Incretin mimetics restore the ER-mitochondrial axis and switch neuronal fate towards survival.

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Abstract

Background and Purpose: Amyotrophic lateral sclerosis with associated frontotemporal dementia, Alzheimer's disease, Huntington's disease, and Parkinson's disease are the major neurodegenerative disorders that afflict more than 7 million people worldwide. There are no disease-modifying or disease-retarding therapeutic agents currently available on the market. All four conditions feature several seemingly-disparate pathological and genetic lesions, which, however, converge into calcium dyshomeostasis and a disturbed function of the axis of the endoplasmic reticulum (ER) and mitochondria. Experimental Approach: Incretin mimetics – traditionally anti-diabetic therapeutic agents – have been repeatedly shown to exert neurotrophic effects in neuroblastoma cells, rodent primary neurones, and murine models of neurodegeneration. Herein, for the very first time, we assess the pharmacological effects of Liraglutide and the dual incretin DA-CH3 in terminally differentiated human neurones under conditions of calcium-dependent chronic ER stress and additionally assess their efficacy in one of the most critical regulatory point for neurones, the mitochondrial respiration and dynamics. Key Results: Liraglutide and DA-CH3 rescue the arrested oxidative phosphorylation and glycolysis. They mitigate the suppressed mitochondrial biogenesis and hyper-polarisation of the mitochondrial membrane, all, to re-establish normalcy of cellular bioenergetics under conditions of chronic ER stress. These effects correlate with a resolution of the unfolded protein response and the autophagic arrest to halt the excessive synaptic and neuronal death, with the dual incretin displaying a superior anti-apoptotic effect. Conclusions: Our findings pave the way for a therapeutic strategy for disorders with a considerable social-economic burden and deepen our understanding of the spectrum of the incretin-signalling functions.

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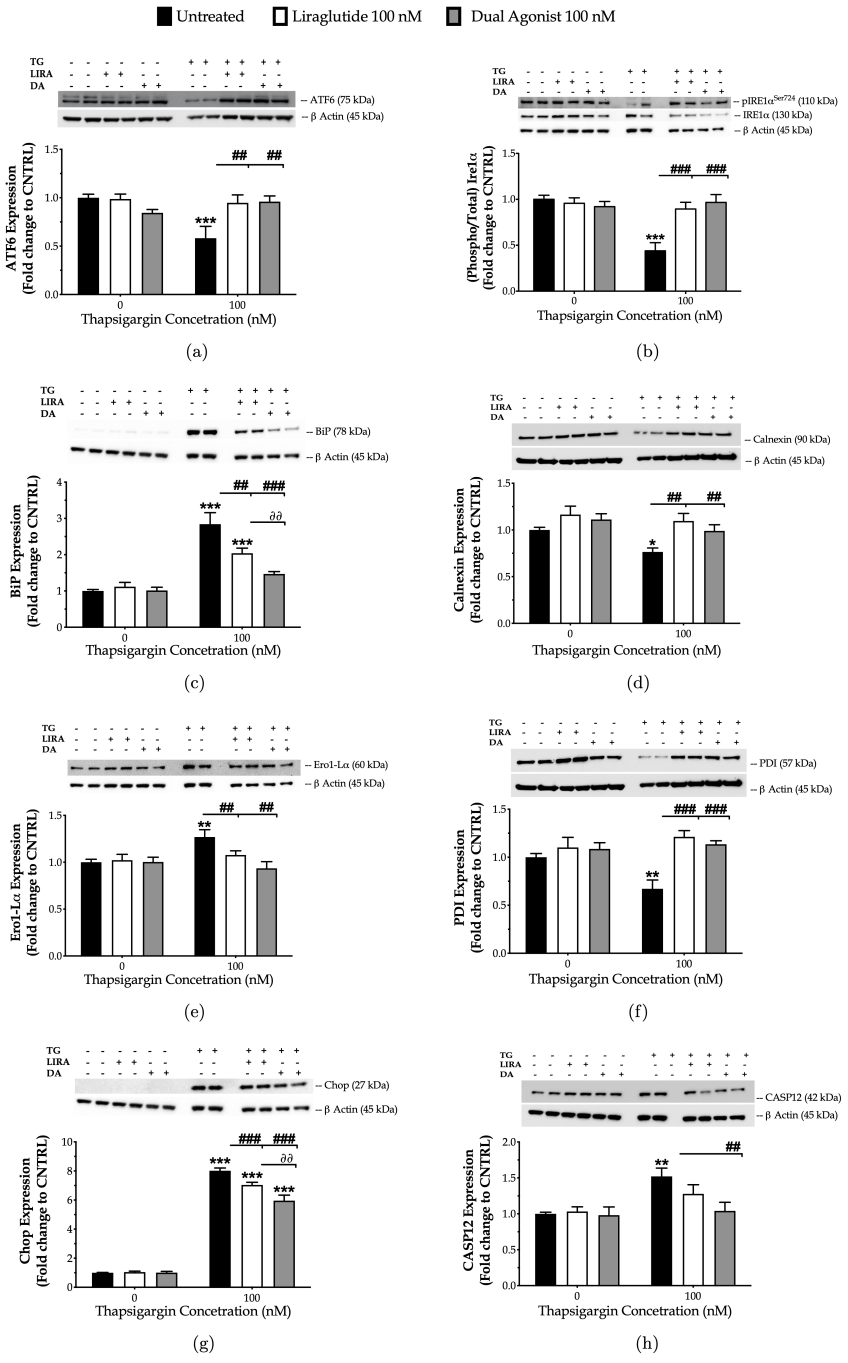
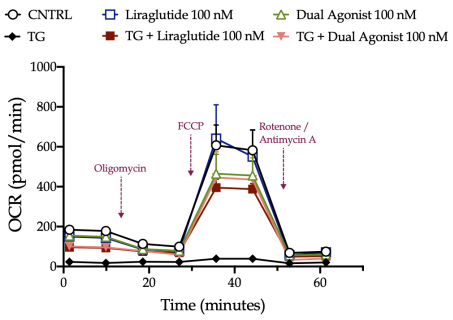
Name	**Amino acid sequence**	**MW** (Da)	**Reference**
Liraglutide	HAEGTFTSDVSSYLEGQAA[Lys-γE-C16 acyl]EFIAWLVRGRG–OH	3751.26	[?]
GLP-1/GIP dual agonist	YXEGTFTSDYSIYLDKQAAXEFVN WLLAGGPSSGAPPPS[Lys-C16]–NH_2	4234.63	[?]





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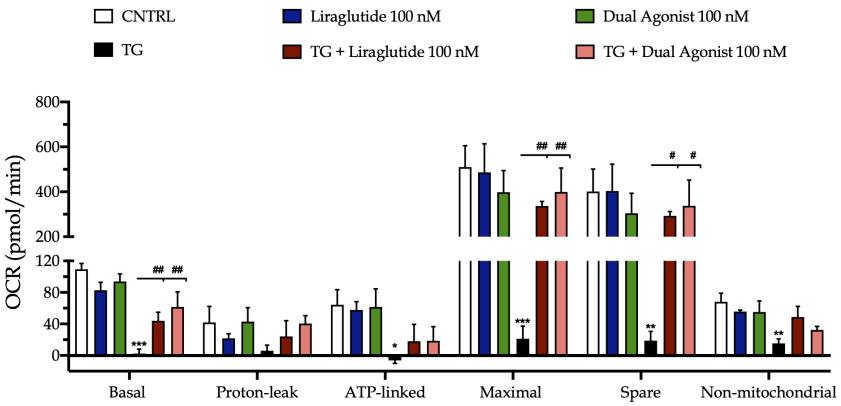

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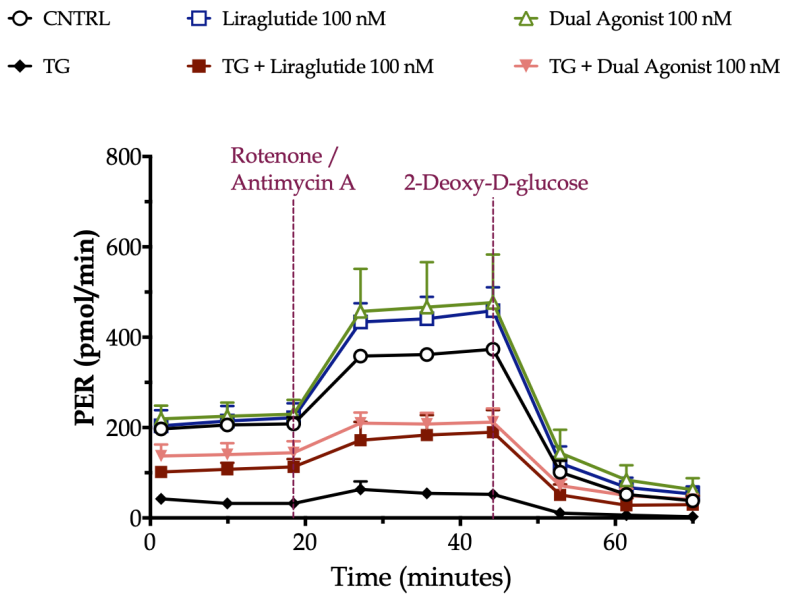

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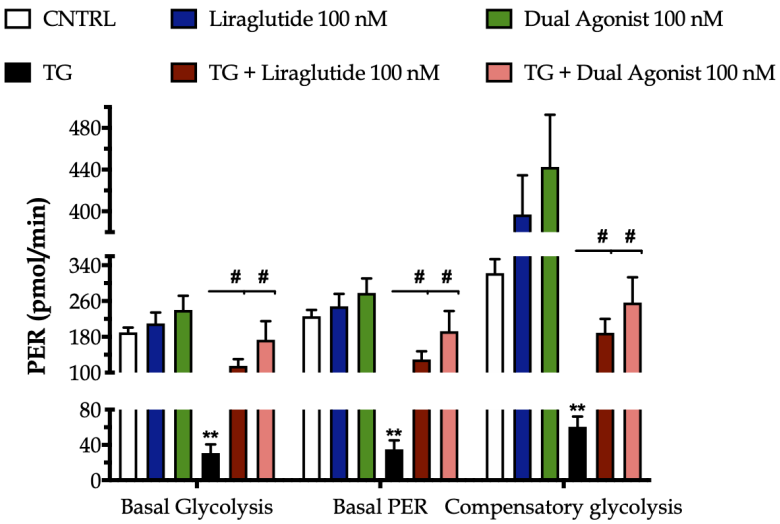

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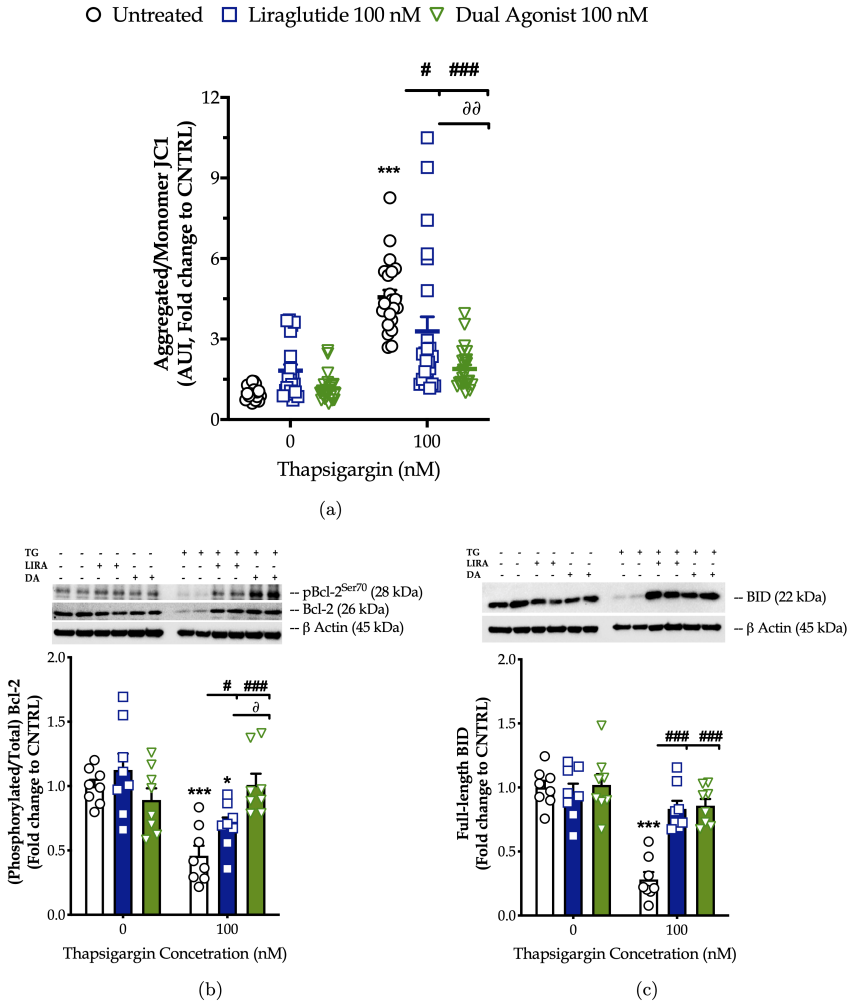

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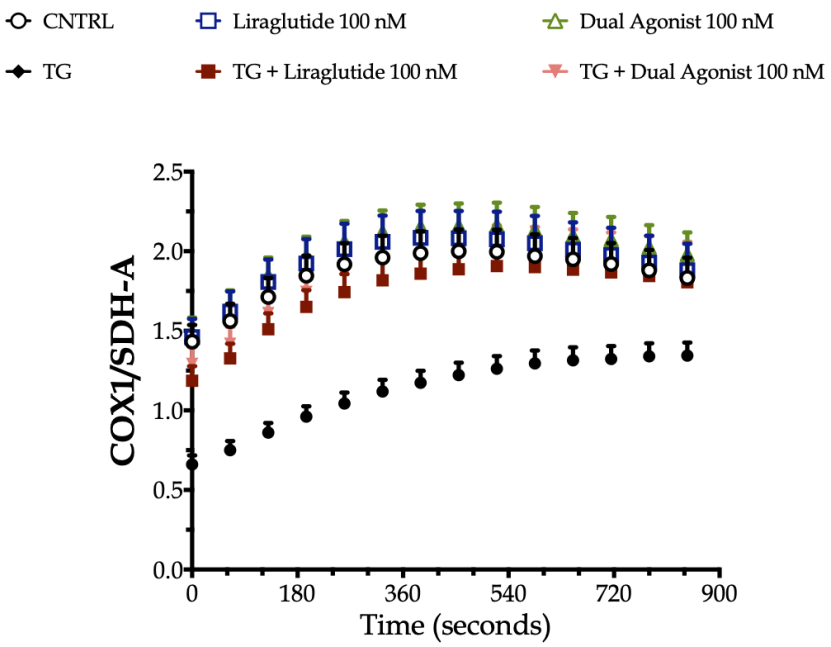

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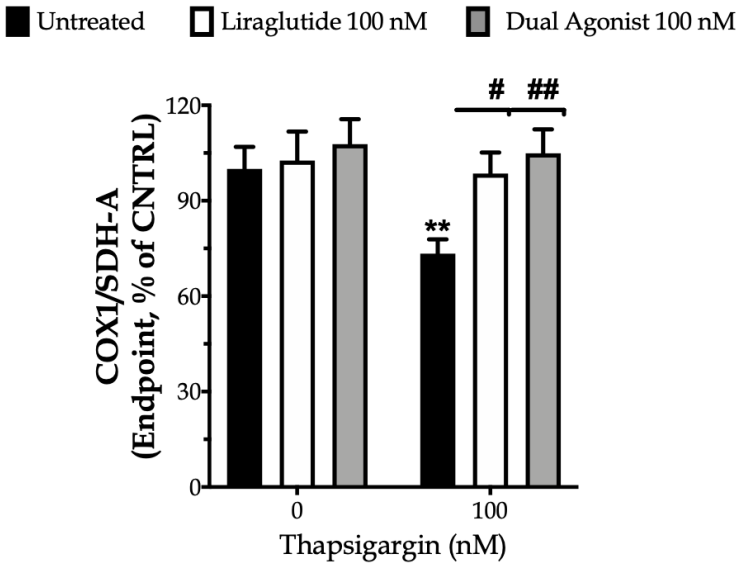

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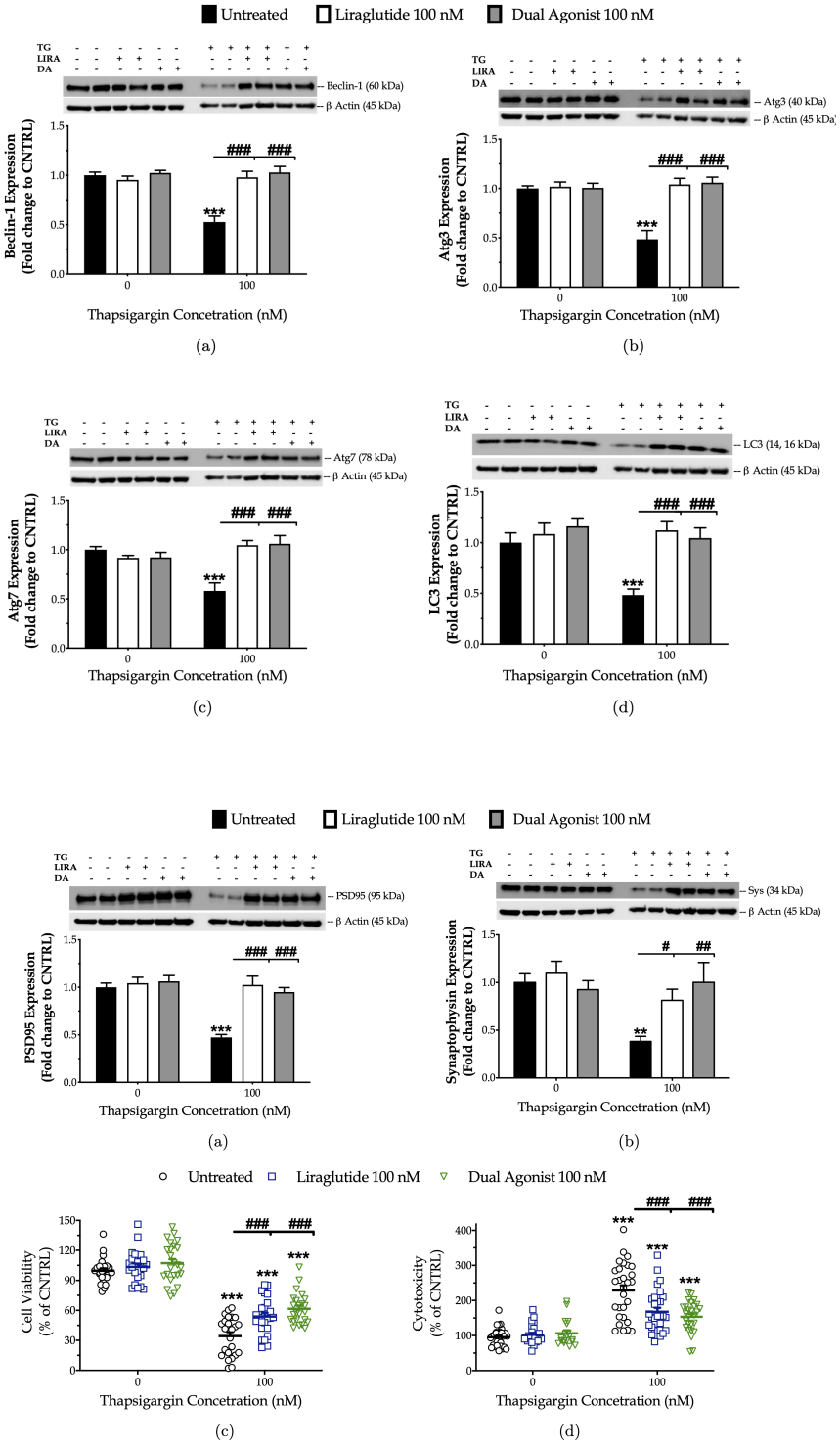

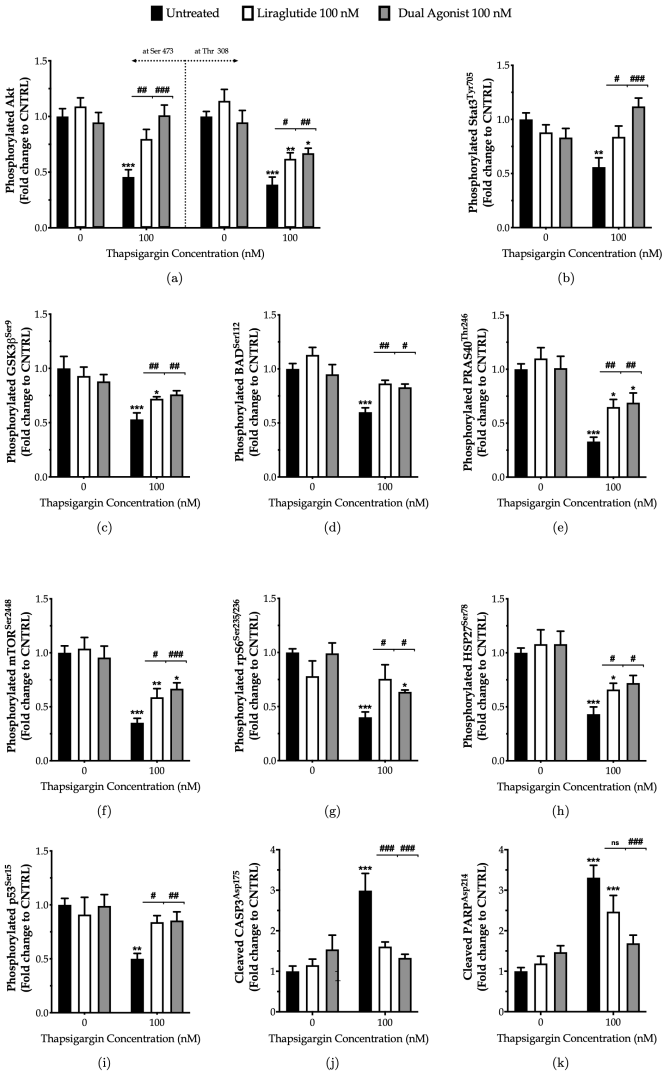

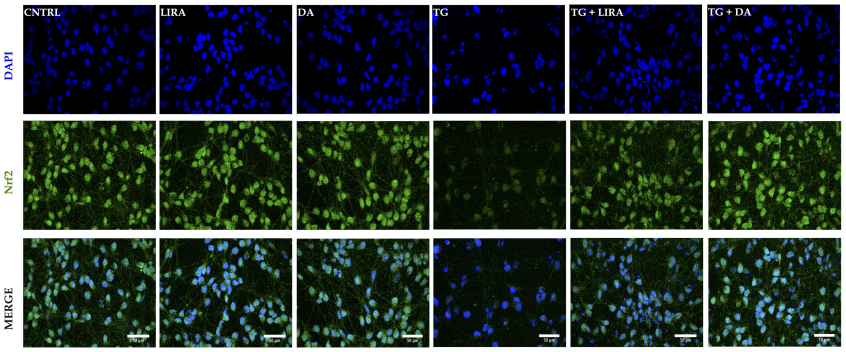

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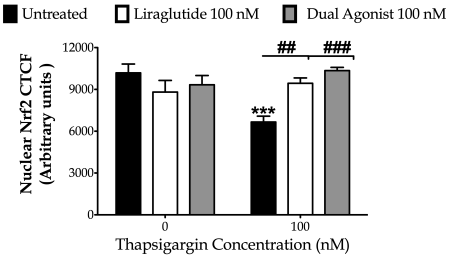

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