ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKADE SUPPRESSES NLRP3 INFLAMMASOME AND IL-1β, WHILE INCREASING BDNF LEVEL IN OVARIECTOMIZED FEMALE RATS

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INTRODUCTION

Several lines of evidence suggest that hormonal changes after menopause may play an important role in the incidence of cognitive dysfunction, and also in the development of Alzheimer's disease (AD)(1). The brain has its own renin angiotensin system (RAS). Accumulating evidence indicates that over-stimulation of RAS is associated with β-amyloid induced apoptosis, oxidative stress, neuroinflammatory response and neurodegeneration in Alzheimer's disease. Several studies have shown angiotensin receptor blockers (ARBs) have neuroprotective effects (2). The nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation contribute to inflammation in hippocampus upon to deprivation of ovary. Activation of NLRP3 inflammasome subsequently activates caspase-1 and induces the secretion of IL-1β (3).
Brain derived neurotrophic factor (BDNF) can exert protective effects by increasing the survival time of neurons and promoting neuronal repair. Estrogen regulates the expression of BDNF expression (4). Many studies have reported a relationship between estrogen depletion and activation of the RAS (5).

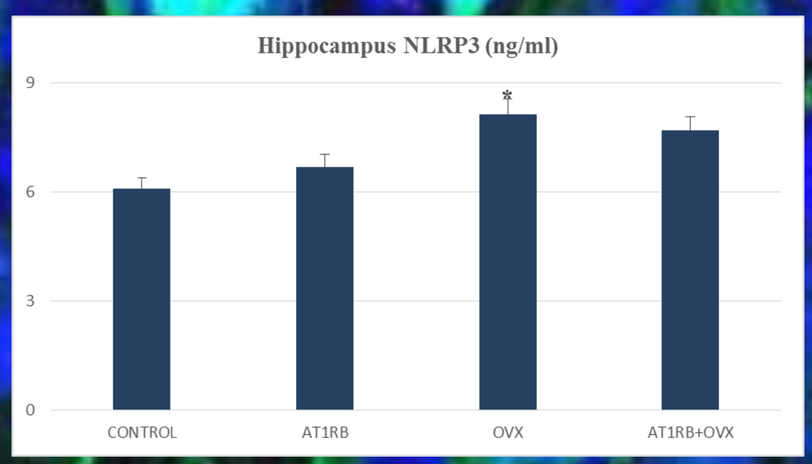
OBJECTIVES

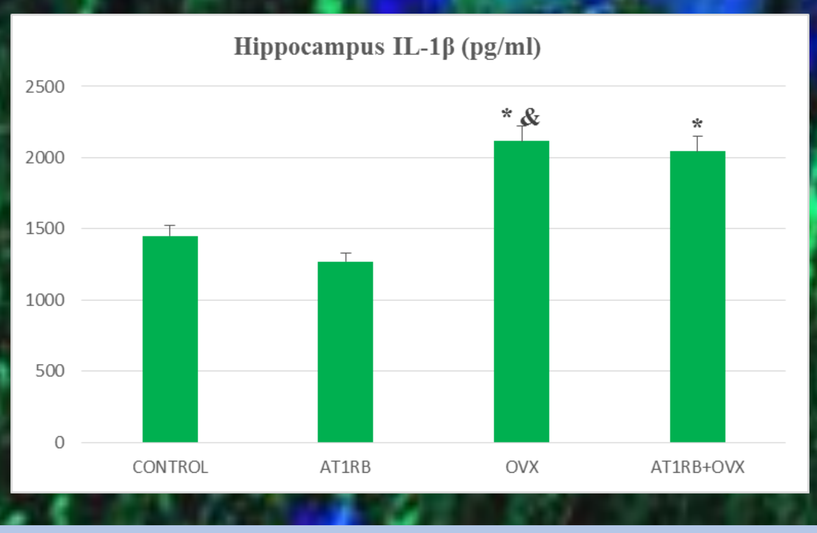
The aim of this study was to investigate the possible protective effects of blocking of angiotensin II type 1 receptor by determining the levels of NLRP3, IL-1β, BDNF in the hippocampus in ovariectomized rats.

METHODS

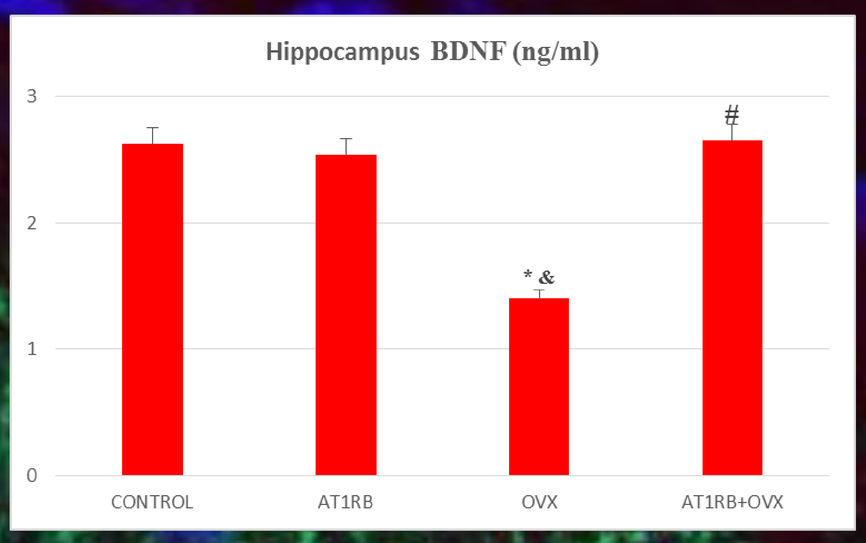
In this study, 32 female Wistar albino rats (200-220 g) were used. Rats were ovariectomized bilaterally to remove the principal source of endogenous estrogen. After 2 weeks of recovery, the rats were divided into four groups (each group n = 8) as follows: Sham control (control), angiotensin II type 1 receptor blocker (AT1RB) treated group, ovariectomized model (OVX), ovariectomy + AT1RB (OVX + AT1RB). AT1RB, valsartan, was administered at a dose of 40mg/kg/ day by intragastric gavage for 14 days. Hippocampus tissue levels of NLRP3, IL-1β, BDNF and CREB were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits.
Statistical analyses of data were performed by Kruskal Wallis and Dunn Tests.

RESULTS

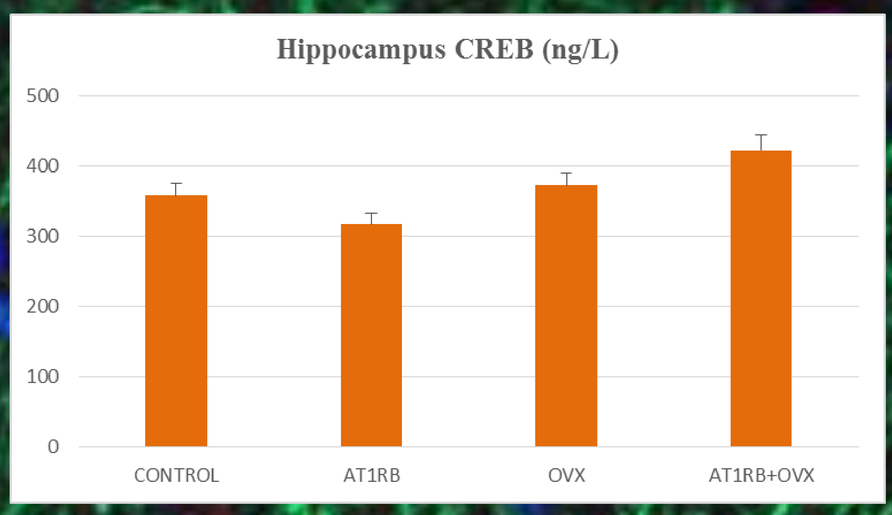




Our results showed that IL-1 and NLRP3 levels were significantly increased in hippocampus of OVX rats ($p<0,05$).
AT1RB did not supressed the levels of NLRP3 and IL-1β in OVX rats ($p>0,05$).



OVX resulted a decreased in BDNF levels in the hippocampus. AT1RB produced a significant increase in hippocampal BDNF levels in OVX rats ($p<0,05$).



The levels of CREB did not change both by OVX and AT1RB treatment ($p>0,05$).

* shows the difference compared to the control group.
- # indicates the difference compared to the OVX group
- & shows the difference compared to AT1RB treated control group (*, **#, & $p<0,05$).**

DISCUSSION

Decreased estrogen levels, due to menopause or ovariectomy, may contribute to memory impairments and neurodegeneration in rats.(1)
In the present study, we demonstrated that ovariectomy resulted in elevation of NLRP3 inflammasome in hippocampus, and subsequently led to an increase in IL-1β in hippocampus.
AT1RB could not reverse the increase of NLRP3 inflammasome and decrease the level of IL-1β in hippocampus of OVX rats. It is well known that there is a correlation between estrogen defciency and RAS components, as both can cause progression of AD and deposition of Aβ in neurons (5).
Our results also confirmed that after ovarian ablation, the level of BDNF in the hippocampus was significantly reduced. This result is accordance with previous studies (4). Valsartan treatment increased the level of BDNF in the hippocampus.

CONCLUSION

Our data indicate that AR1Bs have neuroprotective potential in the loss of ovarian function by increasing BDNF levels.

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