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Progestin therapy to prevent preterm birth: History and effectiveness of current strategies and development of novel approaches

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ABSTRACT

In the 1930s the “progestin” hormone produced by the corpus luteum was isolated and found to be a Δ^4-keto-steroid. It was aptly named progesterone (P4) and in the following 30 years the capacity of P4 and derivatives to prevent preterm birth (PTB) was examined. Outcomes of multiple small studies suggested that progestin prophylaxis beginning at mid-gestation decreases the risk for PTB. Subsequent larger trials found that prophylaxis with weekly intramuscular injections of 17α-hydroxyprogesterone caproate (17HPC) beginning at mid-gestation decreased PTB risk in women with a history of PTB. Other trials found that daily vaginal P4 prophylaxis, also beginning at mid-gestation decreased PTB risk in women with a short cervix. Currently, prophylaxis with 17HPC (in women with a history of PTB) or vaginal P4 (in women with a short cervix) are used to prevent PTB. Recent advances in understanding the molecular biology of P4 signaling in uterine cells is revealing novel progestin-based targets for PTB prevention. One possibility is to use selective P4 receptor (PR) modulators (SPRMs) to boost PR anti-inflammatory activity that blocks labor, while simultaneously preventing PR phosphorylation that causes loss of P4/PR anti-inflammatory activity. This may be achieved by SPRMs that induce a specific PR conformation that prevents site-specific serine phosphorylation that inhibits anti-inflammatory activity. Further advances in understanding how P4 promotes uterine quiescence and how its labor blocking actions are withdrawn to trigger parturition will reveal novel therapeutic targets to more effectively prevent PTB.

1. Introduction

The steroid hormone progesterone (P4) is essential for the establishment and maintenance of pregnancy and its withdrawal is the key trigger event for parturition. The history of P4, as described by George Corner [1], starts in the mid 1600s when physician and anatomist Regnier de Graaf observed in cows that the presence and number of corpora lutea (CL) on the maternal ovaries correlated with pregnancy and the number of fetuses, and that removal of the ovaries during pregnancy caused parturition. That observation led Louis-Auguste Prenant and Gustav Born in the late 1800s to propose that the CL is an organ of internal secretion (this led to the field of endocrinology), and that it secretes a substance necessary for pregnancy. This was subsequently confirmed in the early 1900s when it was found that crude extract from rabbit CL sustained pregnancy in ovariectomized animals. Those observations prompted George Corner and Willard Allen to propose the term “progestin” to describe the factor produced by the CL that exerts “pro-gestation” activity [2–4]. In 1934, Corner and Allen purified and crystalized progestin from organic extract of rabbit CL [5,6] and around the same time Adolf Butenandt determined that progestin is a Δ^4-keto-steroid [7], and it was aptly named “progesterone”.

Those discoveries motivated basic and clinical research to determine how P4 maintains pregnancy. A leader in that effort was Arpad Csapo, who in the 1950s proposed that P4 maintains pregnancy by blocking parturition (referred to as the P4 block hypothesis), and that withdrawal of the P4 block induces labor [8]. That hypothesis was later expanded by Csapo's “seesaw” hypothesis, which posits that P4 maintains pregnancy by counteracting pro-labor stimuli and that withdrawal of the P4 block allows pro-labor stimuli to prevail [9]. It is now generally accepted that P4 is essential for the establishment and maintenance of pregnancy and that labor is triggered by its withdrawal. There is also consensus, in principle, that P4 activity could be exploited therapeutically to prevent preterm birth (PTB).

2. Progestin prophylaxis for the prevention of PTB

In the late 1950s initial trials of P4 to suppress active labor produced mainly negative outcomes [10,11]. On balance the data indicated that P4 treatment has no tocolytic activity and does not

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suppress labor once it initiates. Despite the negative tocolytic data, progestin activity of P4 was demonstrated in a small clinical trial reported by Lars Bengtsson in 1962 [10]. In that study, P4 or placebo was administered as an intramuscular injection to women prior to pregnancy termination at mid-gestation by either artificial rupture of the fetal membranes that caused intrauterine infection leading to parturition or by injection of formalin into the amniotic fluid that killed the conceptus leading to a decrease in maternal P4 and parturition. P4 treatment did not prevent infection-induced parturition in which endogenous P4 levels remained elevated. However, P4 prevented formalin-induced (and presumably infection-free) parturition. Thus, P4 therapy sustained human pregnancy only in the absence of infection and in the context of endogenous P4 deficiency. Importantly, the data suggest that endogenous or exogenous P4 progestin activity can be overridden by intrauterine infection.

During the late 1940s and early 1950s researchers at Schering AG, a major German pharmaceutical company, found that in animal models 17α-substituted derivatives of P4 had higher progestin activity than P4. One of the most potent compounds was the caproic acid ester of 17α-hydroxyprogesterone [12,13]. In the 1950s Squibb, a major US pharmaceutical company, established the safety of 17α-hydroxyprogesterone-caproate (17HPC) and introduced it under the brand name Delalutin that gained FDA approval (NDA 10-347) in 1956 for treatment of menstrual disorders, uterine cancer and threatened miscarriage [14]. Clinical trials conducted between 1960 and 1990 of 17HPC prophylaxis to prevent PTB produced mixed outcomes due mainly to differences in patient cohorts, treatment regimens (some trials used P4 or 17HPC to prevent early miscarriage), study design, and statistical power [15–19]. Nonetheless, a meta-analysis of the pre-1990 placebo-control trials showed that 17HPC prophylaxis reduced PTB risk by ∼50% in women with existing increased risk for PTB [20]. This justified a larger trial in the late 1990s by the Maternal-Fetal Medicine Units (MFMU) Network of the National Institute of Child Health and Human Development [21] who found that weekly intramuscular injection of 200 mg 17HPC in oil beginning at 16–20 weeks and ending at 36 weeks or delivery decreased the incidence of PTB compared with weekly injection of placebo (36.3% for 17 HPC vs 54.9% for placebo). That outcome encouraged the clinical use of 17HPC prophylaxis for PTB prevention, albeit in a specific sub-set of women. However, the high incidence of PTB in the placebo group of 54.9% compared with the *a priori* expected rate of ∼37%, remains problematic. At around the same time a trial reported by de Fonseca et al. [22] found that progestin prophylaxis with 100 mg P4 administered by daily vaginal suppository decreased the incidence of PTB compared with placebo (13.8% P4 vs 28.5% placebo). Interestingly, the incidence of PTB in the placebo group (28.5%) was less than that of the placebo group in the MFMU study (54.9%) even though the inclusion criteria for high PTB risk were essentially identical. Thus, by the early 2000s much clinical enthusiasm existed for the use of 17HPC (intramuscular weekly) or P4 (daily vaginal suppository) for the prevention of PTB in women at risk for PTB.

Several clinical trials subsequently tested the effectiveness of vaginal P4 prophylaxis to reduce PTB risk [23–27]. O'Brien et al. [28] found that vaginal P4 did not reduce the rate of spontaneous PTB (≤32 weeks) in women with a history of spontaneous PTB but instead appeared to have beneficial effects in women with a short cervix (≤25 mm) detected by vaginal ultrasound at around 20 weeks of gestation. A similar outcome was reported by Fonseca et al. [24] and this effect was confirmed by Hassan et al. [25] who found that prophylaxis with vaginal P4 decreased the incidence of PTB (< 33 weeks) compared with placebo (8.9% for P4 vs 16.1% for placebo) in women with a sonographic short cervix (10–20 mm) at mid-gestation. A meta-analysis of all vaginal P4 prophylaxis trials up to that time confirmed that vaginal P4 prophylaxis reduces the rate of PTB in women with a mid-gestation cervical length of ≤25 mm [26]. Those results prompted a large multicenter placebo controlled trial (referred to as OPPTIMUM) in the UK that tested the effect of daily vaginal P4 administered between 22 and 34 weeks of gestation in women with a singleton pregnancy who were at risk for PTB based on a previous spontaneous PTB at ≤ 34 weeks or a cervical length ≤ 25 mm. No significant beneficial effect of vaginal P4 prophylaxis on the rate of spontaneous PTB (< 34 weeks) was detected by the OPPTIMUM trial regardless of PTB risk factor [29]. Follow-up analyses showed that vaginal P4 had no detectable adverse effects on the infants up to 2 years of age [30] which is consistent with studies in animals showing that P4 therapy during pregnancy has no adverse effect on fetal or neonatal neurodevelopment [31].

Despite the negative (with respect to PTB prevention) outcomes of the OPPTIMUM trial, an updated meta-analysis that included the OPPTIMUM data showed that vaginal P4 prophylaxis to women with singleton pregnancy and a mid-gestation sonographic cervical length ≤ 25 mm decreased the risk of PTB (≤34 weeks) by ∼35% (18.1% for women receiving P4 vs 27.5% for women receiving placebo) [32]. Based on that analysis, the current consensus is that daily vaginal P4 prophylaxis should be administered to women with a sonographic cervical length ≤25 mm at mid-gestation to reduce the risk for PTB. However, controversy persists since the negative outcomes of the OPPTIMUM trial cast significant doubt on the effectiveness of vaginal P4 prophylaxis to decrease PTB risk.

In contrast to vaginal P4 therapy, consensus for the beneficial effects 17HPC prophylaxis to prevent PTB is not as strong. The only clinical trial of 17HPC performed after the MFMU trial is that of Rouse et al. [33] who found that 17HPC (250 mg/wk from 16 to 20–36 weeks) had no effect on preventing PTB (< 35 weeks) in twin pregnancies (41.5% in the 17HPC group vs 37.3% in the placebo group). Further 17HPC trials are needed to resolve this issue.

3. Mechanism by which progestin prophylaxis prevents PTB

The core rationale for progestin prophylaxis is that it corrects a progestin deficiency that increases risk for PTB. The endocrine milieu of human pregnancy, however, is dominated by P4, with uterine cells exposed to high levels of P4 throughout pregnancy and during term and preterm labor and delivery [34]. This explains the failure of P4 therapy to prevent miscarriage in women with normal P4 levels, and its failure to inhibit labor and delay normal term parturition. Progestin deficiency as a cause for PTB is therefore difficult to reconcile and, as such, the biological plausibility of adding exogenous progestin to an already progestin-rich milieu is questionable. Nonetheless, clinical data suggest that progestin therapy may act via diverse mechanisms since the effectiveness of progestin prophylaxis is specific to the type of progestin (P4 vs 17HPC), its route of administration (vaginal vs intramuscular), and the PTB risk factor (short cervix vs PTB history).

The mechanism by which vaginal P4 decreases the risk for PTB appears to be related to the pathophysiology of cervical remodeling during the prelude to parturition. A short cervix at mid-gestation may reflect a trajectory leading to subsequent PTB. Vaginal P4 prophylaxis may restore the normal trajectory leading to term parturition. Correction of a P4 deficiency, at least at the level of the cervix, may be involved. Studies suggest that P4 withdrawal occurs locally in cervical stromal cells by the enzymatic metabolism of P4 to an inactive form [35,36] and the subsequent generation of unliganded PRs that promote the expression of genes encoding contraction-associated proteins [37]. The direct application of P4 to the cervix may increase local P4 levels to exceed the capacity for its metabolic inactivation leaving residual bioactive P4 to inhibit the shortening trajectory and restore the normal rate of cervical remodeling. This mechanism would explain why the effectiveness of vaginal P4 is limited to women with a short cervix.

How 17HPC prevents PTB is uncertain. It is clear from the early study at Schering AG that 17HPC has potent (relative to P4) progestin activity in animal models in which endogenous P4 is eliminated by ovariectomy. This may be due to its favorable pharmacokinetics and in vivo stability. It is also possible that 17HPC induces more potent P4 receptor-mediated progestin activity compared with P4 due to its altered structure. It is now recognized that nuclear P4 receptor (nPR) transcriptional activity is cell- and gene promoter-type specific and markedly affected by ligand structure. Thus, the molecular biology and pharmacokinetics of 17HPC may favor augmented progestin activity [38]. Whether this occurs in the context of human pregnancy when 17HPC is expected to compete with endogenous P4 for nPR binding remains unknown.

One interesting hypothesis is that 17HPC decreases the risk for PTB by serving as a precursor for cortisol synthesis by fetal adrenal glands. Cortisol promotes the functional maturation of organ systems (e.g., lungs, gut) essential for the fetus to survive as a neonate [39,40]. Production of cortisol by the fetus begins at around the 30th week of gestation when cells in the transitional zone of the fetal adrenal cortex acquire the capacity to convert cholesterol to cortisol [41,42]. Interestingly, although fetal adrenal cortical cells do not produce cortisol before that time, they express genes encoding enzymes that convert 17-hydroxyprogesterone to cortisol and in vitro can utilize 17-hydroxyprogesterone for cortisol production [41–43]. Under normal conditions, however, the cells are not exposed to 17-hydroxyprogesterone for most of pregnancy until late in the second trimester. It is possible, therefore, that 17HPC treatment provides fetal adrenal cortical cells the key substrate for cortisol synthesis leading to the production of cortisol at a time (i.e., < 30 weeks of gestation) when the glands normally would not produce this steroid. Evidence for this is that salivary estriol in women receiving 17HPC is lower than in women receiving placebo [44]. This can be explained by increased production of cortisol by the fetal adrenals that exerts negative feedback on the fetal hypothalamus-pituitary axis which would decrease adrenal androgen production leading to lowered levels of precursors for placental estriol synthesis. An important caveat of this hypothesis, however, is that esterase activity acting on 17HPC is generally low in human cells limiting the release of 17-hydroxyprogesterone from 17HPC and it is not clear whether cortisol-caproate can be generated from 17HPC [45]. Furthermore, 17-hydroxyprogesterone may also metabolized to pregnenetriol, which is inactive, at least in terms of known progestin activity.

Clearly, understanding of how current progestin-based therapies prevent PTB—albeit in a small cohort of at risk women—is far from complete. Nonetheless, it is generally accepted that P4 blocks labor for most of pregnancy and as such P4-based therapeutics are a rational option to prevent PTB. However, it is also clear that PTB is not due to a deficiency of endogenous P4, and in this context the logic of P4 therapy to prevent PTB is flawed. Clearly, novel progestin-based approaches are needed to prevent PTB. To address these issues, better understanding is needed of how P4 maintains pregnancy and specifically how it blocks labor and promotes uterine relaxation and quiescence, and how those effects are withdrawn to allow for parturition. The following discussion addresses recent progress in this area and how understanding of P4 signaling in uterine cells is revealing novel and innovative approaches for progestin-based therapies to prevent PTB.

4. Role of inflammatory stressors in the pathophysiology of human parturition

In the 1970s, Penti Siiteri and colleagues proposed that P4 blocks labor by immunosuppressive and anti-inflammatory actions [46]. The underlying implication of that hypothesis is that labor is an inflammatory event and that the P4 block to parturition is due to anti-inflammatory effects of P4 on uterine cells. Indeed, studies in the 1950s by Lars Bengtsson (described earlier) [10] showed that labor is induced by intrauterine infection, and more recent studies found that ~50% of PTBs are associated with intrauterine inflammation/infection and/or hyper-distention of the uterine wall [47–50]. In addition, histologic analyses of the gestational tissues show that tissue-level sterile inflammation, characterized by edema, neutrophil infiltration and expression of pro-inflammatory cytokines, chemokines and prostaglandins (PGs), increases during the prelude to labor [51,52]. Whole exome sequencing data also support the concept that parturition has an inflammatory etiology and that PTB may be caused by a hypersensitivity to inflammatory stimuli impacting the gestational tissues [53]. Thus, the complex etiology and pathophysiology of PTB may be due to the diversity of inflammatory/stress stimuli that converge to exert an "inflammatory load” on the uterine tissues [54]. It is possible that P4 blocks parturition for most of pregnancy by desensitizing uterine cells to inflammatory load stimuli (i.e., and anti-inflammatory effect). This mechanism is supported by in vitro studies showing that P4 inhibits the responsiveness of myometrial, decidual and cervical cells to pro-labor/pro-inflammatory stimuli [55–59]. However, as demonstrated by Bengtsson [10], P4 therapy does not prevent infection-induced preterm parturition, suggesting that the anti-inflammatory capacity of P4 is limited and may be overcome by excessive inflammatory load. We propose that an inflammatory load threshold exists above which the anti-inflammatory P4 block to labor is functionally negated leading to unchecked tissue-level inflammation that induced labor [54]. Our model predicts that under normal circumstances the inflammatory load threshold is reached at around the 40th week of gestation and that PTB is caused by an abnormal increase in the inflammatory load such that the threshold is reached before term. Progestin supplementation could boost P4 anti-inflammatory activity such that the threshold is raised and/or the rate of inflammatory load increase is blunted. Based on this reasoning, understanding the functional interaction between P4 and uterine tissue-level inflammation may reveal novel strategies for progestin therapy to prevent PTB.

5. P4/PR signaling in human pregnancy and parturition

Actions of P4 to maintain pregnancy are primarily mediated by the nPR isoforms, PR-A and PR-B, that function as ligand-activated transcription factors [60–63]. Importance of P4/nPR signaling for pregnancy maintenance is demonstrated by clinical and animal studies showing that administration of compounds such as RU486 (aka: mifepristone) and ZK98299 (aka: onapristone) that disrupt nPR actions increases uterine contractility and induces labor and delivery at all stages of pregnancy [64,65].

P4 also may affect the gravid uterus by non-transcriptional/non-genomic mechanisms. These effects are potentially mediated by nPRs functioning in the cytoplasm to directly affect other cell signaling pathways [66,67], by membrane-associated PRs (mPRs) that are coupled to specific intracellular signaling pathways [68–74], and/or by P4 (or its metabolites) interacting with neurotransmitter and peptide hormone receptors [75]. Although the physiology role of putative mPRs as mediators of P4 actions is somewhat controversial [76–78], several studies suggest that certain forms mediate distinct pro-gestational actions of P4 in the myometrium, cervix and fetal membranes [79–86].

The existence of multiple PR types suggests alternative pathways by which progestin prophylaxis may affect the gravid uterus to prevent PTB. It is possible that unlike nPRs that are presumably saturated with endogenous P4, mPRs have lower binding affinity and therefore may be affected pharmacologically by additional exogenous P4 or 17HPC. Moreover, it is possible that nPR signaling in myometrial, cervical and decidual cells may be affected by cross-talk with mPR activity affected by exogenous P4 or 17HPC [81]. Further studies are needed to identify the role of mPRs in the pathophysiology of human parturition and whether they mediate beneficial effects of progestin prophylaxis.

In most species a physiologically controlled prepartum systemic decrease in maternal P4 triggers parturition. This does not occur in women [34,87]. Instead, maternal P4 levels remain high and continue to increase late in pregnancy and during parturition. Nonetheless, disruption of P4/nPR signaling induces human parturition at all stages of pregnancy. This suggests that human parturition is triggered by a functional, rather than systemic, P4 withdrawal mediated by change in nPR (and possibly mPR) function [88–92].

Several mechanisms for functional P4/PR withdrawal have been

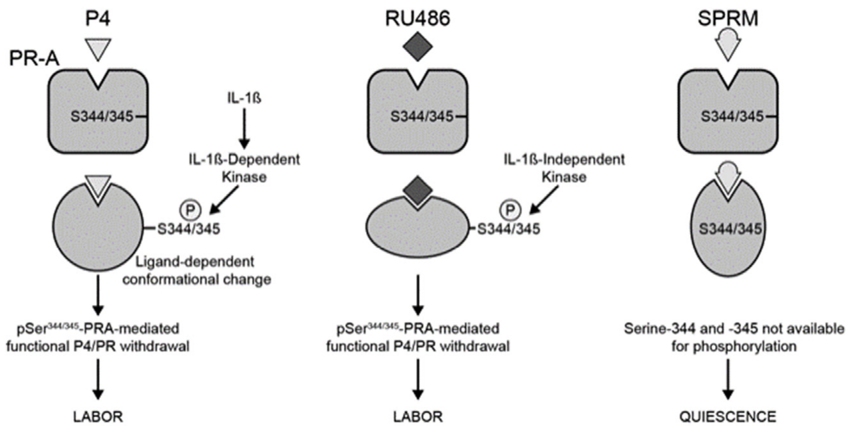

Fig. 1. Model to explain how SPRMs affect PR-A phosphorylation. SPRM binding to the PR ligand binding pocket induces a specific conformational change in the PR that affects the availability of serine-344 and -345 for phosphorylation. pSer$^{344/345}$-PRA inhibits the capacity for P4/PR to maintain uterine quiescence and block labor.

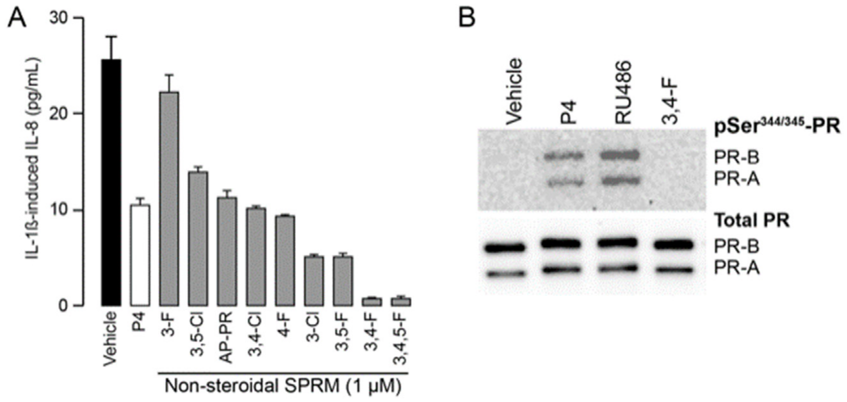

Fig. 2. A: Alpha-ELISA of IL-8 in media of hTERT-HM$^{A/B}$ myometrial cells conditioned to express PR-B and exposed to vehicle, P4 (100 nM) and various SPRMs (each 1 μM) for 24 h and then challenged for 2 h with IL-1β (1 ng/mL). P4 and some SPRMs inhibited IL-1β-induced IL-8 production. There was no effect of P4 or SPRMs in cells not expressing PR-B. **B**: Immunoblot assays of effect of short-term (2 h) exposure to P4 (100 nM), RU486 (10 nM) or various SPRMs (each 1 μM) on ligand-induced generation of pSer$^{344/345}$-PRs in hTERT-HM$^{A/B}$ cells. In hTERT-HM$^{A/B}$ cells P4 induces pSer$^{344/345}$-PR-A and PR-B initially (within 2 h of exposure to P4), but after longterm (~24 h) exposure, and in human pregnancy myometrium, induces only pSer$^{344/345}$-PR-A [54].

proposed, each involving modulation of nPR transcriptional activity [37,90,93,94]. In vitro studies in a variety of cell types show that at some gene promoters the type-A nPR isoform (PR-A) represses the activity of the type-B isoform (PR-B) and as such decreases net P4/nPR responsiveness [95,96]. Those data led to the hypothesis that progestin activity is mediated by P4/PR-B and that human parturition is triggered by increased trans-repressive activity of PR-A [93,97]. The onset of labor at term is associated with increased abundance of PR-A relative to PR-B in myometrial cells [88,91–93,98]. Recent studies show that the abundance of PR-A in myometrial cells is increased by pro-inflammatory stimuli that also increase its trans-repressive activity [99,100]. Taken together the data suggest a mechanism for inflammation-induced parturition whereby pro-inflammatory/pro-labor stimuli induce PR-A-mediated functional progesterone withdrawal.

The key mechanism by which P4/PR is thought to block labor is by decreasing responsiveness of uterine cells to pro-labor/pro-inflammatory stimuli (i.e., an anti-inflammatory effect). In cultured myometrial cells this effect is mediated mainly by PR-B and to a lesser extent by PR-A. Our recent studies show that P4/nPR anti-inflammatory activity is lost when PR-A is phosphorylated at serine residues 344 and 345 (pSer$^{344/345}$-PRA) [54,56]. We also found that abundance of pSer$^{344/345}$-PRA in term myometrium increases in association with the onset of labor at term and in myometrium explant cultures was dependent on P4 and catalyzed by protein kinase activity induced by pro-inflammatory stimuli [99,100]. Based on those data, we proposed that pro-inflammatory stimuli accumulate with advancing gestation leading to a gradual increase in the net inflammatory load on the uterine tissues [54], and that an inflammatory load threshold exists above which specific protein kinase activity in uterine cells is activated that catalyzes the generation of pSer$^{344/345}$-PRA leading to loss of P4/nPR pro-gestation/anti-inflammatory activity. Unopposed pro-inflammatory stimuli then induce tissue-level inflammation that transforms the uterus to the laboring state. Based on this model, therapeutics that alter the inflammatory load trajectory and/or uncouple the generation of pSer$^{344/345}$-PRA by inflammatory stimuli in uterine cells may prevent inflammation-induced PTB. These effects could be achieved by targeting PRs using selective PR modulators (SPRMs).

6. SPRMs to prevent PTB

SPRMs are compounds that compete with P4 for binding to the nPR ligand binding pocket and induce mixed agonist/antagonist (relative to P4) activity [101–107]. Structure-activity relationship (SAR) studies show that agonist or antagonist activity of SPRMs is attributed to how specific ligands affect the conformational state of helix-12 within the PR ligand binding pocket [108–110]. In this context it is noteworthy that 17-HPC may affect nPR signaling differently to P4 due to hydroxylation at the C17 positio and/or existance of the caproate.

SPRM effects on nPR SAR likely extends to the pattern of site-specific serine phosphorylation of the nPRs. Interestingly we found that in term myometrium IL-1β and P4 were necessary for the generation of pSer$^{344/345}$-PRA [54], whereas RU486 alone was sufficient to induce pSer$^{344/345}$-PRA generation (Fig. 1). This observation suggests that SPRMs (RU486 is considered a SPRM) differentially affect nPR function by affecting nPR phosphorylation. This observation is proof-of-concept that SPRMs can be used to induce specific nPR function, in part by regulating the formation specific pSer-PRs. It may be possible, therefore, to improve progestin prophylaxis for PTB prevention using SPRMs that elicit PR anti-inflammatory activity and/or prevent the generation of pSer$^{344/345}$-PRA.

To test this hypothesis, we explored the capacity for several non-steroidal SPRMs to induce nPR-mediated anti-inflammatory activity and pSer$^{344/345}$-PRA generation in human myometrial cells. We found that some compounds exerted potent anti-inflammatory activity that was dependent on nPR expression, and that unlike P4 and RU486 none of the SPRMs derivatives induced the generation of pSer$^{344/345}$-PRs

(Fig. 2). Those data suggest that SPRM compounds can be designed that are P4 agonists based on nPR-mediated anti-inflammatory activity, but unlike P4, do not induce the conformational change in PR-A necessary for the generation of pSer$^{344/345}$-PRA. These compounds may be the next generation of therapeutics for progestin-based inhibition of PTB by promoting P4/nPR anti-inflammatory activity and inhibiting pSer$^{344/345}$-PRA-mediated functional P4/nPR withdrawal.

7. Conclusion

The idea of exploiting progestin activity (mainly by administering P4 or progestin agonists) to prevent PTB is not novel. Current prophylactic therapies are based on the assumption that PTB is due to progestin deficiency that can be corrected by progestin supplementation. However, the endocrinology of human pregnancy is dominated by P4 and as such deficiency of progestin capacity is not likely. This would explain why the effectiveness of current 17HPC and P4 therapies to prevent PTB is limited to a relatively small number of women with existing elevated risk for PTB; both therapies are ineffective in the general population. Nonetheless, the concept of exploiting the progestin activity to prevent PTB remains viable and recent advances in understanding the molecular biology and biochemistry of P4/PR signaling in uterine cells and how it is controlled during human pregnancy and parturition is revealing novel approaches to progestin prophylaxis for PTB prevention. To this end the concept of designing SPRMs that simultaneously boost P4/nPR anti-inflammatory activity and prevent pSer$^{344/345}$-PRA-mediated functional P4 withdrawal is an exciting approach.

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