
MYOMETRIAL RECEPTORS IN RAT PARTURITION

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The present thesis is based on experimental data from seven published papers. Additionally three previously published papers constitute the basis of my entire research in rat myometrial receptors and wherever appropriate those papers have also been addressed in the thesis. The aim of the thesis was to elucidate some of the molecular mechanisms underlying the process of parturition. Pre-term birth is the single most important cause of perinatal morbidity and mortality. In USA and Western Europe three principles are employed in the treatment of pre-term labour namely oxytocin receptor blockade, β_2 -adrenoceptor activation and prostaglandin synthesis inhibition. Since however neither of the treatments in themselves effectively prevent deleterious outcomes of pre-term labour I have found it interesting to focus on the interaction between those hormonal systems.

The oxytocin receptor has been proposed to play a pivotal role in the process of parturition, for the reason that concentrations of functional receptors via an intensified genetic expression increase dramatically at term (Engstrøm et al., VI). It was shown that oxytocin infusions in non-pregnant rats decreased oxytocin receptor function (Engstrøm et al., II). In contrast, oxytocin receptor blockade with atosiban also decreased the number and function of oxytocin receptors in the parturient rat (Engstrøm et al., VI) suggesting that oxytocin receptor stimulation may up-regulate oxytocin receptor function to reinforce the contractile ability of this hormone during delivery. The sex steroids estrogen and progesterone were found to mimic oxytocin receptor function. Thus estrogen up-regulated oxytocin receptor concentrations by means of an increased mRNA production (Engstrøm et al., VII). This effect was curbed by concomitant administration of progesterone and was absent under the influence of progesterone alone (Engstrøm et al., VII) indicating that a positive estrogen/progesterone ratio favors the formation of oxytocin receptors. However, the increased number of oxytocin receptors in the estrogen-dominated myometrium was only followed by an increased oxytocin induced contractile activity when β_2 -stimulation with isoproterenol was additionally employed (Engstrøm et al., VII). Thus isoproterenol

enhanced oxytocin stimulated uterine contractility in non-pregnant rats (Engstrøm et al., VII) and β_2 -adrenoceptor blockade prevented the naturally occurring augmented oxytocin receptor function in the delivering animal (Engstrøm et al., VI).

The myometrial β_2 -adrenergic receptor causes relaxation of the muscle. However, in clinical practice the use of β_2 -agonists to induce tocolysis is limited by the relatively fast development of tachyphylaxis. It was demonstrated that prolonged β_2 -stimulation attenuated the subsequent relaxing ability of further stimulation of the receptor (Engstrøm et al., X). The effect was not followed by a decrease in the concentration of β_2 AR transcripts (Engstrøm et al., X) and therefore appears to take place at a post-transcriptional level. The process was however highly dependent on the presence of estrogen and independent of progesterone (Engstrøm et al., X). Accordingly estrogen per se reduced β_2 -mediated myometrial relaxation and this effect could not be overcome by progesterone, which neither in combination with estrogen nor alone affected the relaxing response (Engstrøm et al., X). In the presence of both estrogen and isoproterenol the diminished response to β_2 -stimulation was considerably impaired. Compared to day 21 of pregnancy β_2 AR mRNA increased four-fold at delivery (Engstrøm et al., VI) and catecholamine levels in maternal and fetal blood are at this time high (Phillippe 1983). Thus a high level of estrogen and catecholamines at parturition may secure that β_2 AR are sufficiently down-regulated under these circumstances to secure a proper transformation of the uterus towards a highly contractile state. On the other hand when the myometrium was under dominance of both estrogen and progesterone isoproterenol did not affect the relaxing response to β_2 -stimulation (Engstrøm et al., X) and therefore β_2 AR function was maintained under these circumstances.

Several evidences support a role for prostaglandins in the process of parturition. Thus indomethacin prevents the normal onset of parturition and mice lacking the gene encoding the $\text{PGF}_{2\alpha}$ -R are unable to deliver at term. In non-pregnant rats the expression of the prostaglandin-promoting enzyme COX-2 was enhanced by estrogen and this effect was curbed by concomitant administration of progesterone (Engstrøm et al., IX). $\text{PGF}_{2\alpha}$ -R mRNA and contractile responsiveness upon $\text{PGF}_{2\alpha}$ challenge were unaffected by any of the two steroids (Engstrøm et al., IX). Isoproterenol in the presence of estrogen down-regulated COX-2 and $\text{PGF}_{2\alpha}$ mRNA (Engstrøm et al., IX). However, in the presence of both estrogen and progesterone those transcripts were unchanged by isoproterenol but the myometrial contractile response to $\text{PGF}_{2\alpha}$ was enhanced (Engstrøm et al., IX). The genetic expression of COX-2 and $\text{PGF}_{2\alpha}$ was measured across pregnancy. The highest levels of both the ligand and the receptor were found at parturition although uterine contractile activity upon $\text{PGF}_{2\alpha}$ challenge was least pronounced at this particular time (Engstrøm et al., VIII). If, however, atosiban was administrated, $\text{PGF}_{2\alpha}$ -R mRNA increased and $\text{PGF}_{2\alpha}$ induced contractility was enhanced almost three-fold (Engstrøm et al., VIII). Thus in the presence of OTR blockade myometrial $\text{PGF}_{2\alpha}$ -R may serve the leading contracting role to secure proper propulsion of the offspring.

Overall it appears likely that the most central occurrence in rodent parturition is the withdrawal of progesterone, since mice who had their ability to decrease plasma levels of progesterone impaired by the lack of expression of the $\text{PGF}_{2\alpha}$ -R were unable to deliver properly (Sugimoto et al. 1997). In accordance with the studies in the present thesis a consequently high estrogen/progesterone ratio at term secures: 1. The induction of OTR,

which in combination with a high adrenergic tone increases OT induced myometrial contractility. 2. A substantial down-regulation of β_2 AR function upon β_2 -stimulation. 3. Up-regulation of COX-2 and PGF_{2 α} -R although the PGF_{2 α} -R remain partly uncoupled to the contractile cascade but still preserve the potential to increase their functionality. The three hormonal systems described in the thesis are, however, to a certain degree mutual redundant. Thus if progesterone withdrawal fails: 1. β_2 AR function remains intact keeping the myometrium in a relaxed state, which may impair labour. 2. To overcome this adverse effect the high adrenergic tone at the same time induces both PGF_{2 α} -R and OTR function in spite of a low estrogen/progesterone ratio. Thus irrespective of the level of progesterone at parturition OTR function may appear critical. If, however, OT is not present as, it is the case in OT knockouts (Nishimori et al. 1996) PGF_{2 α} -R function is enhanced and ensures delivery.

In summary, the mutual redundancy between the β_2 AR, OTR and PGF_{2 α} systems may explain the relatively poor results obtained in the management of pre-term labour when strategies that alone modulate one of the three receptors are employed. Neither of the three is especially vulnerable due to the back up from the other two. From a clinical point of view it is therefore in the future interesting to investigate the effectiveness of a combined treatment of pre-term birth.