Research Update 2011: The Oxytocin Hour

Getting Good Tone: Recent Findings in the Lab
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Objectives: Upon completion of this presentation, participants will be able to understand the phenomenon of desensitization of oxytocin receptors (OTR) and its clinical implications in the pharmacological management of uterine atony.

Summary: Postpartum hemorrhage is one of the leading causes of maternal mortality and morbidity worldwide. It is mainly caused by uterine atony, and hence requires treatment with one or more uterotonic drugs such as oxytocin, ergonovine, carboprost, misoprostol etc., which promote uterine contractions by acting via different mechanisms. Among these drugs, oxytocin is the first-line drug used to restore uterine tone and minimize postpartum blood loss.

Oxytocin is a neurohypophysial hormone, naturally synthesized during pregnancy, which also plays a central role in the contraction of uterine smooth muscles during labor. It mediates its action by binding with OTR on the uterine surface. The oxytocin–OTR complex induces uterine contractility through the activation of phospholipase C, and the release of inositol 1,4,5-triphosphate, 1,2-diacylglycerol and intracellular calcium.

OTRs belong to the family of G-protein-coupled receptors (GPCR), and like other GPCRs, undergo rapid molecular desensitization due to homologous stimulation. This phenomenon has been recently explored in human myometrial tissues, and may have clinical significance in the context of oxytocin-augmented labors. OTR desensitization–induced by in-vivo or in-vitro exposure of the myometrium to oxytocin--reduces the ability of human myometrial culture cells to respond to subsequent administration of oxytocin, and is characterized as a reduction in the concentration of myometrial oxytocin binding sites and OTR mRNA.

In-vitro studies in pregnant rat model myometrial strips have demonstrated the clinical replication of this biomolecular desensitization phenomenon, in the form of inhibition of the oxytocin-induced myometrial contractions after pre-treatment with oxytocin in a concentration-dependent manner. A similar contractility decrease has been observed in the human myometrium of patients undergoing oxytocin-augmented labor; such a decrease is not seen in non-augmented labor or the non-laboring uterus. As the oxytocin-induced desensitization phenomenon is homologous, the uterotonic effects of ergonovine and prostaglandin F2 alpha that act through different receptors do not appear to be affected by this phenomenon in rat myometrial strips. Interestingly, despite the effect of desensitization, the contractions induced by oxytocin in an oxytocin-exposed rat myometrial strip are still superior compared to other uterotonic drugs. Among all the prostaglandins, the myometrial contractions produced by PGF2 alpha are superior compared to other types of prostaglandins but not compared to similar concentrations of oxytocin. A combination of oxytocin and ergot produces even better contractions compared to oxytocin alone in oxytocin-pre-treated rat myometrium or in human myometrium from augmented laboring woman. Further research in this area will eventually guide us in choosing the best combination of pharmacotherapy in the management of uterine atony.

Recent clinical studies have demonstrated poor uterine tone and a higher incidence of postpartum hemorrhage when oxytocin is used for labor augmentation in higher doses and for longer durations. These clinical findings can be explained by the aforementioned desensitization phenomenon and signal attenuation that occurs with oxytocin exposure during labor in a time- and concentration-dependent manner. In view of the fact that repeated or continued high doses of oxytocin after delivery may render the myometrium less responsive, especially in patients with augmented labor, second-line uterotonic agents should be considered early in the event of postpartum bleeding.

Key Points:
1. The desensitization of OTRs is seen after myometrial exposure to oxytocin in a time- and concentration-dependent manner, and is manifested as poor contractile response of the myometrium to additional oxytocin administration.
2. This phenomenon has implications in the control of uterine tone after delivery in women with oxytocin-augmented labor.
3. The best uterotonic therapy in the event of such desensitization remains to be determined, but oxytocin in combination with ergonovine appears to be the most effective option.

Key References: