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Original Article

Small Molecule Compound Nerolidol attenuates Hypertension induced hypertrophy in spontaneously hypertensive rats through modulation of Mel-18-IGF-IIR signalling

Yueh-Min Lin [a, b], Khan Farheen Badrealam [c], Chia-Hua Kuo [d], Jayasimharayalu Daddam [c], Marthandam Asokan Shibu [c], Kuan-Ho Lin [e, f], Tsung-Jung Ho [g, h, i], Vijaya Padma Viswanadha [j], Wei-Wen Kuo [k, l, 1], Chih-Yang Huang [c, m, n, o, p, 1]

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Abstract

Background

Cardiovascular diseases are caused by multitudes of stress factors like hypertension and their outcomes are associated with high mortality and morbidity worldwide. Nerolidol, a naturally occurring sesquiterpene found in several plant species, embodies various pharmacological benefits against numerous health disorders. However, their effects on hypertension induced cardiac complications are not completely understood.

Purpose

The present study is to elucidate the efficacy of nerolidol against hypertension related cardiac hypertrophy in spontaneously hypertensive rats (SHRs).

Study Design

For preliminary *in vitro* studies, H9c2 cardiomyoblasts cells were challenged with 200 nM Angiotensin-II (AngII) for 12 h and were then treated with nerolidol for 24 h. The hypertrophic effect in H9c2 cells were analyzed by actin staining and the modulations in hypertrophic protein markers and mediators were

determined by Western blotting analysis. For *in vivo* experiments, sixteen week-old male Wistar Kyoto (WKY) and SHRs were segregated into five groups (n = 9): Control WKY, hypertensive SHRs, SHRs with low dose (75 mg/kg b.w/day) nerolidol, SHRs with high dose (150 mg/kg b.w/day) nerolidol and SHR rats treated with an anti-hypertensive drug captopril (50 mg/kg b.w/day). Nerolidol treatment was given orally for 8 weeks and were analysed through Echocardiography. After euthanasia, hematoxylin and eosin staining, Immunohistochemical analysis and Western blotting was performed on left ventricle tissue.

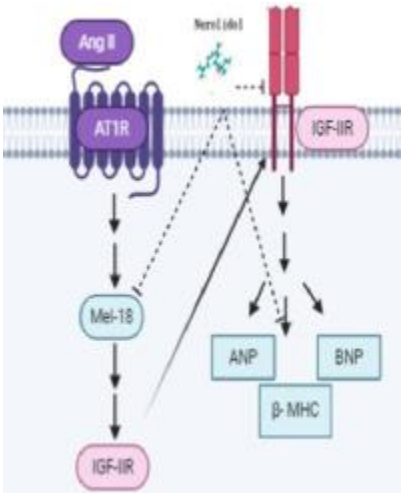
Results

Western blotting analysis revealed that nerolidol significantly attenuates AngII induced expression of hypertrophic markers ANP and BNP in H9c2 cardiomyoblasts. In addition, actin staining further ascertained the potential of nerolidol to ameliorate AngII induced cardiac hypertrophy. Moreover, nerolidol administration suppressed the hypertrophic signalling mediators like calcineurin, GATA4, Mel-18, HSF-2 and IGFIIR in a dose-dependent fashion. In silico studies also ascertained the role of Mel-18 in the ameliorative effects of nerolidol. Further, these intriguing *in vitro* results were further confirmed in *in vivo* SHR model. Oral neraolidol in SHRs efficiently reduced blood pressure and ameliorated hypertension induced cardiac hypertrophic effects by effectively reducing the levels of proteins involved in cardiac MeL-18-HSF2-IGF-IIR signalling.

Conclusion

Collectively, the data reveals that the cardioprotective effect of nerolidol against hypertension induced hypertrophy involves reduction in blood pressure and regulation of the cardiac Mel-18-IGFIIR signalling cascade.

Graphical Abstract



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Keywords

Nerolidol; Hypertrophy; Angiotensin II; Hypertension; SHR

Abbreviations

AngII, Angiotensin-II; ANP, Atrial natriuretic peptide; ATCC, American Type Culture Collection; BLAST, Basic local Alignment search Tool; BNP, Brain natriuretic peptide; BP, Blood pressure; CPTL, Captopril; CVDs, Cardiovascular diseases; DAB, 3,3′-diaminobenzidine; ELISA, Enzyme linked Immunosorbent assay; GATA4, GATA Binding Protein 4; HF, Heart failure; HSF-2, Heat shock factor-2; IGFIIR, Insulin like growth factor II; LVIDd, Left ventricular internal diameter end diastole; LVIDs, Left ventricular internal diameter end systole; NAMD, Nano Molecular Dynamics; RMSD, Root Mean Square Deviation; SHR, Spontaneously hypertensive rats; WKY, Wistar Kyoto rats

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[1] Authors share equal contribution.

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