Effects of Matrix Metallopeptidase 9 Inhibition on Uterine Contraction and Birth Timing

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PRETERM BIRTH

- Birth Prior to 37 weeks gestation
- 15 million babies annually
- Leading cause of mortality for children ages 5 and under
- Survivors face increased lifetime risk of disabilities
- Economic Impact: $26 billion annually

- World Health Organization Preterm Birth Fact Sheet February 2018
MMP2/9 Expression in Preterm Myometrium

- MMP9 increased in the amniotic fluid during term and preterm parturition
- MMPs play a major role in tissue remodeling (cervix)
- MMP9 regulates contraction in other cell types
- MMP2/9 inhibitors rapidly affect contractile response in rat myometrium

* $p<0.05$

- Ulrich et al. (2020) *Biol Reprod* 100:1597
OBJECTIVES

Determine effects of MMP2/9 on uterine contraction in human myometrium

Determine if inhibition of MMP2/9 could delay parturition in mice
MMP2/9 Inhibition Reduces the Contractile Response

*\( p < 0.05 \)
MMP2/9 Inhibition Delays Parturition

Veronica Arinze

D=0
mating

D=16-20
Daily inhibitor
Expected parturition

D=17-20
Monitor for
parturition

Gestational Age at Delivery

*\text{p}<0.05

\text{Ulrich et al. (2020) Biol Reprod 100:1597}
MMP2/9 Inhibition Attenuates the Intracellular Ca^{+2} Response

 Craig Ulrich, Adrian Pena

*\p<0.05

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\begin{itemize}
  \item Ulrich, Pena, and Burkin, unpublished
\end{itemize}
MMP9-Specific Inhibition

Craig Ulrich

**Vehicle**

**MMP9 Inh 1 (AG-L-66085)**

**Estimation Plot**

- *p < 0.01

- Ulrich and Burkin, unpublished
MMP9-Specific Inhibition

- **D=0**
  - Mating

- **D=16-20**
  - Daily inhibitor

- **D=20**
  - Expected parturition

- **D=17-20**
  - Monitor for parturition

- Ulrich, Lambert and Burkin, unpublished
Do MMPs Affect Calcium Reuptake?

- SERCA2a pumps cytosolic Ca\(^{2+}\) into the SR to facilitate relaxation.
- SERCA2a is proteolyzed by MMP-2 in cardiomyocytes.
- MMP inhibition may prevent SERCA2a degradation.

FUTURE DIRECTIONS

- Does MMP inhibition “rescue” preterm birth in mouse models? (Lambert & Burkin)

- Can TIMPS or engineered TIMP variants inhibit contraction and/or delay parturition? (Samazdeh & Burkin)

- How does MMP2/9 inhibition affect intracellular Ca\(^{2+}\) responses to oxytocin? (Leblanc & Burkin)
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