

## ROLE OF GENOMIC AND NON-GENOMIC STEROIDS

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### **Summary**

In the classical model of steroid action, the effect or mechanism involves the binding of steroids either to receptors present in the nucleus or in the cytosol, followed by translocation of the receptor-ligand complex to the nucleus, with subsequent modulation of transcription and protein synthesis. The considerable latency of genomic steroid effects (>30min) is the consequence of these time-consuming steps of action.

**Keywords:** Genomic and Non-Genomic Steroids,

### **Introduction**

Fats and lipids as very simple organic molecule has designed by Nature to play many important roles such as maintenance of cell structure, production and storage of energy and steroid hormones as cell signaling molecule and as rafter for protein and vesicles. Prostaglandin and leukotrienes derived from membrane lipids are released and transported to a variety of target cells. Lipids also help to direct proteins to their proper action in cell. Fats and lipids that absorbed from diet or synthesized by the liver are transported between the adipose tissue and various tissues. These lipids are utilized for the production and storage of energy and cholesterol needed for the cellular structures and synthesis of steroid hormones.

Steroids are small lipophilic molecules derived from cholesterol and synthesized mainly in adrenal cortex and reproductive organs. More than four decades ago their profound impact on nuclear transcription and protein synthesis was recognized. In common theories of steroid action, steroids bind to intracellular receptors and modulate nuclear transcription after translocation of steroid receptor complexes into the nucleus A DNA binding domain allows the ligand receptors complex to bind as homo or heterodimers to specific DNA sequence. Transcription is initiated by a well-organised interaction of co-activator regulators and transcription factors [1].

Due to molecular homologies in receptor structure, intracellular receptors for steroids, vitamin D<sub>3</sub> and thyroid hormones were summarized as the super family of steroid receptor. Despite structural homologies each steroid is capable of producing specific effects in its target organs. For example, sex steroid are primarily acting at reproductive organs. In contrast mineralocorticoid modulates Na<sup>+</sup> transport at the collecting ducts of kidney thus changing body volume and electrolyte balance. These actions are transmitted by modulation of epithelial Na<sup>+</sup> channels and Na-K-ATPase gene expression, probably transmitted by type-I mineralocorticoid receptors [2].

In addition to aldosterone actions on classical target tissues, such as kidney, extra renal localization of mineralocorticoid receptor has been demonstrated. Since steroids play a very vital role in the body so function of steroid has been classified into:

- I. A non-rapid genomic or classical function or action.
- II. Non-Genomic function or non-classical action.

### **GENOMIC STEROID ACTION**

Genomic mode of action is related to the sexual function, which sex hormones perform for example, progesterone plays a vital role in fertilization of fetus in the womb of women during pregnancy.

On the other hand, non-genomic mode of action is not related to the sexual function for example progesterone has anaesthetic effects which occur almost immediately after application. To explain the differences between the genomic and non-genomic mode of steroid actions let us have a look on helpful definition & short historical background of rapid non-genomic steroid action.

### **NON-GENOMIC STEROID ACTION**

In addition to genomic steroid action, non-genomic effects of steroid have received attention during recent years. Non-genomic effects differs from genomic steroid action mainly by their short time lag of action, almost occurring within seconds after addition of steroid furthermore, as transcription and protein synthesis are not involved and non-genomic steroid actions are not blocked by inhibitors of transcription or translation [3].

The first rapid effects of steroid have been described in 1942 Selye demonstrated anaesthetic effects of progesterone occurring almost immediately after application which have been further developed for steroid anaesthesia. Spach and Strutting showed in vitro effects of aldosterone on Na-exchange in canine erythrocyte at physiological steroid concentration [4].

Other non-genomic activity of sex hormones like progesterone is a physiological stimulus of human sperm functions. Progesterone was the first steroid described to have non-genomic effects [5]. In this pioneer study, Selye reported that progesterone induces almost immediately after exposure an anaesthetic effect. Later on it was shown that this effect was indeed specific involving an interaction of progesterone on spermatozoa. Sperm life after ejaculation is characterized by two essential events for the process of fertilization i.e. Capacitation [6] & acrosome reaction. Capacitation occurs during sperm transit in the female genital tract and consists of several biochemical and functional processes ultimately leading to hyperactivated motility [7].

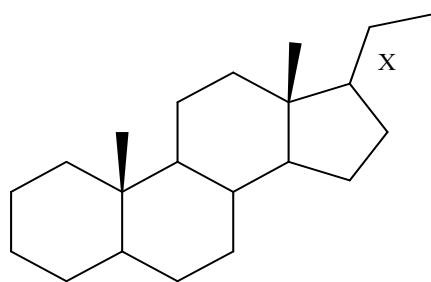
Acrosomal reaction consists of fusion and fenestration of the outer acrosomal membrane with the plasma membrane and release of acrosomal enzyme that aid the spermatozoan to penetrate various investments of oocytes. Evidence for the presence of rapid effect of progesterone on spermatozoan was first reported by Osman *et al.* [8], who showed that progesterone was responsible for the acrosomal reaction inducing activity of the follicular fluid. High concentration (1 to 10  $\mu\text{g/ml}$ ) of progesterone are indeed present in cumulus matrix that surrounds the oocytes, which must be necessarily crossed by the sperm to reach zona pelucida & penetrate it. These concentration are similar to those determining the biological effects of steroids in spermatozoa. Later on these effects were confirmed in other studies and the signal transduction pathway activated by the steroid characterized. It is now clear that the effects of progesterone on human spermatozoa are mediated by a pathway quite distinct from the classic genomic and indeed most of its effect occur within seconds following addition of agonists and can be induced also by a non permeable progesterone analogue and thus cannot be attributed to a genomic effect [9]. Another non-genomic action played by progesterone is the synthesis of myelin sheath. The group headed by Prof. Etienne Emil Baulieu director of INSERM unit 33 at the University of Paris and developer of RU-486 observed that progesterone is present in high concentration in sciatic nerves in mice, some five fold to the level present in plasma. The researchers found that oligodendrocyte also synthesis progesterone and a Schwann cell appears to be the source of progesterone from radio labeled precursors. Schwann cells and oligodendrocyte both produces myelin, Schwann cells in peripheral nervous system and oligodendrocyte in CNS. They measured progesterone levels in the regenerating nerve and studied the effect of progesterone on myelin synthesis. They found that there is an increase in endogenous progesterone in the nerve during regeneration. And when the progesterone inhibitors like trilostane and RU-486 were given it was observed that the layer of myelin in regenerated axons was found to be reduced. When the researchers added progesterone simultaneously with trilostane, the thickness of myelin was much greater than in the control tissue [10]. Another non classical action of steroid is the anesthetic and antiepileptic effect which was exerted by progesterone. The pioneering work of Seyle in 1942 reported that progesterone and other steroids when administered to rats, could produce prolong anesthesia lasting up to 2 hrs or longer. This observation led to the development of variety of steroidal anesthetic. Several of these anesthetics were the  $3\alpha$ ,  $5\alpha$ .  $3\alpha$  &  $5\beta$  forms of progesterone metabolites which reportedly do not bind to classical intracellular progesterone receptors. Recent studies suggest that the anesthetics and antiepileptic properties of these progestins may be due to interaction of GABA<sub>A</sub> receptors system [11]. So it is clear that progestin can exert rapid depressive effect with in CNS. Affirmation of the potent CNS depressant effect of progesterone was further supported by the observation of Backstrom who observed that this incidence of seizure in epileptic women during menstrual cycle was lowest during the period when plasma progesterone level was highest. Further more Rosciszewska et al showed that epileptic seizure activity in women was associated with low level of progesterone metabolite in blood [12]. Non-classical function played by progesterone is neuron excitability. Smith and coworkers found that progesterone significantly enhanced inhibitory responses to rat Purkinje cells of Gamma amino butyric acid (GABA), the principal inhibitory amino acid transmitted in the brain, while it significantly suppressed responses to glutamate the principal excitatory transmitter in brain. In a follow up study, Smith et al found that prior treatment with a protein synthesis inhibitor did not prevent the ability of progesterone to decrease the glutamate response. This finding lends further support to the concept that the effect of progesterone on Purkinje cell responsiveness is exerted through a non genomic mechanism. So it is well established that hormonal action of progesterone on uterine lining is through gene activation by the cytosolic receptors and hence

transcription action. All pregnane compounds are therefore suspected to have transcriptional activity till proved otherwise. It also been established that not all action of progesterone are through gene activation and many of it activities are non genomic. The non genomic actions occur at the membrane level and are not associated with entry into the cell.

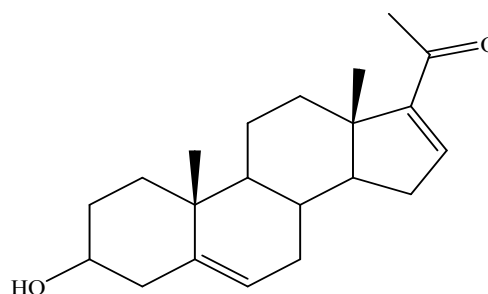
Guggulsterone, isolated from resin of *Commiphora mukul* a reputed plant in *Ayurvedic* system of medicine, 80/574 a pregnane class of compound also has only non genomic activity and no progestational activity. This finding therefore stimulated to explore the non-genomic actions of 80/574 and its analogues and hence their synthesis [13].

### Development of new steroids with hypolipidemic and hypoglycemic activities

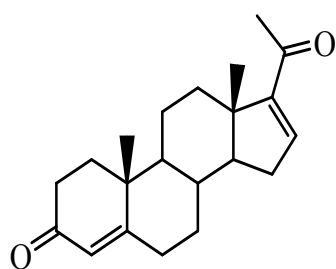
The innovation relates to the novel use of D-ring unsaturated pregnadienols [pregnadienones] represented by general formula I as shown in the accompanying drawings, possessing both marked hypolipidemic and hypoglycemic activities and without androgenic and progestational activities. More particularly the invention relates to the novel use of 3 $\beta$ -hydroxy-pregna 5, 16-dienone which is an important prototype of this class represented by the formula II as shown in the accompanying drawing for the treatment of diabetes and marked hypolipidemic and hypoglycemic activities [15].



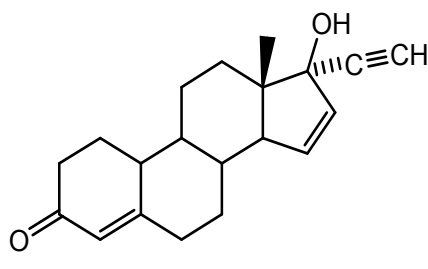
Formula I



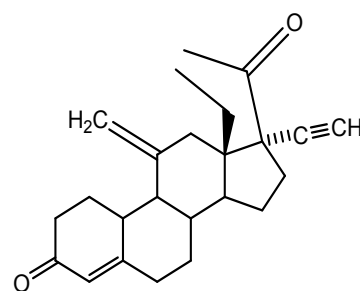
Formula II



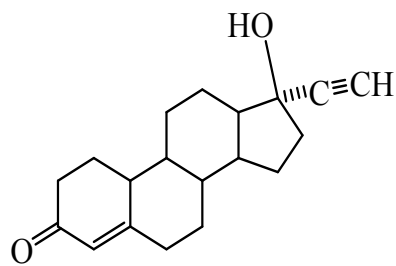
Progesterone



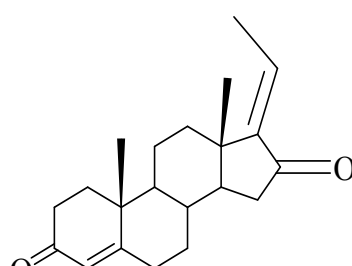
Gestodene



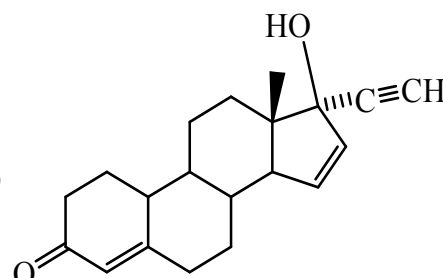
Ketodesogestrel



Levonorgestrel



Guggulsterone



Northisterone

We have earlier discussed about the nongenomic action of steroids specially pregnane class of compounds. We have two pregnane class of compounds viz guggulsterone and 80-574 which have not exhibited any genomic actions. These encouraging findings led us prepare more analogs of these compounds and explore non genomic actions.

Compound 80/574, a close analogue of guggulsterone is a potent antidyslipidemic agent and is currently in phase III clinical evaluation. The compound has a unique mechanism of action and acts by stimulating the farnesoid X receptor/ bile acid receptor (FXR/BAR). There is no other example of any compound other than bile acid or its analogues which is active on this receptor. FXR receptor is a nuclear receptor [16].

### **Conclusion**

Progesterone having action on reproductive and metabolic systems seems to offer the possibility of dissociating these two biological activities by structural modifications. The experience of the development of second-generation progestin's supported this contention. The first generation progestin such as levonorgestral exhibited undesirable pharmacological effects like alteration in carbohydrate and lipoprotein metabolism, weight gain and hypertension which was shown to be related to their intrinsic androgenic activity (anabolic activity) and ability- 1234 -to bind with androgen receptors.

### **Future Policy:**

The action of genomic & nongenomic steroid is as sex hormone. But nowadays many scientist are working on the treatment of diabetics, hypolipidemic and hypoglycemic. Hence it is the new field of development of hypolipidemic and hypoglycemic activity.

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