Sustained expression of K_V7 channels during labour is associated with a highly negative uterine muscle resting membrane potential and dysfunctional labour in women

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Successful vaginal delivery requires strong forceful uterine contractions. Poor contraction, resulting in failure to progress, is associated with prolonged labour and commonly necessitates caesarean delivery (CD). Uterine contractions require calcium influx through voltage-gated calcium channels. Thus, uterine smooth muscle (myometrium) membrane potential is critical for strong labour progress. Dysfunctional labour (DL) is a significant problem in the labour ward, and is the most common indication for caesarean delivery. We recently discovered a marked excessive negative membrane potential in myometrium of both lean and obese DL women. We hypothesized that abnormally high expression and/or activity of potassium channels leads to the large negative resting membrane potential which suppresses opening of voltage-gated calcium channels resulting in weak contractions and DL necessitating caesarean delivery.

Myometrium was obtained during CD at term but before labour onset (NIL) (elective CD) and during established labour (IL). Membrane potential was recorded in strips, using sharp intracellular microelectrodes, simultaneously with contraction. Other myometrial samples from these women were treated with collagenase and ionic currents were recorded from isolated myocytes using patch-clamp electrophysiology. Excess tissue was frozen at -80°C for later western blotting study. Maternal body mass index (BMI) was recorded at first antenatal visit. Most elective CDs were repeats and the reason for a prior CD was ascertained from the clinical histories.

Myometrial strips from women progressing well IL had spontaneous contractions (n=7). DL strips did not contract spontaneously (n=9), although contraction could be achieved using high K solution to evoke experimental depolarization. Resting membrane potential in myometrium from normally progressing women NIL was -58±1mV (n=17) and IL the values were similar (-58±1mV, n=7). DL myometrium was significantly more negative IL (-73±2mV, n=7). Blockade of K_V7 channels, using XE-991, returned resting membrane potential to normal levels (-61±2mV) in high negative DL myometrium. Western blotting revealed that expression of $K_V7.4$ protein was significantly reduced in myometrium from normally progressing IL women (reduced to 36% IL *versus* NIL, P=0.03, n=5 per group). This reduction failed to occur in DL samples. In acutely isolated myometrial cells the K_V7 current (at 20mV) was enhanced in DL (6.1±1.1pA/pF) *versus* normal progress IL tissues (2.5±0.5pA/pF, P=0.02). In DL myometrium, depolarization evoked by oxytocin (10nM) was 8±2mV, usually insufficient to reach threshold for the opening of voltage-gated calcium channels. In addition, oxytocin receptor protein expression was significantly increased in myometrium from normally-progressing labour (P<0.0001) but this increase was not observed in DL tissues.

The results of this study provide novel insights into the complexity underpinning the control of uterine contractility before and during the progression into labour in women. K_V7 channels have a major input into determining the level of membrane potential in human myometrium at term and increased expression of these channels induces excessive negativity which is associated with weak contractions and dysfunctional labour, necessitating caesarean delivery. Oxytocin is widely used to augment labour contractions and expedite delivery, and to reduce post-partum haemorrhage (which is normally prevented by strong uterine contraction following delivery). The effectiveness of oxytocin was blunted in the DL myometrial strips studied and this could help explain the enhanced incidence of post-partum haemorrhage in women following dysfunctional labour. While the excessive myometrial negativity contributes to this, a failure of oxytocin receptor expression to increase at the time of labour is also likely to play an important role.