

NEW APPROACH TO ALZHEIMER'S DISEASE THERAPY

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Research Purpose:

- Search for approaches to treat Alzheimer's Disease and possibly other neurodegenerative diseases on the basis of HLDF-6 peptide application
- Study of molecular mechanisms of HLDF-6 peptide action

Human Leukemia Differentiation Factor (HLDF):

- Isolated from a culture medium of human promyelocyte leukemia HL-60 cells treated with retinoic acid in the laboratory of the hormonal regulation proteins of the IBCh RAS (I.A.Kostanyan et al, FEBS Letters,1994)
- The protein induces differentiation of original cells via the granulocytic pathway
- HLDF exhibits also a non-specific nuclease activity and plays an important role in the promotion of apoptosis in HL-60 cells
- Differentiating and cytotoxic effects of HLDF depend on the factor localization in relation to HL-60 cells (outside or inside the cells).

Human Leukemia Differentiation Factor (HLDF):

*¹AGLMASLKLMLSAGPFVGVWSQMIPFSD
WPRRWHRLKELLTGENHRCGIFVINK⁵⁴*

HLDF-8

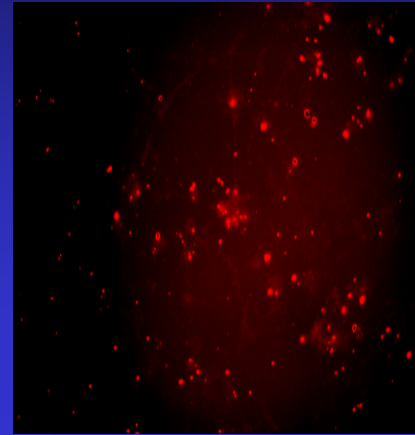
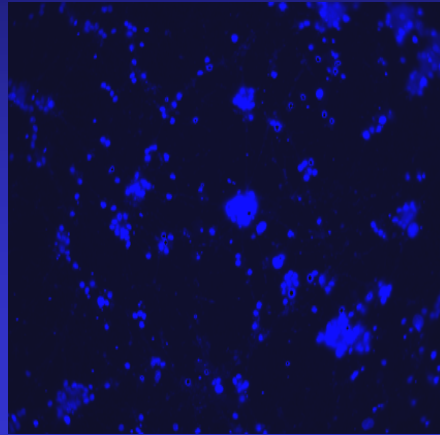
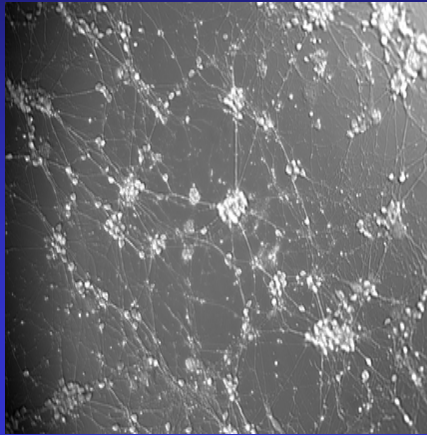
Nuclease activity
**Promotion of
apoptosis**

HLDF-6

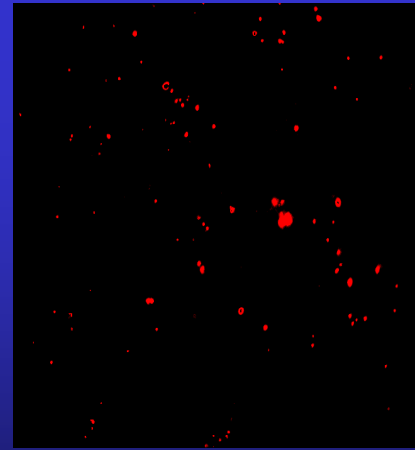
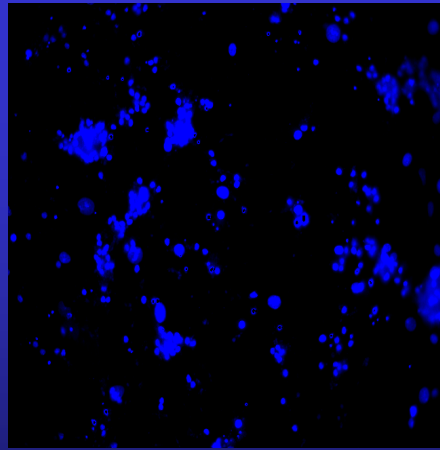
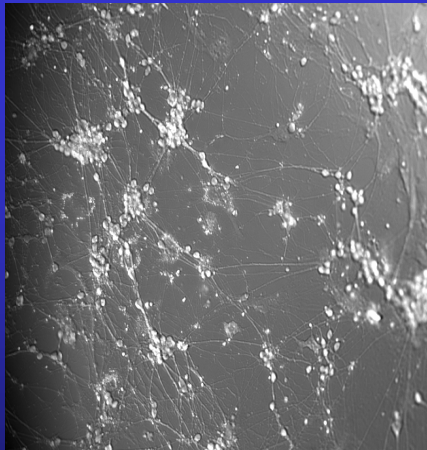
**Differentiation
activity**
**Neuroprotective
activity**

Effect of HLDF-6 peptide on viability of rat cerebella granule neurons in morphine deprivation condition after 6 days of morphinization

A)



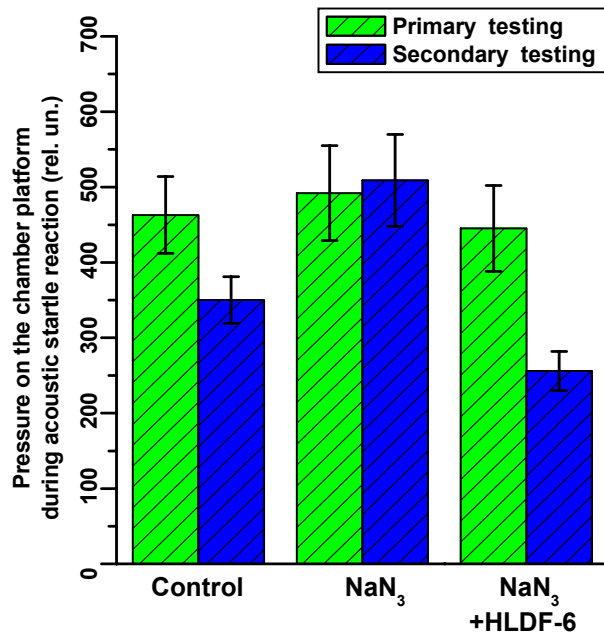
B)



Conclusion: At presence of HLDF-6 peptide the number of apoptotic cells was diminished

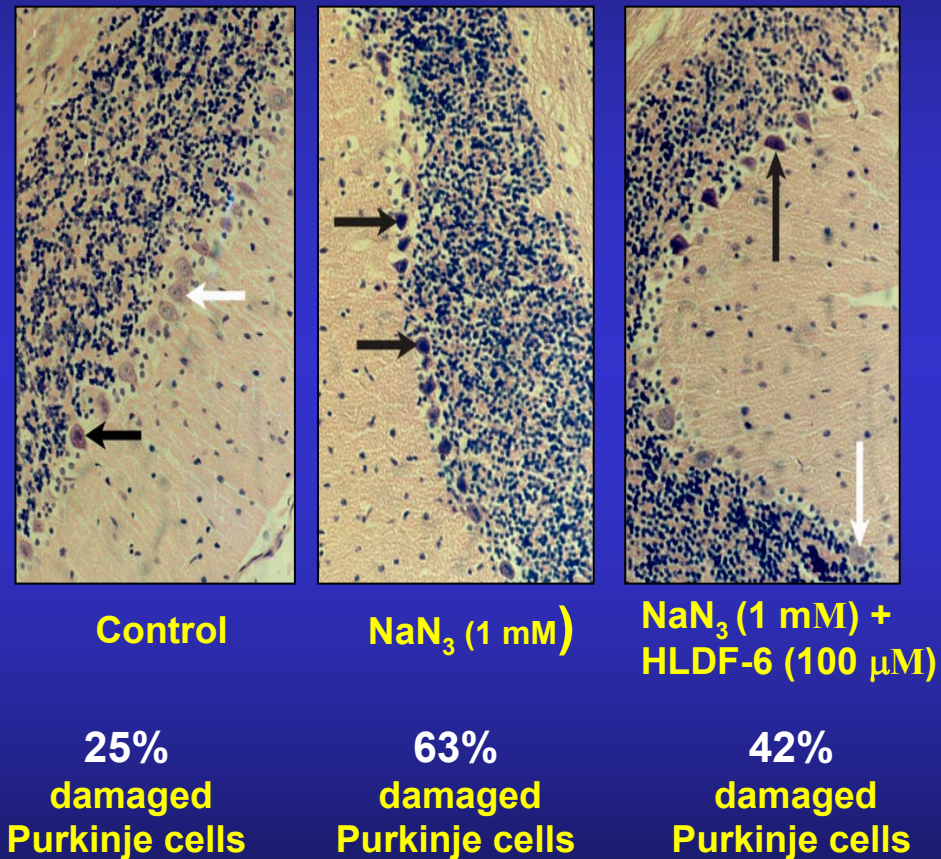
HLDF-6 PROTECTIVE EFFECT AGAINST NaN_3 -INDUCED HYPOXIA IN VITRO

Acoustic startle habituation:



Conclusion: HLDF-6 protects Purkinje cells and recovers normal behavioral reactions in rats which are failed upon chemically induced hypoxia-like state of the vermis cerebelli

Histological slices of the rat *vermis cerebelli*



→ normal Purkinje cells

→ damaged Purkinje cells

Alzheimer's Disease

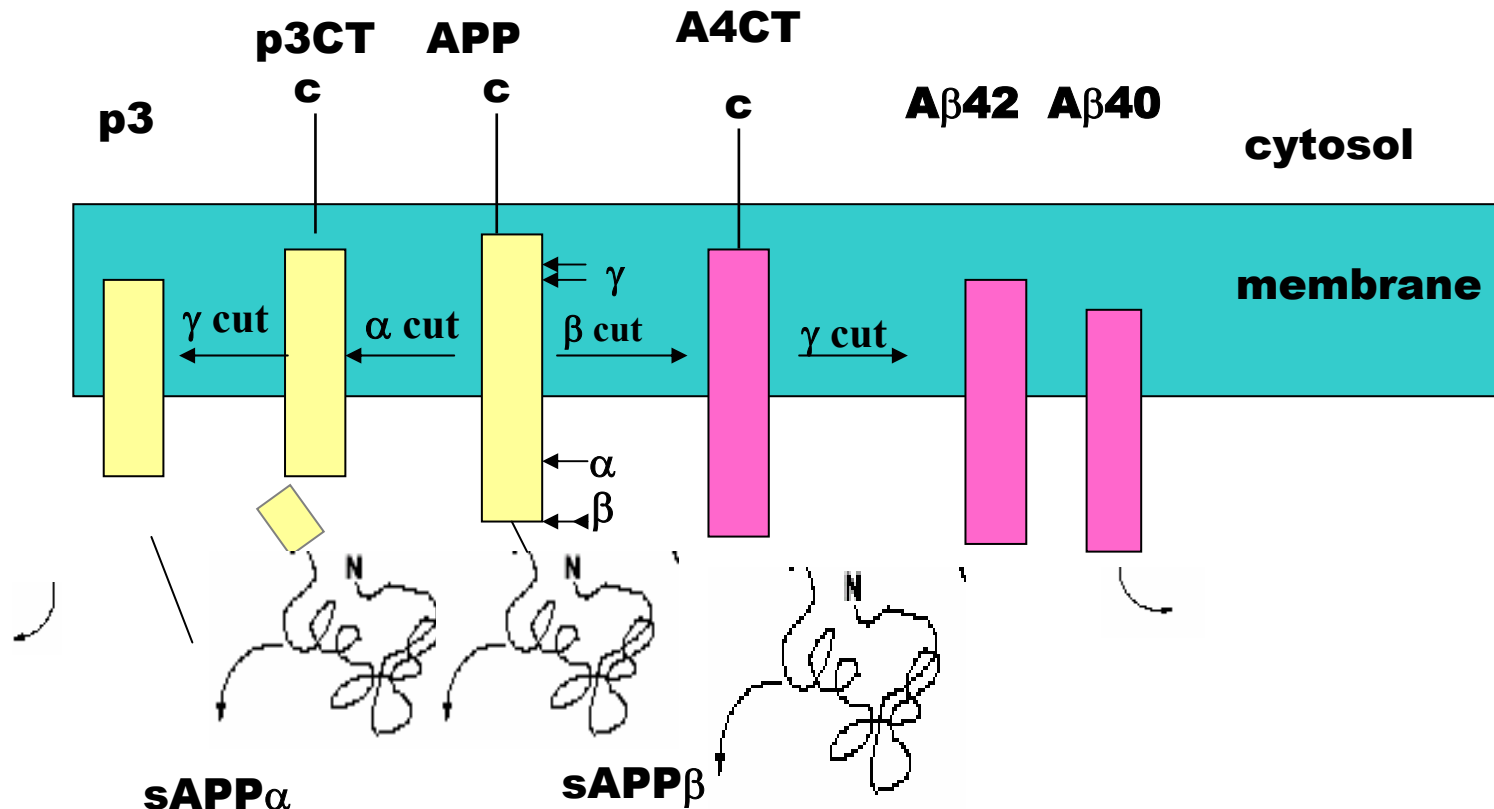
- Most common human neurodegenerative disorder
- Characterized by deterioration of cognitive and mental functions, including learning and memory skills
- Clinically characterized by:
 - Presence of extracellular senile plaques
 - Intracellular neurofibrillary tangles formed by cytoskeletal protein *tau* in the neuronal cell body
 - Neuropili threads in dendrites
 - Synapse and selective neuronal cell loss
- β -amyloid (Ab) peptides represent the major component of senile (amyloid) plaques and are generated during endoproteolysis of a large transmembrane protein:

β -amyloid precursor protein (APP)

Processing of β -amyloid precursor protein (APP) by α -, β - and γ -secretases

Normal pathway

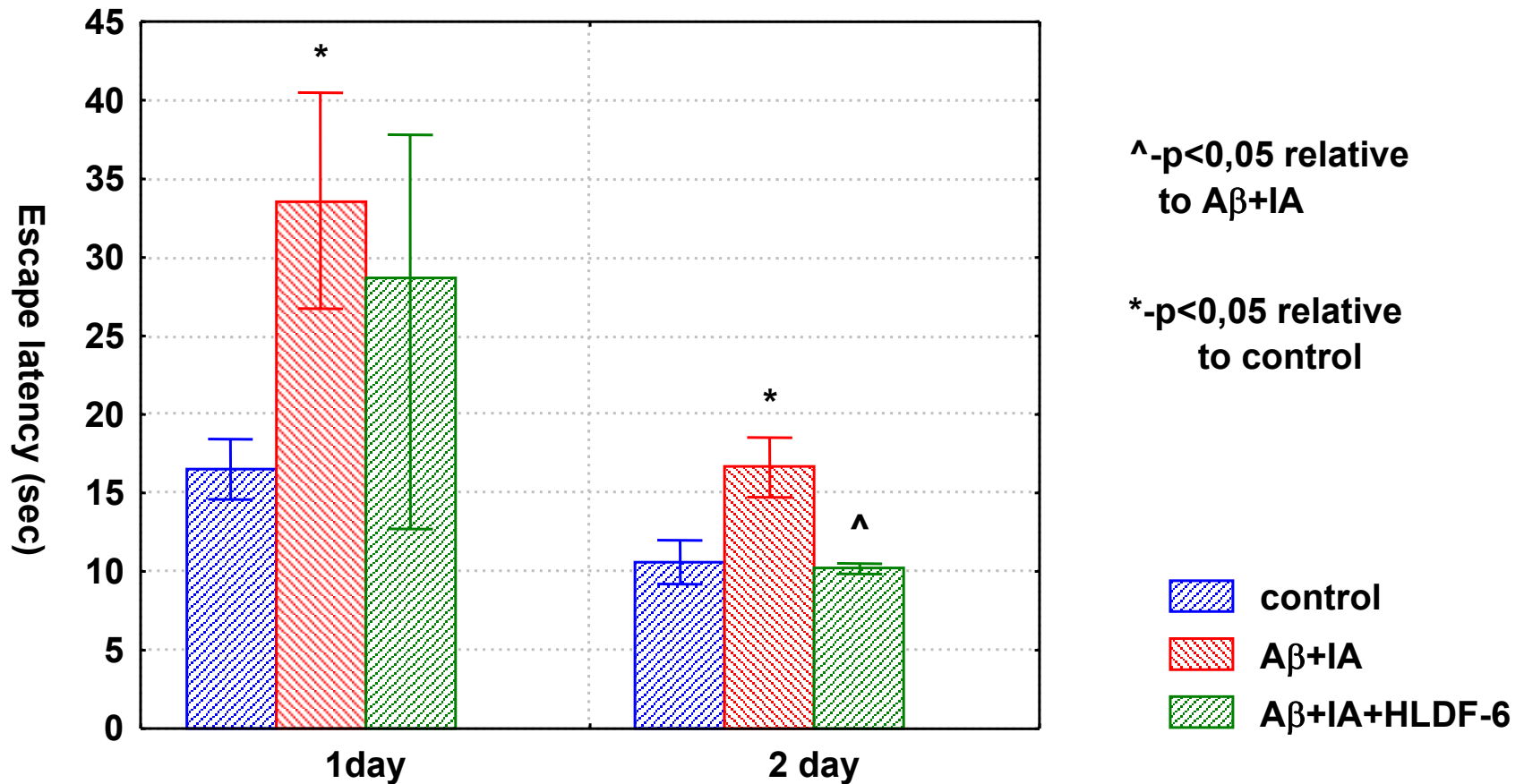
Amyloidogenic pathway



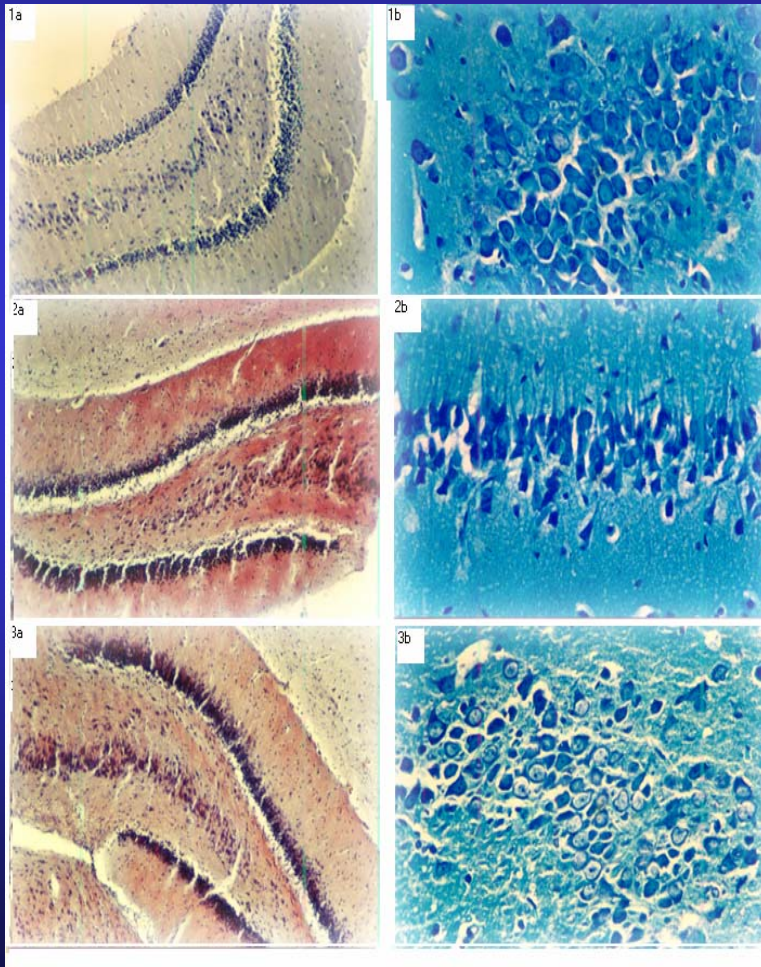
Rodent Model for Alzheimer's Disease used in our study

- Coinjection of β -amyloid ($A\beta$) fragments with ibotenic acid (IA) into rat hippocampus produces drastic neuronal loss

Effects of HLDF-6 on performance in water maze



HLDF-6 effect on Alzheimer's disease experimental model



- 1a, 1b – hippocamp cuts of healthy animals
- 2a, 2b – hippocamp cuts of the rats injected with $A\beta$ +IA
- 3a, 3b - hippocamp cuts of the rats injected with $A\beta$ +IA, administered with HLDF-6

a – staining by Congo red
b – staining according to Nissl

Preliminary research plan

■ Fundamental studies

— Investigation of Influence of HLDF-6 on:

- Amyloid fibrils formation
- Viability of neuronal cells, injured by A β peptides and L-Glu
- Proinflammatory cytokines binding to the cells and their mRNA expression in neuronal cells
- Function of mitochondria, injured by A β peptides
- Protection and differentiating of the stem cells
- Hormonal status of the animals

■ Applied investigations

- Search for optimal doses and protocol of administration for maximal neuroprotective effect of HLDF-6 peptide in experimental injective and transgenic mice models of Alzheimer's disease
- Investigation of modulating influence of HLDF-6 peptide at transplantation of stem cells to the animals with experimental AD

Scientific Significance

- Determination of effects of HLDF-6 peptide on homeostatic functions in animal experimental models of Alzheimer's disease
- Determination of molecular mechanisms of HLDF-6 peptide action to correct neurodegeneration at organism and cellular levels

Applied and Commercial Significance

- Elaboration of properties of HLDF-6 peptide may elucidate novel scientifically justified methods of treatment for neurodegenerative diseases, starting with Alzheimer's.
- Further elaboration of HLDF-6 peptide, production of its analogues, and their properties may eventually allow us to devise a technique for production of a remedy for Alzheimer's disease.

Contact Information



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