New insights into the regulation of uterine contractions in human labour

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Our poor understanding of the processes involved in labour contractions results in limited success in preventing unwanted contractions before term. This leads to preterm labour and delivery, a major cause of perinatal morbidity and mortality. On the other hand, improving contractions when they fail in labour is also restricted. This necessitates caesarean section, which has significant short and long term maternal consequences, as well as childhood issues for the offspring. Thus, clinically safe and effective therapeutic options are limited for both preterm labour tocolysis and dysfunctional labour augmentation. Our aim is to better understand the mechanisms underpinning contraction in human myometrium before and during term labour.

Myometrium was obtained late in pregnancy in women undergoing caesarean delivery in the Royal Women's Hospital, Melbourne. Informed, written consent was obtained prior to surgery by trained research midwives. Membrane potential or cytoplasmic calcium were recorded simultaneously with contraction in myometrial strips from women at term not-in-labour (n=27) and in labour (n=15). Ion channel protein expression was determined using Western blotting (WB).

Contractile amplitude and duration were determined by the duration of the action potential (AP) plateau (similarly to heart). We sought to determine the mechanisms underpinning the duration of the AP plateau. Plateau duration and contraction amplitude were reduced by $CaCC_{inhib}$, which blocks the calcium-activated chloride channel ANO1. Immunohistochemistry demonstrated the presence of ANO1 in human myometrial strips. ANO1 protein expression was significantly increased in myometrium from women in normal labour and this increase failed to occur in tissues from women who failed to progress in labour. Plateau duration was lengthened and contraction amplitude increased by VU-590, which blocks the inwardly-rectifying potassium 7.1 channel ($K_{IR}7.1$). $K_{IR}7.1$ effectiveness and WB $K_{IR}7.1$ protein levels were reduced in normal labour tissues but was significantly increased in tissues from women who failed to progress in labour.

Here we reveal the presence of two ion channels, ANO1 and $K_{IR}7.1$, in term pregnant human myometrium before and during labour. Activity of ANO1 markedly contributes to the development of a long AP plateau and a large contraction amplitude. Increased expression of ANO1 in labour facilitates stronger contractions and expeditious delivery. In contrast, $K_{IR}7.1$ terminates the plateau resulting in a smaller contraction. $K_{IR}7.1$ expression appears to be reduced in labour, blunting the terminating mechanism, thus prolonging the AP and facilitating the increase in contraction amplitude required for successful vaginal delivery. When these labour changes fail to occur labour does not progress well, necessitating caesarean delivery.