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*Full Length Research Paper*

## **Modulating Action of $17\beta$ Estradiol on Urinary Volume and Renal Excretion of Some Electrolytes in Dietary Salt-fed Female Rats**

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### **ABSTRACT**

Body fluid and electrolyte balance are essential for normal cellular function, maintenance of adequate plasma volume and osmolality, yet natural and synthetic female sex hormones have various effects on body fluid and electrolyte balance. This study determined the effect of combined administration of  $17\beta$  estradiol and dietary salt on some renal parameters. Thirty-two female Albino rats were used for this study and they were assigned into four groups consist of eight rats in each group. The group A served as control while groups B, C and D were given daily doses of dietary salt,  $17\beta$  estradiol, and  $17\beta$  estradiol with dietary salt respectively for four weeks consecutively. Twenty four hour urine samples were collected at the end of second and fourth weeks of administration for the determination of some renal parameters. The results were highly significant increase after second and fourth weeks for urinary volume, urinary sodium ions and chloride ion excretion, while there was significant reduction in urinary potassium ion excretion in groups that received dietary salt and  $17\beta$  estradiol ( $p < 0.05$ ) when compared with the control group. It may be concluded that exogenous  $17\beta$  estradiol administration may have some regulatory effect on body electrolytes and fluid in high dietary salt intake female rats.

**Keywords:**  $17\beta$  estradiol, Body fluid, Dietary salt, Electrolytes

### **INTRODUCTION**

The epidemiological, clinical research and one decade of genetic investigation in human and animals have provided remarkable insights on relationships existing between dietary salt (sodium chloride), renal sodium chloride handling and body fluid regulation. The

evidence showed that a chronically high sodium chloride intake participates in the development of hypertension when the kidneys have a reduced ability to excrete sodium chloride (Meneton et al. 2005).

There are gender associated differences in body fluid and sodium regulation in humans and animals. The mechanism responsible for this control is not clear, however, the response to sodium chloride in pre and post-menopausal women and in particular the influence

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of exogenous oestrogen on renal hemodynamic and tubular segmental sodium handling has been poorly investigated (Pechere-Bertschi and Burnier 2004). Oestrogen receptors are found in kidneys involved in fluid regulation (Dubey and Jackson, 2001). The impact of oestrogen on sodium and fluid regulation has important implications for a number of syndromes for which women are at risk, including orthostatic, hypotension and insulin resistance (Fraser and Arieff, 1997). Oestrogen influence the complex, integrated neural and hormonal systems that have evolved to control thirst, fluid intake, sodium appetite, renal fluid and sodium regulation (Stachenfeld, 2008). Pechere-Bertschi and Burnier (2004) reported renal hemodynamic and tubular responses to sodium chloride vary significantly during the normal menstrual cycle and with the administration of oral contraceptives.

Body fluid and electrolyte balance are critical for normal cellular function and maintenance of adequate plasma volume and osmolality, yet natural and synthetic female sex hormones have various effects on body fluid and electrolyte regulation. Whether female sex hormones modulate the renal handling of electrolytes and thereby contribute to the gender associated differences in animal models and in humans is a subject of controversy.

The aim of this study is to investigate the renal excretion of some electrolytes and urinary output in high dietary salt intake female rats administered with exogenous 17 $\beta$  estradiol.

## MATERIALS AND METHODS

### Experimental Animals

Thirty-two female Wistar rats weighing between 180-200g were used for this study. The animals were kept in cages of 90cm x 84cm x 42 cm dimensions with woodchip shavings for bedding which were regularly changed, also standard laboratory conditions of 25°C, 12 hours/12 hours light and dark cycle were maintained. They were fed with standard rat feed and have free access to tap water *ad libitum*. The animals were allowed to acclimatize for one week before grouped into four with eight rats in each.

### Experimental Animals Grouping and Treatment

**Group A** - given the vegetable oil (vehicle) to serve as control;

**Group B** - received 8% dietary salt mixed with feed and each rat was fed independent;

**Group C** - injected intraperitoneally with 0.625 $\mu$ g/kg 17- $\beta$  estradiol;

**Group D** was given 0.625 $\mu$ g/kg 17- $\beta$  estradiol intraperitoneal injection and 8% dietary salt mixed with feed. The injection of 17- $\beta$  estradiol and dietary salt intake were for four weeks consecutively.

### Experimental Procedure

Before the commencement of the administration of drug, dietary salt and vehicle, the rats were housed in metabolic cages for the assessment of food and water intake as well as baseline urine collection overnight. After which administration started, second and fourth urine samples were collected after second and four weeks of administration respectively. Collected urine samples volumes were measured in ml.

Urinary electrolytes were assayed in automated system (NOVA Biomedical Electrolyte Analyzer) at the Chemical Pathology Laboratory of University of Benin Teaching Hospital, Edo State. Creatinine clearance was derived from urine volume and expressed in mM/l

### Statistical Analysis

The results were analyzed with SPSS 17 and statistical significant between the groups was assessed by one way analysis of variance followed by least significant difference test. The results were expressed as mean and standard error of mean.

## RESULTS

After 2 and 4 weeks, there was a significant increase in urinary volume in the rats that were fed with dietary salt, 17 $\beta$  estradiol, and 17 $\beta$  estradiol with dietary salt relative to their baseline in respective groups and when compared with control group (Table 1).

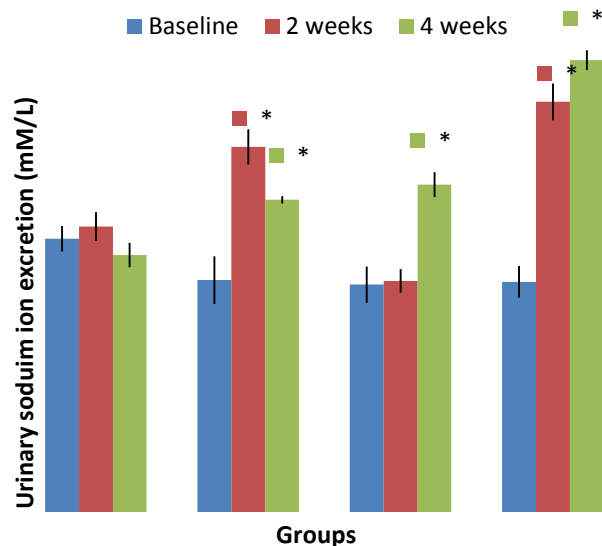
**Table 1:**  
Effect of combined administration of 17 $\beta$  estradiol and dietary salt on urine volume

Groups	Urine volume in ml		
	Baseline	2 weeks	4 weeks
Control	8.7 $\pm$ 2.0	7.1 $\pm$ 1.3	5.2 $\pm$ 0.7
Salt	6.4 $\pm$ 1.5	15.5 $\pm$ 3.1 <sup>a</sup>	11.8 $\pm$ 3.5 <sup>a</sup>
Estradiol	7.4 $\pm$ 1.7	9.4 $\pm$ 2.2 <sup>a</sup>	14.5 $\pm$ 4.2 <sup>a</sup>
Estradiol and Salt	8.4 $\pm$ 4.2	16.7 $\pm$ 3.3 <sup>a</sup>	24.0 $\pm$ 2.4 <sup>a</sup>

Values are expressed in Mean  $\pm$  SEM of 8 rats. <sup>a</sup> is mean significant difference at  $p < 0.05$

Figure 1 shows a significantly increased in renal Na<sup>+</sup> excretion after second week in rats treated with dietary

salt and combination of 17 $\beta$  estradiol and dietary salt groups relative to their baseline and control group, while in the fourth weeks of administration, the results of Na<sup>+</sup> excretion is highly significant in dietary salt, 17 $\beta$  estradiol, and 17 $\beta$  estradiol with dietary salt groups relative to the control group and their baseline.



**Figure 1:**

Effect of combined administration of 17 $\beta$  estradiol and dietary salt on renal Na<sup>+</sup> excretion (mM/L)  
Values are expressed in Mean  $\pm$  SEM of 8 rats. <sup>a</sup> is mean significant difference at  $p < 0.05$

Table 2 revealed a significant reduction in renal K<sup>+</sup> excretion in second and fourth weeks of administration in dietary salt fed rats, 17 $\beta$  estradiol treated rats and 17 $\beta$  estradiol with dietary group relative to control and their baseline.

**Table 2:**

Effect of combined administration of 17 $\beta$  estradiol and dietary salt on renal K<sup>+</sup> excretion (mM/L)

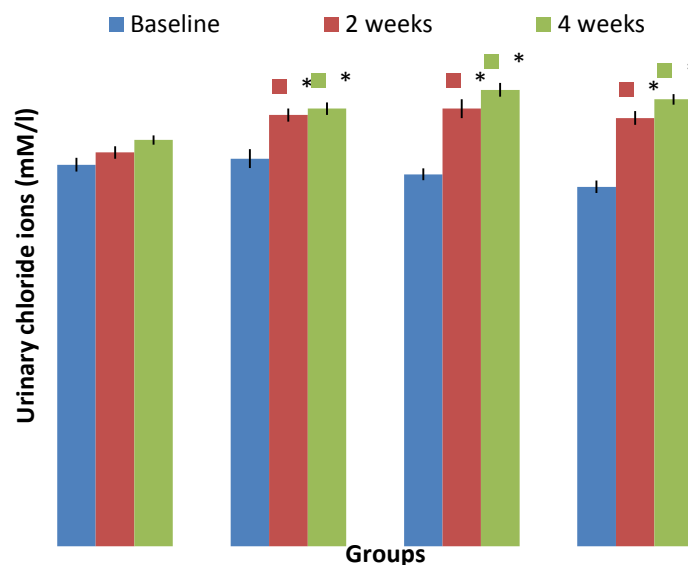
Groups	Renal K <sup>+</sup> excretion (mM/L)		
	Baseline	2 weeks	4 weeks
Control	64.7 $\pm$ 6.9	62.2 $\pm$ 12.6	65.8 $\pm$ 11.2
Salt	67.5 $\pm$ 8.7	35.9 $\pm$ 4.8 <sup>a</sup>	34.8 $\pm$ 5.3 <sup>a</sup>
Estradiol	63.7 $\pm$ 9.0	20.3 $\pm$ 2.7 <sup>a</sup>	16.3 $\pm$ 2.3 <sup>a</sup>
Estradiol and Salt	67.6 $\pm$ 6.3	16.7 $\pm$ 1.3 <sup>a</sup>	14.8 $\pm$ 2.6 <sup>a</sup>

values are expressed in Mean  $\pm$  SEM of 8 rats. <sup>a</sup> is mean significant difference at  $p < 0.05$

Figure 2 shows significant increase in renal chloride ion excretion in groups treated with dietary salt, 17 $\beta$  estradiol, and 17 $\beta$  estradiol with dietary salt after second

and fourth weeks of administration when compared with control group and their baseline.

Table 3 shows no significant difference in creatinine clearance in the rats that received dietary salt, 17 $\beta$  estradiol and combined 17 $\beta$  estradiol and dietary salt when compared with the control and their baseline.



**Figure 2:**

Effect of combined administration of 17 $\beta$  estradiol and dietary salt on renal Cl<sup>-</sup> excretion (mM/L).  
Values are expressed in Mean  $\pm$  SEM of 8 rats. <sup>a</sup> is mean significant difference at  $p < 0.05$

**Table 3:**

Effect of combined administration of 17 $\beta$  estradiol and sodium chloride on renal creatinine excretion (mM/L)

Groups	Renal creatinine excretion (mM/L)		
	Baseline	2 weeks	4 weeks
Control	2.2 $\pm$ 0.8	2.0 $\pm$ 0.5	2.2 $\pm$ 0.3
Salt	2.2 $\pm$ 0.5	2.0 $\pm$ 0.4	2.1 $\pm$ 0.5
Estradiol	2.2 $\pm$ 0.3	2.3 $\pm$ 0.1	2.7 $\pm$ 0.4
Estradiol and salt	2.2 $\pm$ 0.3	2.7 $\pm$ 0.4	3.0 $\pm$ 0.6

Parameters are expressed in Mean  $\pm$  SEM of 8 rats. <sup>a</sup> is mean significant difference at  $p < 0.05$

## DISCUSSION

High dietary Na<sup>+</sup> intake disposes the individual to a higher ECF volume, osmolality and a higher blood pressure (Granger, 2003). 17 $\beta$  estradiol influence the complex and integrated neural and hormonal systems that have evolved to control thirst, fluid intake, sodium

appetite, renal fluid and sodium regulation (Stachenfeld, 2008). The present study investigates the urinary volume, renal excretion of sodium, potassium, chloride ions and creatinine in high dietary salt intake female albino rats administered with exogenous  $17\beta$  estradiol. The results of this study showed significant increase in urinary volume, renal excretion of sodium and chloride ions and decreased in potassium ions excretion in the female rats that received dietary salt,  $17\beta$  estradiol, as well as when  $17\beta$  Estradiol was combined with dietary salt.

The increased in urinary volume observed in combined  $17\beta$  estradiol and dietary salt treated rats was in time dependent manner and may be attributed to low osmotic anti-diuretic hormone threshold in the hypothalamus associated with  $17\beta$  estradiol administration which has been related to the particular subtypes of estrogen receptors (Paech, *et al.* 1997). Anti-diuretic hormone and thirst are highly sensitive to changes in plasma osmolality and volume stimuli via central osmo sodium ion receptors in hypothalamus and peripheral baroreceptor (Stachenfeld, Keefe, 2002; Stachenfeld *et al.* 2001). The observed increased in urinary volume in dietary salt fed rats declined after fourth weeks, this may be a result of increase osmolality by salt loading which has been reported to cause stimulation of renin secretion, anti-diuretic hormone and thirst center in hypothalamus since fluid regulatory mechanisms are far more sensitive to osmotic than volume stimuli (Pechere-Bertschi and Burnier, 2004). Although Stachenfeld (2008) reported increases in fluid retention during estradiol administration, renal free water clearance was unaffected by estrogen administration, they suggested that estrogens may alter renal sensitivity to AVP or even interfere with AVP action in the kidney as has been noted in collecting ducts of rat kidneys.

The urinary sodium ions excretion was initially increased after second week of administration of dietary salt relative to baseline and decline after fourth weeks of administration. This observation may be attributed to the function of kidneys to readjust to salt loading (Meneton *et al.*, 2005). The excretion of urinary sodium ions in rats treated with  $17\beta$  estrogen and dietary salt was significantly increased in time depended way. There is discrepancy between our finding and previous reports which stated that  $17\beta$  estradiol administration in hypertonic infused rats increased sodium ions retention as a result of activation of renin-angiotensin-aldosterone system by estrogen (Kang *et al* 2001; Kuroski, 1999), however, there is some evidence suggesting that  $17\beta$  estradiol may actually protect against a salt-induced water retention, possibly by augmenting the renal

excretion of sodium (Pechere-Bertschi and Burnier, 2004). The modulating action of  $17\beta$  estradiol on sodium ions excretion may also augments urinary volume excretion. The mechanism of this may be as a result of tubuloglomerular feedback and maintenance of glomerulotubular balance (Barrett *et al*, 2010).

The increased in urinary chloride ions observed in  $17\beta$  estradiol and combination of  $17\beta$  estradiol with dietary salt rats in this study may be secondary to the increased in urinary sodium ions excretion.

The insignificant change observed in the level of creatinine excretion in all the groups studied may be attributed to the rate of creatinine production that depends on the rate of turnover of endogenous muscle which may be the same in all the rats used (Schafer, 2003).

This study showed increased in urinary volume, renal excretion of sodium and chloride ions in dietary salt fed female rats treated with  $17\beta$  estradiol compared with dietary salt fed female rats alone. Therefore, it postulated that exogenous  $17\beta$  estradiol administration may modulate blood pressure through the regulation of urinary volume and excretion of sodium and chloride ions in high dietary salt intake female rats.

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