2012-13

Rajnibhai V. Patel
PharmInnova Award
Best M. Pharm Thesis

WINNER

Winner

Mr. Dhaval S Bendale

Research Guide

Prof. Kulbhushan Tikoo

Subject:
Pharmacology

Thesis Title :
17-β estradiol alleviates endothelial dysfunction and downstream angiotensin signaling in estrogen deficient rats fed on high fat diet via activation of SIRT/AMPK pathway

College:
NIPER, SAS Nagar, Punjab

Hormone replacement therapy (HRT) reduces cardiovascular disorders in menopausal women

Outcome of Research:

Women at or after menopause are predisposed to the risk of cardiovascular disorders (CVDs) due to clinical state of estrogen deficiency and effective use of exogenous estrogen as Hormone replacement therapy (HRT) can be beneficial. This study was in its kind the first ever approach to clinically mimic the Post Menopausal Metabolic Syndrome (PMS) in rats by providing High fat diet (HFD) and ovariectomy. In this study, the interplay of various signaling pathways at molecular level has been characterized to better understand the reason of increased cardiovascular risk in PMS and how 17-β Estradiol provides vasoprotective effects by activating intracellular signal (SIRTI/AMPK/eNOS axis). Identifying such key molecular pathways will help to open up new avenues for the novel therapeutic options in the treatment of PMS.

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ABSTRACT

Lifestyle evolution and precisely consumption of high-fat enriched western diet has been credited to worldwide accumulating incidences of Type II Diabetes Mellitus (DM) and cardiovascular disorders (CVDs). Corroborating data from experimental and clinical studies have revealed insulin resistance (IR) as a predisposing factor for endothelial dysfunction (ED). Estrogen has been described as an essential hormone in females critically regulating a myriad of cardio-metabolic functions. Menopause, a clinical condition of estrogen deficiency is associated with various cardiac complications. However, the exact mechanisms of beneficial actions of estrogen are poorly understood. The present study was designed to understand the underlying molecular mechanisms involved in Post-menopausal Metabolic Syndrome (PMS) (i.e. concomitant insulin resistance and menopause).

The primary purpose of the study was to investigate combined effects of insulin resistance and estrogen deficiency [High fat diet (HFD) + ovariectomy (OVX) group – mimicking post-menopausal metabolic syndrome] on endothelial dysfunction, downstream Angiotensin II signaling, and further characterizing the novel mechanisms behind vasoprotective role of estrogen. Our results demonstrate that a 10-week of HFD feeding in OVX rats induces all clinical features of PMS (evident by morphometric measurements and biochemical measurements). Endothelial dysfunction was observed in OVX, HFD and to a greater extent in HFD+OVX rats, which was alleviated by supplementing with 17-β estradiol. Additionally, HFD+OVX also aggravated Angiotensin-II mediated downstream MAP kinase and NOX signaling as compared to OVX and HFD alone. 17- β estradiol was effective in partially reversing these effects. Our findings suggest that vasoprotective effects of 17- β estradiol involve activation of SIRT1/AMPK/eNOS activation. All these changes were accompanied with altered chromatin structure as evident from aberrant histone (H3) phosphorylation. These results support the hypothesis that activation of SIRT1/AMPK/eNOS axis by estrogen in PMS alleviates cardiovascular risk and presents a potential target for understanding its molecular mechanisms. Further understanding of epigenetic regulation of above axis may yield new insights into pathogenesis of PMS.