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M Oettel & AK Mukhopadhyay

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Review

Progesterone: the forgotten hormone in men?

M. Oettel and A. K. Mukhopadhyay*

Jena; *Institute for Hormone and Fertility Research and AgeLab Pharma GmbH, Hamburg, Germany

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ABSTRACT

'Classical' genomic progesterone receptors appear relatively late in phylogenesis, i.e. it is only in birds and mammals that they are detectable. In the different species, they mediate manifold effects regarding the differentiation of target organ functions, mainly in the reproductive system. Surprisingly, we know little about the physiology, endocrinology, and pharmacology of progesterone and progestins in male gender or men respectively, despite the fact that, as to progesterone secretion and serum progesterone levels, there are no great quantitative differences between men and women (at least outside the luteal phase). In a prospective cohort study of 1026 men with and without cardiovascular disease, we were not able to demonstrate any age-dependent change in serum progesterone concentrations. Progesterone influences spermiogenesis, sperm capacitation/acrosome reaction and testosterone biosynthesis in the Leydig cells. Other progesterone effects in men include those on the central nervous system (CNS)

(mainly mediated by 5 α -reduced progesterone metabolites as so-called neurosteroids), including blocking of gonadotropin secretion, sleep improvement, and effects on tumors in the CNS (meningioma, fibroma), as well as effects on the immune system, cardiovascular system, kidney function, adipose tissue, behavior, and respiratory system. A progestin may stimulate weight gain and appetite in men as well as in women. The detection of progesterone receptor isoforms would have a highly diagnostic value in prostate pathology (benign prostatic hypertrophy and prostate cancer). The modulation of progesterone effects on typical male targets is connected with a great pharmacodynamic variability. The reason for this is that, in men, some important effects of progesterone are mediated non-genomically through different molecular biological modes of action. Therefore, the precise therapeutic manipulation of progesterone actions in the male requires completely new endocrine-pharmacological approaches.

INTRODUCTION

From a phylogenetic point of view, the action of the steroid hormone progesterone (4-pregnen-3,20-dione;progesterone) via its nuclear receptor (PR) is a relatively young acquisition in the animal kingdom¹. We find PRs only in birds and mammals in which the progesterone plays an important regulatory role in the oviduct, includ-

ing oviposition, in the uterus including pregnancy, and in the mammary gland including lactation^{2,3}.

Not surprisingly, the main interest of progesterone endocrinology remains focused on the female physiology. Therefore, the history of medical indications for progesterone preparations

Correspondence: Professor M. Oettel, Beethovenstraße 30, D-07743 Jena, Germany

or progestins is a story of gynecological developments, like replacement therapy in oophorectomized women (1934, by Kaufmann), the treatment of oligo- and hypomenorrhea (1937, by von Kehler), the treatment of anovulation (1938, by Clauberg), the treatment of menorrhagia (1953, by Kaufmann), female contraception with norethynodrel (1956, by Pincus), the treatment of endometriosis (1969, by Kistner), and, since the 1970s, postmenopausal hormone replacement therapy with estrogens. Only in the field of hormonal male contraception, has a relatively broader experience been gained, with progestins being clinically administered to men. Antiandrogenically acting progestins are also indicated in some forms of sexual deviation and prostate cancer^{4,5}.

Defined by most encyclopedias and textbooks as a female hormone, the importance of progesterone in the male endocrine system has remained in the shadow. Testicular and adrenal progesterone has been regarded as a physiologically unimportant by-product of steroidogenesis that is not converted to testosterone. But, in many conditions, including aging, the serum progesterone/androgen ratio increases. Only during the past few years has the role of progesterone as a modulator of the male endocrine system become more and more evident⁶.

The aim of this review is to summarize and critically discuss the rather scattered, often controversial results about progesterone and progesterone action in men.

BIOSYNTHESIS/METABOLISM

Pregnenolone is the precursor of progesterone (catalyzed by 3β -hydroxysteroid dehydrogenase) and the main serum metabolites of progesterone are 17α -OH-P (catalyzed by 17 -hydroxylase), desoxycorticosterone (catalyzed by 21 -hydroxylase), and to the main urinary metabolite pregnanediol. Considering that 17α -OH-P gives 11 -deoxycortisol (catalyzed by 21 -hydroxylase), which in turn gives the essential cortisol (catalyzed by 11β -hydroxylase) as well as androstenedione and dehydroepiandrosterone (intermediate steroids in the biosynthesis of androgens and estrogens), the fundamental importance of progesterone for the maintenance of steroid hormone homeostasis independently of

the known, directly sex-specific actions of progesterone is shown⁷. The importance of progesterone as a precursor of the so-called neurosteroids is discussed below. The surprising finding of Nadjafi-Triebsch and colleagues⁸, namely that the serum progesterone levels rise in men after the oral administration of dehydroepiandrosterone (DHEA) (unusual upstream metabolism), does not fit in with the general scheme of biosynthesis and the metabolism of progesterone. On the other hand, only two men were investigated.

3β -Hydroxysteroid dehydrogenase (3β -HSD) has been purified from steroidogenic organs (adrenal cortex, testes, ovaries) of different species, including humans, and has been characterized⁹⁻¹¹. This shows that, in men, progesterone is synthesized not only in the Leydig cells of testicles, but also in the adrenals, and is secreted from there into the circulatory system.

The reference range for progesterone levels in adult men is 0.13 – 0.97 ng/ml¹². Zumoff and colleagues¹³ reported a mean serum progesterone level of 0.18 ± 0.03 ng/ml for men ($n = 7$) and of 0.21 ± 0.05 ng/ml for young women in the follicular phase ($n = 8$). In contrast to this, Muneyirci-Delale and colleagues¹⁴ measured 0.78 ± 0.28 ng/ml for healthy men and 0.26 ± 0.18 ng/ml for postmenopausal women (Coat-a-Count RIA kit).

Data in the literature are contradictory regarding age-dependent changes in blood serum concentrations of progesterone. Collecting 252 saliva profiles from healthy children and adolescents (125 boys and 127 girls), Gröschl and colleagues¹⁵ found that salivary progesterone was highest ($p < 0.001$) in healthy newborns. In children 1–12 months of age, progesterone was decreased to one-third of the values found in newborns. The circadian rhythm with the highest level in the morning and the lowest in the evening was fully developed in children older than 2 years. Surprisingly, Genazzani and colleagues¹⁶ found an age-related decrease in the progesterone levels in 46 men aged 19 to > 60 years. In contrast to these findings, Bélanger and colleagues¹⁷ found no age-related changes in progesterone concentrations in 2423 men (40–80 years old). This discrepancy caused us to reassess the relationship between serum proges-

terone levels and men's ages. The data we show here originate from the cooperation of Jenapharm GmbH & Co. KG/Jena (Germany) with the LURIC study (Ludwigshafen Risk and Cardiovascular Healthy Study), a joint project of the Herzzentrum (Heart Center) in Ludwigshafen and the Universitätskliniken (Teaching Hospitals) in Freiburg and Ulm, Germany¹⁸. We analyzed serum samples from 1015 men aged 20–90 years and serum samples from 330 postmenopausal women aged 50–90 years by a radioimmunoassay for progesterone. We found 1.21 ± 0.41 SD nmol/l (0.38 ± 0.13 ng/ml) for men and 1.24 ± 1.18 SD nmol/l (0.38 ± 0.37 ng/ml) for women, i.e. there were no differences between men and women. As shown in Figure 1, there were no age-dependent changes in serum progesterone levels in both men and postmenopausal women.

No details are given here of the main metabolite of progesterone, 17α -hydroxyprogesterone, and its importance for the diagnosis of congenital adrenal hyperplasia (21-hydroxylase deficiency). In male patients with cytochrome P450C17 (steroid 17α -hydroxylase/17,20-lyase; EC 1.14.99.9) deficiency, the progesterone levels are clearly elevated¹⁹.

PROGESTERONE-MEDIATED SIGNALING

As with all steroid hormones, the classical paradigm of the progesterone action is that intracellular receptors bind to progesterone to modulate the gene expression within the nuclei of target cells. Two progesterone receptors (PRs), termed A and B, are derived from alternate promoters of only one gene located on chromosome 11 q22–23. PR-B contains 933 amino acids while PR-A is a truncated version lacking the initial 164 amino acids (the B-upstream segment). *In vitro* evidence reveals that the PR-A isoform is necessary to oppose the estrogen-induced proliferation as well as the PR-B-dependent proliferation. In contrast to this, PR-A predominance is an early event in mammary carcinogenesis and is associated with poor clinical features^{20,21}. In other words, the cellular ratio of PR-A : PR-B is likely to be an important determinant of the tissue-specific progesterone action^{22–24}. On the other hand, studies with female knock-out mice showed that PR-A is both necessary and sufficient to elicit the progesterone-dependent reproductive responses necessary for female fertility, while the PR-B isoform is required to elicit normal

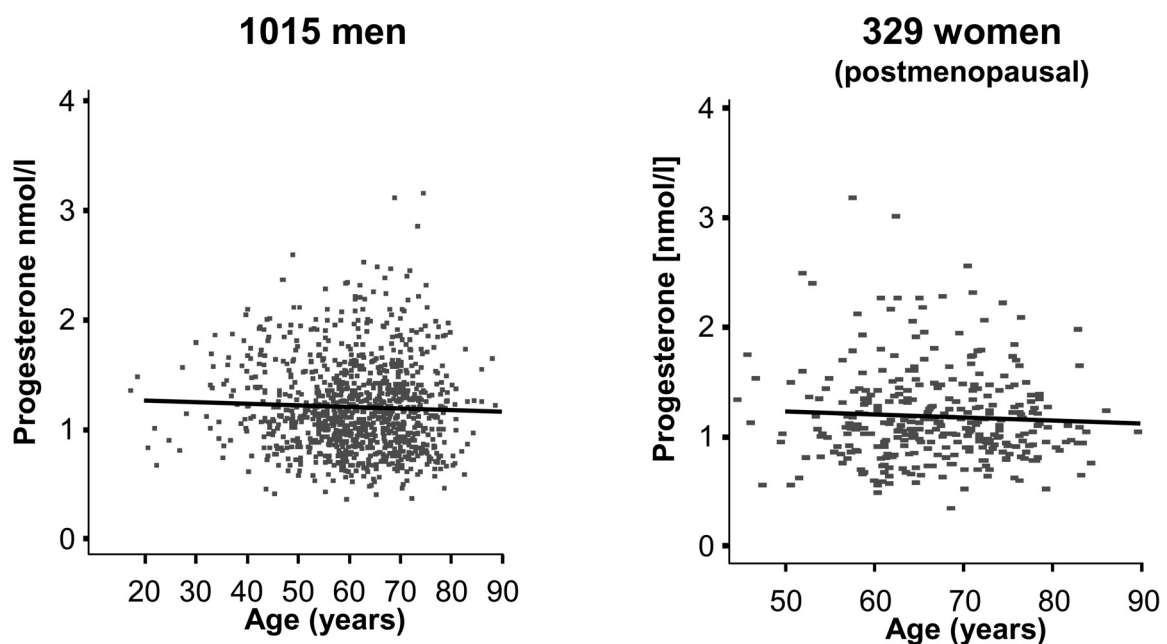


Figure 1 Serum progesterone levels and age (Luric-Jenapharm-study). There are no age-related changes. The mean serum concentrations are 1.21 ± 0.41 SD nmol/l for men and 1.24 ± 1.18 SD nmol/l for postmenopausal women

proliferative and differentiative responses of the mammary gland to progesterone²⁵.

In addition to the classical, genomic action via two nuclear PR isoforms, rapid progesterone effects incompatible with the model of nuclear receptors have been identified. The proposed mechanisms of non-genomic progesterone action are:

- (1) Progesterone acts directly via subsets of the classical intracellular receptor bound to the membrane;
- (2) Progesterone acts directly via one (or more) non-classical membrane-bound receptor;
- (3) Progesterone may interact with a partner ligand via non-PR;
- (4) Progesterone, at high concentrations, may get into the plasma membrane and affect membrane fluidity.

Examples of the membrane-dependent progesterone action in male gender are:

- (1) Sperm capacitation/acrosome reaction (e.g. rapid increase in $[Ca^{2+}]_i$);
- (2) LH receptor expression and subsequent influence on testosterone biosynthesis in Leydig cells;
- (3) Increased classical PR concentrations in prostate (BPH as well as prostate cancer);
- (4) Interactions with the GABA_A receptor complex in the CNS, including sedative and anesthetic actions;
- (5) Progesterone-interactions in adipose tissue and kidney.

This list suggests that many progesterone effects in the male are rapid and therefore non-genomically mediated.

Progesterone-binding membrane proteins have been identified in liver²⁶, sperm^{27,28}, and lens epithelial cells²⁹. Zhu and colleagues³⁰ cloned, expressed, and characterized a membrane PR using fish oocytes. On the basis of the sequence of

the membranous messenger PR, the authors then identified a whole family of mPR proteins from a number of different species, including frog, human, and mouse, some of which bound progesterone^{30,31}.

A variety of other rapid progesterone effects have been demonstrated; however, they occur at non-physiologically high steroid concentrations, rendering their relevance questionable. For example, progesterone at micromolar concentrations induces a dose-dependent relaxation of rat saphenous artery segments (precontracted with norpinephrine). In a similar manner, progesterone dose-dependently decreases the contractile activity of murine jejunum (for review, see reference 28).

Finally, several polymorphisms have been identified in nuclear PRs; they include S344T, G393G, +331G/A, Exon 4 V660L, Exon 5 H770H (C/T), and the PROGINS allele (Al insertion³²). These polymorphisms will be useful markers in the genetic study of disorders affecting female endocrine systems, such as so-called progesterone resistance and breast, uterine, and ovarian cancers. However, nothing is known at present about the diagnostic and therapeutic relevance of functional polymorphisms of PRs in the male.

PROGESTERONE AND THE IMMUNE SYSTEM

Data from both human and animal studies clearly demonstrate that both 17 β -estradiol and progesterone influence most components of innate as well as adaptive immunity. Evidence of these effects is found in the differences in immune responses between females and males. For example, women show more vigorous T and B cell responses and have higher circulating CD4 T cell numbers than men. The incidence of most autoimmune diseases, including multiple sclerosis, is higher in women; and, in many women, the hormone changes associated with pregnancy lessen the severity of the disease³³.

Various *in vivo* and *in vitro* studies have demonstrated that progesterone inhibits the functions of human macrophages and T lymphocytes within physiological concentrations, and thus it has been suggested that progesterone acts mainly as an immunosuppressant during preg-

nancy. However, various immune cells have been shown to lack the classical PR and, hence, the mechanism of anti-inflammatory effects of progesterone still remains more or less unclear³⁴. In this context, studying the so-called FK506-binding proteins could be an interesting approach to answer this question. The ability to bind immunosuppressive drugs such as cyclosporine and FK506 defines the immunophilin protein family, and the FK506-binding proteins form the FKBP subfamily of immunophilins. The large FK506-binding protein FKBP51 is a component of the PR complex and is transcriptionally regulated by the 'pure' progestin R5020 and attenuates progestin responsiveness in hormone-conditioned T-47D cells^{35,36}.

Studies have shown that glucocorticoid receptors can bind progesterone with a high affinity. *In vitro* progesterone and cyproterone acetate have, in some models, antiglucocorticoid effects^{37,38}. But, in contrast to this, it is interesting to note that Alolio and colleagues³⁹ found that high-dose progesterone infusion in healthy men affects neither plasma ACTH levels, nor serum or saliva cortisol. Therefore, under these specific clinical-pharmacological conditions, an antiglucocorticoid action of progesterone can be neglected.

In 132 human thymomas, immunoreactivity for PR-B was dominant (49%) compared with that for PR-A (4%). A significant positive correlation was detected between immunoreactivity for estrogen receptor (ER) α and PR-B. Therefore, the PR-B status in human thymoma may also reflect estrogenic actions in this immune competent tissue. The ER α immunoreactivity was positively correlated with a better clinical outcome and negatively correlated with tumor size, clinical stage, WHO classification, and the Ki-67 labeling index⁴⁰.

PROGESTERONE ACTIONS ON SPERM

Most of the available data about the role of progesterone in sperm function have been obtained in humans (reviewed in references 41–43). The process of capacitation renders the sperm capable of interacting with the oocyte and of engaging acrosome reaction. Progesterone facilitates human sperm capacitation^{44–46}. Acrosome reaction is a process marked by the fusion of the

outer acrosomal membrane with the plasma membrane. The physiological inducer of acrosome reaction in many species is the zona pellucida (ZP) glycoprotein, ZP3. Also, progesterone secreted by cumulus cells and contained in the follicular fluid induces acrosome reaction in humans^{47,48}.

Although early data suggested direct effects of progesterone on sperm⁴⁹, it was not until 1989 that progesterone induction of intracellular free calcium ($[Ca^{2+}]_i$) was found to result in phosphatidylinositol-4,5-bisphosphate hydrolysis in human sperm⁵⁰. In 1990, Blackmore and co-workers⁵¹ demonstrated that high concentrations of progesterone and 17-OH-P rapidly increased $[Ca^{2+}]_i$ in both capacitated and non-capacitated human spermatids, actions which were shown to be blocked by a Ca^{2+} -channel antagonist. Since then, more than 100 studies have investigated, in detail, the action of progesterone on $[Ca^{2+}]_i$ in sperm, in addition to the role of voltage-dependent calcium channels VDCC and sigmoidal dose sensitivity^{6,52,53}. Besides the increasing intracellular calcium concentrations, progesterone has led to a stimulation of activity of phospholipases and tyrosine phosphorylation of sperm proteins (reviewed in reference 41).

Non-genomic progesterone effects have been better demonstrated at the sperm plasma membrane using bovine serum albumin-conjugated progesterone^{48,54}. These progesterone-binding sites in sperm were further characterized and shown to share homology with the steroid-binding site of the genomic progesterone receptor; however, they lacked the long 120-kDa protein. After all, two surface receptors (of 54 and 57 kDa) with different affinity to progesterone (one in the nanomolar and the other in the micromolar range) have been identified in humans. The two proteins were detected after membrane preparation with antibodies directed to the hormone-binding region D of the genomic PR, but are not seen with antibodies to either the DNA-binding domain or the amino-terminal domains of the 'classical' progesterone receptor⁵⁵. The availability of the membranous progesterone receptor on the sperm surface increases during the epididymal transit and after capacitation⁵⁶. Using the hamster egg penetration test for the demonstration of stimulatory effects on the human sperm/oocyte fusion,

Francavilla and colleagues⁵⁷ found that the metabolite of progesterone, 17 α -OH-progesterone, is nearly as active as progesterone itself. The addition of the synthetic progestin levonorgestrel *in vitro* to capacitated spermatozoa from fertile men is associated with a dose-dependently increased rate of acrosome reaction⁵⁸. Both progesterone and the synthetic progestin norethisterone (NET) increased acrosome reaction in porcine spermatozoa, while the 5 α -reduced metabolite of NET, 5 α -NET, not only did not induce this reaction, but was able to block the effect of progesterone⁵⁹. Therefore, 5 α -NET has to be categorized as a 'non-classical' progesterone antagonist in this respect. Other data have demonstrated that these membrane actions of progesterone in sperm are neither mimicked nor blocked using 'classical' progesterone antagonists, such as RU486 (mifepristone)⁴⁶.

Earlier clinical studies showed that sperm obtained from oligospermic semen had reduced responses to progesterone stimulation, suggesting that this membrane effect of progesterone can be crucial for sperm development and fertilizing capacity^{60,61}. Other studies went even further, demonstrating that the absence of progesterone actions on sperm can be the sole reason for some cases of male infertility⁶².

USE OF PROGESTINS IN MALE CONTRACEPTION

Since follicle stimulating hormone (FSH) (through the Sertoli cell), luteinizing hormone (LH) (through the Leydig cell), and testosterone are required for normal spermatogenesis, the two gonadotropins need to be suppressed as strongly as possible for effective male hormonal contraception. Therefore, the exogenous testosterone administration is combined with gonadotropin releasing hormone (GnRH) antagonists or, preferably, with progestins. The gonadotropin suppression by progestins in the human male is mediated by genomic progesterone receptors, whereas the androgenicity of some progestins seems to contribute only minimally to gonadotropin inhibition⁶³. Since excellent reviews on hormonal male contraception have been published recently; this indication for progestins in fertile men will not be treated in greater detail here⁶⁴⁻⁶⁹.

PROGESTERONE AND LEYDIG CELL FUNCTIONS

Generally, the steroidogenic capacity in aging Leydig cells is markedly reduced. This has been explained by an age-related reduction in the expression of a number of genes relevant to testosterone biosynthesis and genes involved on stress/free radical scavenging⁷⁰⁻⁷². Moreover, expression of relaxin-like factor, which is present only in Leydig cells in testis, decreases in parallel with a reduction in the rate of testosterone production in aging testis⁷³. In addition to a quantitative reduction in testosterone biosynthesis, there is a deflection of the direction of testicular steroidogenesis. An example is the increased secretion of progesterone by the aging rat Leydig cell due to lesion at the cytochrome P450 17-hydroxylase/C₁₇₋₂₀ step^{74,75}. Classical nuclear PR is absent in Leydig cells (Mukhopadhyay AK, unpublished data). In murine Leydig tumor cells (mLTC-1 cells), El-Hefnawy and Huhtaniemi⁷⁶ could not demonstrate a classical PR and concluded that progesterone actions in these cells were mediated by a non-classical receptor. The authors found that binding of [³H]progesterone to the mLTC-1-cells revealed a high (K_d , ~9.3 nmol/l) and a low testosterone affinity (K_d , ~284 nmol/l) component, and the binding displayed with specificity (progesterone > dehydroepiandrosterone > 17-OH-P). The binding was apparently different from that of the classical nuclear PR⁷⁶. Also in MA-10 mouse Leydig tumor cells, using reverse transcription-polymerase chain analysis and immunoblotting experiments, the absence of the classical form of PR has been clearly demonstrated, although progesterone was found to have a direct stimulatory effect⁷⁷ on the steroidogenic acute regulatory protein (StAR) and on VEGF production⁷⁸ in these cells. From a variety of data, it appears plausible that progesterone acts on Leydig cells via a non-classical type of receptor, whose specific mode of action remains obscure as yet. The putative progesterone receptor in the Leydig cell is possibly located on the cell membrane, indicating a non-genomic or non-classical mode of progesterone action in this target cell⁷⁹ as well.

In aging men, despite a significant elevation of mean serum LH concentrations⁸⁰, the mean serum testosterone concentrations go down,

indicating an increased LH insensitivity of Leydig cells or a reduction of the number of Leydig cells. Interestingly enough, incubation of Leydig cells with progesterone inhibits the expression of the promoter for the LH receptor gene⁷⁵. In a detailed study, Pirke and co-workers⁸¹ reported that testosterone and its precursors decreased in the testicular tissue of old men. In contrast, progesterone and 17 α -hydroxyprogesterone increased in relation to testosterone in the testicular tissue and in the spermatic vein of old men. Therefore, it is conceivable that a local increase in testicular progesterone concentration may have a detrimental effect on Leydig cell function⁷⁵. A reduced expression of LH receptor may make the Leydig cells in aging testis refractory to LH action. Therefore, it would be logical to consider increasing testosterone secretion in older men with antiprogestins, which may ameliorate the action of increased progesterone in aging testes. This caused us to investigate the effects of progestins and antiprogestins on the testosterone secretion of isolated rat Leydig cells. It is well established that steroidogenesis in Leydig cells is regulated by LH/human chorionic gonadotropin (hCG) via the second-messenger cAMP signal transduction pathway⁸². Therefore, we additionally used the intracellular cAMP levels as a marker of steroidogenesis. Initially, we observed a higher rate of progesterone production by isolated Leydig cells from aged Wistar rats, compared to young ones, with and without stimulation by 8 Br-cAMP or hCG (Figure 2). This was compatible with the observations of Pirke and co-workers⁸¹ in aging human testis (see above). When cells were preincubated with the progestin antagonist mifepristone (RU 486), we found a dose-related increase in testosterone production (Table 1). After that, we investigated several other antiprogestins as well as progestins in this *in vitro* system. All steroids had in common was that they showed 'classical', genomic agonistic or antagonistic activities. They had all been screened previously in the same pharmacological model, the so-called McPhail assay (transformation of the estrogen-primed rabbit endometrium). The findings regarding the influence on the steroid biosynthesis of Leydig cells were very heterogeneous, indicating that conventional screening and selection for 'classical' antiprogestins are not sufficient for specific manipulation of testosterone

biosynthesis in Leydig cells. Sometimes, U-shaped dose-response curves were seen. All things considered, 'classical' screened progestins or antiprogestins have an insufficient influence on Leydig cell function. For the non-classical PR, there is probably a need for a new class of agonists or antagonists different from those which are known to act on the classical PR.

PROGESTERONE AND THE PROSTATE

It has been suggested that prostate cancer cells can survive in an androgen-deprived milieu by using estrogens for their own growth⁸³. Since the PR is a widely accepted marker for a functional estrogen receptor pathway, the evidence of elevated PR concentrations in metastatic and androgen-insensitive adenocarcinomas is considered as proof of a continuing steroid metabolism directed to estrogens. The observed increasing activity of 17 β -hydroxysteroid dehydrogenase type 7 (17HSD7) could lead to the increased intracellular production of 17 β -estradiol during disease progression⁸⁴. In primary tumors, the PR was detectable in 36% of primary Gleason grade 3; 33% of primary Gleason grade 4, and in 58% of primary Gleason grade 5 tumors. None of the 41 primary tumors investigated revealed a significant PR expression in more than 50% of tumor cells. Conversely, moderate to strong receptor expression was observed in 60% of metastatic lesions. Irrespective of grades and stages, the presence of the PR was invariably associated with high steady-state levels of ER α mRNA⁸⁵.

Kumar and colleagues⁸⁶ found that cytosolic PR was detectable in all cases of benign prostatic hypertrophy (BPH) as well as in all cases of prostatic carcinoma. In contrast to this, three other groups observed a higher expression of PR in BPH than in prostate cancer⁸⁷⁻⁸⁹. This raises the question whether progesterone or PR may play an independent role in the etiology of BPH or prostate cancer. Chlormadinone acetate (CMA) and its derivatives cyproterone acetate and TZP-4238 (Osaterone) are steroidal progestins with strong antiandrogenic properties, which are sometimes used in the medical management of human BPH or prostatic carcinoma. The atrophic effects on human BPH have been reported by

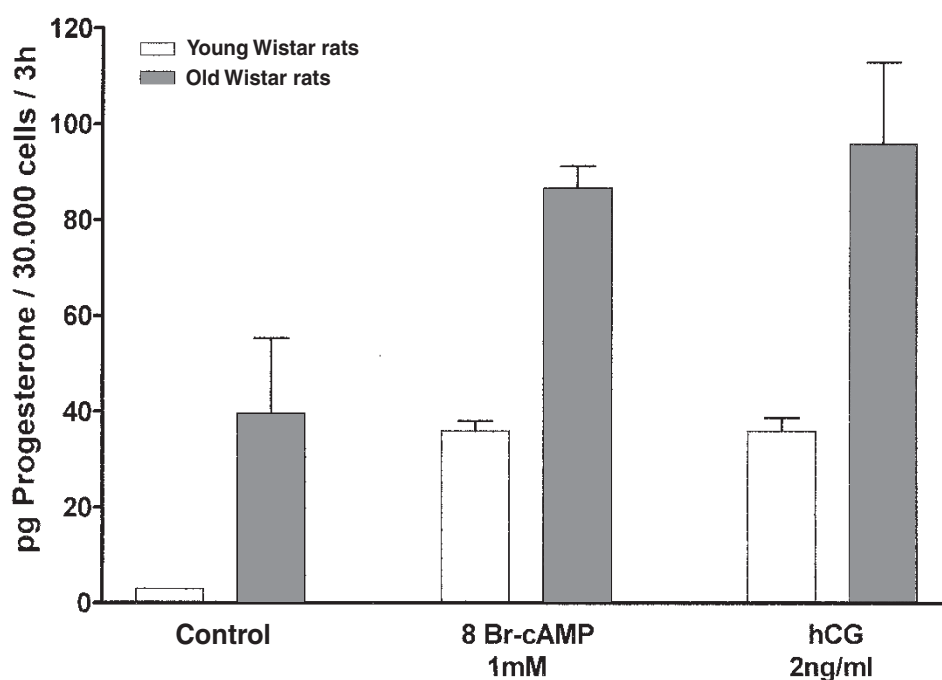


Figure 2 Progesterone secretion by isolated Leydig cells from young and old Wistar rats with or without stimulation by 8 Br-cAMP or hCG. Note the increased progesterone secretion from Leydig cells of aged rats

Table 1 The influence of different progestins administered postnatally on sexual behavior of male Wistar rats. Daily administration of 0.5 mg progestin from day 1 to day 14. Apomorphine (A) was given 10 min prior to mating period (0.1 mg/kg b.w. subcutaneously)

Treatment	Number of males	Number of mounts on one female (ovariectomized and estradiol- and progesterone-substituted) over a 30-min observation period
Vehicle/control	9	26.4
Vehicle'control + A	8	29.3
Progesterone	6	17.1*
Progesterone + A	6	20.0
Chlormadinone acetate	7	31.2
Chlormadinone acetate + A	7	38.8
Levonorgestrel	6	3.0*
Levonorgestrel + A	6	3.8†
Dienogest	4	6.9*
Dienogest + A	4	9.2*†

*Significantly different to the corresponding control group ($p < 0.05$); † significantly different to the respective group alone

several authors. In the prostate cell, these progestins are reported to inhibit the cellular uptake of testosterone and the binding of androgen to its receptor, and to decrease the level of androgen receptors (ARs). The anti-androgenic mechanism has been evaluated biochemically, for example, on the basis of the AR

content and the steroid 5α -reductase activity in the prostate. The reduction of volume of BPH may be due to shrinkage of both glandular and stromal compartments in the prostate tissue^{90–95}.

On the other hand, Tassinari and colleagues⁹⁶ observed rapid progression of advanced 'hormone-resistant' prostate cancer during palliative

treatment with progestins for cancer cachexia. This brings up the question of the sense of antiprogesterin treatment of prostate disorders. *In vitro*, pretreatment with the antiprogesterin mifepristone overcomes the resistance of prostate cancer cells to tumor necrosis factor α -related apoptosis-inducing ligand (TRAIL)⁹⁷. Mifepristone is a potent antiandrogen with minimal androgen agonistic activity. Compared with other known antiandrogens, mifepristone is a very strong inducer of the interaction between androgen receptor and its co-repressors NCoR and SMRT, and, therefore, could be used as a selective receptor modulator. In view of the unique molecular, pharmacological profile of this antiprogesterin, a phase II trial of mifepristone for treatment of progressive prostate cancer seems justified⁹⁸.

OTHER TUMORS

The interrelations between progesterone, PR, and several tumors within the CNS have been of interest for a long time. Progesterone may be involved in the regulation of the growth and development of neurogenic tumors via PR, especially in the inhibition of tumor proliferation via PR-A. Whereas PR-A and PR-B were expressed in equal amounts in meningiomas, in astrocytic tumors and Schwannomas, PR-B was the predominant isoform compared with PR-A. Additionally, there was a statistically significant inverse correlation between PR-A and the proliferation index in meningiomas and astrocytic tumors^{99,100}. ER expression is lost or reduced in non-malignant meningiomas, whereas loss of PR expression is an indicator of increased apoptosis and early recurrence¹⁰¹. A case report indicated that prolonged therapy with the progestin megestrol acetate could promote the growth of benign intracranial meningioma¹⁰². Therefore, it is not a surprise that Eid and colleagues in 2002⁹⁷ announced a phase III clinical study with the antiprogesterin mifepristone (RU486). Unfortunately, at present, nothing is published about the outcome of this study.

McLaughlin and Jacks¹⁰³ found that the majority (75%) of neurofibromas express PR, whereas only a minority (5%) express ER. Within neurofibromas, PR was expressed by non-neoplastic tumor-associated cells and not by

neoplastic Schwann cells. The authors hypothesize that progesterone may play an important role in neurofibroma growth and suggest that antiprogesterins may be useful in the treatment of this tumor.

17 β -Hydroxysteroid dehydrogenase type 2 (17HSD type 2) is a member of the short-chain dehydrogenases/reductases (SDR) enzyme family. Substrate specificity for the enzyme shows that it efficiently converts 17 β -estradiol, testosterone and 5 α -dihydrotestosterone into their corresponding inactive 17-ketoforms, thereby decreasing the influence of sex steroids on various target tissues and organs. On the other hand, it also converts 20 α -hydroxyprogesterone to active progesterone and is expressed in the surface and foveolar epithelium of normal gastric mucosa and in the duodenum. Gender did not have an effect on epithelial expression, but 17HSD type 2 mRNA expression decreased with increasing age. Chronic gastritis was associated with decreased expression. Regenerating epithelium close to ulcers and active gastritis showed up-regulation. Type I intestinal metaplasia also showed up-regulation, while type III metaplasia and gastric cancer showed decreased expression¹⁰⁴. On the other hand, no literature about PR expression in different compartments of the human gastrointestinal tract is available to date. Using bovine samples, PR mRNA was not abundant in the stomach and guts. Interestingly, under these conditions, PR seems not to be estrogen-dependent¹⁰⁵. Wu and colleagues¹⁰⁶ found, in 122 male patients with gastric adenocarcinoma, that the serum progesterone levels were significantly higher than in the male control group (0.26 ± 0.26 vs. 0.14 ± 0.11 ng/ml). Patients with presurgical serum progesterone levels > 0.26 ng/ml survived for significantly shorter periods than those with levels ≤ 0.26 ng/ml.

PROGESTERONE AND THE CENTRAL NERVOUS SYSTEM

In the 1980s, Baulieu and co-workers¹⁰⁷ demonstrated that some steroids, such as the precursor of progesterone, pregnenolone (PREG), DHEA and their sulfates, are present in higher concentrations in the brain than in blood and are synthesized *de novo* in the CNS (e.g. by astrocytes, oligodendrocytes, neurons)¹⁰⁸. Such steroids are now

universally referred to as neurosteroids. They act as modulators of several neurotransmitter receptors (γ -aminobutyric acid_A, *N*-methyl-D-aspartate, and δ 1 receptors), either as stimulators or inhibitors, and are involved in learning and memory performance. The biosynthesis of the neurosteroids in glial cells starts with cholesterol, which is first converted to PREG, progesterone, 5 α -pregnane-3,20-dione (5 α DH-PROG or 5 α -DHP) and then to 3 α -hydroxy-5 α -pregnane-20-one (3 α ,5 α -TH-PROG) or 3 α ,5 α -THP or allopregnanolone^{109,110}. 5 α -Reductase type II, one of the two 5 α -reductase isoforms, is thought to be a key enzyme in the generation of neuroactive steroids in the brain, particularly allopregnanolone. The gene expression of 5 α -reductase type II in the brain is transcriptionally regulated by progesterone¹¹¹. It could be that estrogens induce directly the *de novo* synthesis of progesterone in astrocytes¹¹². In adult rats, neuroactive derivatives of progesterone (i.e. dihydroprogesterone, allopregnanolone) exert direct effects on adult neurogenesis, strongly affecting both neuroblasts and astrocytes of the subependymal layer¹¹³.

Steroids can influence neuronal function through 'classical' binding to cognate intracellular receptors, which may act as transcription factors in the regulation of gene expression. Receptors for gonadal steroids have been identified in several brain areas: amygdala, hippocampus, cortex, basal forebrain, cerebellum, locus ceruleus, mid-brain rafe nuclei, glial cells, pituitary gland, hypothalamus, and central gray matter¹¹⁴. These intracellular steroid hormone receptors have often been considered to be activated solely by cognate hormone. However, during the past decade, numerous studies have shown that the receptors can be also activated by neurotransmitters and intracellular signaling systems, through a process that does not require hormone¹¹⁵.

Neuroactive steroids not only modify neuronal physiology, but also intervene in the control of glial cell function^{110,116}. In addition, certain neuroactive steroids modulate ligand-gated ion channels via non-genomic mechanisms. Especially distinct 3 α -reduced metabolites of progesterone are potent positive allosteric modulators of γ -aminobutyric acid type A (GABA_A) receptors. However, progesterone itself is also an allosteric agonist of the GABA_A receptor¹¹⁷ and, in addition to this, it may act as a functional

antagonist at the 5-hydroxytryptamine type 3 (5-HT₃) receptor, a ligand-gated ion channel, or certain glutamate receptors. There is evidence that neurosteroids interact allosterically with ligand-gated ion channels at the receptor membrane interface. On the other hand, 3 α -reduced neuroactive steroids, too, may regulate gene expression via the PR after intracellular oxidation into 5 α -pregnane steroids. Animal studies have shown that progesterone is converted rapidly into GABAergic neuroactive steroids *in vivo*. Progesterone reduces locomotor activity in a dose-dependent fashion in male Wistar rats. Moreover, progesterone and 3 α -reduced neuroactive steroids produce a benzodiazepine-like sleep EEG profile in rats and humans. In extremely low concentrations, sulfated neurosteroids, such as PREG sulfate, can regulate learning and memory. Femtomolar doses of PREG sulfate infused into the ventricles of mice could enhance memory¹¹⁸. In a presynaptic mode of action, PREG sulfate also increases the spontaneous glutamate release via the activation of a presynaptic G_{i/o}-coupled δ receptor and an elevation in intracellular Ca²⁺ levels¹¹⁹. In men receiving androgen ablation therapy for prostate cancer, treatment with the progestin medroxyprogesterone acetate (MPA) may be an effective and well-tolerated option for the alleviation of hot flashes¹²⁰.

Animal studies have shown neuroprotective effects for progesterone, which protects, for example, against necrotic damage and behavioral abnormalities caused by traumatic brain injury, e.g. by increasing the activity of antioxidative catalase or by modifying the microtubule-associated protein-2 content^{109,121–124}. In this context, progesterone and allopregnanolone inhibited cell death and cognitive deficits, including recovery of select behaviors after a contusion of the rat pre-frontal cortex^{125,126}. Progesterone-mediated neuroprotection has also been reported in peripheral nerve and spinal cord injury¹²⁷. Furthermore, inhibition of 3 α -hydroxysteroid oxidoreductase (3 α -HSOR) by the progestin medroxyprogesterone acetate resulted in enhanced synaptic and extrasynaptic GABA_A receptor-mediated inhibition of neurotransmission in the dentate gyrus but not in the CA1 region in the hippocampus, also indicating a regionally dependent manner of neurosteroid action¹²⁸.

Recent observations have indicated that both the central nervous and the peripheral nervous system are able to synthesize neurosteroids. After cryo-lesion of the male mouse sciatic nerve, blocking the local synthesis or action of progesterone impairs remyelination of the regenerating axons, whereas administration of progesterone to the lesion site promotes the formation of new myelin sheaths^{110,129}. Neuroactive steroids are able to reduce aging-associated morphological abnormalities of myelin and aging-associated myelin fiber loss in the sciatic nerve¹³⁰. Two important proteins are expressed by myelin of peripheral nerves, the glycoprotein (Po; controlled by progesterone via PR) and the peripheral myelin protein 22 (PMP-22; controlled by allopregnanolone via GABA_A receptor^{127,131–133}). Systemic progesterone administration resulted in a partial reversal of the age-associated decline in CNS remyelination following toxin-induced demyelination in male rats¹³⁴. On the other hand, the Charcot-Marie-Tooth disease (CMT-1A) – the most common inherited neuropathy – is associated with overexpression of PMP-22. In a transgenic model for CMT-1A with male rats, daily administration of progesterone elevated the steady-state levels of PMP-22 and myelin protein zero (Mpz) in the sciatic nerve, resulting in enhanced Schwann cell pathology and a more progressive clinical neuropathy. In contrast, administration of the antiprogestin mifepristone reduced overexpression of PMP-22 and improved the CMT phenotype¹³⁵.

Neuroactive steroids affect a broad spectrum of behavioral functions through their unique molecular properties and may represent a new treatment strategy for neuropsychiatric disorders. The background is that both the genomic and the non-genomic effects of progesterone and reduced progesterone metabolites in the brain may contribute to the pathophysiology of psychiatric disorders and the mechanisms of action of antidepressants.

In major depression, there is disequilibrium of 3 α -reduced neuroactive steroids, which can be corrected by treatment with antidepressant drugs. Neuroactive steroids may further be involved in the treatment of depression and anxiety with antidepressants in patients during ethanol withdrawal. A deregulation in concentrations of the neurosteroids allopregnanolone and 3 α ,5 α -tetra-

hydrodeoxycortico-sterone (3 α ,5 α -TH DOC) has been found in depressed patients. Indirect genomic (allopregnanolone) and non-genomic (allopregnanolone and DHEA) mechanisms are involved in the neurosteroidogenic pathophysiology of depression. The neurosteroid levels in depressive patients normalize following treatment with selective serotonin uptake inhibitors. Additionally, studies in patients with panic disorder suggest that neuroactive steroids may also play a role in modulating human anxiety^{136–138}.

Furthermore, blood concentrations of progesterone are significantly lower in catamenial epilepsy patients compared to non-epileptic controls. Over 60 years ago, Selye in 1942¹³⁹ demonstrated that progesterone protected animals against pentylenetetrazol-induced seizures. Ciriza and colleagues¹⁴⁰ showed that the protective effect of progesterone against kainic excitotoxicity *in vivo* in rats is also mediated by the 5 α -reduced metabolites of progesterone. Chronic slow spike-and-wave discharges (SSWDs) induced by the cholesterol synthesis inhibitor AY9944 in Long Evans rats were exacerbated by the administration of both progesterone and allopregnanolone. This effect was not blocked by mifepristone¹⁴¹.

Cyclic natural progesterone administration may lessen the seizure frequency in women with catamenial seizure exacerbation. Under clinical conditions, the progesterone-efficacy can be diminished by the concomitant administration of the 5 α -reductase inhibitor finasteride, indicating that 5 α -reduced metabolites rather than progesterone itself are responsible for improved seizure control. In contrast to convulsive epilepsy, progesterone seems to aggravate absence seizures^{142,143}. Interestingly, the antiprogestin mifepristone failed to affect the electroconvulsive threshold or the efficacy of antiepileptic drugs in maximal electroshock in mice¹⁴⁴.

Although progesterone is relatively well tolerated, certain hormonal side-effects, such as disturbances of the mineral balance due to the metabolism of progesterone to desoxycorticosterone or (perhaps) breast tenderness, may occur. The short half-life makes it inconvenient to administer to men. Neurosteroid analogs that do not mimic progesterone's genomic actions and have improved pharmacokinetic properties may overcome these drawbacks (for a review see references^{138,145,146}).

PROGESTERONE AND SLEEP

Intramuscular injection of 200 mg progesterone produces mild sedative-like effects in men and women¹⁴⁷. A single oral administration of 300 mg micronized progesterone at 21.30 induced a significant increase in the amount of non-rapid eye movement (non-REM) sleep in nine healthy male volunteers. The EEG spectral power during non-REM sleep showed a significant decrease in the slow wave frequency range (0.4–4.3 Hz), whereas the spectral power in the higher frequency range (> 15 Hz) tended to be elevated. Some of the observed changes in the sleeping pattern and sleep-EEG power spectra are similar to those induced by agonistic modulators of the GABA_A receptor complex and appear to be mediated in part by the conversion of progesterone into its GABA-active, 5 α -reduced metabolites¹⁴⁸. The oral administration of progesterone at the same dosage and at the same time (300 mg in the evening) produced no consistent effects on attention performance. Thus, dosages of progesterone that are sufficient to modulate sleep in men are not likely to exert sedative hangover effects¹⁴⁹. It seems that only progesterone including its 5 α -reduced metabolites is involved in positive sleep regulation, whereas, in contrast to this, the synthetic progestin megestrol acetate reduces REM sleep¹⁵⁰.

PROGESTERONE AND SEXUAL FUNCTION

Administering various progestins, including progesterone, to male rats postnatally (critical hypothalamic differentiation phase), we found that some progestins (progesterone, levonorgestrel and dienogest) were able to reduce mating activities. In the case of levonorgestrel and dienogest, the additional application of apomorphine 10 min prior to the 30-min mating periods caused only a marginal improvement of sexual activity, indicating a more peripheral effect of inhibition of mounting behavior by progesterone and selected progestins. These experimental-pharmacological results also substantiate what we already know from a variety of clinical observations that a progestin is not a progesterone. For example, the progestin with distinct antiandrogenic action, chlormadinone acetate, was

unexpectedly ineffective in our model, indicating that the influence of progestins on the maturation of the hypothalamus is independent of given antiandrogenic effects (Table 1).

The antiandrogenically acting progestins MPA and CPA are widely used in Europe and in the USA for the treatment of deviant behavior of male sex offenders. Given orally in a high dosage or intramuscularly as weekly injections of 200–600 mg, the two progestins have been reported to reduce a variety of paraphilias, including pedophilia, incest, sadism and rape^{4,5}. Interestingly, testosterone and sexual experience increase the levels of plasma membrane binding sites for progesterone in the male rat brain¹⁵¹. In this context, the down-regulation of sex hormone receptors, including PR, in the aging rat penile crura is associated with erectile dysfunction¹⁵².

PROGESTERONE AND THE RESPIRATORY SYSTEM

Hasselbach recognized progesterone's potential role in the regulation of ventilation already in 1912^{153,154}, when he reported hyperventilation in pregnant women. Moreover, he found that women also hyperventilate during the luteal phase of the menstrual cycle. Consequently, these cyclic breathing variations disappear in postmenopausal women¹⁵⁵. A direct effect of progesterone is suggested here, because the concentrations of progesterone in the rat lung are much higher than those of the progesterone metabolites; the P/P metabolites ratio is 6:1¹⁵⁶. PR-A is the predominant progesterone receptor isoform in the rat lung, in an A:B ratio of 2:1¹⁵⁷. The classical PR is also present in the mouse fetal lung tissue and reveals distinct developmental profiles, with the highest expression during the prenatal period¹⁵⁸.

Logically, synthetic progestins (MPA and chlormadinone acetate, CMA) have also been used for respiratory stimulation in men, mainly within the management of chronic obstructive pulmonary disease (COPD). Clinical studies have reported some improvement in blood gas levels and in number or duration of apneic and hypopneic events (for a review, see reference 159). A recent publication underlines the usefulness of another progestin, megestrol acetate (MGA), for selected patients with COPD¹⁶⁰.

Also, the combination of the carbonic anhydrase inhibitor acetazolamide with either CMA or MPA seems to be effective for the treatment of COPD^{161,162}.

MISCELLANEOUS

Here, we will discuss briefly the renal action of progesterone, the influence of progestins on kidney, the cardiovascular system, some effects of progesterone on the adipose tissue metabolism, and, finally, the clinical use of progestins for stimulating weight gain in men.

The kidney is one of the sites in the body expressing progesterone receptors, as reported in various studies. The incubation of rabbit proximal tubules with progesterone had no influence on the Ca^{2+} or Na^{+} transport by brush border membrane vesicles. By contrast, the hormone significantly increased the Ca^{2+} and decreased the Na^{+} uptake by the distal tubule luminal membranes. These effects were significant following 1 min of incubation. Finally, 10^{-11} mol/l progesterone also enhanced the Ca^{2+} uptake by distal tubules-membranes through a direct non-genomic mechanism¹⁶³. In the same context, the group of W. Oelkers¹⁶⁴ found enhanced downstream metabolism of progesterone in human kidney. This may be the mechanism responsible for the protection of the mineralocorticoid receptor (MR) from the antimineralocorticoid action of progesterone, by which water balance is maintained.

As far as we know, the influence of progesterone or progestins on the hemostatic system in men has been described in only one publication. A single intramuscular 200-mg dose of the depot-progestin norethindrone enanthate (NET-EN) alone to seven healthy white men, aged 28–38 years, led to a significant suppression of serum free and total testosterone and of serum 17β -estradiol on day 14 *post injectionem*. There was a marked shift in hemostatic parameters with increasing levels of Factor XIIc, fibrinogen, antithrombin, F1 + 2, and plasmin- α_2 -antiplasmin complex (PAP), whereas levels of Factors VIIc and VIIa decreased¹⁶⁵. The intravenous infusion of progesterone dilated mesenteric, renal, and iliac circulations in pigs. This dilatative effect on the arteries was inhibited by N-nitro-L-arginine methylester (NAME), indi-

cating the involvement of NO-dependent mechanisms¹⁶⁶. Plasma membrane-bound PR in vascular endothelial cells may regulate the non-genomic actions of progesterone^{167,168}. Additionally, progesterone at physiological concentrations inhibits the cell proliferation in cultures of aortic smooth muscle cells¹⁶⁹ in a dose-dependent manner.

Progesterone acts as an antiglucocorticoid in adipose tissue *in vivo*. When progesterone was given concomitantly, the glucocorticoid effects of dexamethasone on adipose tissue mass, lipolytic activity, and lipolysis were blocked³⁷. The expression of each adrenergic receptor (AdR) subtype gene is distinctly regulated by sex hormones (naturally besides norepinephrine) in brown adipocytes. Testosterone-treated cells had lower lipolytic activity and increased expression of antilipolytic receptors α_{2A} -AdR. Both 17β -estradiol and progesterone decreased α_{2A} -AdR expression and α_{2A}/β_3 -AdR protein ratio, but progesterone had a higher potency than 17β -estradiol, increasing β -AdR levels, mainly β_3 -AdR expression, and enhancing lipolysis stimulated by norepinephrine¹⁷⁰. The uncoupling protein 1 (UCP1) is the main mediator of brown adipose tissue (BAT). Progesterone stimulated *in vitro* the norepinephrine-stimulated UCP1 mRNA expression at very low concentrations (10^{-9} mol/l). Surprisingly, the antiprogestin and antiglucocorticoid mifepristone (RU486) acted in this model as a progesterone agonist, strengthening the progesterone activity¹⁷¹. This observation possibly indicates that the effects of progesterone on adipose tissue are non-genomically mediated.

The synthetic progestin, megestrol acetate (MGA), is used clinically to treat a reduction in appetite and weight loss in AIDS and cancer patients and in elderly people who are underweight^{172–174}. However, the composition of the body mass gained with MGA in AIDS and cancer patients has been shown to be predominantly or entirely fat. This may be due to the reduction in serum testosterone associated with MGA ingestion. Lambert and colleagues¹⁷⁵ performed a randomized, controlled, clinical trial with 30 older men (body mass index < 25) and found that the progestin (800 mg/day administered orally over 12 weeks) depressed serum testosterone levels greatly, reduced the thigh-muscle cross-sectional area, and enhanced the thigh-fat

cross-sectional area. Despite a significant weight gain, MGA appears to have an anti-anabolic effect on muscle size, even when it is combined with testosterone replacement. However, when the progestin administration was combined with resistance exercise, the total body muscle strength was significantly increased. However, in a MGA therapy, the possibility of an induction of adrenal insufficiency should always be taken into account as a serious side-effect¹⁷⁶.

Finally, there are some unclear relationships between serum progesterone and certain physiological or pathological conditions. For example, the serum Mg^{2+} concentration in young healthy men was directly and significantly related to the progesterone level, and the Ca^{2+}/Mg^{2+} ratio was inversely related to the serum progesterone level¹⁴. At the end, serum progesterone concentrations were elevated significantly in HIV-positive men at different stages of their disease¹⁷⁷. In this context, there are positive correlations between serum ACTH and progesterone levels¹⁷⁸.

CONCLUDING REMARKS

Is progesterone the forgotten hormone in men? To answer this question, we have three possibilities to explain the physiological role of this steroid in male gender:

- (1) Progesterone is a physiologically unimportant by-product in steroidogenesis;
- (2) The expression and the function of the progesterone receptors are only the result of the action of estrogens;
- (3) Progesterone plays a specific physiological and pathophysiological role in men with smart possibilities for new therapeutic approaches.

Naturally, depending on the given tissue or cell type or state of scientific clearing up, all three opportunities are applicable. Despite the relative broad knowledge about the progesterone actions in the male (reviewed in this paper), the exact physiological ranking of progesterone in comparison with other steroids and the therapeutic value of progestins and antiprogestins in the male for

gender-specific approaches remains more or less unclear.

The situation is furthermore complicated by the fact that the obviously important progesterone-dependent conditions in males are mediated either by the uncommon PR isoform A (e.g. lung) or by membraneous progesterone-effects (Table 2). Both targets are not typical of the hitherto performed screening for selecting progestins or antiprogestins. Therefore, the precise pharmacological manipulation of progesterone actions in the male requires completely new molecular biological approaches. But this investment could be valuable because it seems reasonable to identify new compounds for male contraception, stimulation of endogenous testosterone biosynthesis in aged Leydig cells, prostate cancer and/or BPH, meningioma/fibroma, chronic obstructive pulmonary disease, weight loss and – last but not least – specific diseases of the central nervous system.

Progesterone – the forgotten hormone in men? This title is not quite correct for a publication at the beginning of the 21st century. We have to wait for the future with new pharmacological and clinical results, hopefully.

Table 2 Expected genomic and non-genomic actions of progesterone in the male

<i>Genomic actions</i>
Central nervous system/neurosteroids (partially)
Tumors in the central nervous system (meningioma, fibroma)
Gonadotropin blockage
Spermiogenesis
Immune system
Respiratory system
Physiology and pathology of prostate (benign prostatic hypertrophy, prostate cancer)
Weight gain/appetite
<i>Non-genomic actions</i>
Sperm capacitation/acrosome reaction
LH receptor expression in the outer membrane of Leydig cells
Testosterone biosynthesis in Leydig cells
Increase in progesterone receptor concentrations in the prostate
Central nervous system/neurosteroids (partially)
Kidney
Adipose tissue

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