Progesterone as an Anti-Inflammatory Drug

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The specific regulation of inflammatory processes by steroid hormones has been actively studied, especially by progesterone (P4) and progestins. The mechanisms of the anti-inflammatory and immunomodulatory P4 action are not fully clear. The anti-inflammatory effects of P4 can be defined as nonspecific, associated with the inhibition of NF-κB and COX, as well as the inhibition of prostaglandin synthesis, or as specific, associated with the regulation of T-cell activation, the regulation of the production of pro- and anti-inflammatory cytokines, and the phenomenon of immune tolerance. The specific anti-inflammatory effects of P4 and its derivatives (progestins) can also include the inhibition of proliferative signaling pathways and the antagonistic action against estrogen receptor beta-mediated signaling as a proinflammatory and mitogenic factor. The anti-inflammatory action of P4 is accomplished through the participation of progesterone receptor (PR) chaperones HSP90, as well as immunophilins FKBP51 and FKBP52, which are the validated targets of clinically approved immunosuppressive drugs. The immunomodulatory and anti-inflammatory effects of HSP90 inhibitors, tacrolimus and cyclosporine, are manifested, among other factors, due to their participation in the formation of an active ligand–receptor complex of P4 and their interaction with its constituent immunophilins. Pharmacological agents such as HSP90 inhibitors can restore the lost anti-inflammatory effect of glucocorticoids and P4 in chronic inflammatory and autoimmune diseases. By regulating the activity of FKBP51 and FKBP52, it is possible to increase or decrease hormonal signaling, as well as restore it during the development of hormone resistance. The combined action of immunophilin suppressors with steroid hormones may be a promising strategy in the treatment of chronic inflammatory and autoimmune diseases, including endometriosis, stress-related disorders, rheumatoid arthritis, and miscarriages. Presumably, the hormone receptor- and immunophilin-targeted drugs may act synergistically, allowing for a lower dose of each.

Keywords: progesterone (P4) ; FKBP51 ; cyclosporine A (CsA) ; HSP90 ; inflammation

1. Introduction

The goal is to highlight the possibility of using P_4 and its derivatives as alternative steroid hormones to glucocorticoids in the treatment of inflammatory diseases, especially chronic inflammatory diseases accompanied by resistance to hormone therapy.

Acute inflammation is simultaneously a typical pathological process and a protective reaction of the body in response to infections and tissue damage. When one of the main regulators of inflammation—the transcription nuclear factor kappa B (NF-κB)—is constitutively activated due to translocation to the nucleus, the inflammation is no longer an acute, rapid protective reaction of the body to pathogens, but in itself is a stimulus for the development of serious pathologies, including cancer and autoimmune diseases [1]. In the case of acute inflammation, the moderate production of proinflammatory cytokines serves as a protective factor, while in chronic inflammation and autoimmune and allergic reactions, it acts as a negative factor for the body's immune homeostasis. It is well known that steroid hormones are endogenous regulators of inflammation and cytokine production. In particular, glucocorticoids (GCs) are known to be potent immunosuppressive agents with anti-inflammatory activity [2][3]. GCs are the most widely prescribed class of drugs worldwide and their effectiveness in treating acute or chronic inflammation is undeniable [4]. However, there are some limitations to their clinical application. In addition to the gradually emerging resistance to GCs, serious side-effects of their usage are hyperglycemia with the further possibility of insulin resistance, sodium retention, and hypertension, muscle atrophy, osteoporosis, features of Cushing's syndrome, etc. [5]. The response to GC relies on several factors, including the duration of the stimulus (acute or chronic) and the physiological state of the immune system. In pathological situations, GCs may function as anti-inflammatory molecules to control the process. In contrast, under normal physiological conditions, they may play a proinflammatory role [2][6].

An alternative to GCs can be progesterone (P_4) due to its anti-inflammatory and immunomodulatory effects. Progesterone at an equal concentration of 0.3–1 ng/mL is present in both men and women. During pregnancy, its concentration increases to 300 ng/mL, and in the luteal phase, it increases to 14 ng/mL. Both in menopausal women and in men over

the age of 60, the P_4 concentration decreases, being equal to 0.38 ± 0.13 ng/mL in men aged 20–90 years and 0.38 ± 0.37 ng/mL in postmenopausal women aged 50–90 years [7]. This fact may explain a more severe course of infectious and autoimmune diseases in people over 60 years old, when the protective effect of P_4 is reduced.

Recently, some unique anti-inflammatory and immunomodulatory effects of P_4 have been shown, particularly its anti-inflammatory role in COVID-19 therapy. In 2021, a study was completed on 42 men with severe COVID-19, where the patients were treated with P_4 in addition to the standard of care. The participants needed 3 days less supplemental oxygen (median, 4.5 vs. 7.5 days) and were hospitalized for 2.5 fewer days (median, 7.0 vs. 9.5 days) as compared with control subjects [8]. A decrease in circulating progesterone levels has been noted in patients with SARS [9]. Sex steroid hormones, particularly P_4, may be useful in preventing and managing severe COVID-19; related clinical trials are ongoing [10][11]. It was revealed that P_4 decreases the production of IL-1β, IL-6, TNFα, and IL-12, as well as the production of chemokines (e.g., monocyte chemoattractant protein-1 MCP-1/CCL2); moreover, due to its good tolerability and neuroprotective properties, P_4 could be a very useful addition to established COVID-19 therapy [12].

The possible side-effects with progesterone usage as an anti-inflammatory drug should be extremely minimal or absent. For progestins with affinity for GR, MR, or AR, some side-effects may be associated with the concomitant glucocorticoid, mineralocorticoid, or androgenic activity, which may be accompanied by water retention, verification, and acne (levonorgestrel, gestodene, drospirenone, and MPA). Progestins dydrogesterone and dienogest have no adverse hormonal activities [13] and could be adequate drugs for the therapy of inflammatory processes.

In general, all progestins are classified as low-toxicity substances, and their usage during pregnancy, as well as in assisted reproductive technologies, testifies to the absence of general and reproductive toxicity [14].

The usage of P_4 in men is not well studied. P_4 is the essential hormone for the normal functioning of the male endocrine system, i.e., for spermatogenesis, testosterone biosynthesis in Leydig cells, and neuroprotective function in the brain [15]. For example, the lack of RP expression in germ cells leads to male infertility [16].

The neuroprotective role of P_4 has been confirmed in both men and women; there are results of a number of clinical studies confirming the high therapeutic efficacy of P_4 against necrotic damage and behavioral abnormalities caused by traumatic brain injury (TBI) [17][18][19][20].

Importantly, there was no adverse event after the administration of progesterone, at least at 1 $mg \cdot kg^{-1}$ per 12 h, as well as no further late toxicity up to 6 months in both women and men in the trial [18]. Therefore, side-effects should not be expected in men, and progesterone treatment can be a potential therapy not only for TBI, but also for other inflammatory diseases [21], as well as an established pharmacologic therapy for TBI.

Recently, it was shown that intranasal delivery of progestin segesterone acetate may be an efficient strategy to promote recovery after stroke in males and realize cerebroprotection via PR in the brain [22]. Later, the role of mitochondrial metabolism and oxidative protection in segesterone acetate's therapeutic effects in stroke have been confirmed [23].

2. Progesterone Regulates Inflammation via FKBP51

The action of P_4 is realized through nuclear, mitochondrial, and membrane progesterone receptors. The active cytosolic/nuclear progesterone receptor complex exists in dynamic interactions with chaperones HSP90, HSP70, and p23, as well as cochaperone immunophilins FKBP51 and FKBP52 [24]. Studies have implicated alterations in the expression or function of PR coactivators, chaperones, and cochaperones that are bound to the mature form of the cytosolic PR before activation and nuclear translocation in the development of P_4 resistance [25].

P23 is a small acidic protein with intrinsic molecular chaperone activity. It is best known as a cochaperone of the major cytosolic molecular chaperone Hsp90. P23 inhibits both the basal and the substrate-stimulated ATPase activity of Hsp90, resulting in its stabilization [26]. Hence, targeting p23, as well as other members of the active PR complexes, can modulate PR- and GR-mediated responses. p23 functioning is not as well studied as FKBP51 and FKBP52 functioning.

FKBP51 and FKBP52 are members of the immunophilin protein family, named because they bind the immunosuppressive drugs tacrolimus FK506, sirolimus (rapamycin), and cyclosporin A (CsA), which play a role in immune regulation and basic cellular processes involving protein folding and trafficking. FKBP51 has *cis–trans* prolyl isomerase activity, which is inhibited after FKBP51 binding using the abovementioned immunosuppressive drugs. Binding with immunosuppressants also mediates the calcineurin inhibition. FKBP51 interacts with mature progesterone receptor hetero complexes, as well as glucocorticoid and mineralocorticoid complexes with HSP90 and p23 proteins. Via a short feedback loop, FKBP51

regulates hypothalamic–pituitary–adrenal axis activity. FKBP51 expression is increased by GC or P_4 and acts on GR or PR in an inhibitory manner; then, cortisol synthesis is decreased, which downregulates inflammation [27].

FKBP51 has the potential to control inflammation in steroid-insensitive patients in a steroid-dependent and -independent manner; thus, it may be worthy of further study as a drug target. Its role in inflammation has been extensively studied, especially in the regulation of the IKK complex, NF-κB signaling, etc., with a focus on its role in hormone-resistant inflammation. It is assumed that the downregulation of FKBP51 expression can restore steroid sensitivity.

For example, the blockade of FKBP51 in a bronchial epithelial cell line resulted in a tenfold increase in the effectiveness of dexamethasone in suppressing IL-6 and IL-8, while the overexpression of FKBP51, on the contrary, reduced sensitivity to prednisolone in a model of pneumonia in mice [28]. FKBP51 silencing also decreased NF-κB translocation to the nucleus [28].

It can be hypothesized that FKBP51 inhibition would increase hormone sensitivity and attenuate inflammation. FKBP51, unlike FKBP52, does not bind to dynein and, thus, does not move GR into the nucleus [27]. That is, FKBP51 overexpression inhibits GR signaling. Upon steroid binding, the steroid receptor heterocomplex exchanges FKBP51 for FKBP52. After this, FKBP52 is able to interact with dynein and further promotes the transcriptional activity of nuclear steroid receptors [29]. It is assumed that, by regulating FKBP51 expression and post-translational changes, it is possible to increase or decrease the response to P_4 or GC during inflammatory processes [30].

As FKBP51 was described as a regulator of NF-κB (nuclear factor binding near the κ light-chain in B cells) signaling in different cell types, it has been suggested as a drug target for the treatment of NF-κB-mediated inflammation and cancer [31]. FKBP51 interacts with the subunits of the IKK complex [31]. Therefore, FKBP51 ligands can modulate the PR-mediated influence on inflammation, as well as restore the sensitivity to steroid hormones.

FKBP51 ligands can reduce inflammation and proliferation. It was shown that the FKBP51 ligand FK506 inhibits both PR and GR found in T47D breast cancer cells [32]. When needed, this feature can be used to protect against the action of GR, PR, or possibly AR. Indeed, in LNCaP (prostate cancer) cells, another FKBP51 ligand CsA was a highly effective inhibitor of both AR-dependent and -independent proliferation, while FK506 inhibited only AR-dependent growth. Indeed, some studies have shown that AR can be a molecular target for both CsA and FK506 [32].

The localization and functioning of FKBP51 are still under investigation. It is assumed that FKBP51 is a mitochondrial protein present in various cell lines and rat organs, which undergoes nuclear–mitochondrial shuttling [33]. It was also shown that FKBP51 forms complexes in the mitochondria with the glucocorticoid/progesterone receptor and with the Hsp90/Hsp70-based chaperone heterocomplex [33]. Furthermore, FKBP51 is an inhibitory cochaperone for PR, AR, and GR. Conversely, FKBP52 is a stimulatory cochaperone for these receptors. The cytoplasmic FKBP52 is localized to microtubules and, after hormone binding, activates dynein, which moves the mature GR or PR complex to the nucleus for downstream genomic signaling [27]. Thus, FKBP51 is responsible for the binding to the ligand, while FKBP52 is responsible for the transfer of the receptor–ligand complex to the nucleus via dynein binding [29]. Hence, immunosuppressants such as tacrolimus revealed potential therapeutic benefits for their use in treating female infertility due to the enhanced progesterone receptor sensitivity [27].

The role of FKBP51 in the regulation of glucocorticoid-mediated inflammation is also the subject of interest. FKBP51 may provide an additional instrument to regulate the glucocorticoid-mediated pathways especially in the case of pathologies associated with high glucocorticoid levels, where the suppression of the FKBP51 function may help to restore the anti-inflammatory action of glucocorticoids [6]. Therefore, FKBP51 functioning is still not fully studied, but FKBP51 targeting may be promising in inflammation, cancerogenesis, and stress-related disorders. P_4 and its analogues should be strong regulators of FKBP51 activity, but the exact mechanisms of regulation remain to be explored. FKBP51 ligands such as tacrolimus or CsA can cause immunosuppressant and anti-inflammatory action not only via calcineurin inhibition, but also by increasing sensitivity to steroid hormones. P_4 and synthetic progestins bind FKBP51 and regulate its expression and activity.

FKBP51 also acts as a negative regulator of AKT since FKBP51 is responsible for binding indirectly through Hsp90 to AKT [34]. Consequently, researchers can assume that, upon FKBP51 binding with P_4 or immunodepressants, Akt signaling is decreased, which can be an additional mechanism to increase progestin or GK sensitivity.

However, there are conflicting data on this issue. It is possible that the effect of progestins on FKBP51 is different depending on the dose of progestin and the time of exposure. For example, an inducing effect of the PR agonist R5020

and P_4 itself on FKBP51 mRNA expression, leading to resistance to P_4, has been demonstrated [35]. The FK506-binding immunophilin FKBP51 is transcriptionally regulated by progestin and attenuates progestin responsiveness [36].

The opposite action of FKBP51 on the responsiveness to P_4 was also demonstrated [37]; FKBP51 decreased cell proliferation and increased progestin sensitivity of human endometrial adenocarcinomas by inhibiting Akt. Furthermore, FKBP51 overexpression in progesterone receptor-positive Ishikawa cells sensitized them to medroxyprogesterone acetate (MPA; progestin) treatment by repressing Akt signaling.

As observed, FKBP51 levels are lower in endometrial adenocarcinoma than in normal endometrium tissues [37]. Conversely, FKBP51 expression is higher in the secretory-phase endometrium than in the proliferative phase. Furthermore, FKBP51 expression is higher in younger women than in older women. Thus, the interaction between P_4 and FKBP51 and the influence of P_4 on FKBP51 expression and functioning should be more extensively studied with respect to their role in acute and chronic inflammation, as well as in hormone-resistant inflammation and cancer.

3. Other Evidence of the Anti-Inflammatory and Immunomodulatory Action of Progesterone

3.1. The Influence on Chemokine Production

A number of studies have shown that P_4 and synthetic progestogens are able to suppress the production of chemokines and change chemokine–chemokine receptor profiles. P_4 (10 μM) caused a 50–70% inhibition of RANTES, MIP1α, and MIP1β secretion in $CD8^+$ cells of the peripheral blood mononuclear fraction [38].

Specific downregulation of the monocyte chemoattractant protein-1 (MCP-1) has been observed in human endometrial stromal fibroblast cells under the action of P_4 and MPA, LNG, and NETA, progestins structurally related to progesterone and testosterone. All progestins downregulated not only MCP-1, but also IL-6, TGFβ1, and matrix metalloproteinase-3 in this culture [39].

The role of contraceptive intravaginal progestins in possible protection against HIV is currently being actively investigated. It is assumed that P_4 protects against HIV-1 infection by reducing the expression of CCR5, the main co-receptor for HIV entry into human cells. The synthetic progestins etonogestrel and MPA increase the rate of virus penetration, although this may be due to the thinning of the endometrium [40].

3.2. Inhibition of WNT and MAPK Pathways

Recently it has been shown that the main role in inflammation in endometriosis is played by MAPK and WNT/β-catenin cascades. Since endometriosis is a chronic inflammatory disease, their inhibition may be a therapeutic strategy for endometriosis [41]. Progestins at high dosage inhibit both MAPK and WNT/β-catenin pathways; therefore, this effect may also be one of the mechanisms of their anti-inflammatory action [42][43].

3.3. Diminution of Estrogen Action by P_4

E2 has proinflammatory and mitogenic properties [44]. COX-2 promotes mammary adipose tissue inflammation, local estrogen biosynthesis, and carcinogenesis by inducing the secretion of cytokines and prostaglandins from peritoneal macrophages [45]. Estrogen receptors, particularly ER-β, are known to interact with some inflammasome components such as NLRP3 sensor and caspase 1 to activate IL-1β production. P_4 downregulates ER, representing an additional anti-inflammation mechanism [46].

3.4. GR-Mediated Anti-Inflammatory Action of Progestins

The anti-inflammatory effects of progestins may be associated with partial agonism of GR if they have agonistic activity toward GR, as in the case of MPA. Thus, in the endocervical epithelium cell line model, MPA, unlike NET-acetate and P_4, increased mRNA expression of the anti-inflammatory GILZ and IκBα genes [47]. Similarly, MPA, unlike NET-A, decreased the expression of the proinflammatory IL-6, IL-8, and RANTES genes, as well as the level of IL-6 and IL-8 proteins. Marinello et al. also demonstrated an anti-inflammatory GR-mediated action of MPA [48]. In primary human amnion mesenchymal cells, MPA had an anti-inflammatory effect via the inhibition of IL-1β-induced MMP-1 and IL-8 expression. This effect of MPA was blocked with the inhibition of glucocorticoid receptor expression by small interfering RNA transfection [48].

4. New Aspects in the Application of Progesterone and Progesterone Receptor Chaperones to Reduce Inflammation

The anti-inflammatory action of P_4 was described above, and the main mechanisms were shown. An additional intriguing aspect is the possibility to potentiate the P_4 anti-inflammatory action by targeting PR chaperones, such as immunophilins. As immunophilins are involved in the formation of active progesterone receptor complexes, they can regulate the specific pharmacological activity of progesterone, androgens, and glucocorticoids [24].

Immunophilins FKBP52 and FKBP51 are Hsp90-associated cochaperones. However, if HSP90 inhibitors have a broader spectrum of action, since HSP90 folds a great number of signal proteins in the cell (so-called “clients”), then FKBP52 or FKBP51 inhibitors should be much more specific and their influence, should not be global across the organism.

The significance of FKBP52 and FKBP51 was recently demonstrated in animal models with the knockout of these genes. Mice deficient in the FKBP52 gene were insensitive to androgens, glucocorticoids, and progesterone, but no more severe effects were observed. Thus, after inhibiting FKBP52, the action of these steroid hormones could be carefully eliminated when necessary. Moreover, a pharmacological target in FKBP52 has already been established, i.e., a proline-rich loop in the FK1 catalytic domain [49][50][51]. As for FKBP51/FKBP52 double-knockout mice, embryonic lethality took place in all cases [49].

FKBP52 is a validated target of the clinically approved immunosuppressive drug, FK506 (tacrolimus). Thus, the development of FKBP52-specific small-molecule inhibitors is predicted to be a highly targeted strategy with potential for the treatment of any disease that is dependent on functional AR, GR, and/or PR signaling pathways. Thus, the action of progestins, androgens, and GK can be enhanced by tacrolimus. In this way, it is possible to decrease the dosage of the appropriate hormone and the FK506 immunosuppressant.

With regard to HSP90 inhibitors, their elaboration is also a fast-developing pharmaceutical direction, with several drugs in clinical trials, most of which are aimed at anticancer therapy [51][52]. However, in some cases, small-molecule inhibitors of Hsp90 have been found to be cardiotoxic. Considering this connection, specific targeting of Hsp90 via modulation of post-translational modifications (PTMs) seems to be a more appropriate strategy [53]. Surprisingly, increased HSP expression and functioning may even be protective for the myocardium. The therapeutic enhancement of intracellular HSP activity with commercially available drugs (e.g., geranylgeranyl acetone, an antiulcer drug that supports HSP70) has been experimentally shown to provide protection against myocardial infarction [54].

For FKBP51 immunophilin targeting, there are not as many intensively explored mechanisms. As described above, FKBP51 expression has a dual role in inflammation and stress-related signaling; specifically, it is positive in protecting against oxidative stress and negative in the case of already activated NF-κB-related gene networks [55]. FKBP51 overexpression protects cells against oxidative stress, while FKBP51 knockdown makes them more sensitive to injury [33].

It should be noted that there are strong interactions between HSP90 and FKBP51, since Hsp90 inhibitors promote the reversible translocation of FKBP51 from the mitochondria to the nucleus. These data suggest that the unexpected mitochondrial localization of FKBP51 may be related to its antiapoptotic effect [33].

P_4 also demonstrated a unique action on mitochondria [56]; thus, considering the expression of FKBP51, together with the finding that mitochondrial PR also exists in mitochondria [57], the translocation of FKBP51 from the mitochondria to the nucleus may have great importance. Hsp90 inhibitors favor FKBP51 translocation from the mitochondria to the nucleus in a reversible manner. After radicicol treatment, FKBP51 no longer resides in the mitochondria and concentrates in the nucleus. When the situation returns to normal, FKBP51 rapidly cycles back to the mitochondria, completing its cycle. Because both p53 and NF-κB are mitochondrial proteins, it may be that FKBP51 interacts with them in the mitochondria [33].

In inflammatory diseases, both the activation of the NF-κB pathway and the activation of the p53 pathway can occur [58]. P53 is required for the suppression of NF-κB by anti-inflammatory drugs, particularly GC and possibly P_4. Loss of p53, a tumor suppressor protein, impairs transcriptional repression of the NF-κB target gene by glucocorticoids. Thus, p53 plays a key role in the repression of NF-κB [59].

P53 and the GR are transported to the nucleus in a similar manner. The complexes of steroid hormone receptors with HSP90 and FKBP52 are transported to the nucleus by dynein, while the p53 complex with HSP90 and FKBP52 is transported in the same way upon DNA damage and cellular stress [60][61].

The identity transport of steroid receptor complexes and P53 complexes with immunophilins into the nucleus indicates that pharmacological regulation of this transport can reduce or induce the transcription of the corresponding genes.

The trafficking from the nucleus to the mitochondria is an important process, and it can be pharmacologically regulated. It was noted that toxicants induced an accumulation of NF-κB and p53 proteins in the nucleus, while the inhibitor of NF-κB nuclear translocation SN50 blocked the increase of p53 expression and suppressed the expression of *COX-2* and TNF-α [58]. The further exploration of the role of mitochondrial PR in oxidative stress, injury, and inflammation can open up new perspectives for regulation by targeting PR chaperones. This can be especially useful in the treatment of neurological and cardiac diseases.

More and more publications are appearing with respect to FKBP51 as a stress-related protein [62]. When the stress-related protein FKBP51 partners with Hsp90, this formidable chaperone protein complex prevents clearance from the brain of the toxic tau protein associated with Alzheimer's disease. Hsp90 supervises the activity of tau inside nerve cells. Chaperone proteins typically help ensure that tau proteins are properly folded to maintain the healthy structure of nerve cells [58].

Polymorphisms in FKBP51 have been associated with a number of neurological conditions including depression, suicide, and Alzheimer's disease [63]. Therefore, FKBP51 is a new treatment target for diseases with tau pathology. FKBP51 emerged as a key player in several diseases such as stress-related disorders, chronic pain, and obesity. The historically first FKBP51 inhibitor FK506 was shown to have neuroprotective effects and induce neuronal regeneration, suggesting significant roles for FKBPs in neural growth, injury, and regeneration. Linear analogues of FK506 called SAFit were shown to be highly selective for FKBP51 over its closest homolog FKBP52, allowing proof-of-concept studies in animal models.

Recently, newly synthesized macrocyclic inhibitors in complex with FKBP51 showed the desired selectivity-enabling binding mode, confirming that macrocyclization is a viable strategy to selectively target the shallow FKBP51 binding site [64].

As FKBP51 associates with HSP90 and appears in functionally mature steroid receptor complexes [65], the universal molecules for their inhibition are P_4, progestins, or other known PR ligands. In this case, tacrolimus and cyclosporine may potentiate the action of progestins.

Tacrolimus also affects various physiological functions, especially those mediated by glucocorticoid receptors [26]. Improvement in systemic and ovarian immune function, expression of endometrial progesterone receptors and co-receptors, and adaptation of uterine vessels to pregnancy were signs of increased sensitivity of progesterone receptors in a mouse model of the disease treated with low doses of tacrolimus. It is possible that these effects are mediated by the restoration of P_4 insensitivity [25]. A clinical trial of cyclosporine in RSA was recently initiated in China. As a background for its implementation, the researchers suggest that CsA in the cytoplasm forms a special complex with cyclophilin that binds calcineurin phosphatase and prevents lymphocyte proliferation, as well as the transcription of lymphocyte factors (TNF-α, IL-2, and IFN-γ), by inhibiting serine threonine protein phosphatase activity, which leads to immunosuppression. Thus, CsA may improve pregnancy outcomes in women with RSA, primarily in those with elevated Th1 immune-response phenotypes [66]. Combinations of progestins with CsA or tacrolimus require further preclinical studies devoted to the P_4 resistance.

Another little-explored role of in the suppression of inflammation is related to the fact that the specific target of progesterone action is the kappa-type opioid receptor agonist [67], the activation of which reduces pain, one of the main signs of inflammation. Through the action of its agonist on this receptor, P_4 may help reduce chronic pain, as observed in endometriosis, rheumatoid arthritis, and other inflammatory diseases. Although this assumption is based on a small number of publications [68][69], the study of the regulation of the kappa-type opioid receptor by P_4 appears to be important in understanding the role of P_4 in the regulation of inflammation.

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