Complex interacting mechanisms regulating contraction and inter-contraction relaxation in labouring human myometrium

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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). On the other hand, strong contractions must be separated by full uterine relaxation since this is essential for the restoration of placental blood flow, mandatory in the long hours of human labour. Failure of adequate relaxation results in non-reassuring fetal welfare, also necessitating CD. Obesity increases the risk of failure to progress in labour, with an increase in neonatal deaths, morbidity, maternal hypertension and diabetes, a doubling of CD rate, increasing the incidence of life-threatening events, such as placenta praevia or accreta, in subsequent pregnancies. The aim of this study was to investigate the role and nature of potassium (K) channels in determining the resting membrane potential (RMP) and the relaxation between contractions before and during established labour.

Myometrium was obtained during CD at term before labour (elective CD) and during established labour. Membrane potential was recorded in strips, using sharp intracellular microelectrodes, simultaneously with contraction. Following collagenase treatment, ionic currents were recorded from isolated myocytes using patch-clamp electrophysiology. 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 prior CD was ascertained from the clinical histories.

RMP was similar when comparing data across the groups lean, obese, before and during labour. However, when the data were regrouped according to normal progress, failure to progress, before and during labour, the failure to progress tissues had RMPs that were 11±2mV more negative, irrespective of whether or not the woman was in labour. (1) This additional negativity was abolished by agents that blocked either K_V7 or $K_{IR}7.1$ channels. The inwardly rectifying segment of the K current was sensitive to $K_{IR}7.1$ blockers. $K_{IR}7.1$ protein levels were significantly reduced in normally-progressing labour but were elevated in failure to progress. All tissues with RMP of -58±1mV had spontaneous contractions, each underpinned by a complex action potential (AP), which included a plateau to -25±1mV. APs were separated by an after-hyperpolarization, which determined contraction frequency. (2) The spike of the AP was increased by 20mV by tetraethyl ammonium (TEA) but not by other K channel blockers. (3) Blockers of $K_{IR}7.1$ and K_V7 and other K_V channel blockers, barium, TEA, 4-aminopyridine and dofetilide (which blocks hERG channels), markedly increased the duration of the plateau, likely reflecting an effect on the repolarizing K current. (4) The after-hyperpolarization was blunted by all except dofetilide (the hERG blocker) and hence all those other K channel blockers tested gave rise to an increase in the frequency of contraction and a reduction in contraction spacing.

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. We show that failure to progress in labour results from an excessive influence of K_V7 and/or $K_{IR}7.1$ channels. However, blocking these channels, to expedite the labour process, would likely give rise to a dangerous increase in contraction frequency with insufficient time for adequate restoration of placental blood flow between contractions and hence would threaten fetal wellbeing. However, agents that activate these K channels might be considered as candidates for suppressing preterm labour, but much additional investigation is required.