterm labour. Furthermore, existing therapies are far from being the ideal tocolytics. The recent findings that *KCNQ*- and (*ERG*) *KCNH*-encoded K^+ channels have a major impact on myometrial contractility and that the functional impact of *KCNH*-encoded channels diminishes in an animal model of term pregnancy represent progression towards answering some of these questions.

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Additional Information

Competing interests

None declared.

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