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Nuclear factor-kappa-B/steroid hormone receptor interactions as a functional basis of anti-inflammatory action of steroids in reproductive organs

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The transcription factor, nuclear factor-kappa-B (NF-κB), can be induced by pro-inflammatory cytokines and is important in immunological and inflammatory processes because it directs transcription of chemoattractants, cytokines (including the NF-κB-inducing cytokines themselves), cytokine receptors and cell adhesion molecules. We and others have recently found that NF-κB and the glucocorticoid or progesterone receptor mutually suppress each other's activity. Because of its central role in signal transduction in immunological and inflammatory responses, inhibition of NF-κB activity by glucocorticoids and progestins provides an explanation for the anti-inflammatory and immunosuppressive activity of these molecules. Since suppression of inflammatory processes leading to menstruation and parturition are among the key functions of progesterone, the repression of NF-κB activity by the progesterone receptor may prove to be essential in the regulation of these processes. Recent data show that it may be possible to select progesterone receptor ligands that are more efficient suppressors of NF-κB activity, and which may therefore be more effective in modulating these major reproductive processes.

Key words: cytokine/inflammation/menstruation/parturition/progesterone receptor

Introduction

Steroid hormones bind to specific members of the superfamily of nuclear hormone receptors, which via a process referred to as transactivation, enhance transcription of specific target genes upon ligand binding (Truss and Beato, 1993). Recently, it has been discovered that many of these receptors can not only transactivate but also efficiently repress target genes through inhibition of major growth factor- and cytokine-induced signalling molecules (Pfahl, 1993). In the case of the retinoid (Lafyatis *et al.*, 1990; Nicholson *et al.*, 1990), glucocorticoid (Jonat *et al.*, 1990; Schüle *et al.*, 1990) and progesterone (Shemshedini *et al.*, 1991) receptors mutual transrepression has been described with the transcription factor AP1. AP1 is a dimeric transcription factor important in transducing the signals of a plethora of growth and differentiation-inducing agents. Inhibition of AP1 activity by these nuclear receptors plays a role in their inhibition of several metalloproteinases and their growth suppressive effects (Lafyatis *et al.*, 1990; Schüle *et al.*, 1990; Shemshedini *et al.*, 1991; Fanjul *et al.*, 1994; Van der Burg *et al.*, 1995; Chen *et al.*, 1995). More recently it has been established that the glucocorticoid (Mukaida *et al.*, 1994; Ray and Prefontaine, 1994; Van de Stolpe *et al.*, 1994; Caldenhoven *et al.*, 1995; Scheinman *et al.*, 1995), the progesterone (Kalkhoven *et al.*, 1996), and the oestrogen (Ray *et al.*, 1994; Stein and Yang, 1995) receptor can inhibit the activity of nuclear factor-κ-B (NF-κB). Because of its central role in signal transduction in immunological and inflammatory responses, inhibition of NF-κB activity by steroids could provide an explanation for their anti-inflammatory and immunosuppressive activity. Beside playing a role in immuno-modulation this interaction seems highly relevant in non-lymphoid tissues in which the mutual presence of cytokines and these steroid receptors has been described including bone, ovaries, endometrium and mammary gland, and especially relevant to those processes which resemble inflammatory responses such as menstruation, parturition and ovulation

The steroid/thyroid hormone superfamily

Lipophilic hormones, including steroids, retinoids and thyroid hormone, act through the dimeric nuclear receptors belonging to the superfamily of steroid/thyroid receptors which, upon binding of the hormone, *trans*activate gene expression following recognition of palindromic hormone response elements in the promoter region of target genes (Truss and Beato, 1993; Figure 1). The nuclear receptors have structural similarities and several functional domains can be distinguished, including a DNA binding domain, transactivation domains and a ligand binding domain. In addition, it has been found recently that several of these receptors can interfere with transcription through physical interaction with major transcription factors including AP1 (Pfahl, 1993). These interactions mostly lead to mutual repression, and the ratio between the numbers of receptors and interacting molecules determines the biological outcome.

Transcription factor NF-κB as a transducer of inflammatory and immunological triggers

The NF-κB proteins and the protein product of the *c-rel* proto-oncogene are all members of the NF-κB/Rel family and show

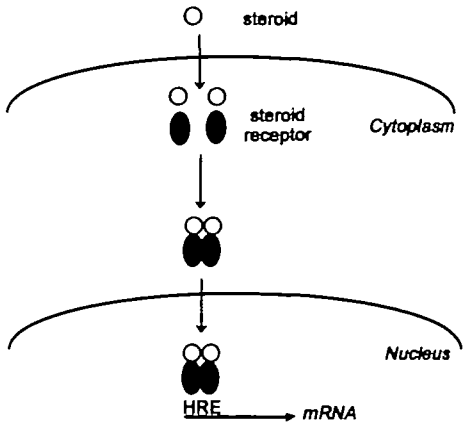

Figure 1. When activated by their ligands steroid receptors bind to hormone responsive elements (HRE) in promoter regions of target genes and enhance mRNA transcription of these genes.

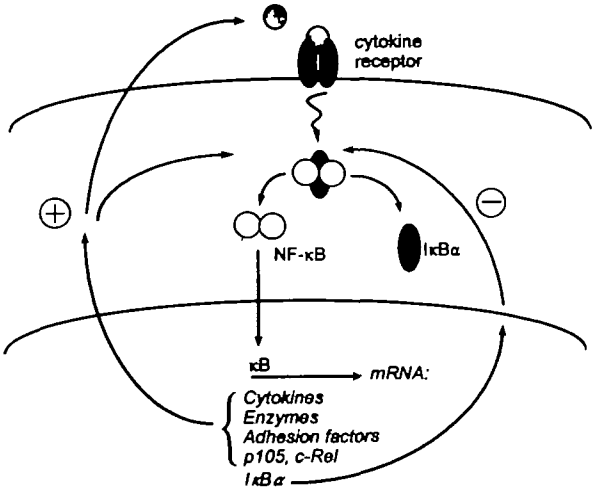

Figure 2. Nuclear factor-kappa-B (NF-κB) is a major transcription factor in immunological and inflammatory responses and its activity is induced by a number of pro-inflammatory cytokines. Recent data strongly suggest a major role of NF-κB directed inflammatory responses in menstruation, parturition and ovulation. NF-κB activation occurs as a result of the release of an inhibitory molecule, IRB. NF-κB directs transcription of a number of molecules involved in positive feedback (+), such as pro-inflammatory cytokines, certain adhesion factors, NF-κB components and enzymes. A major negative feedback loop (–) is the activation of $I_\kappa B_\alpha$ transcription.

a high degree of homology within a 300 amino acid long region, termed the Rel homology domain (Baeuerle and Henkel, 1994; Siebenlist *et al.*, 1994). This region mediates DNA binding, dimerization, nuclear localization, and interactions with an inhibitory molecule, IκB. The NF-κB transcription factor is found in a constitutively active form in B-cells, while in most other cells it is highly inducible, playing a major role in signal transduction by cytokines. Normally, NF-κB is present in an inactive form in the cytoplasm where it is associated with the inhibitory molecule IκB (Figure 2). Induction of NF-κB can be attained by a variety of agents including the pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, phorbol esters, physical or oxidative stress, and bacterial and viral proteins. Upon activation NF-κB is released from IκB, which is rapidly degraded. NF-κB subsequently translocates to the nucleus where it forms a homo- or hetero-dimer composed of 50 kDa (NFKB1) and 65 kDa (RelA) DNA-binding subunits and activates transcription. The RelA protein contains a *C*-terminal transactivation domain that is absent from the NFKB1 protein and is primarily responsible for the transactivation function in a heterodimer (Baeuerle and Henkel, 1994; Siebenlist *et al.*, 1994).

NF-κB directs transcription of a variety of genes, many of which are important in immunological and inflammatory processes, including chemoattractants, cytokines (among which the NF-κB-inducing cytokines themselves), cytokine receptors and cell adhesion molecules (Figure 2). Because the protein products of many NF-κB target genes will either directly or indirectly (through lymphocyte attraction) lead to NF-κB induction, a cascade of events is triggered. Normally this response is shut down by negative feedback loops of which NF-κB induction of IκB provides a major one (Baeuerle and Henkel, 1994; Siebenlist *et al.*, 1994).

Immunosuppression by steroids

Steroid hormones have long been known for their immunomodulatory effects with, as a hallmark, the potent immunosuppressive action of glucocorticoids. Glucocorticoids have a widespread use in the treatment of allergic reactions and the prevention of tissue rejection after transplantation (Barnes and Adcock, 1993). Also the sex steroids progesterone and testosterone have prominent immuno-suppressive effects, of which the ability of progesterone to suppress the rejection of the fetus by the maternal immune-system has long been recognized (Kelly, 1994). Non-pregnant females, however, have a stronger immune response compared to males. This has been related to immuno-suppression by androgens in males, while oestrogens tend to be less potent or even stimulatory (Morell, 1995). The effects of oestradiol on immuno-responsiveness are complex and differ between tissues, varying between stimulatory and inhibitory (Morell, 1995). Generally, however, there is an increase in responsiveness prior to ovulation, which is linked to rising oestradiol concentrations, while after ovulation this response decreases along with the rising progesterone concentrations. Because of the more restricted expression of sex steroid receptors their effects are more localized compared to those of glucocorticoids. Glucocorticoids and sex steroids are stronger repressors of the cellular than of the humoral immune response. In contrast to these steroid hormones, thyroid hormone and retinoids, after binding to their cognate nuclear receptors, are able to enhance immune responses (Grossman, 1991; Blomhoff and Smeland, 1994).

Hormonal repression of inflammatory responses

Closely related to the immunosuppressive effect of steroids is their anti-inflammatory action. Glucocorticoids are very effective suppressors of inflammation and are also used to treat inflammatory diseases such as asthma and rheumatoid arthritis (Cutolo *et al.*, 1995). The ubiquitous expression of

the glucocorticoid receptor throughout the body allows the use of glucocorticoids as standard anti-inflammatory drugs. The sex steroids, particularly progestins and androgens, share the anti-inflammatory potency of glucocorticoids, but again the more restricted expression of their receptors leads to more localized effects. Nevertheless, suppression by androgens of the severity of rheumatoid arthritis is documented (Robertson *et al.*, 1992). In addition, the anti-inflammatory action of sex steroids may play an essential role in reproductive organs.

Emerging evidence suggests a prominent role for cytokines as local regulators of endocrine-acting hormones including steroids (Robertson *et al.*, 1992). Cytokines are involved in regulation of proliferation, cell adhesion, lymphoid infiltration and angiogenesis, and are produced in a highly regulated fashion in all human organs. Particularly in those organs, such as the endometrium and ovary, which are subject to cyclic hormonally-regulated tissue remodelling, a role for cytokines can easily be envisaged. A complex interplay between endocrine hormones, cytokines and growth factors is known to regulate all stages of ovarian and endometrial development during the menstrual cycle and pregnancy (Robertson *et al.*, 1992). In these organs the most obvious examples of processes in which a crucial role of cytokines has been recognized are menstruation, parturition and ovulation, which bear many characteristics of acute inflammatory responses. In these processes the cytokines and lymphoid infiltrates induce a rapid cascade of events leading to the destruction of tissues which had been built up gradually under the influence of hormones. The evidence for the role of cytokines in the latter processes will be reviewed briefly with special attention to their role in antagonizing the response of steroid hormones.

Cytokine/steroid antagonism in the endometrium

During pregnancy rejection of the fetus is prevented by progestins, and anti-progestins including RU486 can induce labour at any time, particularly in combination with prostaglandin E_2 (Baulieu, 1989). Normally, human parturition is thought to be initiated by an endogenous progesterone antagonizing trigger of unknown origin (Kelly, 1994). A first hint that cytokines and inflammatory responses may be involved in antagonizing progesterone action and the onset of labour comes from the observed increased incidence of abortion following uterine infections that lead to induction of the pro-inflammatory cytokines TNFα and IL-1 (Radetsky, 1994).

Both parturition and menstruation have been compared with an inflammatory response, and many of the characteristic inflammatory cytokines have been detected during these processes, together with massive invasion by lymphoid cells (Kelly, 1994). Uterine infiltration of leukocytes can also be induced experimentally in pregnant sheep following removal of ovarian progesterone (Staples *et al.*, 1983). In humans, rising concentrations of the pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNFα can be measured during progression of the menstrual cycle (De *et al.*, 1992; Philippeaux and Piguet, 1993; Simon *et al.*, 1993; Kelly *et al.*, 1994). Along with these NF-κB target genes intercellular adhesion molecule (ICAM)-1 and NF-κB itself are subject to cyclic regulation (Shyamala and Guiot, 1992; Tawia *et al.*, 1993). At the end of the cycle, progesterone concentrations drop, which will allow the inflammatory response to commence. Experimentally, the bleeding and apoptosis characteristic of menstruation can be induced in mice by TNFα and interferon (IFN)-γ. Cytokines are abundantly expressed throughout pregnancy (Robertson *et al.*, 1994). Parturition can be seen as a delayed menstruation in which the continuously rising concentration of progesterone delays the onset of an inflammatory response. In line with this is the observation that in knockout mice lacking the progesterone receptor, a strong inflammation in the uterus occurs (Lydon *et al.*, 1995). The activity of the progesterone receptor may decline sharply through interaction with NF-κB formed during the inflammatory response (see below).

Prostaglandins have been suggested to play a central role in the initiation of menstruation and labour, and can be used to terminate pregnancy (Kelly, 1994). Cyclo-oxygenase-1 (COX-1) is a more or less constitutively active enzyme involved in prostaglandin production, while COX-2 is a form highly inducible by cytokines including TNFα and IL-1 (O'Banion *et al.*, 1992). Progesterone interferes with prostaglandin production through enhanced breakdown by stimulation prostaglandin dehydrogenase production. In addition, both progestins and glucocorticoids can repress transcription of the cytokine-inducible COX-2 gene, thereby further reducing prostaglandin concentrations (Ishihare *et al.*, 1995).

Cytokine/steroid antagonism in the ovary

Recent data show that the ovary is a site of pro-inflammatory cytokine production and lymphocyte infiltration, the abundance of which increases before ovulation (Brännström and Norman, 1993). At that time a range of pro-inflammatory cytokines is present, and their role in ovulation can be illustrated by the fact that both IL-1β (Brännström *et al.*, 1993) and TNFα (Brännström *et al.*, 1995) induce ovulation in perfused rat ovaries. Progesterone receptors clearly are expressed in granulosa cells (Stouffer and Duffy, 1995), raising the possibility that progestins are involved in suppressing the onset of an inflammatory response by cytokines. However, since ovulation occurs earlier in the menstrual cycle than menstruation it seems that the balance between inflammatory and anti-inflammatory responses is disturbed earlier in the ovary compared to the endometrium in favour of inflammation, which may be related to the relative local activity of the two players in this interaction, the ligand-activated progesterone receptor, and NF-κB.

Mutual transrepression by NF-κB and steroid receptors

Although negative regulation by glucocorticoids can be mediated through so-called negative glucocorticoid-response elements (nGREs) no such sequence is present in promoters of negatively regulated genes such as ICAM-1 and IL-8. Interestingly, we and others found that glucocorticoid repression of these genes is almost exclusively mediated through

NF-κB elements in their promoters (Mukaida *et al.*, 1994; Van de Stolpe *et al.*, 1994). Repression is mutual and cytokine-induced NF-κB can strongly repress transactivation by the glucocorticoid receptor (GR). Since NF-κB has a major role in inflammatory and many immunological responses, transrepression of GR on transactivation by NF-κB may provide an important molecular basis for the anti-inflammatory properties of glucocorticoids.

In vitro a direct protein-protein interaction between RelA and GR has been demonstrated, which is consistent with a bi-directional repression of transcriptional activation (Ray and Prefontaine, 1994; Caldenhoven *et al.*, 1995; Scheinman *et al.*, 1995). Mutational analysis has shown that both the DNA binding domain (DBD) and ligand-binding domain (LBD) of GR are essential for this interaction. Hybrid receptor constructs in which the GR-DBD had been exchanged for the DBD originating from the retinoic acid receptor (RAR) were not able to repress transactivation by RelA (Caldenhoven *et al.*, 1995). On the other hand, a point mutation in GR-DBD causing a different DNA-binding specificity of GR was still able to carry out repression. These results demonstrate that, although the DBD of GR plays a crucial role in mediating repression, specific GRE binding is not essential (Caldenhoven *et al.*, 1995).

We also found that the progesterone receptor (PR) is able to repress RelA-mediated transcriptional activation, and can bind to this protein *in vitro* (Kalkhoven *et al.*, 1996). Again repression was mutual and induction of NF-κB in cells by TNFI or hydrogen peroxide leads to repression of induction of the progesterone target gene fatty acid synthetase. In addition, in this study evidence was presented suggesting that the PR/NF-κB interaction does not prevent DNA binding (Kalkhoven *et al.*, 1996), which resembles the GR/AP1 interaction which also occurs on DNA (König *et al.*, 1992). Thus, probably a DNA binding complex is formed in which transactivation of both partners is prevented (Figure 3).

Recently, evidence for an additional mechanism of NF-κB suppression by glucocorticoids has been presented, which relies on the induction of IκB by glucocorticoids (Auphan *et al.*, 1995; Scheinman *et al.*, 1995). The induction of two different NF-κB repressive mechanisms by glucocorticoids may explain their strong immunosuppressive effects, and stresses the relevance of NF-κB suppression in this process. Prevention of IκB induction by blocking protein synthesis, however, did not diminish repression of ICAM-1 by glucocorticoids (Van de Stolpe *et al.*, 1994), suggesting that this process is mediated through transrepression only.

The androgen and oestrogen receptors are also able to transrepress NF-κB (Ray *et al.*, 1994; Stein and Yang, 1995; S.Wissink *et al.*, unpublished data), and it was demonstrated that oestrogens are able to repress the IL-6 promoter activation through this interaction. Repression of this promoter has been suggested to be important in the protective effect of oestrogens against osteoporosis (Ray *et al.*, 1994; Stein and Yang, 1995). Repression of NF-κB activity by oestrogen receptors has not been found in all cell lines tested (Caldenhoven *et al.*, 1995; Stein and Yang, 1995), suggesting that cell type-specific factors are involved in modulating the oestrogen receptor/

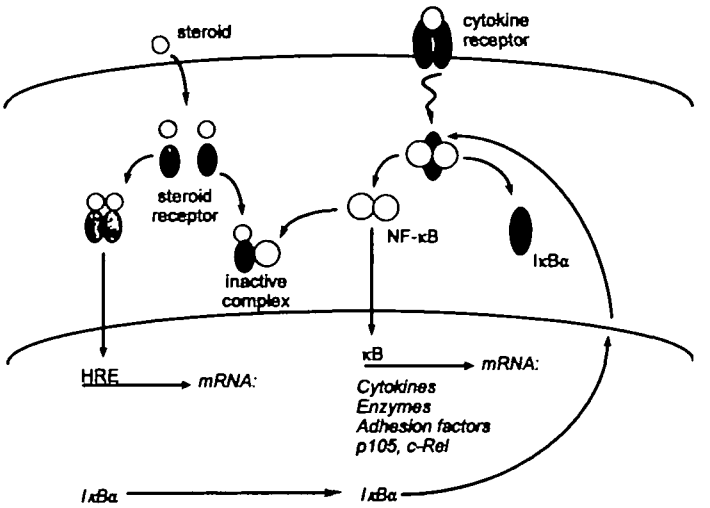

Figure 3. Steroids, such as glucocorticoids, but also oestrogens and progestins are able to repress nuclear factor-kappa-B (NF-κB) activity, which gives an explanation of their potent anti-inflammatory properties. Two mechanisms have been found to be operative in this respect. In the first place, ligated steroid receptors are able to prevent NF-κB-mediated transcriptional activity through formation of a transcriptionally inactive complex with NF-κB. It is unclear if this interaction occurs between monomers, as depicted, or between dimers. In the second place, it has been shown that glucocorticoids induce enhanced production of the NF-κB inhibitor IκB.

RelA interaction. Such cell type-specific differences are also prominent in the case of AP1/steroid hormone receptors (Shemshedini *et al.*, 1991). Interestingly, however, the mutual transrepression of RelA and the PR or GR has consistently been found in a wide variety of cell lines (Mukaida *et al.*, 1994; Ray and Prefontaine, 1994; Van de Stolpe *et al.*, 1994; Caldenhoven *et al.*, 1995; Scheinman *et al.*, 1995; Kalkhoven *et al.*, 1996), suggesting that cell type-specific proteins are of little importance in this interaction. However, it has been found that AP1 over-expression can prevent RelA transrepression by GR (Scheinman *et al.*, 1995), suggesting that *in vivo* situations may also be found in which the GR transrepression is attenuated.

Interestingly, no suppressive effect of related nuclear receptors for retinoids or thyroid hormone has been found, but rather stimulation of NF-κB activity (Caldenhoven *et al.*, 1995; S.Wissink *et al.*, unpublished data), which is consistent with the mainly immuno-stimulatory activity of their ligands (Grossman, 1991; Blomhoff and Smeland, 1994).

Although the NF-κB transrepression by steroid hormone receptors seems of particular importance in mediating anti-inflammatory and immuno-suppressive effects of steroids, it should be kept in mind that transrepression of other transcription factors, including AP1 and NF-IL6, may also be instrumental in some of these effects (Jonat *et al.*, 1990; Ray *et al.*, 1994; Stein and Yang, 1995). However, the biological relevance of the NF-κB/steroid receptor interactions in the immunomodulatory and anti-inflammatory action of steroids seems the most important. This can be inferred from the importance of NF-κB in such inflammatory responses which is highlighted by the fact that many of the major NF-κB target genes,

including ICAM-1, IL-6, IL-8, granulocyte–macrophage colony-stimulating factor (GM-CSF), TNFα, and COX-2 (Collart *et al.*, 1990; Van de Stolpe *et al.*, 1993; Kato and Schleimer, 1994; Kelly *et al.*, 1994; Mukaida *et al.*, 1994; Ray *et al.*, 1994; Van de Stolpe *et al.*, 1994; Ishihare *et al.*, 1995) are subject to steroid suppression *in vitro* and *in vivo*. The regulation of many other NF-κB target genes by steroids has not yet been studied, but in the light of the above it would not be surprising to find that many of them are subject to direct negative regulation by steroid hormones.

The negative regulation of NF-κB and its target cytokines by sex steroids cannot explain the rising concentrations of these molecules along with rising sex steroid concentrations during progression of the menstrual cycle (De *et al.*, 1992; Philippeaux and Piguet, 1993; Simon *et al.*, 1993; Kelly *et al.*, 1994). Possibly, the transactivation function of steroid hormone receptors is responsible for enhanced cytokine expression. Interestingly, expression of the IFNγ gene is enhanced by oestrogens through the transactivation function of its receptor (Fox *et al.*, 1991), while M-CSF production is enhanced by progestins in endometrial stromal cells (Hatayama *et al.*, 1994). Particularly, expression of IFNγ could play a role in initial lymphocyte attraction and could indirectly lead to expression of more cytokines.

Development and use of anti-inflammatory steroids

Normally, receptor agonists induce both transrepression and transactivation. Interestingly, however, nuclear receptor ligands have been described which can preferentially induce either transrepression or transactivation of the transcription factor AP1 (so-called dissociating ligands; Heck *et al.*, 1994). Some classical antihormones that repress transactivation have been found to be effective agonists with respect to transrepression (Heck *et al.*, 1994; Caldenhoven *et al.*, 1995; Scheinman *et al.*, 1995; Kalkhoven *et al.*, 1996). For example RU486, which is an established antagonist of both glucocorticoid and progesterone receptor transactivation, is a potent agonist with respect to transrepression of AP1 activity (Heck *et al.*, 1994). Interestingly, biological systems have sometimes been found to react in a similar way to hormones and antihormones. For instance, breast tumours can be efficiently treated with both progestins and antiprogestins, suggesting that both types of receptor ligands share a common property (Horwitz, 1992). This property is possibly due to transrepression of transcription factors like AP1 and NF-κB, of which enhanced expression has been implicated in tumorigenesis (Kalkhoven *et al.*, 1996). The common property of progesterone receptor agonists and antagonists to repress NF-κB (Kalkhoven *et al.*, 1996) may also be important in their activity as contraceptives.

In the case of retinoids a systematic search for dissociating ligands has resulted in the identification of a number of retinoids that can selectively address these functions in the AP1/RAR interaction (Fanjul *et al.*, 1994; Chen *et al.*, 1995). However, GR- or PR-mediated transrepression of NF-κB was only partly induced by antihormones (Caldenhoven *et al.*, 1995; Scheinman *et al.*, 1995; Kalkhoven *et al.*, 1996). Therefore, other ligands have to be identified which are more efficient in dissociating the transrepression of NF-κB from the transactivation function of nuclear receptors. These may be used as important tools to study the relevance of NF-κB/steroid receptor interactions *in vivo*. They may also provide us with tools to be used to modulate reproductive functions and to treat inflammatory diseases, avoiding side-effects related to either transactivation or transrepression.

Conclusions

NF-κB is a major transcription factor in immunological and inflammatory responses. The recent finding that not only glucocorticoids but also progestins can repress the activity of NF-κB gives a simple and plausible explanation for the strong immuno-suppressive and anti-inflammatory activity of these hormones. Particularly the female reproductive organs are subject to strong hormonally directed changes which are cyclically terminated by inflammation-like processes. The current data strongly suggest that progesterone is involved in suppressing these inflammatory processes through suppression of NF-κB activity. However, as soon as a certain threshold of cytokines has been reached NF-κB is activated and an inflammatory response is initiated. This response may further be enhanced since NF-κB can repress the activity of the progesterone receptor. Therefore, the balance between NF-κB and the progesterone receptor may be important in regulating processes including menstruation, ovulation and parturition.

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