Tau protein is essential for stress-induced brain pathology

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Tau protein and its role in brain pathology

Alzheimer’s disease & Tauopathies

Sholz and Mandelkow *Cell Mol Life Sci* 2014 71;18, 3139;
Predisposing / Risk factors for Alzheimer’s disease

- Aging
- Mutations
- Gender
- Environment
- Stress
Stress role on brain structure and function

- In many Alzheimer patients, cortisol levels are elevated.
- Stress is suggested risk of AD.

Stress/GC induces:
- Neuronal atrophy
- Memory deficits

Stress/GC induces:
- Depressive behavior
- Anxiety

Glucocorticoid (GC)

Cortisol levels

- High GC levels impair hippocampal function
- Depressed patients exhibit elevated GC levels

Inhibitory signal

Stress

Hypothalamus

Glucocorticoid (GC)

Cortisol

Cortisol levels

Cognitive function

Hippocampal volume

Normal

Stress/AD

Stress/GC induces:

- Dendritic atrophy
- Synaptic loss

* Depressed patients exhibit elevated GC levels

Control

Depressed

nmol/l
Common symptomatology, common mechanisms?

Conclusions: A history of depression may confer an increased risk for later developing AD. This relation may reflect an independent risk factor for the disease.

Arch Gen Psychiatry. 2006;63:530-538

• Aβ levels are elevated in CSF of depressed patients while its levels may mark the transition from depression to the onset of AD (Post et al 2006; Sun et al., 2007).

• History of depression is correlated with increases of amyloid plaques and NFT (Rapp et al., 2006).
AD-related mechanisms in stress-driven pathology?

**Stress**

Alzheimer’s disease animal models
(Aβ- & Tau-based AD models)

**GC**

Stress-driven pathology (WT mice, WT rats)

Hyperphospho-tau

Accumulated tau

AD neuropathology & memory decline

Depressive pathology & cognitive deficits

Tau

Tau-KO mice
Similar physiological responses to chronic stress in WT and Tau-KO mice

Lopes et al., PNAS 2016; Lopes et al., Cer Cortex 2016
Absence of Tau blocks stress-driven depressive and anxious behavior

**Depressive-like behavior**

- **Forced swim** (learned helplessness)
- **Tail Suspension**

**Anxiety**

- **Elevated Plus Maze test**

**Sucrose Preference Test** (anhedonia)

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*Lopes et al., PNAS 2016*
In contrast to WTs, Tau-KO exposed to chronic stress do not exhibit cognitive deficits

Cognition

Y-Maze

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% Distance in novel arm

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% Time in novel arm

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NOR

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Discrimination Index

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MWM

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Distance (cm)

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Lopes et al., PNAS 2016
Stress-induced neurostructural changes are Tau-dependent.

Lopes et al., PNAS 2016
Neurochemical alterations induced by stress are abolished in Tau-KO animals.

HPLC analysis

Tryptophan → 5-Hydroxytryptophan → 5-Hydroxytryptamine (5HT) → 5-Hydroxyindole Acetic Acid (5HIAA)

Lopes et al., PNAS 2016
Mechanisms of synaptic plasticity are damaged by chronic stress in WT, but not Tau-KO, hippocampus

Electrophysiological analysis

WT

KO

Mn-enhanced MRI

Lopes et al., PNAS 2016
Are you stressed?
Then, your Tau moves to your synapses!!

Lopes et al., PNAS 2016; Pinheiro et al., Mol Neurobiol 2015
Tau protein is essential in the stress-driven depressive pathology and cognitive deficits

Lopes et al., PNAS 2016; Lopes et al., Cer Cortex 2016
Stress-driven brain pathology - What do you believe in?

Are you a Baptist?
(Aβ believer)

a Tauist?
(Tau believer)

a Baptized Tauist

Mood and Cognitive status
Age (years)

Neuronal malfunction & atrophy

Depression
AD/PD

Price 2009
European College of Neuropsychopharmacology Fellowship award 2009
AD/PD Young Faculty Award 2015
Research Award 2015

Price
Thank you very much

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