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FACULTY OF MEDICINE SIRIRAJ HOSPITAL

The effect of Thai herbal medicine on learning & memory mechanisms, and vascular dementia

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Brain functions

Introduction

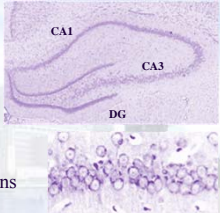
- **Sensation, movement, language, thought, and etc.**
- **Learning**
 - ✓ A process: new information is acquired
- **Memory**
 - ✓ A process: the previously acquired knowledge is stored and maintained for later use
- **Behaviors**
 - ✓ The response of an individual, group, or species to its environment
 - ✓ Affected by Learning and memory
 - ✓ Normal vs Abnormal behaviors

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Learning and Memory

Introduction

- **Human brain**
 - ✓ A network of more than 100 billion individual neurons
 - ✓ Neurons are interconnected in systems
 - ✓ Neural circuits
- **Hippocampus**
 - ✓ Medial temporal lobe
- **Long-term potentiation**
 - ✓ A putative neural mechanism
 - ✓ associative memory formation and storage in mammalian brains

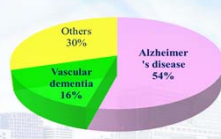


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Dementia

Introduction

- Impair functions of multiple brain systems
- Learning & memory and cognitive dysfunctions
- Interfere with daily activities & the quality of life



Types of dementia with late onset (> 65 years)
Lobo et al., 2000;
Alonso et al., 2009

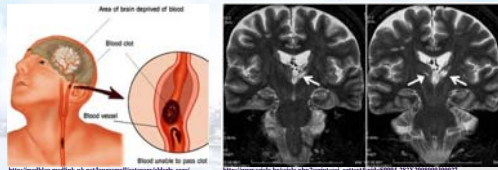
Hofman et al., 1991; Zhang, 1990; Laschke et al., 2005; Ustun et al., 1999; Jitapunkul et al., 2001; Malouf et al., 2004; Alonso et al., 2009.

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Vascular dementia (VaD)

Introduction

- **Blockage of cerebral blood vessels**
 - ✓ Chronic cerebral hypoperfusion
- **Progressive decline in cognition**
 - ✓ Cognitive & memory impairments
- **Neuronal death and white matter damage**



Nolan et al., 1998; Ronnenmaa et al., 2011; Scheel et al., 1999

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Pathophysiology of Chronic cerebral hypoperfusion

Introduction

- **Oxidative stress**
- **Neurovascular pathology**
 - ✓ Microvascular basement membrane thickening
 - ✓ Collagen deposition
- **Neuronal damage**
 - ✓ Apoptosis
- **Glial activation (astrocyte and microglia)**
 - ✓ Pro-inflammatory cytokines and chemokines
- **Inflammation** (Doyle et al., 2008)


Learning and memory impairment

Farkas et al., 2007; Panickar & Norenberg et al., 2005; Eisel et al., 2006

Bacopa monniera (BM); Brahmi

Introduction

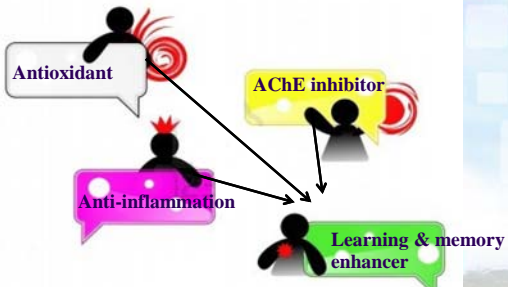
- A Thai herbal medicine
- Asian countries such as Nepal, India and Thailand
- Learning & memory, intelligence enhancer; antiepileptic activity
- Active ingredient: saponin glycosides
 - Non-polar glycosides (Rajan et al., 2011; Abascal et al., 2011)
 - Cross the blood brain barrier (BBB) (Pardridge WM., 1999)



Thorne Research, 2004; Boonyapraph et al., 1999; Kumar et al., 2006; Alternative Medicine Review., 2004

Effects of BM extract on learning & memory

Introduction



Russo and Borrelli, 2005; Bhattacharya et al., 2000; Kishore and Singh, 2005; Shabana Channa et al., 2006

Protective effect against Chronic cerebral hypoperfusion

Drug administration

- H₂O
- BM 120 mg/kg of BW
- BM 160 mg/kg of BW
- BM 240 mg/kg of BW

Histological study

- Cresyl violet staining
- Mean total number of survival neurons in CA1, CA3 & DG

Transcardial perfusion

2 step 2-VO model

- Chronic cerebral hypoperfusion

Behavioral study

- MWM
- Mean escape latencies
- Mean retention times

Acute hippocampal recording

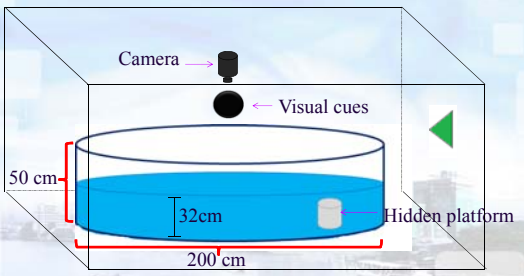
- Long-term potentiation

2-VO = 2-vessel occlusion; MWM = Morris water maze

Behavioral study

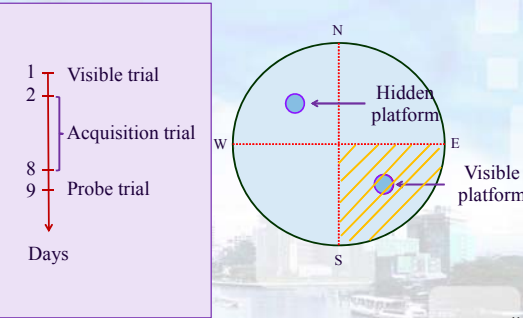
Material and methods

- Morris water maze (MWM) task**



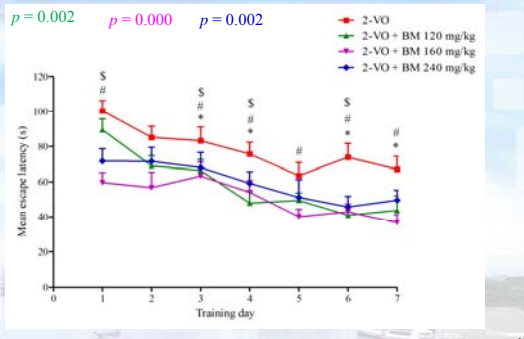
Morris water maze (MWM) task

Material and methods



Effects of BM extract on Spatial learning & memory

Result



Material and methods

The mean total numbers of surviving hippocampal neurons

CA1
CA3
DG

345 x 300 μm^2 /crop or 0.1 mm^2
→ Total area = 0.3 mm^2

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Result

Effects of BM extract on surviving neurons in CA1 subregion

Sham
2-VO
2-VO + BM 120 mg/kg
2-VO + BM 160 mg/kg
2-VO + BM 240 mg/kg

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Result

Effects of BM extract on the mean total number of surviving hippocampal neurons

Region	Sham	2VO	2VO + BM 120 mg/kg	2VO + BM 160 mg/kg	2VO + BM 240 mg/kg
CA1	~140	~100	~135	~130	~145
CA3	~100	~60	~85	~80	~105
DG	~145	~115	~140	~135	~155

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Material and methods

Effects of BM extract on Long-term potentiation

- Acute hippocampal recording
 - Stimulation
 - Schaffer collateral fibers
 - Record
 - Dendritic layer of CA1 area
 - Excitatory postsynaptic potential (EPSP)
- Long-term potentiation
 - Long-term enhancement of postsynaptic response

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Result

Effects of BM extract on Long-term potentiation

Normalized EPSP slope (%)

Duration [min]

Basal phase
Test phase

Control group
BM (80 mg/kg)
BM (160 mg/kg)
BM (240 mg/kg)

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Introduction

Conclusion

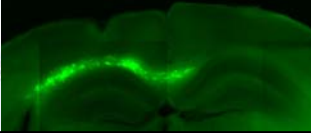
- Brahmi extract demonstrated neuroprotective effect against chronic cerebral hypoperfusion
 - Prevent the learning and memory impairment
 - Reduce of hippocampal cell death
 - May be mediated by anti-inflammatory and anti-oxidative activities
- Memory enhancing effect of the extract to exhibit its activity in hippocampal synapses
 - Enhance of LTP magnitudes
 - Maybe mediated by anti-acetylcholinesterase activity

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Material and methods

Ongoing projects

- **The effect of Brahmi extract on molecular cascades in chronic cerebral hypoperfusion**
 - ✓ Molecular techniques
- **The role of sodium leak channel, non-selective (NALCN) in learning and memory**
 - ✓ Induction of siRNA into neurons via viral vectors
 - ✓ Blockage of NALCN gene expression



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