Controlling contractions in human myometrium; an eye on channels

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Introduction: Human myometrial contractions are controlled by calcium influx through voltage-gated calcium channels during the action potential (AP). We have shown that the hERG K channel curtails the duration of the AP and associated contraction during pregnancy, that the influence of hERG is inhibited during normal labour, facilitating strong contraction, and that this inhibition fails to eventuate in obese women, providing a supportive mechanism for the commonly observed failure to progress in labour in many obese women (Parkington *et al.*, 2014). More recently, we have also recorded large negative membrane potentials in myometrium from obese women in labour. In the present study we addressed the issue as to (1) what ion channels are responsible for the large negative potential in obesity and (2) whether blocking hERG permitted the retention of the relaxation between contractions, as these are essential for fetal oxygenation between contractions and fetal survival during the hours of human labour.

Methods: Myometrium was obtained from consenting lean and obese women at term, before or after labour onset. Membrane voltage was recorded simultaneously with contractions in strips using sharp microelectrodes, ion channel activity was recorded in acutely isolated myometrial smooth muscle cells using patch clamp technology and protein levels were analysed using Western blotting.

Results: The level of negativity of the membrane potential was resistant to blockade of most classes of potassium channels. Depolarization of these tissues occurred upon blockade of two-pore potassium channels. Interestingly, membrane voltage in human myometrium was exquisitely sensitive to blockade of the Na/K ATPase pump, especially in tissues from obese women. As for the action potential, blockade of big-conductance, calcium-activated potassium (BKCa) channels significantly increased the amplitude of the initial spike component of the AP, but was without an effect on resting membrane potential. Blockade of the hERG potassium channel increased the duration of the plateau phase of the AP and contraction and caused a significant hyperpolarization between APs. This hyperpolarization was due to activation of the Na/K ATPase pump.

Conclusions: Resting membrane potential and contraction in human myometrium is set predominantly by two-pore potassium channels and the Na/K ATPase pump, and manipulating these restored membrane potential and contraction in quiescent tissues obtained from obese women with failure to progress in labour. Of critical importance, blockade of hERG increases contraction strength and duration while retaining the ability of the tissues to fully relax between contractions, essential for survival of the fetus.

Parkington HC, Stevenson J, Tonta MA, Paul J, Butler T, Maiti K, Chan E, Sheehan PM, Brennecke SP, Coleman HA, Smith R (2014). Diminished hERG K^+ channel activity facilitates strong human labour contractions but is dysregulated in obese women. *Nature Communications*, **5**: 4108.