Regulation of Steroidogenesis in Reproductive, Adrenal and Neural Tissues by Cytokines

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Abstract: Steroid hormones have a large number of functions in the organism, including the regulation of stress response, the electrolytic balance, and reproduction. The synthesis of these hormones is mediated by a series of enzymes, which produce glucocorticoids, mineralocorticoids, progestins, androgens and estrogens using cholesterol as the metabolic main precursor. In this general way, steroid synthesis regulation depends on signals constituted by proteinic hormones (corticotrophin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) in the case of glucocorticoids, and (gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), and follicle stimulating hormone (FSH) in the case of sex hormones, which bind to their specific receptors. However, this is not the only regulatory mechanism of the steroidogenic pathway. It has been observed that the neuroendocrine axes also interact with the immune system. Thus, this bidirectional communication between these two systems has currently been accepted. Steroids can regulate some functions of the immune system, and, viceversa, molecules secreted by the immune system modulate steroid synthesis. This is the case of cytokines. These molecules participate in the immune response and are secreted by different immunological cells. Their functions include activation and proliferation of the immune cells as well as mediation of the inflammatory process. Gonadal and adrenal steroidogenesis regulation by direct or bidirectional communication between the immunologic and neuroendocrine systems has been well established. Cytokines play a key role in this interaction, and their production is influenced by the direct action of hormones and neurohormones on immune system cells. The action of some of the main cytokines produced by the immunologic system on the regulation of gonadal (ovarian and testicular), adrenal and neural steroidogenesis is summarized in this review.

Keywords: Steroids synthesis, cytokines, neuroimmunoendocrine.

INTRODUCTION

In recent years, interest has grown regarding the interactions of the systems in an organism that regulate its homeostasis. These interactions have currently been solidly documented, and they include the nervous, endocrine and immunological systems. Interactions are bidirectional and several substances are known to be produced by the three systems and to act at target cell level through specific receptors, which are frequently common to different cell-types [1].

Among these soluble substances, the nervous system secretes the classical neurotransmitters (such as histamine, dopamine, serotonin and enkephalins), which act at immunological cell level either stimulating or inhibiting specific functions. The immune system produces cytokines, which are soluble products generated by an array of immune cells, but mainly by lymphocytes and macrophages as a response to external stimuli. Cytokines can in turn, modify nervous or endocrine system functions as a result of their autocrine, paracrine or endocrine action on diverse target tissues [1, 2]. The neuroendocrine system secretes two types of hormones, which have diverse effects on the immunologic system: peptide and steroid hormones [2]. These two hormone types have been amply studied. They are capable of regulating differential cytokine secretion, of promoting antibody synthesis, the change of immunoglobulin isotype, inhibiting the major histocompatibility complex (MHC) antigen expression, T-cell receptor expression, T lymphocyte maturation, cell adhesion molecules and, consequently, cell adhesion for cell communication, among other functions [2-4].

The studies on neuroimmunoendocrine communication have led to the very interesting concept that the immunological system may be an internal sensor organ. The immune system may sense stimuli that are not recognized by the central and peripheral nervous system. These have been labeled non-cognitive stimuli and include phenomena (such as presence of bacteria, tumors, viruses and antigens in general) which could otherwise go unnoticed within the organism. Recognition of these non-cognitive stimuli by immune cells is then converted into information in the form of peptide hormones, steroid hormones, cytokines, neurotransmitters, which stimulate the neuroendocrine system and lead to physiological changes [2, 3]. On the other hand, the recognition of cognitive stimuli by the central and peripheral nervous system leads to neurohormonal information, which is recognized by immunocyte receptors, leading to immunological changes [3, 4]. Thus, the sensor

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function of the immune system mimics the neuroendocrine system in the sense that a given stimulus produces a particular hormone combination that leads to physiological responses and changes [4]. If this is the case, then the pathologies that are associated with a particular infectious agent, antigen or tumor could in part be related with the set of hormones produced by the immune system.

In this way, if the internal homeostasis of the organism is being altered, the nervous system is notified by chemical communication via cytokines, which stimulate the immunological system to respond. Once the malfunction has been controlled, the neuroendocrine system responds producing hormones and neurohormones that regulate the immune response, and prevent it from becoming aggressive towards the organism. Thus, the immunologic system not only regulates the magnitude of the response to an antigenic stimulus by means of intrinsic signals from its own cells – cytokine secretion and the idiotype-anti-idiotype network– but receives extrinsic signals from the neuroendocrine system that regulate the magnitude of the response [5, 6]. Analogous to this, the substances of the immunological system such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, IL-6 and interferons (IFN, especially -α -γ), and thymic hormones, regulate the secretion of diverse neuroendocrine gland products, such as hypothalamic releasing factors (corticotrophin releasing hormone (CRH), thyrotropin releasing hormone (TRH), gonadotropin releasing hormone (GnRH)), hypophysial peptide hormones (prolactin, melatonin, adrenocorticotropic hormone (ACTH), gonadotropins), adrenal and gonadal steroids (glucocorticoids, estradiol, progesterone and testosterone), among others [1-5]. The cells of the neuroendocrine system are also able to produce cytokines (the pituitary produces IL-6, IL-1, migration inhibitory factor (MIF) and IFN) [6], and immune cells have similar capacities to endocrine cells (macrophages can metabolize testosterone to dihydro testosterone (DHT)). On the other hand, sex hormones play a regulatory role in the humoral and cellular immunologic responses, which can in turn affect hormone levels. The suggestion that gonadal steroids play an important role in the immune response is based on several observations: differences between males and females in immune response level, changes in the immune response during pregnancy, after gonadectomy or sex hormone replacement, and the presence of receptors for certain gonadal hormones in lymphoid organs and circulating immune cells [3-5].

Cytokines are soluble polypeptides released by immune system cells, mainly by macrophages and activated T cells, which may be liberated during the inflammatory process or as a response to antigenic stimuli, acting as local response coordinators and endocrinologically affecting a large number of tissues [2]. Cytokines have traditionally been divided into various specific factors produced by a lymphocyte type or by other immune cells and based on their interleukin action. They are numbered from 1 to 29, which correspond to the order in which they were discovered.

Although there is a large number in cytokines that are able to interact with different systems, only a few have been associated to the regulation of the steroidogenic pathway. Such molecules and their immune function are listed below.

IL-1 production increases during the acute phase of infection in response to antigens, bacterial toxins, or tissue damage. This proinflammatory cytokine mediates many responses during disease, including fever, sleep, neutrophilic leukocytosis, acute phase protein synthesis as well as endocrine changes, such as increased release of insulin, glucagon, growth hormone (GH), prolactin, ACTH, thyroid stimulating hormone (TSH), and vasopressin [7, 8].

IL-2 is produced by activated T lymphocytes which acts as an autocrine factor on the growth and differentiation of T cells, and stimulates macrophages. *In vitro*, it increases the tumoricidal activity of blood peripheral mononuclear cells and induces the formation of natural killer cells (NK) and lymphocyte eliminating cells (LAK). When administered to rats for long periods, it increases ACTH levels.

IL-3 is a lymphokine secreted by T helper cells (Th1) and participates in cellular immunity. It promotes the generation of neutrophils, monocytes and macrophages at a microbial infection site, and also stimulates the mechanisms of respiratory discharge and phagocytosis in these cells. It is also known to act directly on T lymphocytes, causing an enzymatic activity exclusive of steroid cells: an increase in the activity of 20α-hydroxysteroid dehydrogenase (20α-HSD).

IL-6 acts as a differentiation factor in B-cells and it is produced by T-cells. In addition, it is also known to be produced by a large variety of cells such as fibroblasts, endothelial cells, monocytes, hypophysial, and hypothalamic cells. Its levels increase during the acute phase response; it is a growth factor of hematopoietic cells and increases T cell proliferation (Th2). It acts synergistically with IL-1 and can indirectly mediate some of its actions. Receptors to IL-6 are known to be present in neuroendocrine tissue; the binding of the molecule to its receptors modifies the response of these cells.

In recent years, it has been established that IFNs are not only important host defense molecules against viral infections and resistance to tumors, but also regulate some normal physiological processes. In fact, the 3 known types of IFN share many biological actions. IFNs have been detected in human amniotic fluid and murine placenta in absence of viral or any other type of infection. These molecules have been suggested to participate in the regulation of fetal development, or in the immunoregulation of the mother's acceptance of the product.

TNF-α is produced by macrophages in response to a tumorigenic transformation within the organism. In many of its effects, TNF-α resembles IL-1, however, they are not homologous, since TNF-α has its own receptor and does not directly activate lymphocytes. The injection of this cytokine causes fever, hypotension, response to acute phase proteins, lipase inhibition and release of stress hormones.

CYTOKINE REGULATION OF GONADAL STEROIDOGENESIS

Testicular Steroidogenesis

At testicular level, IL-1 is expressed constitutively in adult rat testis and acts on germ, Sertoli and Leydig cells to regulate germ cell proliferation and steroidogenesis [9]. Specifically, IL-1α up-regulates the steroidogenic acute

regulator (StAR) protein expression and phosphorylation [10], this protein (particularly its phosphorylated form) regulates the translocation of cholesterol from the outer to the inner mitochondrial membrane where steroidogenesis rate limiting step occurs [11]. Both isoforms IL-1α and IL-1β stimulate basal progesterone [12] as well as testosterone [12, 13], DHT [13] and androstenedione [12] secretion by Leydig cells *in vitro*. In contrast, when stimulated by gonadotropins, particularly by luteinizing hormone (LH) or human Chorionic Gonadotropin (hCG), IL-1α inhibits testosterone secretion [14-19] in Leydig cells. The mechanism by which IL-1 inhibits LH/hCG stimulated steroidogenesis in Leydig cells is dependent on cyclic AMP (cAMP) levels [15, 20]. IL-1 inhibits the steroid production by direct effect on the enzyme, P450 cholesterol side chain cleavage (P450scc), which stimulates the transformation of cholesterol into pregnenolone, the step of cholesterol entry into steroidogenesis as well as at the level of 17α-hydroxylase/C17-20 lyase (P450c17) that converts progestins into androgens. This effect of IL-1 is due to the decrease in the mRNA that transcribes this enzyme and its protein levels [15, 20, 21] as well as in P450c17 [12, 15, 20]. This regulation seems to be located downstream of cAMP, since Leydig cells cultured in the presence of cAMP analogs still show a dose-dependent decrease in testosterone production [15]. Studies at different ages suggest a similar behavior, administration of IL-1 to immature Leydig cells stimulates testosterone while adult Leydig cells do not show response [22]. In immature hemicastrated rats, local injection of IL-1β induced a significant rise in testosterone secretion [23]. IL-1 effect on Leydig cells seems to be dependent on the presence of IL-1 receptor (IL-1R). In male mice lacking a functional IL-1R, IL-1 has not the steroidogenic effect [24]. Other studies showed that testicular innervation and serotoninergic receptors in the testis as well as IL-1β are important features for testosterone production [23].

IL-2 is a potent inhibitor both of hCG-stimulated steroidogenesis and of cAMP formation in Leydig cells. Since it blocks forskoline and 8-bromo cAMP-induced testosterone production, as well as pregnelonone, progesterone, 17α-hydroxypregnelonone and 17α-hydroxyprogesterone, and has no effect on dehydroepian-drosterone and androstendione production, the enzyme that specifically inhibits is P450c17 [25]. The addition of cholesterol does not revert the effect, meaning that P450scc may also be affected. This suggests that the effect of IL-2 is specific on the steroidogenic enzyme system, and it is not due to a toxic effect of the molecule on the cells [26]. The mentioned effect on the steroidogenic enzyme system could be achieved by hindering the steric enzyme-substrate recognition, since IL-2 can modify the binding site in a non-competitive irreversible way.

In macrophages, IL-2 can stimulate the conversion of testosterone to dihydrotestosterone, by increasing the enzymatic activity of 5α-reductase [27].

Regarding steroidogenesis, in healthy male subjects, it has been observed that subcutaneous administration of IL-6 increases its circulating levels, and consequently produce a suppression in testosterone levels without affecting LH [28].

INFs are known to have a large variety of effects on the endocrine system. IFNs have direct action on gonadal steroidogenesis. It has been established that treatment with reduces serum progesterone and estradiol concentrations, with no apparent change in LH/hCG and Follicle Stimulating Hormone (FSH) levels. IFN-α inhibits the FSH-stimulated conversion of testosterone to estradiol by cultured Sertoli cells.

Pre-treatment of Leydig cells with α or IFN-γ diminishes steroidogenesis and, if the treatment is combined, the effect is summatory. In these systems it has been shown that gonadal inhibition is caused by the capacity of IFN-γ to inhibit the accumulation of basal and LH/hCG stimulated mRNA molecules that code for StAR protein and enzymes P450scc and P450c17 [29] and testosterone production in Leydig cells [30-32].

It has also been shown that IFN-γ can stimulate steroidogenesis in testes, increasing the activity of both, 17β-hydroxysteroid dehydrogenase (17β-HSD) and 5α-reductase [29-32]. TNF-α has been demonstrated to inhibit steroidogenesis in Leydig cells. *In vitro*, it does not affect the expression of StAR protein on the synthesis of progesterone [33], while intratesticular administration induces a reduction on StAR protein expression and testosterone byosinthesis [34]. TNF is known to suppress gonadotropin (LH/hCG) and cAMP (8-Br-cAMP) induced steroid secretion by Leydig cells [35]. Downstream it suppresses the cAMP Responsive Element (CRE) activity but this is not mediated by the NFκB pathway and the levels of CRE Binding Protein (CREB) or P-CREB are not affected [35]. At the transcriptional level, TNF-α induces the recruitment of the Nuclear Factor κB (NFκB) to the promoter of P450c17 causing the repression of this gene [36]. In a similar behavior to IL-1 TNF-α inhibits cAMP stimulated testosterone production, as well as mRNA and protein of P450scc, P450c17 [14,20], 3β-HSD [20], basal expression of 3β-HSD [20] but not P450scc basal expresión [14]. TNF-α also reduces in a dose dependent mannerLH/hCG induced StAR levels of mRNA and protein [37]. It also promotes the conversion of testosterone to dihydrotestosterone . Therefore, the enzimatic targets of this moelcules are inhibitions of P450scc and P450c17 in the ovary adn the increase of 5α-reductase activity in the testicle.

Transforming growth factor (TGF)β-1 plays an important role in the hypothalamic-pituitary-gonadal axis [38]. This multifunctional cytokine is implicated in gonad and secondary sex organ development, steroidogenesis, and spermatogenesis. The absence of this cytokine decreases serum and intratesticular testosterone and serum androstenedione. However this deficiency is secondary to disrupted pituitary gonadotropin secretion since serum LH and FSH were reduced. Interestingly when exogenous LH/hCG is administrated normal testosterone levels are reestablished.

Ovarian Steroidogenesis

IL-1 has shown similar effects both at testicular and ovarian level. IL-1β stimulates basal progesterone secretion by human granulosa and theca cells [39] and small and large follicles [40] *in vitro* and also IL-1β induce and increase levels of progesterone and PGF2-α in equine granulosa and cumulus cells which demonstrated that IL-1 is involved in equine oocyte *in vitro* maturation [41]. When stimulated by gonadotropins, IL-1β inhibits both LH/hCG and FSH

stimulated progesterone [39, 42-47] and estradiol [39, 47, 48] secretion by follicular theca and granulosa cells, affecting cAMP production [43], suggesting an follicle-stage dependent regulatory role of IL-1 on ovarian follicles [40]. In the same fashion, progesterone and estradiol are stimulated by IL-1 in small follicles while in antral gonadotropin-dependent follicles their secretion is inhibited [40]. Similarly to the Leydig cells, granulosa cells cultured in the presence of cAMP analogs show an IL-1 induced decrease in estrogen production suggesting an interleukin steroidogenic downstream regulation [48]. Thus, IL-1β is involved in follicular development in the ovary and it is an important regulator for steroidogenesis and gamete production.

IL-2 has no effect on LH/hCG induced steroid secretion, while it increases FSH induced progesterone synthesis and has no effect on estradiol [49]. In ovary cells in culture, it provokes an increase in progesterone production by stimulating the 3β-HSD activity [50].

In FSH-stimulated granulosa cells, increasing amounts of IL-6 produce a significant suppression of progesterone biosynthesis. However, basal progesterone production is not influenced by this cytokine [51] but it does not seem to affect LH-induced estradiol or progesterone levels by the ovary although it increases basal progesterone synthesis [52]. IL-6 has a stimulatory effect on estradiol production since it can stimulate aromatization of testosterone to estradiol, increasing the enzymatic activity of P-450 aromatase (P-450 arom) in cultured mammary cancer cells. Moreover, in cultured granulosa cells, the addition of IL-6 and testosterone induces in few hours high levels of estradiol, which are not produced with the sole direct addition of testosterone in the same period. Thus, the possible enzymatic targets of IL-6 are the following enzymes: stimulating P450scc and 3β-HSD stimulated by FSH, increasing the capacity of P-450 arom. The mechanisms of action remain to be determined. In the ovary IFN-α has no effect on progesterone or estradiol production by luteal cells [53].

IFNs also interfere with the enzyme fixation of the substrate (cholesterol) without modifying its structure. In ovaries disaggregated in bioassay, IFN-α inhibits both the basal and the hCG-stimulated production of testosterone and estradiol in a dose-dependent and temporary way. The effect of IFN-α inhibition is caused by interference with substrate (cholesterol) fixation by the enzyme 17β-HSD, and with the accumulation of P-450 arom 1 and 2 mRNA.

In granulosa and theca cells, IFN-γ reduces LH/hCG stimulated progesterone secretion [53-55] and FSH stimulated estradiol secretion as well as gonadotropin dependent cAMP levels [50, 54]. It also reduces progesterone secretion in response to cAMP analogue [54]. At follicular cells, addition of IFN-γ inhibits the formation of the LH/hCG receptor [50].

TNF-α has been found to induce complex dose-dependent alterations in progesterone and androsterone synthesis, but not in estrogen synthesis. It is interesting to note that TNF-α inhibits gonadotropin-dependent differentiation in isolated murine granulosa cells increasing its proliferation in a dose dependent manner. This effect is mediated by its type 1 receptor (TNFR1): in the TNFR1 knockout TNF administration did not induced granulosa cell proliferation. At steroidogenic level, TNF inhibits basal progesterone production in granulosa and theca cells and stimulates estradiol from small follicles but not cAMP levels [56]. It also reduces intracellular levels of StAR protein in granulosa cells [57] and gonadotropin stimulated progesterone and estradiol secretion [58, 59]. It lowers the LH/hCG-induced androstendione production by thecal cells from large follicles [60-62] and basal and FSH stimulated progesterone production in preovulatory follicles [63]. In the theca cells, it enhances the conversion of cholesterol to pregnenolone [63], but it does not show any effect on cAMP [58]. The data suggest a cAMP downstream down-regulation by inhibiting PKA [61] The TNF receptor does not seem to be implicated in the regulation of these effects since in the TNFR1 knockout mice, administration of TNF does not affect LH/hCG-stimulated accumulation of progesterone, estradiol or cAMP [58] In follicular fluid the estradiol and progesterone levels are lower when TNF is detectable [64].

CYTOKINE REGULATION OF ADRENAL STEROIDOGENESIS

During inflammation, cytokines like TNF-α, INF-α, -INF-γ, IL-1, IL-2, and IL-6, they influence the cross-talk between the immune system and the hypothalamic-pituitary-adrenocortical (HPA) axis [65-71] and then affect the corticosteroids produced in the adrenal gland. Interestingly, the adrenal and the immune cells contained within in this gland (the reticularis and the fasciculate zone specifically) are the two principal sources of cytokines. However, this is not the only way in which HPA axis is affected; the secretion of CRH and ACTH by the immune system is also regulated. The rate limiting step in the synthesis of corticosteroids is the transfer of cholesterol molecules from the cytoplasm to the inner mitochondrial membrane where the P450 scc and StAR proteins have a key role to convert the cholesterol into prenenolone. Cytokines in some cases favor or inhibit the expression or the activity of the proteins implicated in the corticosteroids synthesis pathway.

Macrophages in the zona reticularis of the adrenal cortex secrete different cytokines such as IL-1, IL-6 and TNF-α besides of its phagocytic activity. Also IL-1 and IL-6 mRNA are produced by adrenocortical cells predominantly in the zona reticularis as well [69, 70]. In the case of IL-1, both IL-1α and IL-1β stimulate the secretion of corticosteroids, and inhibit angiotensin II-induced secretion [72]. IL-2 stimulates the secretion of corticosteroids in rats. IL-3 and IL-6 stimulate the cortisol secretion, however, the IL-3 action is through the lipooxygenase pathway, whereas the action of IL-6 is by the cyclo-oxygenase pathway in human adrenocortical cells [73]. The corticosteroid production by IL-6 show an important effect on the release of adrenal androgens via ACTH [74]. TNF-α and its receptors are expressed in the hypothalamus and the anterior pituitary gland. This inflammatory cytokine, mediate communication between the immune system and the HPA axis [75-82] regulating this axis at several levels. For example, TNF-α increases CRH release from the hypothalamus that increased the ACTH production in the pituitary gland which leads a stimulation of adrenal steroidogenesis [76, 78, 79, 83]. Also it has been suggested that TNF-α is an important intraadrenal regulator of steroidogenesis [84-87].

Macrophages and adrenocortical cells expressing and producing TNF-α are located in the fasciculate and reticular zones and the density of these cells increases toward the medulla [71]. However, the effects of TNF-α are variable depending on the species or the developmental stage of the adrenal cells. For example, *in vivo* experiments in rats, TNF-α stimulated corticosterone production [76, 78, 79] but inhibit the ACTH-stimulated corticosterone and aldosterone release *in vitro* [88]. In recent findings using the adrenocortical cell line NCI-H295R, it was showed that the treatment with TNF-α increased the basal production of cortisol, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) and aldosterone. That was also corroborated by the increase of the expression of genes encoding for StAR, 3β-HSD-2, and P450c17 [89]. However, when TNF-α is added to cultured human fetal adrenal cells, suppression of the ACTH-induced steroid production and the expression of steroidogenic enzyme genes is observed [84, 88, 90, 91].

Interleukins also play an important role during the stress response in adrenal cells. The IL-6, a pleiotropic cytokine, is a potent activator of the human HPA axis and stimulates this axis *in vitro* and in animals at different levels [92-98]. IL-6 regulates adrenal synthesis of mineralocorticoids, glucocorticoids, and androgens *in vitro*. Also it is well known that the adrenal gland is the main source the IL-6 [99] and it is not surprising that IL-6 promotes the production of IL-6 and IL-6R mRNAs in normal human adrenals and adrenal adenomas [100, 101]. On adrenal cells in primary culture stimulated with IL-6, those cells induced an increase secretion of aldosterone, cortisol and DHEA. In humans, chronic administration of IL-6 leads to a substantial elevation of cortisol, whereas ACTH levels in plasma decreased [102, 103]. During acute stress it has been showed that IL-18 mRNA production is promoted by glucocorticoid-producing adrenocortical cells, which suggested that IL-18 plays an immunostimulatory role during this stress [104, 105]. Other cytokine that may play a role in the regulation of adrenal steroidogenesis is the LIF (leukemia inhibitory factor) because LIF and its receptor (LIF-R) are expressed in the normal human adrenal cortex and in the NCI-H295 cell line and moreover because LIF enhances the release of both basal and ACTH-induced cortisol and aldosterone [106].

On the other hand, there is evidence that the functions of growth factors are beyond to their mitogenic activity. In this way, TGFβ1 is now well recognized as a multifunctional regulator of cellular processes including cell differentiation, cell migration, immunosuppression and steroidogenesis [107]. TGFβ1 exerts a strong inhibitory effect on adrenocortical cell steroidogenesis. In this regard, TGFβ1 inhibits the basal and ACTH-induced cortisol production by decreasing the expression of StAR and steroid P450c17

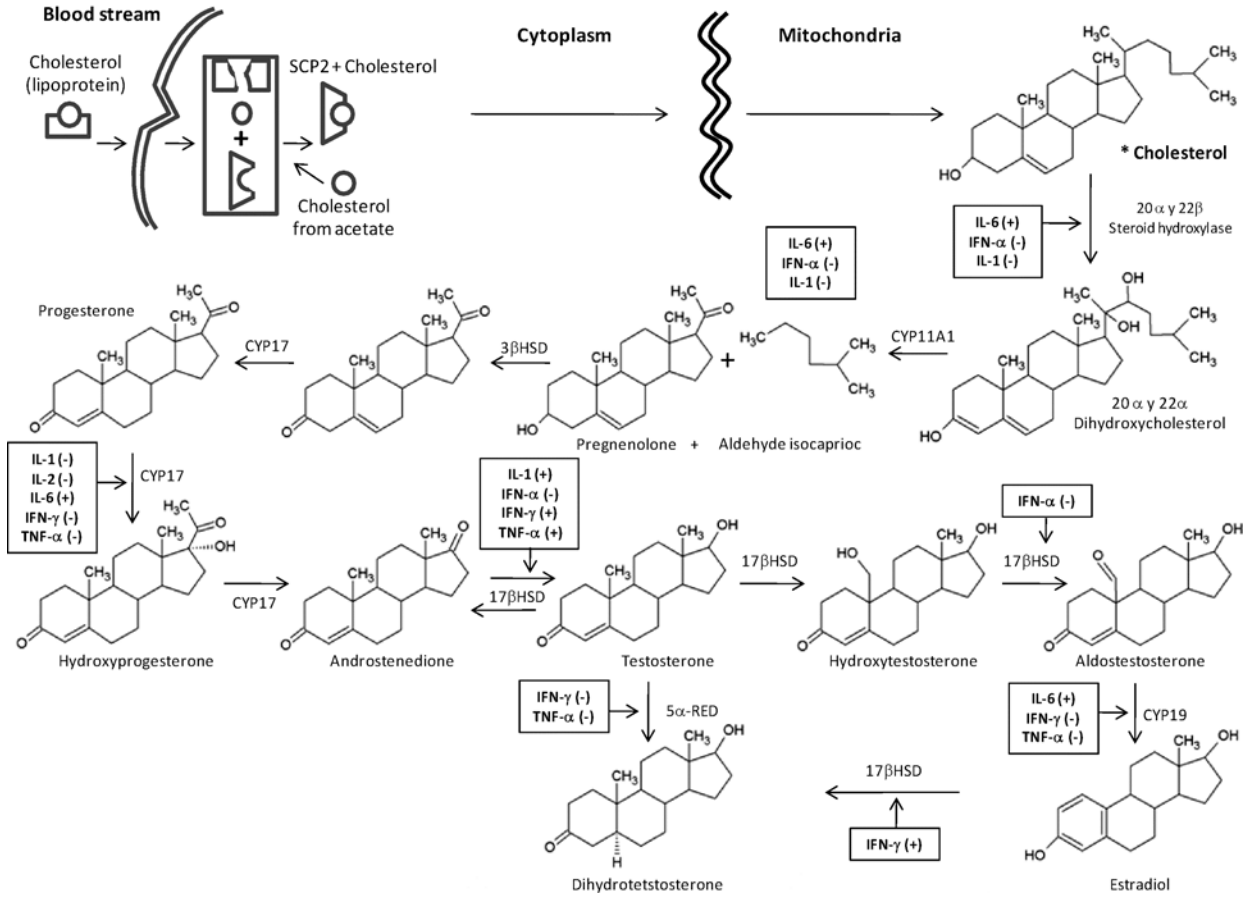

Fig. (1). Role of cytokines in the regulation of steroidogenesis. Different interleukins and other cytokines inhibit the expression and function of steroidogenic enzymes and steroid hormone secretion. The chart shows whether an inhibitory action (-) or a stimulatory effect (+) is exerted by cytokines on those steroidogenic enzymes in which an effect has been reported.

enzymes in bovine adrenocortical fasciculata cells [108-110]. In fasciculata cells of adult human cells, TGFβ1 shows inhibition of DHEAS synthesis in the absence of any effect on cortisol synthesis [111]. Evenmore, in the human NCI-H295R adrenocortical cancer cell line, after treatment with TGFβ1, the cortisol and aldosterone biosynthetic pathways are reduced. In this case, the enzymes steroid 11β-hydroxylase (P450c11) coded by the gene (*CYP11B1*) and the aldosterone synthase (P450 aldo) coded by (*CYP11B2*) gene, which catalyze the last steps of the biosynthesis pathways of cortisol and aldosterone are profoundly inhibited. It is important to mention that in humans and rodents, specific expression of *CYP11B2* in the glomerulosa zone and *CYP11B1* in the fasciculata zone are responsible for the functional zonation of the adrenal cortex [107].

CYTOKINE REGULATION OF NEUROSTEROID SYNTHESIS

Crucial roles of cytokines have been demonstrated recently at the nervous system level, including neurotransmission, neuroregeneration, neurodegeneration, behaviors such as sickness behavior and sleep. It could be hypothesized that in a similar fashion as has been described at gonadal and adrenal levels, cytokines could be involved in the regulation of neurosteroid synthesis in the brain. Nevertheless, no data are available to date that demonstrate that cytokines have a regulatory role on neurosteroidogenesis

CONCLUDING REMARKS

The aforementioned data suggest that different cytokines are important regulators of steroidogenesis in gonads (testes and ovaries) as well as gamete production and the adrenal cortex. Most of the reviewed molecules have been shown to be produced by steroidogenic cells. Paracrine and autocrine roles have also been demonstrated for them. Here, we paid particular attention on steroidogenesis but other neuroendocrine functions have been shown to be altered by cytokines such as ovulation and spermatogenesis. Most of the experimental data show basal stimulation and gonadotropin-stimulated down-regulation of sex steroids synthesis. Local or systemic up regulation of these cytokines, as it happens when an infection occurs, could modify steroidogenic functions, and it explains the lack or the loss of reproductive capacities when the immune system is highly activated.

In summary, regulation of the steroid production depends not only on the complex normal endocrine regulation by the neuroendocrine axis, but on certain cell-types: lymphocytes (B and T), monocytes, macrophages, and on several representatives of the leukocyte strain, which are normal residents of the steroidogenic tissue, and regulate steroidogenesis by secretion of interleukins (Fig. **1**).

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