Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice


Ines Ana EDERER, JC 12.10.2015
Introduction

- What are heterochronic parabionts?

### Aging
- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

### Rejuvenation
- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?
Introduction

Hippocampus - special vulnerability to aging
- downregulation of plasticity-related genes
- reduced spine density
- decreased synaptic plasticity
- impairments in associated cognitive functions
I. Molecular, structural and functional changes
Genome-wide microarray analysis

Biological pathways involved in synaptic plasticity using IPA software based on differentially expressed genes in isochronic and heterochronic parabionts.

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Immunohistochemical analysis of Egr1, c-Fos, and pCreb in the DG

Quantification of immunostaining
Golgi stain image and quantification of dentritic spine density in granule cell neurons in the DG
Extracellular population spike amplitude (PSA) recorded from the DG of aged parabionts – representative LTP levels for isochronic and heterochronic parabionts
II. Cognitive changes
Testing hippocampal-dependent cognitive functions:

1. RAWM – spatial learning and memory

2. Contextual fear conditioning
Administration of young blood plasma in aged mice (18 months), n=8/group.
Aged mice given young plasma exhibit enhanced learning and memory for hidden platform location during testing phase.
Mice receiving young plasma demonstrate increased freezing in contextual memory testing.
Additional fear-conditioning experiment: saline, young plasma or heat-denatured young plasma to aged animals

Rejuvenation through heat-labile factors?!
III. Creb signaling
llla.

Adult mice infected with AAVs encoding K-Creb in tandem with GFP.
Western blot analysis of K-Creb overexpression in isolated hippocampi
IIIb.

Dendritic spine density in DG assessed by AAV-mediated neuronal tracing
Confirmation of results through shRNAs in N2A neuronal cell line and in the hippocampi of adult mice: Consistent with previous data.
Illc.

Phosphorylated Creb in the DG of aged animals
AAV Stx injection 16 Plasma administration 40 RAWM 42 43 Fear conditioning

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Contextual fear conditioning after plasma treatment

![Graph showing percentage freezing with different plasma treatments.](image-url)
RAWM after plasma treatment

- GFP aged plasma
- GFP young plasma
- K-Creb aged plasma
- K-Creb young plasma

Errors

Day 1 training
Blocks
Day 2 testing

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cognitive improvements after administration of young plasma are partly mediated by Creb.
Summary

• Exposure of aged animals to young blood can counteract effects of brain-aging at the molecular, structural and cognitive level.

• Heterochronic parabiosis enhances dendritic spine density and synaptic plasticity in aged hippocampus and elicits a plasticity-related expression profile.

• Administration of young blood plasma improves hippocampal dependent cognitive functions such as spatial learning and memory.

• Creb is one member of the regulatory network underlying cognitive and structural enhancements in the aged hippocampus.
Comment/Criticism

• cued memory testing vs contextual memory testing (p. 9)
• “pro-aging” vs “pro-youthful” factors (p. 5)
• conflicting conclusion (p. 3 Golgi, LTP)
• reproducibility (p. 5)

• popular topic and complex (!) methods (many data not published – 19 pages of supplementary tables)
• transferability of results into human being – PRP?!
Thank you for your attention!