REVIEW ARTICLE

ROLE OF ANTIPROGESTERONE ON THE ENDOMETRIUM RECEPTIVITY- A REVIEW

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Estrogen produces proliferation in the functional layer of the endometrium and the differentiation in the ciliated and secretory epithelium of the uterine tube. Progesterone produces differentiation in the functional layer of the endometrium and the produces mitosis in the stroma of the endometrium. These effects of the estrogen and progesterone are mediated through interactions with specific intracellular receptors[1]. Mifepristone (RU 486) is a steroid hormone with a chemical structure similar to natural hormone progesterone. It has been proposed that antiprogestins may be useful in the treatment of endometrial inflammatory disease and carcinoma +breast because these conditions are dependent on the ovarian receptors and have receptors for estrogen and progesterone. Anti-progesterone compounds can antagonize the biological action of the progesterone or inhibit the synthesis of progesterone. Mifepristone, (RU 486) has been found to be the most effective and is now used in practice.

Keyword: Antiprogestins, Endometrial changes, Uterine bleeding.

Synthesis of Mifepristone and its analogues

Mifepristone is an orally active synthetic steroid with antiprogesterone and antiglucocorticoid activities[1-3]. Mifepristone, behaves different from progesterone and causes conformational changes in the receptor[4]. Roussel Uclaf accomplished a comprehensive study in the mid 1980s announcing the safety of the molecule and allowing mifepristone to be used in humans[5]. In sub chronic toxicity studies performed on rodents for 30 days and 26 weeks, daily doses of mifepristone up to 200 mg/kg or 125 mg/kg, respectively, presented no toxicity but caused effects related to the antihormonal effects of the drug[6]. The antiprogesterone effects caused recurrent estrus, decrease in weight of the uterus, development and suppression of menstruation and a decrease in serum progesterone in monkeys[7].

Treatment with Mifepristone triggered a fall in estrogen levels with reversion in the dominant follicle. Lactate dehydrogenase (LH) and follicle stimulating (FSH) intensities had a tendency to reduce but successively augmented with reinitiating growth of follicles and manifestation of an LH ovulatory gush 13 days later[8]. Antiglucocorticoid effects were detected with a surge in weights of kidneys and adrenal glands of animals and increases in serum adrenocorticotropic hormone (ACTH) and cortisol levels[9]. Mifepristone establishes antiglucocorticoid action, which is displayed at doses of 400 mg and overhead (single administration). This antiglucocorticoid process affects all the systems of the body. Mifepristone does alter the mineralocorticoid receptors[10]. The drug has moderate antiandrogenic effects. When the diverse actions of mifepristone are linked in the same species, the dosage for the antiprogesterone and antiglucocorticoid activities is about 3 mg/kg, whereas it is about 30 mg/kg for antiandrogenic activity[11]. Female mice missing both PRs display compromised sexual behavior, neuroendocrine gonadotropin regulation, anovulation, uterine dysfunction, and impaired ductal branching lobuloalveolar components of the mammary gland. PRs also play a crucial role in the cardiovascular system through regulation of endothelial cell proliferation[12].

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Receptors for progesterone have also been identified in the brain[13].

Receptors

Physiological Spectrum of Steroid Receptor Action

The molecular mode of action of estrogen and progesterone receptors, together with molecular genetic lines to inspect the physiological concerns of receptors as co regulator protein ablation, have provided important vision into how physiological miscellany of female steroid hormone action is attained. Developing from these experiments is the general principle that the flexible nature of receptors allows ligand, tissue and agent specific interaction with select subsets of co regulators capable of expounding discrete transcriptional responses to steroid. There is a study observing the elevation in endometrial receptors after prolonged consumption of antiprogestin[14]. Depressed regulation of the progesterone receptor has been revealed to be extremely related with expansion of endometrial receptivity[15]. RU 486 appears to act by high binding to the progesterone receptor, converting it into an inactive DNA-receptor compound[16]. The data on the inhibitory action by RU 486 therefore strongly suggests that the proliferative effects of progesterone are mediated through its receptor[17]. Mifepristone action in the endometrium is facilitated by the PR with higher affinity of mifepristone for the PR linked with ER. The high efficacy of Mifepristone administered at a dose of 1mg/kg could also be demonstrated in glands and luminal epithelium where progesterone–prompted vacuolization was inhibited[18]. Epithelial PR can directly facilitate anti proliferative effects of mifepristone and stromal PR is also enhanced, an heightened sensitivity of the stroma to hormones could block any progesterone-dependent, stromal–epithelial interfaces involved in glandular mitosis. Therefore the suggested mechanism of action probably has a cell explicit property[19]. The progesterone-mediated decrease in ER protein has been shown more recently in breast cancer cells to result from decreased cellular ER mRNA levels, likely to reflect decreased transcription of the ER gene, since the result was seen rapidly without shortening of the ER mRNA half-life[20]. Abundant proof in the text demonstrates that steroid hormones play an important part in adaptable cyclic endometrial vascular modifications, arterial permeability which is important for endometrial physiology and for successful implantation and reproduction[21]

Endometrial arteries regrow at the beginning of the ovarian cycle, increase and branch during the follicular phase, and then coil into thick-walled spiral arteries in the luteal period to endure breakdown and sloughing at menses[22]. Prolonged antiprogestines intake inhibits estrogen-dependent endometrial cell proliferation and growth. This endometrial antiproliferative effect is the basis of the clinical use of antiprogestines to control certain conditions such as endometriosis[23].

Using mifepristone for 3 months was as effective with the end result being; a 50 percent shrinkage in fibroid size .Besides this, it was much better tolerated since it caused minimal hot flashes and Mifepristone also does not cause loss of bone density since it doesn't repress estrogen levels . Another advantage of mifepristone is that it is cost effective as compared to other drugs[24].

Therapeutic Effects

Anti-abortion movements and politics have been active recently and have brought the larger clinical trials, validating mifepristone's efficacy and safety in treating fibroids, to a stop. Mifepristone's medical potential is vast as it can treat numerous conditions that mainly affect women for e.g. uterine cancer, ovarian cancer, uterine fibroids , endometriosis and breast cancer and based upon this, the Feminist Majority Foundation has initiated the "Mifepristone and Women's Health" campaign, calling for more clinical trials exploring mifepristone's medical potential. Fibroid research with mifepristone is crucial in equipping women with a better tolerated, safe and effective non-surgical relief in the management and treatment of fibroid tumors[25].

Experimental results indicate that, under physiological conditions, two generally used anti-progestin's fail to evoke the efficient binding of PR to HRE in the natural context of the MMTV promoter in vivo, while the mechanistic claims remain presumptive. Thus it can be said that the mechanism of action of anti-progestin's, which is of major importance for the designing of pharmaceutical strategies for hormone therapy, has to be seriously reconsidered. The dispensing of the anti-progesterone RU486 during the dioestrous phase of cyclic rats produces ovulatory impairment and this effect of RU486 is dose dependent. This effect is elaborated by the example that although 0.2 mg RU486 day"1 has no effect and 10 mg RU486 day"1 is fully effective in blocking ovulation, while 2 mg RU486 day-1 reduces both the number of rats ovulating and the number of ova per ovulating rat . The anti-progesterone RU486 also induces a reduction in the amount of ovulatory LH released as well as inadequate follicular development at the time of the LH surge and a dual mechanism has been suggested for the an ovulatory action of RU486 in rats on the basis of this evidence. The reduction in the ovulatory LH released justifies the action of RU486 on ovulation but it is still not clear by which procedure the follicular responsiveness is reduced by RU486 treatment[26].

Intrauterine devices (IUDs) that release progesterone are extremely functioning contraceptives, but they produce breakthrough bleeding that some women find unbearable. Progesterone (P) antagonists (AP) are known to reduce the proliferation of the endometrium causing amenorrhea, and constrain fertility. Antiprogestines IUDs may provide an effective contraceptive that also switches endometrial bleeding. The reverse of the anti-fertility effects of prolonged, low-dose antiprogestin management supports the clinical practicability of effective antiprogestins as potential contraceptives for women[27].

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

AUTHORS CONTRIBUTION

Khadija Qamar, conception, Rubina Mushtaq, medical writing, Humaira Arshad, interpretation of text and review.

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