Presentation 6 - Ya Fang Liu

Assessment of a role of stress-activated kinases in the pathogenesis of Gulf War Syndrome

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Part I

Introduction

Stress-activated kinases

They are a group of enzymes or kinases that are activated in response to stressful stimuli such as UV light, γ–irradiation, inflammatory cytokines, certain chemicals, toxins.

Activation of these kinases indicates that cells or neurons are undergoing cellular stress.

MKK4

- Mitogen-activated protein kinase kinase 4 (MKK4) controls activation of c-Jun-N-terminal kinase (JNK).

Physiological role of JNK

- JNK1 controls differentiation and cytokine production in Th2 lymphocytes (immune cells).
- JNK2 controls differentiation and cytokine production in Th1 lymphocytes.
- JNK1 and JNK2 are involved in the regulation of inflammatory responses

Physiological role of p38MAPK

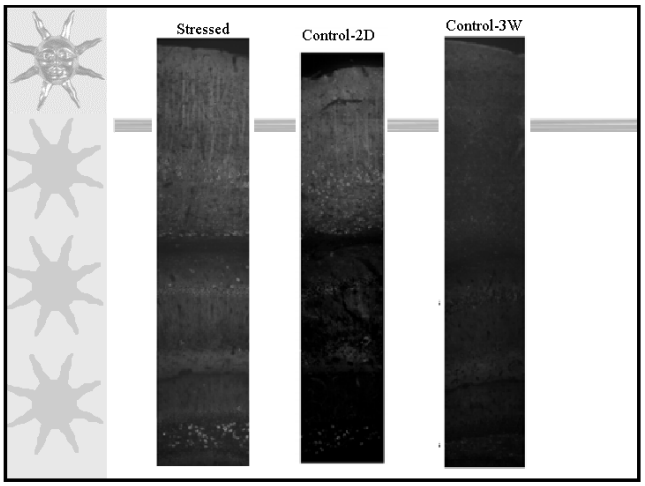
- Regulate differentiation and cytokine production in Th1 lymphocytes.
- Regulate inflammatory responses.

Pathological role of stress-activated kinases

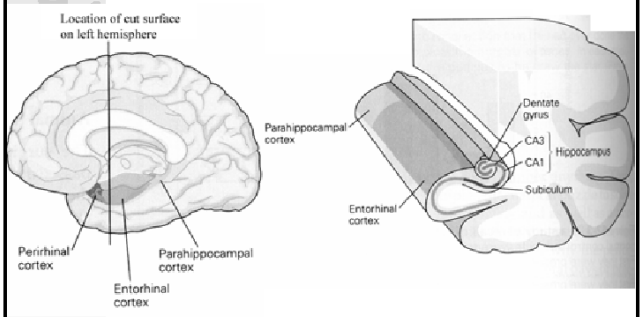
Over-activation of stress-activated kinases can induce dysfunction of central nervous and immune systems.

Stress

- Psychological stress;
- Physical stress;
- Environmental stress: cold, hot, new environment, transportation, high mountain attitude, high humidity, strange odors from chemicals or animals, noise, etc.
- Stress is a physiological response.
- Excess stress is the foundation of many illnesses.



Cognition and the hippocampal formation



Stress and the brain

- The Hypothalamus (Corticotropin-releasing factor,CRF)-Pituitary (adrenocorticotropic hormone,ACTH)-adrenal gland (cortisol): the HPA axis: stress responses.
- Dysfunction of the HPA axis has been implicated in chronic fatigue and sleeping disorders
- Amygdala: stress and emotional memory: dysfunction of the amygdala has been implicated in post-traumatic disorder (PTSD)

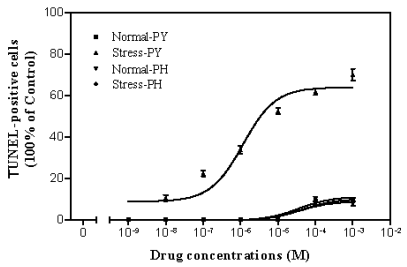
Part II

Hypothesis

Factors that may contribute to GWS

- Chemicals: such as pyridostigmine (PB), permethrin, DEET, serine, etc.
- Stress: physical stress, psychological stress, and environmental stress.
- Vaccinations: Challenge of the immune system.

Pyridostigmine is a potential neurotoxin



Pyridostigmine is a potential neurotoxin

- PB induces neuronal death when neurons are undergoing cellular stress or stress-activated kinases are activated. .
- PB-induced neuronal toxicity is independent of its inhibition of acetylcholine esterase.

Hypothesis

Stress, vaccination, and exposure to one or more chemicals may synergistically act on stress-activated kinases. Over-activation of these stress-activated kinases may lead to dysfunction in the central nervous and immune systems, contributing the majority of symptoms observed in patients with GWS

The Goal of the Project

- Identifying the molecular mechanism(s) underlying the pathogenesis of Gulf War Syndrome (GWS).
- Development of effective prevention and treatment for GWS.

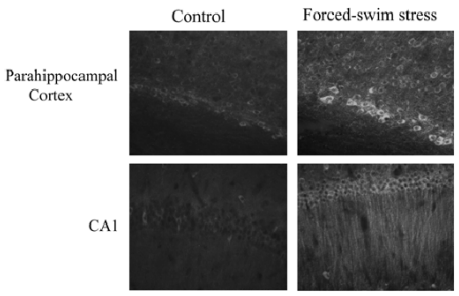
Part III

Stress Studies

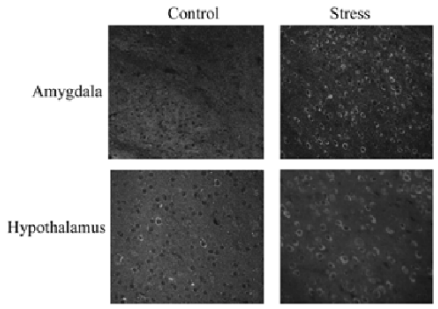
Forced-swim stress

- Physical stress
- Psychological stress
- Environmental stress

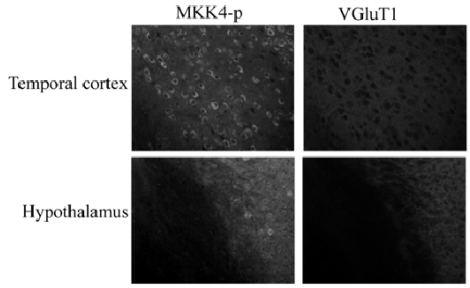
Forced-swim stress induces MKK4 activation in the cortex and the hippocampus



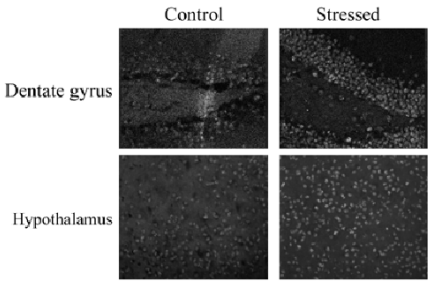
Forced-swim stress induces MKK4 activation in the hypothalamus and the amygdala



Forced-swim stress induces MKK4 activation in VGluT1-positive neurons



Forced-swim stress induces activation of JNK in the dentate gyrus and hypothalamus



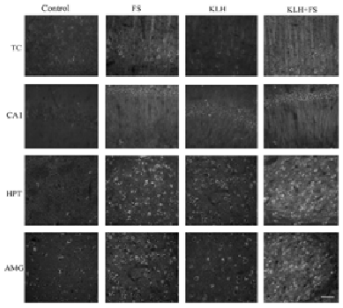
Summary

- Forced-swim stress induces activation of MKK4 and JNK in the hippocampal formation, the amygdala, and the hypothalamus.
- Forced-swim stress induces activation of MKK4 and JNK in glutamatergic neurons.

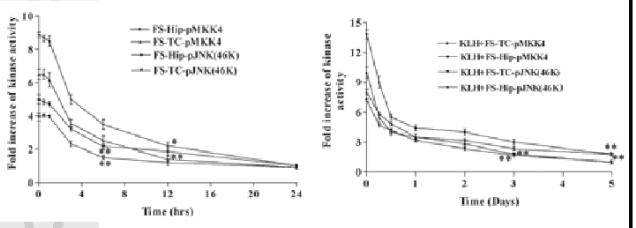
Part IV

Vaccination

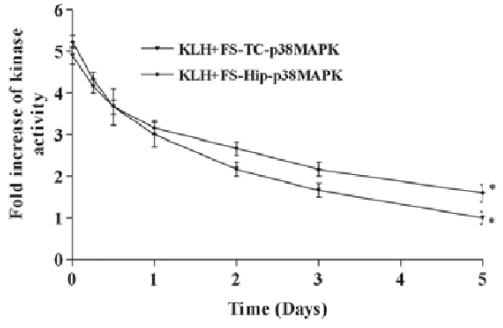
KLH immunization significantly increases activation of MKK4 in the brain

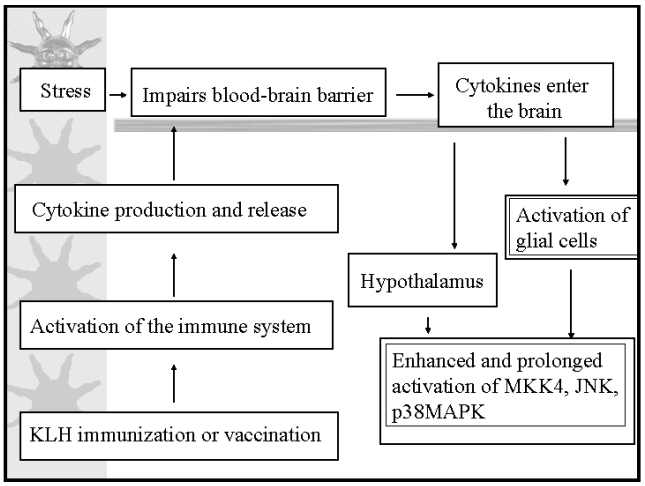


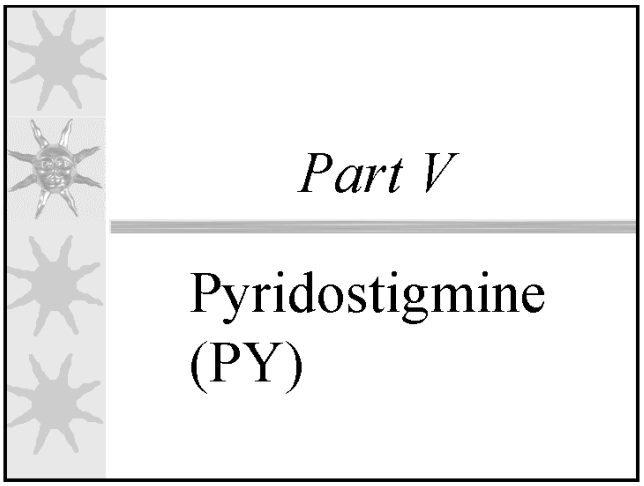
KLH significantly prolongs activation of MKK4 in the brain

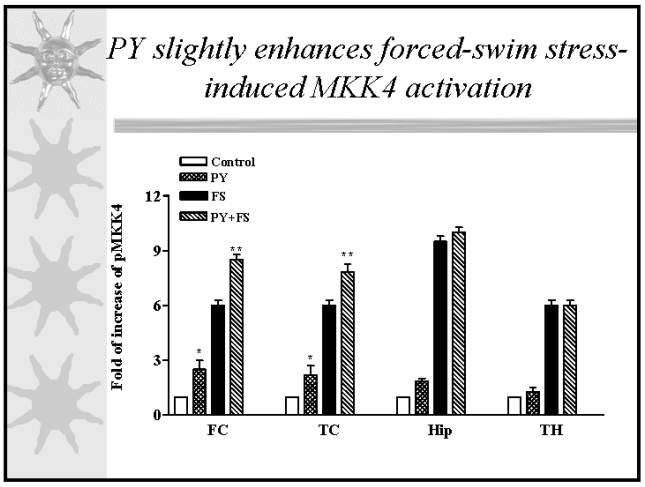


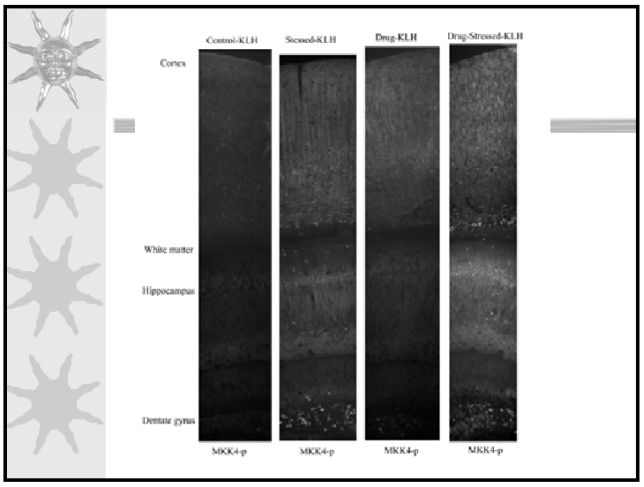
KLH immunization in combination with forced-swim stress triggers activation of p38MAPK



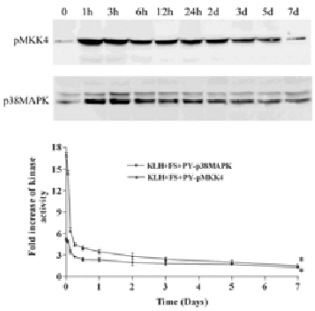

Stress
Impairs blood-brain barrier
Cytokines enter the brain
Cytokine production and release
Activation of glial cells
Hypothalamus
Activation of the immune system
Enhanced and prolonged activation of MKK4, JNK, p38MAPK
KLH immunization or vaccination


Part V
Pyridostigmine (PY)


PY slightly enhances forced-swim stress-induced MKK4 activation
Control
PY
FS
PY+FS
Fold of increase of pMKK4
12
9
6
3
0
FC
TC
Hip
TH


Control-KLH
Stressed-KLH
Drug-KLH
Drug/Stressed-KLH
Cortex
White matter
Hippocampus
Dentate gyrus
MKK4-p
MKK4-p
MKK4-p
MKK4-p

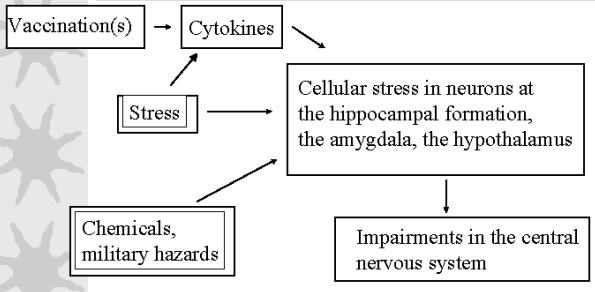
PY further prolongs activation of MKK4 and p38MAPK



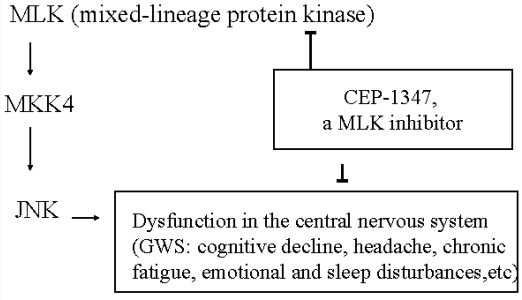
Summary

- Administration of pyridostigmine further promotes and prolongs activation of stress-activated kinases induced by forced-swim stress in combination with KLH immunization.

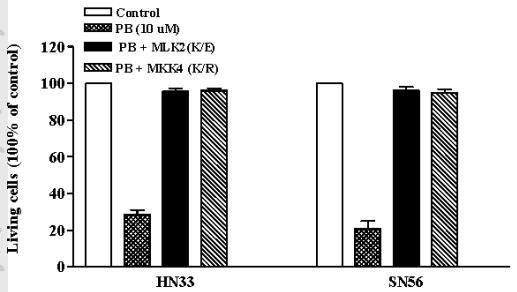
Relationship to GWS



Signaling pathway of stress-activated kinases



Inactivation of MLK2 or MKK4 blocks neuronal toxicity induced by PB



Future Studies

- Effects of other chemicals such as DEET, permethrin;
- Generate chronic stress model;
- Effect of the MLK inhibitor, CEP-1347 on our mouse models
- MLK2 knockout mice