Leveraging Stretch-Activated Channels in the Uterus to Develop Novel Therapeutic Approaches to Halt Preterm Labor
SACs as Mediators of Myometrial Quiescence

Review

A role of stretch-activated potassium currents in the regulation of uterine smooth muscle contraction

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Novel identification and modulation of the mechanosensitive Piezo1 channel in human myometrium

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How does $\text{Ca}^{2+}$ influx promote quiescence?

-- Piezo1 Activates $\text{BK}_{\text{Ca}}$ --
Piezo1/BK$_{Ca}$ are interesting targets as they are down-regulated in preterm laboring myometrium.
Our Approach

**Hypothesis**: Mechanosensitive signaling in pregnant human myometrium regulates quiescence, and this effect can be bolstered through the co-administration of small molecule agonists, which will additively decrease the intensity of contractions.
How does agonism/antagonism of TREK-1 and Piezo-1 affect uterine myocyte membrane potential?
Effects of Piezo1 Modulation on Uterine Myocyte Membrane Potential
Effects of TREK-1 Modulation on Uterine Myocyte Membrane Potential

TREK-1 activation stabilizes membrane potential
Do these effects translate to whole tissue?

Whole human myometrium (cesarean section)

Organ bath
TREK-1 and Piezo-1 Relax to Agonists Dose-Dependently

Barnett, et. al, 2022
Combination Tocolysis

TREK-1 Activation: 45% ↓ in AUC
Piezo-1 Activation: 48% ↓ in AUC
Piezo-1 + TREK-1 Activation: 74% ↓ in AUC

Combination tocolysis greatly increases the negative inotropic effects of TREK-1 and Piezo-1 agonism.
In Conclusion

• Stretch-activated channels are essential for maintaining uterine quiescence during pregnancy

• Piezo-1 and TREK-1 operate in concert to hyperpolarize the membrane through K$^+$ efflux

• Small molecule activation of Piezo-1 and TREK-1 enhance quiescence beyond stretch alone

• Combination tocolysis using yoda1 and ML335 results in additive negative inotropic effects, intimating strong therapeutic potential
Thank you to the MW CTR-IN for supporting our research!

QUESTIONS?