PRESENTING AUTHOR(S) NAME & RESEARCH TITLE

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

PURPOSE/BACKGROUND

Evidence suggests that matrix metallopeptidase 9 (MMP9) is involved in the process of parturition and the regulation of birth timing. MMP9 concentrations remain stable in maternal plasma until labor starts and increase in women experiencing either term or preterm labor. MMP9 activity is increased in the amniotic fluid of patients undergoing spontaneous rupture of membranes and parturition. We have recently shown that MMP9 is elevated in preterm laboring uterine myometrial tissue (and therefore locally available to affect the contractile response) and that inhibition of MMP2/9 reduces contractile responses in human uterine tissue. Together, these observations led us to hypothesize elevation of MMP9 is sufficient to increase the oxytocin-induced contractile response in the pregnant uterus. We performed experiments to determine to specific effects of MMP9 inhibition on uterine contraction and birth timing.

MATERIALS & METHODS

Uterine myometrial tissues were obtained from term nonlaboring patients undergoing elective C-section, dissected into strips, suspended in a tissue bath filled with Krebs solution at 37 °C, and connected to a force transducer. Tissue strips were maintained under 2-3 g basal tension for at least 30 min and stimulated with 60 mM KCl followed by washes in Krebs buffer. Uterine strips were stimulated with 10 nM oxytocin for 20 m, followed by the addition of AG-L-66085 to 1 μM and changes in isometric tension were recorded.

C57BL/6 female mice were mated to induce pregnancy and successful matings were confirmed by the presence of a vaginal plug. Mice were randomly assigned to two groups and administered 30 mg/kg JNJ0966 or vehicle control every 12 h by oral gavage beginning on gestational day 15. Animals were closely monitored and delivery times recorded for 15 animals per group.

RESULTS

We observed a 48% reduction in the contractile response as measured by area under the curve over time in tissue treated with MMP9 inhibitor compared to a 31% reduction in the vehicle treated controls ($p<0.05$). In addition, we observed a 16% reduction in peak contraction height (g) compared to a 4% reduction in vehicle-treated control tissues. ($p<0.05$). The observed effects were reversible after drug washout.

We did not observe differences in gestational length, maternal weight, or litter size between JNJ0966-treated animals and vehicle-treated controls. We did observe a small reduction in weight of pups born to JNJ0966-treated mothers ($p<0.01$).

DISCUSSION/CONCLUSION

We have shown that MMP9 specific inhibition is sufficient to rapidly reduce oxytocin-induced human myometrial contractions, suggesting this effect is likely due to mechanisms other than extracellular matrix remodeling. We did not observe a difference in time to parturition between mice treated with JNJ0966 and vehicle controls, suggesting the parturition delay in response to MMP2/9 inhibition cannot be attributed solely to MMP9 catalytic activity. These data could be explained by one of the following mechanisms: 1) the pro-MMP9 isoform present in JNJ0966-treated animals can compensate for the absence of catalytically active MMP9; or 2) MMP2 can compensate for the absence of MMP9 in the myometrium or other tissues to regulate birth timing.