INFLUENCE OF ESTRADIOL VALERATE (PROGYNova) ON AGED FEMALE ALBINO RATS WITH REFERENCE TO CARBOHYDRATE METABOLITES

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ABSTRACT

The present study was designed to evaluate the efficacy of estradiol valerate on glucose and glycogen in aged female albino rat tissues. Wistar strain albino rats at 20 months age group were administered with estradiol valerate at dose 8mg/Kg body weight/day orally for one week. The glucose and glycogen levels were estimated in young, aged and aged administered with estradiol valerate. The administration revert the glucose levels in ovary, no changes in uterus, and in vagina further depletion of glucose takes place. Aging does not altered glucose levels in heart and liver but estradiol valerate administration slightly increased as estrogens mobilizes glucose levels. After administration glycogen levels were regained in ovary. Elevated glycogen levels in heart have been shown to have cardio protective effects. The liver glycogen storage capacity was diminished in aged rats and elevated by the administration.

KEYWORDS: Menopause, Estradiol valerate, Glucose, Glycogen.

INTRODUCTION

Increasing female age is perhaps the greatest enemy of fertility. Menopause is associated with a very little change in overall circulating insulin level, there is increasing insulin resistance with age, predisposing postmenopausal women to the development of type 2 diabetes. Care of postmenopausal women with diabetes mellitus is therefore one of the serious clinical issues of concern due to the high prevalence of diabetes in aging population. In humans, the menopause transition marks the cessation of ovarian function and dramatic reductions in circulating estrogen and progesterone concentrations. Glucose plays critical roles in the regulation of glucose metabolism and maintenance of insulin sensitivity. Although the
ovarian hormones operate primarily in reproduction, they also make an important contribution to carbohydrate metabolism.\(^5\)

The clinical application of estradiol replacement in menopausal women results in altered glucose tolerance in about 40% of the subjects studied. Alka et al., (2003)\(^6\) have reported that women when randomly assigned to hormone replacement therapy (HRT) had a 35% lower risk for diabetes than those assigned to placebo, but at the end of the treatment, there was a small increase in the random serum glucose level in the hormone replacement therapy group. Hence the present study was focused to evaluate the effect of estradiol valerate on female aged albino rats.

**MATERIAL AND METHODS**

In the present study healthy female albino rats were used. The rats were purchased from Sri Raghavendra Enterprises, Bangalore, India and divided into three groups, each group containing 6 rats. First group are young rats (4 months), second group are aged rats (20 months) and third group are aged rats administered with estradiol valerate (progynova tablets, Bayer Zydus Pharma Pvt. Ltd) (8mg/Kg body weight/day), \(^7\) orally for one week with gastric gavages method. Animals were housed in a clean polypropylene cage under hygienic conditions in 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 usage 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. The reproductive tissues like ovary, uterus, vagina and non reproductive tissues like heart and liver were isolated, chilled immediately and used for biochemical analysis, glucose\(^8\) and glycogen \(^9\) were estimated in young, aged and estradiol valerate administered aged female rats.

**RESULTS AND DISCUSSION**

Glucose acts both as a source of energy and as a source of starting material for nearly all types of biosynthetic reactions. The liver is the major metabolic regulatory organ. About 90% of all circulating glucose not derived directly from the diet comes from the liver. In the present findings the glucose levels (Table-1) were depleted in ovary and vagina, elevated in uterus by aging. EV administration to aged rats revert the glucose levels in ovary, no changes in uterus, and in vagina further depletion of glucose takes place.
Glucose plays critical roles in the regulation of glucose metabolism and maintenance of insulin sensitivity. Although the ovarian hormones operate primarily in reproduction, they also make an important contribution to carbohydrate metabolism [5]. Growing evidence suggests that the ovarian hormones have major effects on lipid and carbohydrate metabolism and may also play a major role in up-stream molecular signaling mechanisms for regulating substrate metabolism. It appears that the absence of estrogen can impair glucose uptake.

The rate of glucose transport into cells is regulated by both gonadotropins and steroid hormones. Hence there were reduced glucose levels. Due to insufficient glucose, as energy sources, ovary does not produce follicles, leads to cessation of ovulation and cycles in aged rats. This is also due to more glucose efflux in to blood from tissues, which leads to diabetes as mentioned in earlier reports in postmenopausal women. [2] These were reverted by the administration of estradiol valerate.

Uterus, as it is an accessory sex organ depends on estrogens, secreted from ovary. Elevation in glucose levels may be due to 17β-estradiol which was secreted from uterus. Estradiol valerate administration does not show any effect on these glucose levels. The depleted glucose levels in vagina by age were further decreased by estradiol valerate administration. Some studies reveal that adequate glucose uptake and metabolism are essential for the proper differentiation of the uterine endometrium toward a receptive state capable of supporting embryo implantation. Glucose transporters may play in normal uterine physiology as well as the pathological conditions of infertility, endometrial cancer, and polycystic ovarian syndrome. [10]

Aging does not altered glucose levels in heart and liver (Table-2) by age but EV administration slightly increased as estrogens mobilizes glucose levels. [11]

The data represented in (Table-3) indicates the glycogen levels in reproductive tissues like ovary, uterus & vagina in young, aged and aged administered with estradiol valerate female albino rats. The ovarian glycogen content enhanced in aged rats over young and EV administration also enhanced further. In sex accessory organs uterus does not shows significant changes in aged and enhanced by EV administration. In vagina significant reduction in aged and no significant changes by administration. The presence of glycogen in the reproductive organs is of importance for many reproductive phenomena such as formation of decidualmata and uterine proliferation, implantation, nidation, uterine receptivity, vaginal
cornification, transport in the female genital tract. The glycogen in human fallopian tubes, localized mostly in the ciliated cells, exhibits cyclic changes in concentration and localization during the menstrual cycle.\textsuperscript{12}

In the present study the glycogen content were reduced in ovary and vagina while in uterus no changes takes place in aged rats. Glycogen synthesis is generally a function of estrogen; it varies markedly among reproductive tissues and among species. The glycogen synthesis response to estrogen in a particular species may be related to the number of estrogen binding sites, or to the ability of estrogen to convert the dependent form of glycogen synthetase.\textsuperscript{13} Hence, due to lowered levels of estrogens in aged rats glycogen synthesis was lowered in which the functional activities of these tissues were affected. In uterus the glycogen levels were not altered due to the presence of some estradiol in uterus itself.

However, after administration, glycogen levels were regained in ovary. But in uterus there was elevation in glycogen synthesis after administration. The estrogen treatment showed its ability to elevate uterine glycogen levels. Thus, increase in glycogen by general proliferative changes in the uterus. The vaginal glycogen does not alter after administration of estradiol valerate.

The data represented in (Table-4) indicates the glycogen levels in heart and liver. In heart the glycogen was elevated slightly in aged rats. EV administration does not alter these changes. Glycogen is an immediate source of glucose for cardiac tissue to maintain its metabolic homeostasis. However, its excess brings about cardiac structural and physiological impairments.\textsuperscript{14} Elevated glycogen levels in heart have been shown to have cardio protective effects against ischemic injury.\textsuperscript{15} The heart can use a variety of substrates to oxidatively regenerate ATP depending upon availability. During ischemia and hypoxia, the coronary circulation is unable to deliver metabolic substrates to the heart to support aerobic metabolism. Under these conditions, the heart is able to utilize glycogen (a storage form of carbohydrate) as a substrate for anaerobic production of ATP and the formation of lactic acid. However, the amount of ATP that the heart is able to produce by this pathway is very small compared to the amount of ATP that can be produced via aerobic metabolism. Furthermore, the heart has a limited supply of glycogen, which is rapidly depleted under severely hypoxic conditions. Increased glycogen levels will have positive effects on cardiac function. The hepatic glycogen levels were reduced in aged rats. However, EV administration enhanced two fold. The two major sites of glycogen storage are the liver and skeletal muscle. Glycogen
stores in the liver are used to maintain a constant blood glucose concentration. The major factor that controls glycogen metabolism in the liver is the concentration of phosphorylase alpha. Indeed, this enzyme catalyzes the limiting step of glycogen breakdown and, by controlling the activity of synthetase phosphatase, also regulates glycogen synthesis. Hence the liver glycogen storage capacity was diminished in aged rats and elevated by the administration. Thus, glycogenesis was lowered by age and enhanced by EV administration.

Table 1: The levels of Glucose (mg/g wet wt) in reproductive tissues of young, aged and estradiol velerate administered aged female rats.

<table>
<thead>
<tr>
<th>Name of the tissue</th>
<th>Young (1)</th>
<th>Aged (2)</th>
<th>% Change (1&amp;2)</th>
<th>Estradiol velerate Administered aged (3)</th>
<th>% Change (2&amp;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>4.310±0.321</td>
<td>3.912±0.299</td>
<td>-9.23***</td>
<td>4.251±0.301</td>
<td>+8.66***</td>
</tr>
<tr>
<td>Uterus</td>
<td>3.173±0.213</td>
<td>3.631±0.245</td>
<td>+14.43**</td>
<td>3.714±0.251</td>
<td>+2.28NS</td>
</tr>
<tr>
<td>Vagina</td>
<td>2.942±0.198</td>
<td>2.742±0.156</td>
<td>-6.79***</td>
<td>2.394±0.132</td>
<td>-12.69**</td>
</tr>
</tbody>
</table>

Mean± SD of six individual observations. * indicates P<0.001, **indicates P<0.01, ***indicates P<0.05 the level of significance, NS- indicates non significant changes

Table 2: The levels of Glucose (mg/g wet wt.) in non reproductive tissues of young, aged and estradiol velerate administered aged female rats.

<table>
<thead>
<tr>
<th>Name of the tissue</th>
<th>Young (1)</th>
<th>Aged (2)</th>
<th>% Change (1&amp;2)</th>
<th>Estradiol velerate Administered aged (3)</th>
<th>% Change (2&amp;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>2.370±0.195</td>
<td>2.471±0.197</td>
<td>+4.26NS</td>
<td>2.670±0.199</td>
<td>+8.05***</td>
</tr>
<tr>
<td>Liver</td>
<td>3.031±0.29</td>
<td>2.912±0.146</td>
<td>-3.92NS</td>
<td>3.101±0.201</td>
<td>+6.49***</td>
</tr>
</tbody>
</table>

Mean± SD of six individual observations. ***indicates P<0.05 the levels of significance, NS- indicates non significant changes.

Table: 3 The levels of Glycogen (mg/g wet wt) in reproductive tissues of young, aged and estradiol velerate administered aged female rats.

<table>
<thead>
<tr>
<th>Name of the tissue</th>
<th>Young (1)</th>
<th>Aged (2)</th>
<th>% Change (1&amp;2)</th>
<th>Estradiol velerate Administered aged (3)</th>
<th>% Change (2&amp;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>5.230±0.341</td>
<td>4.013±0.299</td>
<td>-23.26*</td>
<td>4.99±0.310</td>
<td>+24.34*</td>
</tr>
<tr>
<td>Uterus</td>
<td>3.123±0.167</td>
<td>3.001±0.151</td>
<td>-3.90NS</td>
<td>4.012±0.240</td>
<td>+33.68*</td>
</tr>
<tr>
<td>Vagina</td>
<td>2.741±0.163</td>
<td>2.132±0.129</td>
<td>-22.21*</td>
<td>2.091±0.102</td>
<td>-1.92NS</td>
</tr>
</tbody>
</table>

Mean± SD of six individual observations. * indicates P<0.001 the level of significance, NS- indicates non significant changes
Table 4: The levels of Glycogen (mg/g wet wt.) in non reproductive tissues of young, aged and estradiol valerate administered aged female rats.

<table>
<thead>
<tr>
<th>Name of the tissue</th>
<th>Young (1)</th>
<th>Aged (2)</th>
<th>% Change (1&amp;2)</th>
<th>Estradiol valerate Administered aged (3)</th>
<th>% Change (2&amp;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>4.121±0.31</td>
<td>4.570±0.37</td>
<td>+10.89***</td>
<td>4.982±0.36</td>
<td>+9.01 NS</td>
</tr>
<tr>
<td>Liver</td>
<td>3.572±0.29</td>
<td>3.011±0.146</td>
<td>-15.7*</td>
<td>3.987±0.154</td>
<td>+32.41*</td>
</tr>
</tbody>
</table>

Mean± SD of six individual observations. * indicates P<0.001, ***indicates P<0.05  the levels of significance, NS- indicates non significant changes

CONCLUSIONS

Due to lowered levels of estrogens in aged rats glycogen synthesis was lowered in which the functional activities of these tissues were affected. The liver glycogen storage capacity was diminished in aged rats and elevated by the estradiol valerate administration. Hyperglycemia was not recommended by EV administration.

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REFERENCES


