Scott D. Barnett, Ph.D.

Laboratory of Dr. Iain L.O. Buxton
Pharmacology Department
UNIVERSITY OF NEVADA, RENO SCHOOL OF MEDICINE

University of Nevada, Reno
School of Medicine

MW CTR-IN

Leveraging Stretch-Activated Channels in the Uterus to Develop Novel Therapeutic Approaches to Halt Preterm Labor

Mountain West CTR-IN Program

November 18th, 2022

SACs as Mediators of Myometrial Quiescence

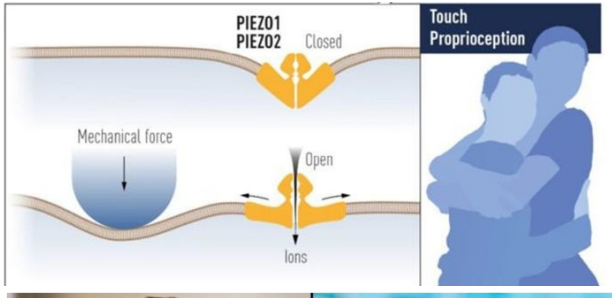
Acta Pharmacologica Sinica (2011) 32: 758–764
 1671-4083/11 $32.00
www.nature.com/aps

Review

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

Iain L O BUXTON*, Nathanael HEYMAN, Yi-ying WU, Scott BARNETT, Craig ULRICH

Myometrial Research Laboratory, University of Nevada School of Medicine, Reno, Nevada 89557–0573, USA



J Physiol 0.0 (2022) pp 1–16

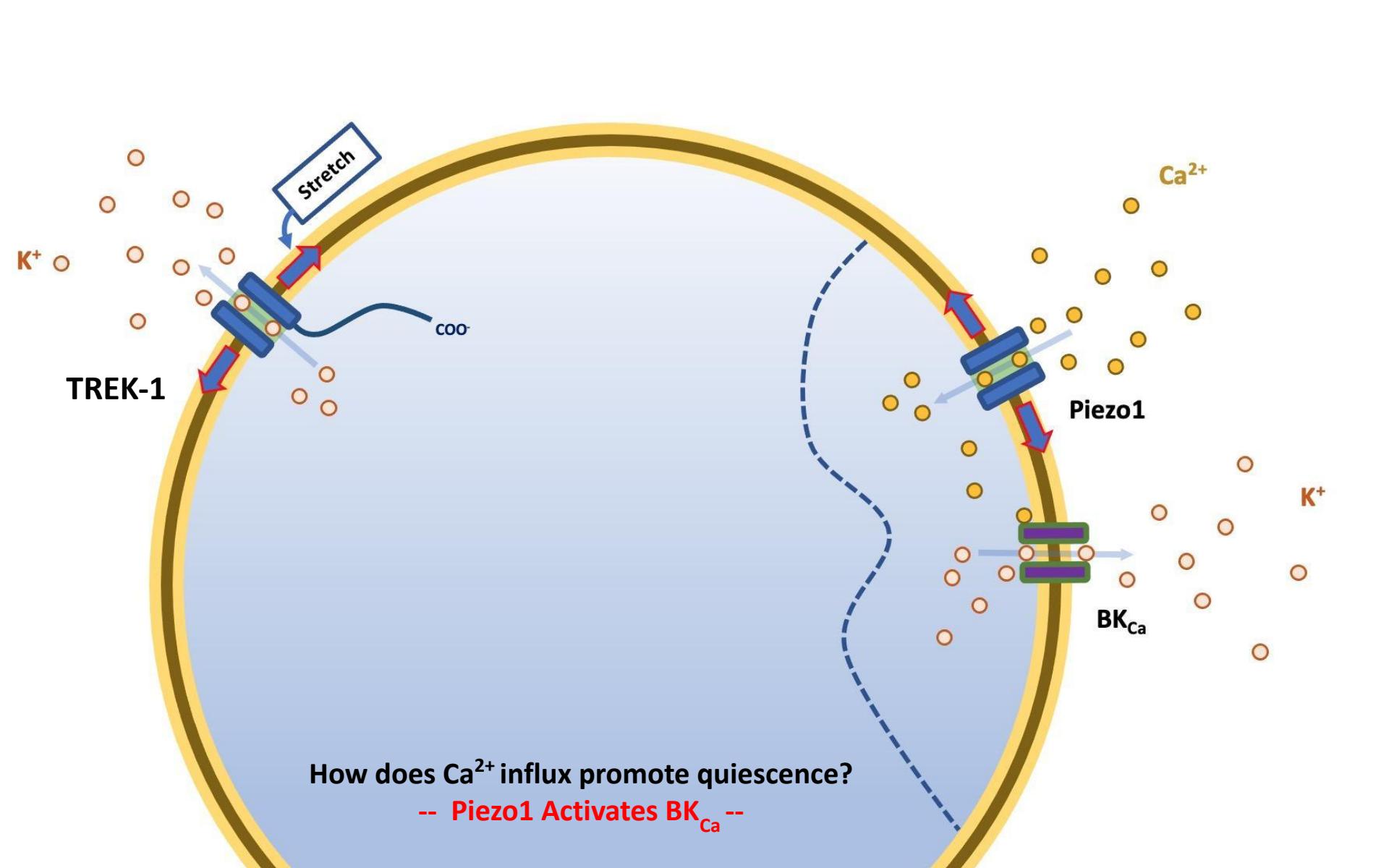
1

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

Scott D. Barnett, Hazik Asif and Iain L. O. Buxton

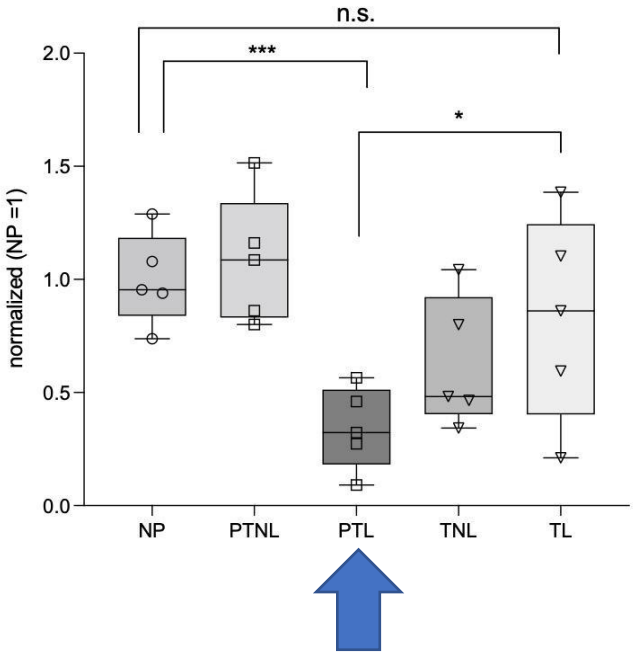
Department of Pharmacology, Center for Molecular Medicine, Reno School of Medicine, University of Nevada, Reno, NV, USA

Ardem Patapoutian (L) and David Julius (R), recipients of the 2021 medicine Nobel prize. Credit: Scripps Research/Noah Berger

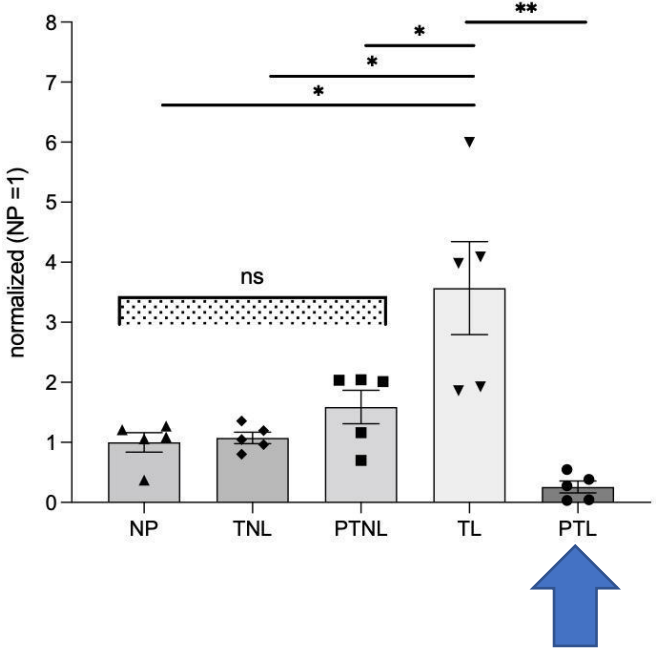

Stretch
K+
COO-
TREK-1
Ca2+
Piezo1
K+
BKCa
How does Ca2+ influx promote quiescence?
-- Piezo1 Activates BKCa --

Piezo1/BK_{Ca} are interesting targets as they are down-regulated in preterm laboring myometrium

BK_{Ca} Protein Expression



Piezo-1 Protein Expression

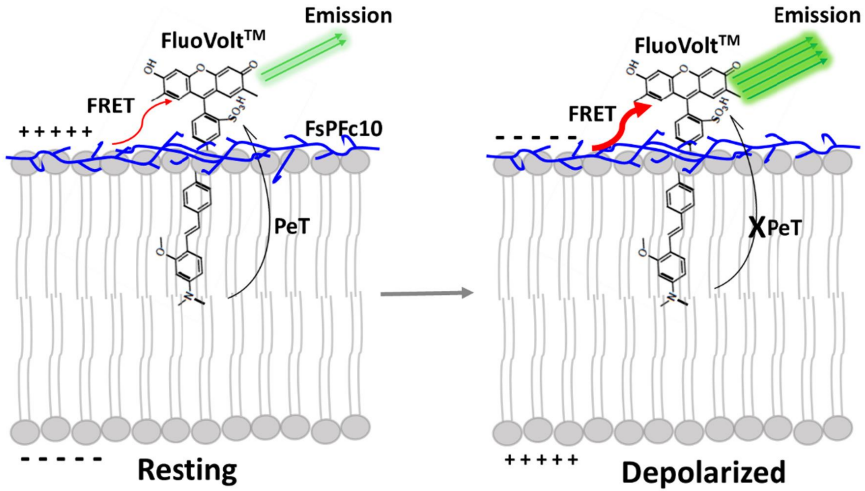


Our Approach

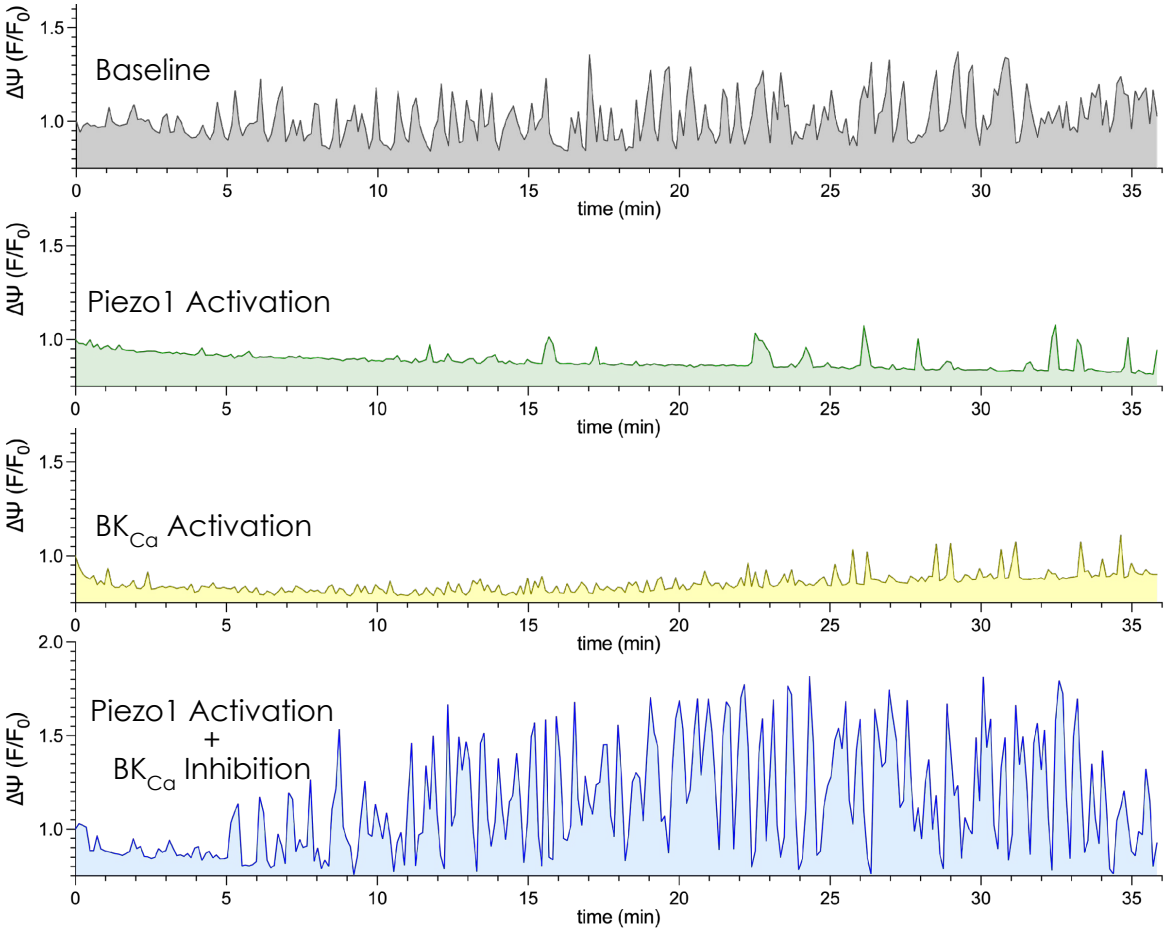
Hypothesis: Mechanosensitive signaling in pregnant human myometrium regulates quiescence, and this effect can be bolstered through the co-administration of small molecule agonists, which will additively decrease the intensity of contractions.

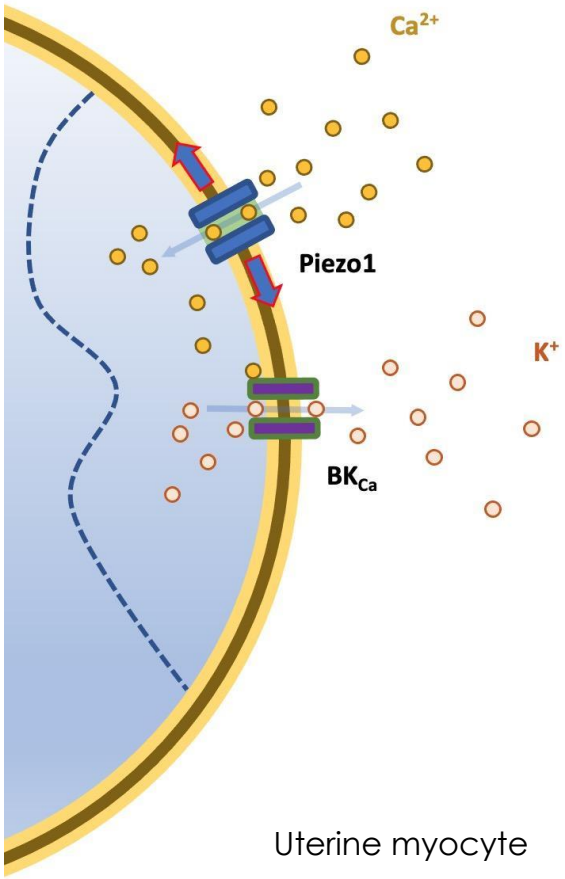
Effects on Membrane Potential

How does agonism/antagonism of TREK-1 and Piezo-1 affect uterine myocyte membrane potential?



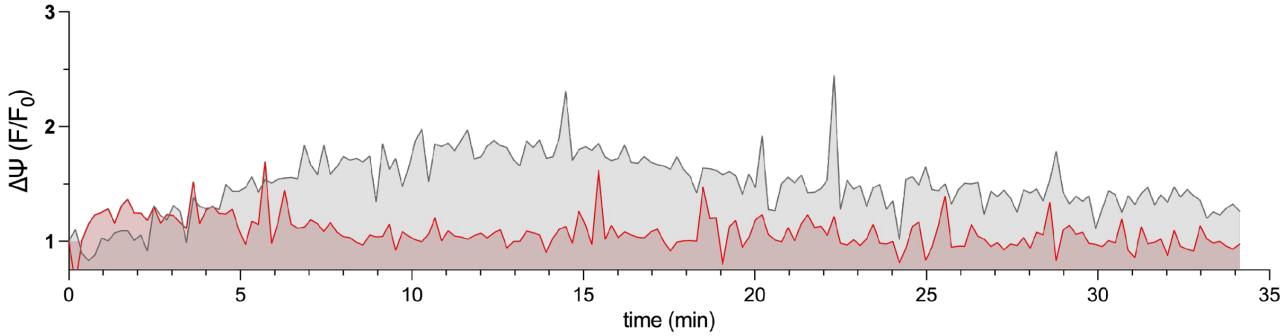
Effects of Piezo1 Modulation on Uterine Myocyte Membrane Potential





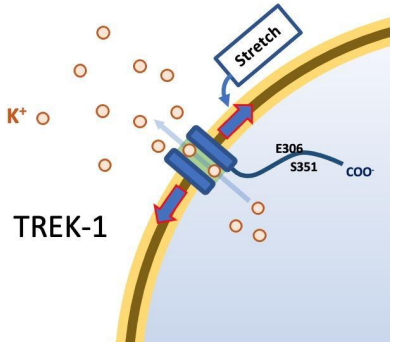
Effects of TREK-1 Modulation on Uterine Myocyte Membrane Potential

TREK-1 activation stabilizes membrane potential



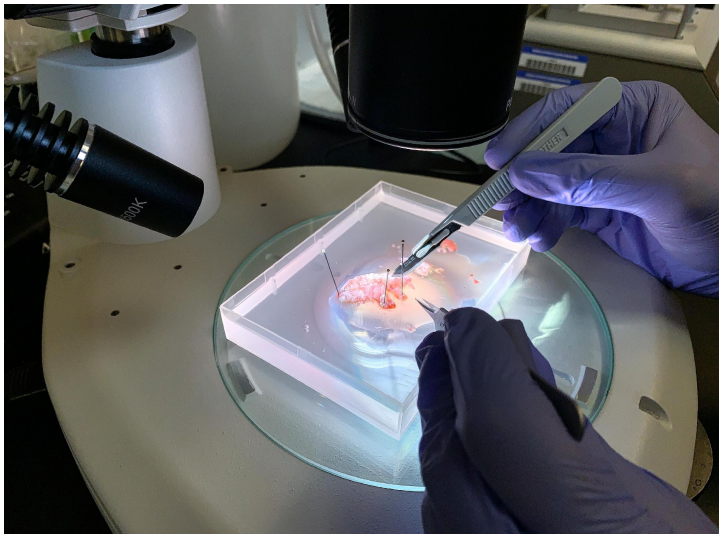
TREK-1 Inhibition

TREK-1 Small Molecule Activation

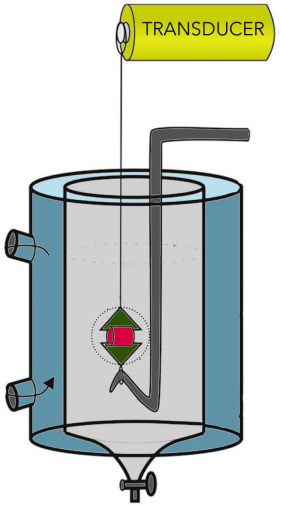


Uterine myocyte

Do these effects translate to whole tissue?



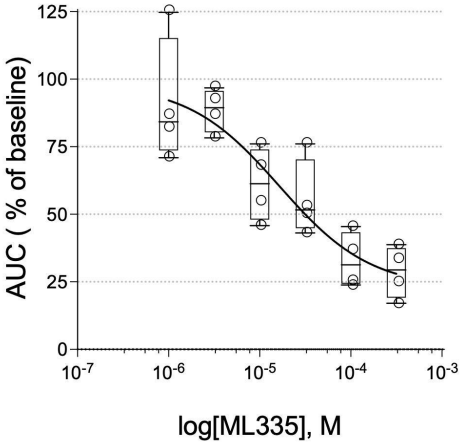
Whole human myometrium
(cesarean section)

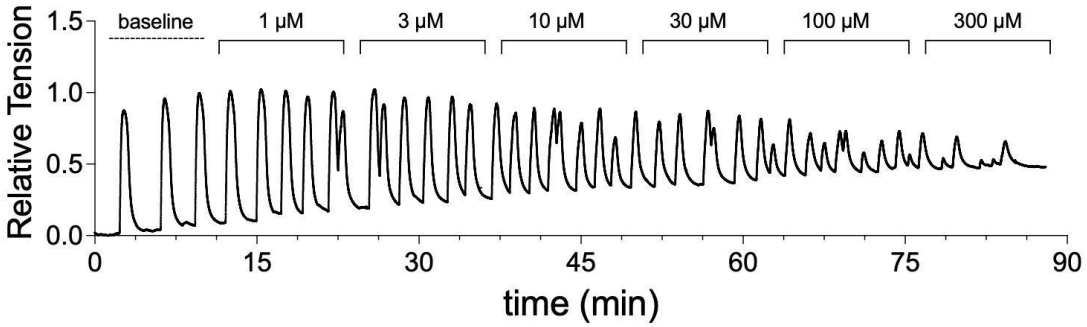


Organ bath

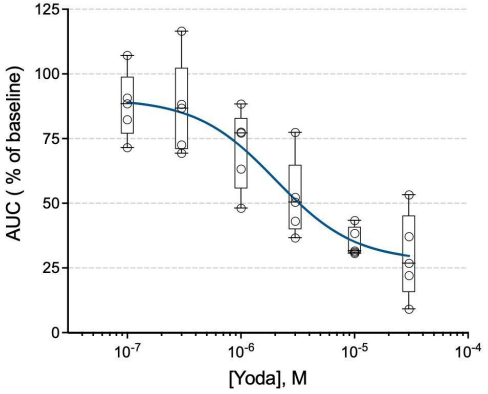
TREK-1 and Piezo-1 Relax to Agonists Dose-Dependently

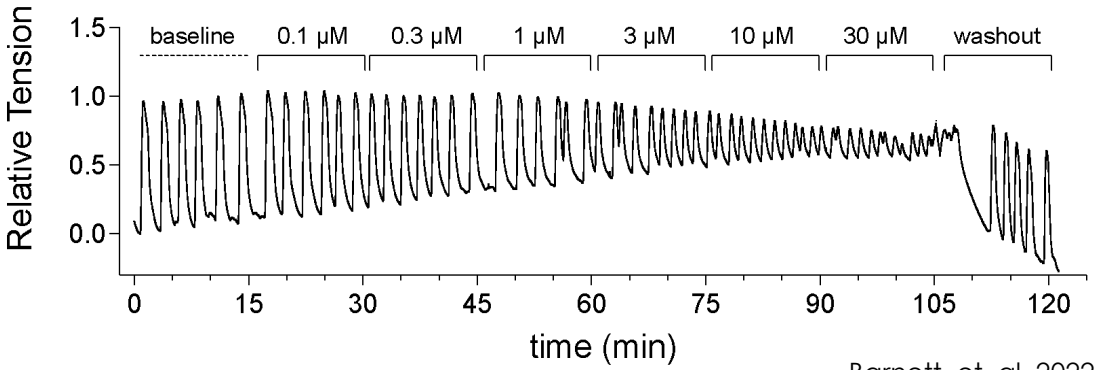
TREK-1





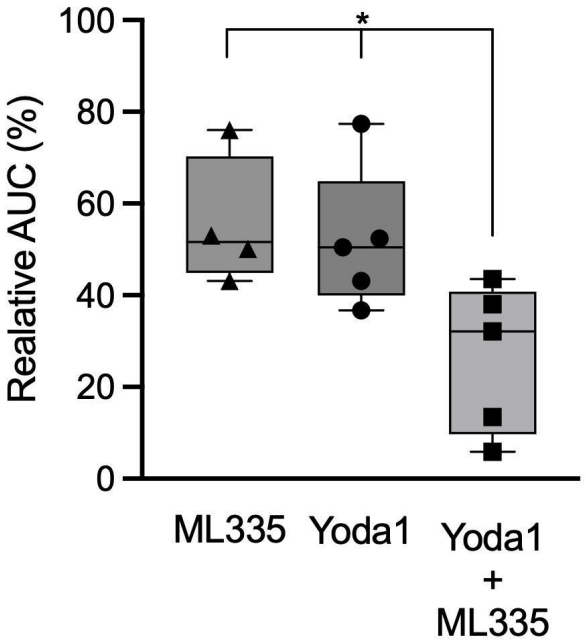
Piezo-1





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**

University of Nevada, Reno
School of Medicine

MW CTR-IN

Thank you to the MW CTR-IN for supporting our research!

QUESTIONS?