TARGET IDENTIFICATION

Putting the brakes on preterm labour

> In [mouse models of] preterm labour … intraperitoneal injections of the TRPV4 inhibitor HC-067047, given 8 hours after the labour-inducing stimulus, substantially increased the time until delivery

Preterm labour is a substantial contributor to perinatal mortality, and few effective strategies exist to prevent premature birth. Ying *et al.* now identify the inhibition of transient receptor potential vanilloid 4 (TRPV4), a receptor on myometrial smooth muscle cells (mSMCs) that regulates Ca^{2+} influx and therefore muscle contractility, as a potential therapeutic intervention.

The activity of myometrial smooth muscle is tightly regulated during pregnancy; this tissue must remain relaxed as the fetus grows and must then contract to deliver the fetus. Oxytocin initiates smooth muscle contractions during labour, predominantly by increasing receptor-mediated Ca^{2+} entry. Although L-type Ca^{2+} channels are involved in this Ca^{2+} influx, the use of inhibitors of these channels is restricted owing to their associated adverse effects on cardiac function.

The authors therefore investigated whether inhibition of other channels that mediate Ca^{2+} entry could prevent preterm labour. They found that levels of the TRPV4 channel in mSMCs increase with gestation, especially in the plasma membrane where this channel is active. In mSMCs from pregnant rats, activation of these channels using small molecules increased the intracellular Ca^{2+} concentration; this effect was much smaller in mSMCs from non-pregnant rats. In human mSMCs, depletion of TRPV4 using siRNA decreased oxytocin-mediated contraction in collagen gel assays. Similarly, in uterine muscle strips from pregnant mice, oxytocin-induced contractions required the activity of TRPV4 channels. These findings indicate that TPRV4 may be an important mediator of intracellular Ca^{2+} concentration in mSMCs during the latter part of pregnancy.

During pregnancy, TRPV4 may be regulated by β-arrestin, a cytoplasmic protein that binds to and internalizes numerous activated receptors, often targeting them for degradation. Levels of β-arrestin in smooth muscle tissue from mice decreased during pregnancy, and mice deficient for β-arrestin were hypersensitive to lipopolysaccharide-induced preterm labour.

The authors then investigated the use of TRPV4 inhibitors in mouse models. In preterm labour induced either by inhibition of the progesterone receptor or by lipopolysaccharide, intraperitoneal injections of the TRPV4 inhibitor HC-067047, given 8 hours after the labour-inducing stimulus, substantially increased the time until delivery. Multiple, smaller doses (10 mg per kg administered every 8 hours) of HC-067047 were more effective than a single, large dose in both of these models.

Together, these data suggest that TRPV4 could be an important target for therapies designed to prevent preterm birth. TRPV4 inhibitors are currently in Phase II clinical trials for the treatment of congestive heart failure, which could pave the way for investigating their use in preterm labour.

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ORIGINAL ARTICLE Ying, L. N. *et al.* The transient receptor potential vanilloid 4 channel modulates uterine tone during pregnancy. *Sci. Transl. Med.* **7**, 319ra204 (2015)