Molecular and Cellular Endocrinology 441 (2017) 31–45

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

# Progestins used in endocrine therapy and the implications for the biosynthesis and metabolism of endogenous steroid hormones

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ARTICLE INFO

*Article history:*
Received 28 June 2016
Received in revised form
1 September 2016
Accepted 7 September 2016
Available online 9 September 2016

*Keywords:*
Progestins
Contraception
Hormone replacement therapy
Adrenal steroidogenesis
Ovarian steroidogenesis
Hydroxysteroid dehydrogenase

ABSTRACT

Steroidogenesis refers to the *de novo* synthesis of steroid hormones from cholesterol by a number of sequential enzyme catalysed reactions in the adrenal and the gonads. In addition, circulating steroid hormone precursors are further metabolised in selected peripheral tissues. It has been suggested that the biosynthesis of endogenous steroid hormones can be modulated by progestins, used widely by women in female reproductive medicine. However, as a number of structurally diverse progestins with different pharmacological properties are available, it is possible that these synthetic compounds may vary in their effects on steroidogenesis. This review summarises the evidence indicating that progestins influence the biosynthesis of steroid hormones in the adrenal and gonads, as well as the metabolism of these endogenous hormones in the breast, highlighting the limitations to the current knowledge and directions for future research.



## 1. Introduction

Progestins are a class of synthetic compounds that were developed to mimic the biological action of the endogenous sex steroid hormone progesterone (Prog), which plays a pivotal role in female reproduction (Geller et al., 1999; Graham and Clarke, 1997). These progestins have many therapeutic applications in female reproductive medicine, and are used instead of Prog as they have better bioavailabilities and half-lives (Hapgood et al., 2004; Speroff, 1996; Stanczyk et al., 2013). Therapeutic applications include contraception, hormone replacement therapy (HRT), cancer therapy as well as the treatment of gynaecological disorders such as endometriosis (Africander et al., 2011; Schindler, 2014; Stanczyk et al., 2013). In addition to these beneficial effects, a number of side-effects have been reported with the clinical use of progestins. However, since progestins differ in their chemical structures and their biological activities, it is likely that not all progestins will display beneficial effects and side-effects to the same extent. It is thus crucial to improve our understanding of the risk/benefit profile of progestins used in hormone therapy. Progestins were designed to elicit their intracellular actions via the progesterone receptor (PR), but many progestins also bind to other members of the steroid receptor family such as the glucocorticoid, androgen and mineralocorticoid receptors (MR). Although these actions of progestins via steroid receptors are suggested to be the main mechanism of the differential intracellular actions, other factors such as metabolism, pharmacokinetics, bioavailability and effects on steroidogenesis cannot be excluded. In contrast to the numerous studies on progestin actions via steroid receptors, not much research has been devoted to the effects of progestins on endogenous steroid hormone biosynthesis. While it is known that the first-generation progestin medroxyprogesterone acetate (MPA) (Van Veelen et al., 1984) suppresses steroidogenesis by inhibiting the hypothalamic-pituitary-adrenal (HPA)-axis, studies investigating the direct inhibition of specific steps in the steroidogenic pathway by MPA, and other progestins, are limited. Furthermore, since it has been suggested that progestins do not always act in a similar manner, an important question is whether, and to what extent, progestins from different generations modulate these steps. A number of reviews have described the molecular mechanisms of action of progestins via steroid receptors (Africander et al., 2011; Kuhl, 1990; Schindler et al., 2003; Stanczyk et al., 2013) and will thus not be replicated in this review. Instead, we will describe the different generations of progestins and the enzymes involved in

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http://dx.doi.org/10.1016/j.mce.2016.09.004
0303-7207/

**Abbreviations**

| | |
|---|---|
| 3βHSD | 3β-hydroxysteroid dehydrogenase |
| 5α-dione | 5α-androstanedione |
| 11βHSD | 11β-hydroxysteroid dehydrogenase |
| 17βHSD | 17β-hydroxysteroid dehydrogenase |
| 11OH-A4 | 11β-hydroxyandrostenedione |
| 16OH-Prog | 16α-hydroxyprogesterone |
| 17OH-Preg | 17α-hydroxypregnenolone |
| 17OH-Prog | 17α-hydroxyprogesterone |
| A4 | androstenedione |
| Ald | aldosterone |
| CBG | corticosteroid binding globulin |
| CMA | chlormadinone acetate |
| COC | combined oral contraceptive |
| CORT | corticosterone |
| CPA | cyproterone acetate |
| CYB5A | cytochrome *b5* |
| CYP11A1 | cytochrome P450 side-chain cleavage |
| CYP11B1 | cytochrome P450 11β-hydroxylase |
| CYP11B2 | cytochrome P450 aldosterone synthase |
| CYP17A1 | cytochrome P450 17α-hydroxylase/17,20-lyase |
| CYP19A1 | cytochrome P450 aromatase |
| CYP21A2 | cytochrome P450 21-hydroxylase |
| DHEA | dehydroepiandrosterone |
| DHEA-S | dehydroepiandrosterone sulfate |
| DHT | dihydrotestosterone |
| DNG | dienogest |
| DOC | 11-deoxycorticosterone |
| DRSP | drospirenone |
| DSG | desogestrel |
| E1 | estrone |
| E1-S | estrone sulfate |
| E2 | estradiol |
| E2-S | estradiol sulfate |
| EE | ethinyl estradiol |
| FSH | follicle-stimulating hormone |
| GES | gestodene |
| HRT | hormone replacement therapy |
| HPA | hypothalamic-pituitary-adrenal |
| LH | luteinizing hormone |
| LNG | levonorgestrel |
| MA | megestrol acetate |
| MPA | medroxyprogesterone acetate |
| MR | mineralocorticoid receptor |
| MWS | Million Women Study |
| NES | nestorone |
| NET | norethisterone |
| NET-A | norethisterone acetate |
| NET-EN | norethisterone enanthate |
| NoMAC | nomegestrol acetate |
| PCOS | polycystic ovary syndrome |
| PR | progesterone receptor |
| Preg | pregnenolone |
| Prog | progesterone |
| SRD5A | steroid 5α-reductase |
| StAR | steroidogenic acute regulatory protein |
| STS | sulfatase |
| SULT1E1 | sulfotransferase family 1E member 1 |
| SULT2A1 | sulfotransferase family 2A member 1 |
| TMG | trimegestone |
| WHI | Women's Health Initiative |
| WISDOM | Women's International Study of Long Duration Oestrogen after Menopause |

steroidogenesis, while highlighting the effects of progestins on steroid biosynthesis likely via the regulation of expression and/or enzyme inhibition.

## 2. Progesterone and the classification of progestins

Prog and progestins are generally referred to as progestogens; compounds known to exhibit progestational activity. Prog is a natural progestogen, while progestins are synthetic progestogens developed to mimic the activity of Prog. The *de novo* synthesis of Prog occurs in various steroidogenic tissues, including the ovaries, adrenal gland and central nervous system (Capper et al., 2016; Hu et al., 2010; Miller and Auchus, 2011; Payne and Hales, 2004; Schumacher et al., 2012), with the ovary being the major site of biosynthesis in females (Graham and Clarke, 1997; Norman and Litwack, 1987). The physiological roles of Prog are dependent on the particular target tissue where it exerts its physiological effects by binding to the PR (Li et al., 2004; Scarpin et al., 2009). In the uterus and ovary, for example, Prog is crucial for the development and release of oocytes, support of implantation of a fertilised ovum and the maintenance of pregnancy (Gellersen et al., 2009; Graham and Clarke, 1997). In the mammary gland, Prog is required for the development of lobular-alveolar and the inhibition of milk protein synthesis during pregnancy (Graham and Clarke, 1997; Savouret et al., 1988), while in the brain Prog regulates signals required for sexual responsiveness and elicits neuroprotective effects (Brinton et al., 2008).

The list of available progestins has grown substantially since their first appearance more than five decades ago (Greenblatt, 1958; Inhoffen and Hohlweg, 1938; Kuhl, 2011; Mansour, 2005), and they are currently classified into four consecutive generations (Schindler, 2014; Sitruk-Ware, 2006). The newer, fourth-generation progestins have been developed to be closer in activity to Prog than progestins from the first three generations. It should be noted that although a large number of progestins have been developed, many are no longer commercially available. Tables 1 and 2 list examples of progestins commonly used. Most progestins are structurally related to either Prog (Table 1) or testosterone (Table 2) (Schindler et al., 2003; Sitruk-Ware, 2004; Stanczyk et al., 2013), with only one, the fourth-generation progestin drospirenone (DRSP), being derived from the MR antagonist, spironolactone (Table 2) (Fuhrmann et al., 1996; Krattenmacher, 2000). Those progestins structurally related to Prog can be subdivided into compounds with and without a methyl group at carbon 10. Progestins containing the methyl group are referred to as 17α-hydroxyprogesterone (17OH-Prog) derivatives, while 19-norprogesterone derivatives lack the methyl group (Sitruk-Ware, 2004; Stanczyk et al., 2013). The first-generation progestins MPA, megestrol acetate (MA), chlormadinone acetate (CMA) and cyproterone acetate (CPA) are examples of 17OH-Prog derivatives, while the fourth-generation progestins nestorone (NES), nomegestrol acetate (NoMAC) and trimegestone (TMG) are examples of 19-norprogesterone derivatives. Progestins structurally related to testosterone, the 19-nortestosterone derivatives, include the first-generation progestin norethisterone (NET), second-generation progestin levonorgestrel (LNG), third-generation progestins desogestrel (DSG), norgestimate and