

## THE EFFECT OF ESTRADIOL VALERATE ON SEX HORMONE LEVELS IN AGED FEMALE ALBINO RATS

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### ABSTRACT

The study was carried out to evaluate the levels of sex hormones (follicle stimulating hormone, luteinizing hormone, prolactin, testosterone and estradiol) in young, aged and aged administered with estradiol valerate female rats. The gonadotropin levels were declined in aged rats, which were elevated drastically by estradiol valerate administration, stimulating the hypothalamic-pituitary axis in aged rats. Elevation in testosterone levels represents elevation in bone mineral density and decreases fracture risk and risk of coronary heart disease events.

**Keywords:** Post menopausal changes, Hormonal replacement therapy, Gonadotropins, Testosterone, Prolactin.

### INTRODUCTION

Aging is an important event in the life of mammals including human beings, during which a number of metabolic and hormonal changes take place. In post-menopausal women, having a low concentration of estradiol and progesterone, there is an increased risk of various health problems such as diabetes, cardiovascular complications, osteoporosis and others [1, 2]. Menopause, a normal state of ovarian hormone deficiency, dramatically affects older women, often producing disabling consequences. The incidence of metabolic syndrome also called insulin resistance syndrome, increases substantially during menopause and advancing age [3]. The free levels of sex hormones were decreased during aging, which may indicate an important role of sex hormones in metabolic homeostasis. Estradiol hormone replacement in post-menopausal women exhibits positive changes on a wide range of metabolic parameters, including improved peripheral vascular reactivity, increased HDL levels [4], reduced abdominal obesity, enhanced overall insulin sensitivity, lower lipid levels, lower blood pressure [5, 6] as well as prevention of new type 2 diabetes cases.

Follicle-stimulating hormones help to control and regulate the woman's menstrual cycle and are also partially responsible for the production of ova, or eggs, in the ovaries. Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) act synergistically in reproduction [7]. Thus, it is believed that the mechanisms involved in the causation of reproductive senescence probably involve changes in hypothalamic function and/or changes in pituitary responses to hypothalamic input. A number of hypothalamic neuroendocrine changes occur during reproductive ageing that may play a role in, or

be causal to, reproductive senescence. Hence the present study was focused to evaluate the effect of estradiol valerate on serum hormone levels in female aged albino rats.

### MATERIALS AND METHODS

In the present study healthy female albino rats were used. The rats were purchased from Sri Raghavendra Enterprises, Bangalore, India and divided in to three groups, each group containing 6 rats. First group is young rats (4 months), second group is aged rats (20 months) and third group is aged rats administered with estradiol valerate (progynova tablets, Bayer Zydus Pharma Pvt. Ltd) (8mg/Kg body weight/day) [8] orally for one week with gastric gavages method. Animals were housed in a clean polypropylene cage under hygienic conditions in the well ventilated clean air conditioned room, with photoperiod of 12 hours light and 12 hours dark cycle at 25±2°C, with a relative humidity of 50±5%.

The rats were fed with standard laboratory feed supplied by Hindustan Lever Ltd, Mumbai and water *ad libitum*. The use of animals was approved by the institutional animal ethical committee, in its resolution no: 13/2012-2013(i)/a/CPCSEA/IAEC/SVU/CC - AL dt.01-07-2012. Twenty four hours after the last dose, the animals were autopsied and blood was collected, separated serum and used for hormonal analysis. Serum samples were assayed for Follicle stimulating hormone, Luteinizing hormone, Prolactin, Testosterone and Estradiol. The hormones were estimated by using the ELFA technique (Enzyme Linked Fluorescent Assay). It is an aid in the diagnosis and management of conditions involving excess or deficiency of these hormones.

**Table 1: The levels of serum Follicle Stimulating Hormone, Luteinizing hormone, Prolactin, Testosterone and Estradiol levels in young, aged and EV administered aged female rats**

S. No.	Name of the hormone	Young (1)	Aged (2)	% Change (1&2)	EV administered aged (3)	% Change (2&3)
1.	FSH (mIU/ml)	1.88 ±0.072	0.76 ±0.013	-59.57*	1.63 ±0.059	+114.4*
2.	LH (mIU/ml)	0.28 ±0.02	0.01 ±0.001	-96.42*	0.19 ±0.01	+1800*
3.	Prolactin (ng/ml)	0.32 ±0.014	0.02 ±0.001	-93.75*	0.36 ±0.021	+1700*
4.	Testosterone (ng/ml)	1.09 ±0.05	0.01 ±0.001	-99.08*	0.14 ±0.001	+1300*
5.	Estradiol (pg/ml)	699.9 ±30.12	612.6 ±27.11	-12.47*	672.9 ±29.01	+9.84**

Mean± SD of six individual observations. \* indicates P<0.001, \*\*indicates P<0.01 the level of significance

## RESULTS AND DISCUSSION

The data represented in table-1 indicates serum FSH, LH, Prolactin, testosterone and estradiol levels in young, aged and aged administered with estradiol valerate (EV) female albino rats. All hormones were reduced by age over young and elevated by EV administration over aged rats.

### Follicle-stimulating hormone (FSH)

Normal patterns of gonadotropin secretion are absolutely required for reproduction. The secretion of follicle-stimulating hormone (FSH) by the anterior pituitary gland is regulated by the interaction of hypothalamic and gonadal hormones. Follicle-stimulating hormone (FSH) regulates the development, growth, pubertal maturation, and reproductive processes of the body. Follicle-stimulating hormone and luteinizing hormone (LH) act synergistically in reproduction. In the present findings, Follicle-stimulating hormone levels were lowered by age and these become doubled by EV administration. As a woman nears pre menopause the number of small antral follicles recruited in each cycle diminishes and consequently insufficient inhibin B is produced to fully lower Follicle-stimulating hormone, by menopause any remaining small secondary follicles no longer have Follicle-stimulating hormone receptors. The increase in serum estradiol levels causes a decrease in Follicle-stimulating hormone production by inhibiting GnRH production in the hypothalamus [9]. Diminished secretion of Follicle-stimulating hormone can result in failure of gonadal function (hypogonadism), cessation of reproductive cycles.

### Luteinizing hormone (LH)

Follicle-stimulating hormone and Luteinizing hormone play a critical role in folliculogenesis [10]. The low Luteinizing hormone level may negatively affect other Luteinizing hormone – dependent physiologic functions including ovulation. On the other hand, the elevation of Estradiol and Progesterone levels with a concomitant significant suppression of Follicle-stimulating hormone in the female animals is consistent with a compensatory response arising from reduced negative feedback on the hypothalamus-pituitary levels by the lowered Estrogen and Progesterone levels [11]. These observations suggest that the altered circulatory levels of steroids are in response to altered profiles of Follicle-stimulating hormone and Luteinizing hormone secretion. In the present observations Luteinizing hormone levels were nearly 100 folds depletion in aged rats which were reverted 1000 folds by EV administration.

### Prolactin (PRL)

Besides its well-known lactogenic properties, prolactin is also a highly versatile hormone whose functions are related to reproduction, growth and development, metabolism, immune regulation, brain function, and behavior [12, 13]. Prolactin also takes a crucial part in regulating whole-body insulin sensitivity and glucose metabolism by increasing b-cell proliferation [14]. Prolactin and growth hormone is necessary for mammary gland development in young animals and will, at sufficiently high levels, stimulate some growth in the absence of steroids [15].

In the present findings it is observed that PRL levels were drastically depleted in aged rats. But EV administration enhances more. Prolactin cell of estradiol valerate treated female rats were characterized by hypertrophy, small nucleo cytoplasmic ratio and eccentrically placed nucleonema [16]. These observations suggest that hypertrophy of prolactin cells induced more secretion of prolactin (hyper prolactinemia) by the EV administration. Highly elevated levels of prolactin decrease the levels of sex hormones-estrogen in women and testosterone in men [16]. Thus the gonadotropin levels were declined in aged rats, 60% in FSH and 95% in luteinizing hormone & prolactin (hypogonadotropins) which were elevated (thousand folds) drastically by EV administration (hypergonadotropins).

It is well established that aging is associated with dramatic changes in gonadotropin secretion in healthy subjects. In women, after the initial elevation of serum gonadotropins that characterizes the menopause, a progressive decline in both follicle-stimulating

hormone (FSH) and luteinizing hormone (LH) levels occurs with age in the later post-menopausal years [17]. The progressive decline of both follicle-stimulating hormone and luteinizing hormone with age in normal postmenopausal women that probably involves changes occurring at the level of both the hypothalamic gonadotropin releasing hormone (GnRH) pulse generator and the pituitary gonadotroph. Hence, estradiol valerate stimulate the hypothalamic-pituitary axis in aged rats.

### Testosterone

In the present study, reduced serum testosterone levels were observed in aged female rats while 1000 fold elevation with estradiol valerate administration. Testosterone production is critical for women. Testosterone is a major precursor for estradiol production, and it acts directly on androgen receptors throughout the body. In healthy premenopausal women, circulating testosterone levels are approximately 10-fold greater than circulating estradiol levels. Testosterone levels decline with age across the reproductive years; by the time women reach their late 40s, their blood testosterone levels are approximately half what they were in their 20s [18]. Importantly, testosterone levels do not decline across the natural menopausal transition [18]. Testosterone may also be important for the maintenance of bone and muscle mass. Observational studies have reported that low serum testosterone is associated with lower bone mineral density and increased fracture risk in postmenopausal women. A large study has reported an increased risk of coronary heart disease events in women who had low levels of total and bio available testosterone [19, 20]. Thus administration of estradiol valerate increases the bone mineral density and decreases fracture risk and risk of coronary heart disease events in postmenopausal women.

### Estradiol

Ovaries gradually produce estrogen in the period up to menopause, then its blood level decline as a result [21]. The declining levels of estrogen can cause distressing symptoms with increased incidence of osteoporosis, cardiovascular disease [22]. In the present findings the estradiol levels were reduced in aged rats, supported by earlier reports [23]. Estrogen hormones play a key role in sexual development and reproduction in women. Estradiol is the most active hormone. Its blood levels are particularly high during the active reproductive period. After the menopause, the ovarian function ceases, leading to a significant drop in estrogen levels in the blood (the adipose tissue then becomes the main source of estrogen). During menopause, estrone is the predominant circulating estrogen. However, low concentrations of these hormones do continue to circulate and may still exert biological actions. The administration of estradiol valerate revokes the estrogen levels to some extent.

## CONCLUSION

Administration of estradiol valerate stimulate the hypothalamic-pituitary axis in aged rats.

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