Targeting Matrix Metallopeptidase 9 to Modulate Uterine Contraction

Heather R. Burkin[1], Lauren L. Parker[1], and Craig C. Ulrich[1]

[1]Department of Pharmacology, University of Nevada, Reno School of Medicine

Matrix metallopeptidase 9 (MMP9) expression is elevated in maternal tissues and fluids during both term and preterm labor. We performed experiments to test the hypothesis that MMP9 contributes to labor by enhancing uterine contractions and that targeting this enzyme could serve as a mechanism to relax the uterus. Ex-vivo experiments were performed with human uterine tissues donated by women undergoing Cesarean-sections at term. Uterine tissue was immediately transported to the laboratory in physiological buffer and myometrial samples dissected into 10x1x1 mm strips which were suspended in tissue organ baths filled with Krebs solution at 95% O_2, 5% CO_2 at 37 °C. One end of each strip was connected to a force transducer and changes in isometric tension were recorded. Tissues were maintained under 2-3 g basal tension for at least 30 min and then primed with 60 mM KCl for 3 min. Baseline spontaneous or oxytocin-induced (0.6 IU/mL) contractions were recorded for 30 min and served as the baseline for comparison of treatments with recombinant human MMP9 or the specific inhibitor AG-L-66085. Statistical analyses were performed using Prism version 10.0.1. Addition of MMP9 to physiologically relevant levels (10 nM) enhanced the oxytocin-mediated contractile response over time (n=6 patients, p=0.0003), primarily by increasing contraction frequency compared to vehicle (PBS) (p<0.0001). Specific inhibition of MMP9 with 1 micromolar AG-L-66085 reduced the oxytocin-mediated contractile response over time (n=8 patients, p=0.0075) by dampening both contraction amplitude (p<0.0001) and frequency (p=0.0498) compared to vehicle (DMSO). Effects of AG-L-66085 on spontaneous contractions (in the absence of peptide agonist) were highly variable, with contractions completely abolished in two patient samples. AG-L-66085 had an inhibitory effect in six additional uterine samples, reducing the contractile response over time (p=0.0415) and contraction amplitude (p=0.038) compared to vehicle (DMSO). These data suggest MMP9 contributes to the physiology of labor and could serve as a molecular target to regulate this process.