Small-molecule inhibitors of protein aggregation and ER stress as a novel strategy against neurodegeneration in the course of synucleinopathy

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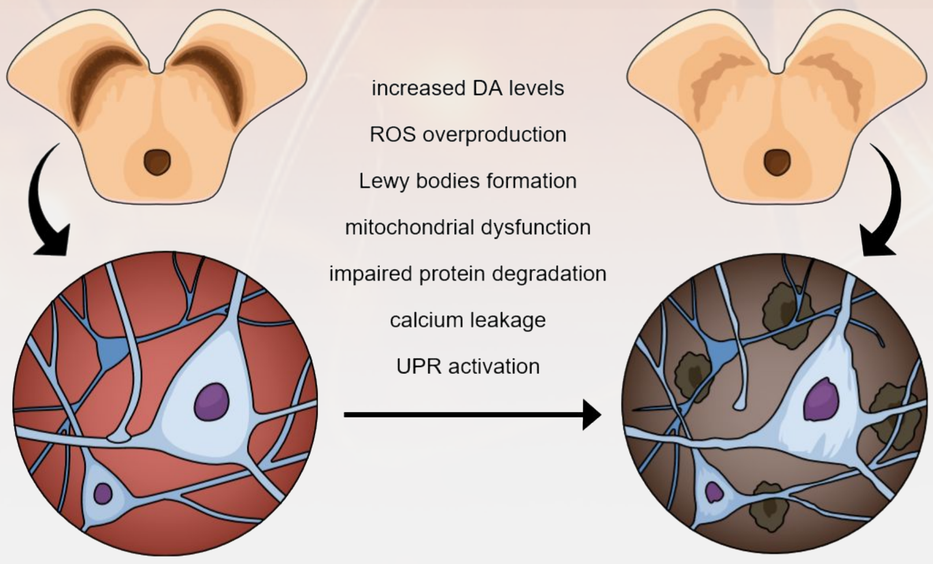
INTRODUCTION

- **Neurodegeneration in Parkinson's disease (PD) is associated with accumulation of α-synuclein and induction of Endoplasmic Reticulum (ER) stress in dopaminergic neurons.**
- **Under such conditions, the PERK branch of the UPR signaling pathway is activated.**
- **PERK orchestrates neural cell apoptosis via upregulation of specific, pro-apoptotic genes.**



OBJECTIVES

The primary objective of the present study was to evaluate the effectiveness of the selected small-molecule PERK inhibitor LDN-87357 (LDN) in PD *in vitro* model.

METHODS

1. XTT assay was used for the cytotoxicity analysis. SH-SY5Y cells were exposed to LDN at 0.75-100μM + 50mM or 0.1% DMSO (solvent). Cell viability upon treatment with LDN was also assessed in cells exposed to an ER stressor, thapsigargin (Th), at 500nM. Cells treated with Th only served as a positive control, and untreated cells as a negative control.

2. To assess the mRNA expression levels of specific pro-apoptotic ER stress-related genes, qPCR was performed. Cells were treated with LDN at 0.75 and 50μM, 0.1% DMSO, 500nM Th or with LDN+Th. Untreated cells constituted a negative control.

RESULTS

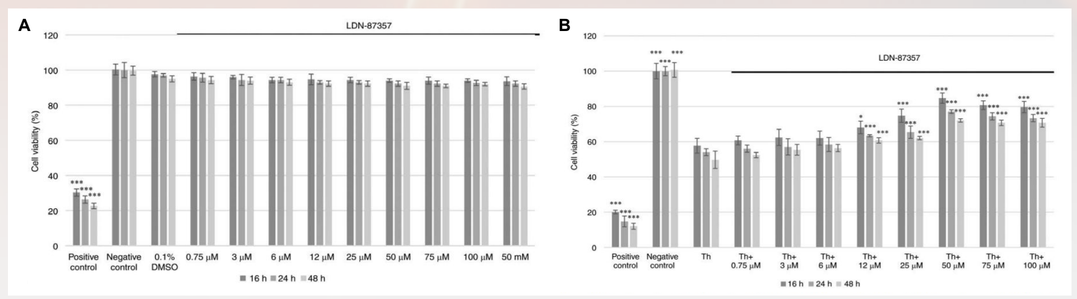


Fig. 1. Cytotoxicity analysis in SH-SY5Y cells treated with LDN (A) or LDN+Th (B) using XTT assay. The data are presented as mean ± SE. *P<0.05, and ***P<0.001 vs. negative control (A) or Th (B).

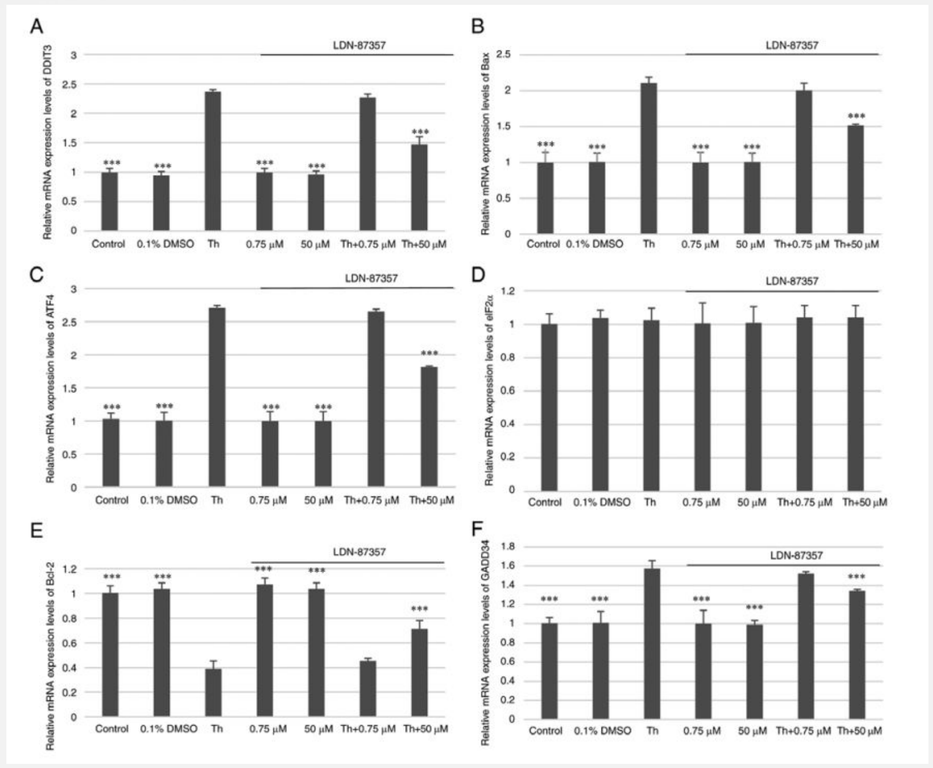


Fig. 2. The mRNA expression levels of *DDIT3* (A), *Bax* (B), *ATF4* (C), *eIF2α* (D), *Bcl-2* (E) and *GADD34* (F) in SH-SY5Y cells treated with Th, LDN or LDN+Th. The data are presented as mean ± SE. ***P<0.001 vs. Th.

CONCLUSIONS

Small-molecule PERK inhibitor LDN is effective against neurodegeneration in PD *in vitro*. Thus, we assume that it may contribute to development of novel, targeted therapy against PD.

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