Angiotensin-II receptor type one gene expression in ovariectomized rats under estradiol therapywith either beta- 1receptor or angiotensin- II receptor blockers

Thesis

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SUMMARY

Postmenopausal hypertension is a major health problem; the prevalence of hypertension in postmenopausal women is increasing dramatically worldwide. Postmenopausal hypertension is characterized by complications affecting several organs, including the heart and the kidney. It was found that activation of the RAAS which results in imbalance sodium and water regulation, and estrogen regulation to the AT1 gene in the target tissues are involved in the pathogenesis of postmenopausal hypertension.

There is mounting evidence to support the notion that estrogen can prevent, and even reverse, many early changes in the cardiovascular and renal tissues from ovariectomized animals.

This study was carried out in order to clarify the protective effect of estrogen supplementations on blood pressure control in ovariectomized animals and its possible mechanism of antihypertensive action alone and in combination with of the beta-1 blocker and angiotensin- II receptor blocker.

This study was carried out on 7 main groups (each contains 10 rats) of adult female albino rats. The first of them is the sham operated control group received no medications. All the other groups were ovariectomized. The 2nd group was ovareiectomized rats received no treatment. The 3rd OVX group received conjugated estrogen at dose (50µg /kg),it was administrated daily for 8 weeks. The 4th OVX group received atenolol at a dose of (30 mg /kg),it was administrated daily for 8 weeks. The 5th OVX group receivedboth conjugated estrogen at a dose of (50µg /kg) and atenolol at dose (30 mg/kg) orally. Both were administrated for 8 weeks. The 6th OVX group received valsartan at a dose of (10mg/kg),it was administrated daily for 8 weeks. The 7th OVX group receivedboth conjugated estrogen at a dose of (50µg /kg) and valsartan at dose (10 mg/kg) orally. Both were administrated for 8 weeks.

The parameters used to evaluate the ovarictomy and estrogen replacement treatment consequences were serum renin, aldosterone, angiotensin- II, sodium, potassium and bicarbonates Also urinary sodium and potassium level were measured. The kidney function was evaluated by the serum urea and creatinin.

While the AT1 receptor gene expression was measured by Quantitative real time PCR in the heart, kidney and adrenal glands.

The obtained results of this study could be summarized as follow:

- The ovariectomy of the rats resulted in activation of the RAAS manifested by a significant increase in the serum levels of renin, aldosterone and angiotensin -II and also was associated with significant increase in the serum creatinin, serum urea and serum sodium and significant decrease in serum potassium and bicarbonates levels. The examination of AT1 gene showed significant increase in all examined tissues.
- On studying the prophylactic effect of estrogen by a dose (50µg /kg) there were a significant decrease in the serum levels of renin, aldosterone, angiotensin- II, sodium, urea and creatinin. While there were a significant increase in the serum levels of potassium and bicarbonates. Also there were a significant increase in the urinary levels of sodium and significant decrease in urinary level of potassium. Also there were a significant decreasein the gene expression of angiotensin- II type I receptors in the heart tissue, kidney and adrenal glands.The blood pressure both systolic and diastolic were lowered by estrogen.

- On studying the effect of atenolol by a dose (30mg/kg) there were a significant decrease in the serum levels of renin, aldosterone, angiotensin-II, sodium, urea and creatinin. While there were a significant increase in the serum levels of potassium and bicarbonates. Also there were a significant increase in the urinary levels of sodium and significant decrease in urinary level of potassium. Also there were a significant decreasein the gene expression of angiotensin- II type I receptors in the heart tissue, kidney and adrenal glands. The blood pressure both systolic and diastolic were lowered.

- On studying the effect of valsartan by a dose (10mg/kg) there were a significant decrease in the serum levels of renin, aldosterone, angiotensin-II, sodium, urea and creatinin. While there were a significant increase in the serum levels of potassium and bicarbonates. Also there were a significant increase in the urinary levels of sodium and significant decrease in urinary level of potassium. Also

there were a significant decreasein the gene expression of angiotensin- II type I receptors in the heart tissue, kidney and adrenal glands. The blood pressure both systolic and diastolic were lowered.

- On studying the prophylactic effect of both conjugated estrogen by a dose (50µg /kg) and atenolol by a dose (30mg/kg) or valsartan by a dose (10mg/kg), there were a significant decrease in the serum levels of renin, aldosterone, angiotensin-II, sodium, urea and creatinin. While there were a significant increase in the serum levels of potassium and bicarbonates. Also there were a significant increase in the urinary levels of sodium and significant decrease in urinary level of potassium. Also there were a significant decreasein the gene expression of angiotensin- II type I receptors in the heart tissue, kidney and adrenal glands. The blood pressure both systolic and diastolic were lowered.

- By comparing the treated groups together, the estrogen combined valsartan group there were significant decrease in the serum levels of renin, aldosterone, angiotensin- II, sodium, urea and creatinin. While there were a significant increase in the serum levels of potassium and bicarbonates. Also there were a significant increase in the urinary levels of sodium and significant decrease in urinary level of potassium. Also there were a significant decreasein the gene expression of angiotensin- II type I receptors in the heart tissue, kidney and adrenal glands. The blood pressure both systolic and diastolic were lowered, having the nearest levels to normal control group in most of the parameters, so we could consider it the best combination group in our study.

From the above results we conclude that the pathogenesis of postmenopausal hypertension is mediated even partially through estrogen effect on the RAAS and especially the AT1 gene expression and that estrogen and valsartan combination have a more cardioprotective effect.

RECOMMENDATIONS

- Further studies on the prophylactic effects of estrogen on hypertension in humans could have clinical application or not yet. We only demonstrate the effect of estrogen alone and combined with atenolol or valsartan on the RAAS system and at the level of gene expression in different tissues.
- Further studies on estrogen if they could have a possible curative effect in cases of postmenopausal hypertension.