Contributions of translational behavioral neuroscience to the advanced diagnostic and therapeutic approaches towards dementia

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Old age is the zenith of life,
a time for rest, reflection,
wisdom and truth

Goethe
But...

Goethe and Bergman are not always right
A complex pattern

Germany, 1907

- female, 51 years old
- cognitive impairment
- amnesia
- aphasia
- apraxia
- dementia
- paranoid illusions
- violent behavior
- postmortem brain pathology
  - neuritic deposits
  - neurofibrillar tangles
The Umbrella effect
Lydia Giménez-Llort, 2014
The Umbrella effect
Lydia Giménez-Llort, 2014
The Umbrella effect
Lydia Giménez-Llort, 2014
The other patient
A complex clinical history

Dementia
1. STM & LTM
2. Abstract thinking
3. Judgement
4. High cognitive functions

BPSD Behavioral and Psychological symptoms of dementia
Agitation, aggressive, psychosis, anxiety
5-15% AD + major depression
20-40% AD + illusions and hallucinations
Sundawning behavior
Pathways away from

- Genetic
- Environmental
- Production BA

Pathways towards to

- Synaptic disfunction
- Oxidative Stress disregulation Ca++
- Impaired Plasticity and Neurogenesis

REDUCTION of RISK

- Cognitive Stimulation
- Exercise
- Caloric restriction
- Immunization BA
- BACE i g-secretases Inhibitors
- Fatty acids modulators (cholesterol)

TREATMENT

- Immunization BA
- Quelants Cu+ i Fe++
- BACE i g-secretases inhibitors
- Antioxidants and B vit
- Antiinflammatory agents
- Neurotrophic factors
- Fatty acids modulators (cholesterol)
- Cholinergic enhancers
- Antidepressants

Mattson, Nature 2004
The complexity of the therapeutical strategies

The unique
The best
The exclusive one

Cognition & Memory
Cholinergic deficits

Behavioral Alterations
Neurotransmitters

Neuroprotection & Regeneration
Glutamate antagonists
Genetic Strategies
Growth Factors
Validation (Guideliness)
Screening and validation of the model
Behavioral Neuroscience

- Validation (Guideliness)
- Screening and validation of the model
- Multidimensional: focus BPSD and DLA
- Translational, Longitudinal
- Gender dependent

- Life events + Life style (Non-Pharmacological)
- External intervention (Pharmacol, Molecular, other)

- Prevention + Therapeutics

Ademuz, 1968
Mice deficient in BACE1, the Alzheimer’s B-secretase, have normal phenotype and abolished B-amyloid generation.

Nat Neurosci. 4: 231-232.

Alzheimer-like neuropathology in transgenic mice overexpressing V171F B-amyloid precursor protein


Senescence Accelerated Mice
Premature Aging Mice
Administration of Beta-amyloid

Games et al., 1995

Engel et al.
Neurobiol Aging 2005

Oddo et al.
Triple-transgenic of Alzheimer’s disease with plaques and tangles: Intracellular AB and synaptic dysfunction.

Neuron 2003; 39: 409-421
Oddo et al.

Triple-transgenic of Alzheimer’s disease with plaques and tangles: Intracellular AB and synaptic dysfunction.

*Neuron* 2003; 39: 409-421
Modeling behavioral and neuronal symptoms of Alzheimer’s disease in mice: A role for intraneuronal amyloid


Abstract

The amyloid Aβ peptide (Aβ) is suspected to play a crucial role in the cascade leading to AD as the pathology that causes neuronal and synaptic dysfunction and, eventually, cell death. Therefore, it has been the subject of a large number of clinical and basic research studies on this disease. Aβ is typically found aggregated in extracellular amyloid plaques that occur in specific brain regions affected in AD. In Alzheimer’s disease (AD) and Down syndrome (DS), Advances in the genetics of its familial and sporadic forms, together with those in gene transfer technology, have provided valuable animal models that complement the traditional cholinergic approaches, although modeling the neuronal and behavioral deficits of AD in these models has been challenging. More recently, emerging evidence indicates that intraneuronal accumulation of Aβ may also contribute to the cascade of neurodegenerative events and strongly suggest that it is an early pathological biomarker for the onset of AD and associated cognitive and other behavioral deficits. The present review covers these studies (in humans, in vivo and in vitro) in numerous models, also providing more evidence that adult 3xTg-AD mice harboring PS1M146V, APPSwe, tauP301L transgenes, and mimicking many critical hallmarks of AD, show cognitive deficits and other behavioral alterations at ages when overt neuropathology is not yet observed, but when intraneuronal Aβ, synaptic and cholinergic deficits can already be described.

Keywords: Intraneuronal amyloid; Animal models; 3xTgAD mice; Learning and memory; Neuropsychiatric-like symptoms; Activity; Circadian rhythms; Emotional; Psychosis

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doi:10.1016/j.neubiorev.2006.07.007
BPSD-like changes
2.5 month old 3xTgAD mice

Open-field

Total horizontal activity

Total vertical activity

Number of entries

Latency to white area

Time in white area

Latency to explore

Time head-dipping

Entries OA

Time in OA

Head-dips

Repetitions

Black-white box

Plus-maze

Boissier’s hole-board
Changes BPSD-like in 6 month old 3xTgAD mice

- **Open-field**
  - Number of crossings over time
  - Total horizontal activity
  - Number of rearings over time
  - Total vertical activity

- **Black-white box**
  - Latency
  - Time in white area

- **Plus-maze**
  - Entries OA
  - Time in OA
  - Head-dips
  - Repetitions

- **Boissier’s hole-board**
Alterations BPSD-like 12 month old 3xTgAD mice

- **Open-field**
  - Horizontal activity
  - Vertical activity
  - Total horizontal activity
  - Total vertical activity

- **Corner test**
  - Number of corners
  - Number of rearings

- **Dark-light box**
  - Latency
  - Time in lit area

- **Boissier’s hole-board**
  - Latency
  - Time head-dipping
  - Head-dips
  - Vertical activity
Changes and deficits
Exploration and Spontaneous Activity

Actimeter cages (5 min)

A. EXPLORATORY ACTIVITY
B. SPONTANEOUS ACTIVITY + HABITUATION

Horizontal activity
Total horizontal activity
NTg 3xTgAD

Vertical activity
Total vertical activity
NTg 3xTgAD

Activity counts
1 min intervals
NTg 3xTgAD

Horizontal activity
Total horizontal activity
NTg 3xTgAD

Vertical activity
Total vertical activity
NTg 3xTgAD

Activity counts
10 min intervals
NTg 3xTgAD

Activity counts
10 min intervals
NTg 3xTgAD
Sundawning-like behavior

**Actimeter (24h)**

**Activity Counts**

- **Non-Tg**
- **3xTgAD**

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
<th>Total</th>
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<tbody>
<tr>
<td>Non-Tg</td>
<td>200000</td>
<td>250000</td>
<td>300000</td>
</tr>
<tr>
<td>3xTgAD</td>
<td>250000</td>
<td>300000</td>
<td>450000</td>
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</tbody>
</table>

**Night/day relationship**

- Non-Tg: 2
- 3xTgAD: 3
Learning and Memory Deficits

2.5 month old

6 month old

Morris Water Maze
Learning and Memory deficits

12 month old

Morris Water Maze
<table>
<thead>
<tr>
<th>Behavioral screening of 3xTgAD mice</th>
<th>Activity cages</th>
<th>Open-field</th>
<th>Plus-Maze or Corner test</th>
<th>Hole-board</th>
<th>Dark/light box</th>
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<tr>
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<td>Total horizontal activity</td>
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<td>PM Entries OA</td>
<td>Latency to explore</td>
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<tr>
<td>6 month-old</td>
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<tr>
<td>Total horizontal activity</td>
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<td></td>
<td>PM Entries OA</td>
<td>Latency to explore</td>
<td>Latency to white area</td>
</tr>
<tr>
<td>Total vertical activity</td>
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<td>Number</td>
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<td>12 month-old</td>
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<tr>
<td>Total horizontal activity</td>
<td></td>
<td></td>
<td>CT Number of corners</td>
<td>Latency</td>
<td>Latency</td>
</tr>
<tr>
<td>Total vertical activity</td>
<td></td>
<td></td>
<td></td>
<td>Number</td>
<td>Number</td>
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<td></td>
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</tbody>
</table>

**Notes:**
- PM: Plus-Maze
- OA: Open Area
- CT: Corner Test
- NTg: Non-Tg
- 3xTgAD: Three-Tg Alzheimer's Disease
- **:** p < 0.05
- ***:** p < 0.01

**Images:**
- Equipment setup for behavioral tests
- Graphs showing activity data for different age groups
<table>
<thead>
<tr>
<th>Behavior parameters</th>
<th>Onset (2.5 m)</th>
<th>Early stages (4 m)</th>
<th>Moderate stages (6 m)</th>
<th>Advanced stages (12 m or more)</th>
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</thead>
<tbody>
<tr>
<td>Increased sensorimotor function</td>
<td>n.s.</td>
<td>n.s.</td>
<td>+</td>
<td>++</td>
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<tr>
<td>BPSD-like symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotionality</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Neophobia</td>
<td>n.s.</td>
<td>+</td>
<td>n.s.</td>
<td>+++</td>
</tr>
<tr>
<td>Reduced exploration in anxiogenic places</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Anxiety-like behaviors</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>Desinhibition</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Reduced novelty seeking</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dysfunction of startle response</td>
<td>n.a.</td>
<td>n.a.</td>
<td>+</td>
<td>n.a.</td>
</tr>
<tr>
<td>Dysfunction of prepulse inhibition</td>
<td>n.a.</td>
<td>n.a.</td>
<td>+</td>
<td>n.a.</td>
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<tr>
<td>Cognition</td>
<td></td>
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</tr>
<tr>
<td>Spatial Working memory deficits</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Spatial Short-term memory deficits</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>Spatial Long-term memory deficits</td>
<td>n.s.</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Instrumental conditioning deficits</td>
<td>n.s.</td>
<td>n.a.</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alteration Circadian rhythms</td>
<td>n.s.</td>
<td>n.a.</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Notes: Genotype effects: n.s. non-significant differences. n.a. not assessed in our colony of mice. +, ++, +++: higher levels in 3×Tg-AD than NTg mice (P < 0.05, P < 0.01, and P < 0.001, respectively). The appearance of AD pathology at different ages: 2.5 months (onset of AD; no neuropathological manifestation); four months (early stages; intracellular Aβ immunoreactivity); six months (moderate stages; extracellular Aβ deposits but still no tau alterations); 15 months (advanced stages; Aβ deposits in many cortical regions and tau hyperphosphorilation). Refs. [30, 60, 63–65].
Spatial memory deficits in APP and 3xTg-AD mice

A, B, C: Graphs showing the path length over days for WT and APPind, APPSw,Ind, and 3xTg-AD mice.

D, E, F: Graphs showing the percent time in each quadrant for WT and APPind, APPSw,Ind, and 3xTg-AD mice.

G, H, I: Graphs showing platform crossings for WT and APPind, APPSw,Ind, and 3xTg-AD mice.
Transgenic mice:
- APP_Sw, Ind
- APP_Ind
- 3xTg-AD

Fear conditioning: context and cued

BLA: Basolateral amygdala
Age-dependent fear symptoms in APP<sub>Sw,Ind</sub> transgenic mice

- **Graph:** Bar graph showing the percentage of time freezing at 2, 6, and 12 months for WT and APP<sub>Sw,Ind</sub> mice. Significant differences are indicated by asterisks (*, **).

- **Western Blot:** Western blot analysis with bands for APPs<sub>α</sub>, APP fl, APP CTFs, and α-tubulin, labeled with the respective months (2, 6, 12, 6).

- **Scatter Plot:** Scatter plot with the percentage of time freezing plotted against the memory index (target platform crossings), showing a linear trend line with a coefficient of determination ($r^2 = 0.1608$) and a p-value of 0.0423.
Intraneuronal Aβ accumulation in the basolateral amygdala of AD mice

<table>
<thead>
<tr>
<th></th>
<th>GABAergic</th>
<th>GLUTergic</th>
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<tr>
<td>WT</td>
<td></td>
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<td>APP&lt;sub&gt;Ind&lt;/sub&gt;</td>
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<td><img src="image3" alt="Image" /></td>
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<td>3xTg-AD</td>
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<td>2G3</td>
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<tr>
<td>WT</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>3xTg-AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>pTau</th>
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<tbody>
<tr>
<td>WT</td>
<td>PHF1</td>
</tr>
<tr>
<td>3xTg-AD</td>
<td>PHF1</td>
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<tr>
<td>AD</td>
<td>CP13</td>
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</tbody>
</table>
Intraneuronal β-Amyloid Accumulation in the Amygdala Enhances Fear and Anxiety in Alzheimer’s Disease Transgenic Mice

Judit España, Lydia Giménez-Llort, Jorge Valero, Alfredo Miñano, Alberto Rábano, José Rodriguez-Alvarez, Frank M. LaFerla, and Carlos A. Saura

Background: Alzheimer’s disease (AD) is characterized by progressive memory decline and neuropsychiatric symptoms. Despite common emotional symptoms in AD such as anxiety and fear being associated with a more rapid cognitive decline, the pathological mechanisms involved in these behavioral changes remain largely elusive. In this study, we examined the pathological mechanisms of emotional behavior in well-established AD transgenic mice expressing human mutant β-amyloid (Aβ) precursor protein (APP<sub>sw,ind</sub> and APP<sub>sw,ind</sub>) and tau (3xTg-AD).

Methods: We evaluated unconditioned and conditioned fear-induced freezing behavior and spatial memory in APP<sub>sw,ind</sub> and APP<sub>sw,ind</sub> and 3xTg-AD transgenic mice. The Aβ and tau pathologies and signaling pathways involved in emotional processing were studied by immunohistochemistry and immunoblotting analyses.

Results: The APP<sub>sw,ind</sub> and 3xTg-AD transgenic mice displayed at early ages enhanced innate and conditioned fear symptoms and spatial memory deficits coinciding with enhanced accumulation of Aβ in γ-aminobutyric acid (GABA)ergic and glutamatergic neurons, respectively, of the basolateral amygdala (BLA). Similarly, the number of neurons with intraneuronal Aβ40 and Aβ42 was significantly increased in the BLA of human AD brains. Fear responses might reflect an influence of anxiety, because the anxiolytic compounds valproate, diazepam, and buspirone reduced efficiently unconditioned and conditioned fear responses in APP transgenic mice. In addition, phosphorylation of extracellular signal-regulated kinase (ERK)1/2, which is critical for acquisition and consolidation of fear conditioning, was increased in the amygdala of APP transgenic mice after cued conditioning.

Conclusions: We propose a deleterious role of intraneuronal Aβ on amygdala-dependent emotional responses by affecting the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway.
Behavioral Neuroscience

✓ Validation (Guidelines)
✓ Screening and validation of the model

☐ Neuroimmunosenescence
☐ White Paper for the Use of Atypical Antipsychotics in AD patients
☐ Metabolic syndrom
Behavioral Neuroscience

✓ Validation (Guideliness)
✓ Screening and validation of the model

✓ Life events + Life style (Non-Pharm)
✓ Ethogram + Social behavior
  ❑ Soledad
  ❑ Permanent Family Structure
  ❑ Carmen
Validation (Guideliness)

Screening and validation of the model

Life events + Life style (Non-Pharm)

- Early postnatal and Late Handling
- Environmental Enrichment
- Exercice_ Forced (Treadmill)
- Exercice_Voluntary (Wheel)
Behavioral Neuroscience

✓ Validation (Guideliness)
✓ Screening and validation of the model
✓ Life events + Life style (Non-Pharm)
✓ External actions (Pharmacol, Molecular)
  - Huprine X, Huperzina A, Dine 3
  - Memantine + Mynocycline
  - New Marine drugs
  - 5HT4
  - sc-Fv-h3D6
Models of Aging of Neuroimmunomodulation: Strategies for Its Improvement

AGING

Chronic oxidative and inflammatory stress

Ax anti-inf

ROS pro-inf

Impaired homeostasis

Models for study of NIM aging (humans and rodents)

A) Poor response to stress, anxiety and depression
B) Males versus females
C) Menopausal models
D) Obesity

Models of Aging of Neuroimmunomodulation: Strategies for Its Improvement

Nervous system (behavior parameters)

Endocrine system (hormonal levels)

Immune system (immune cell functions)

ROS, pro-inf (NFκB over-expression)

Strategies for improvement of NIM in aging

Nutrition (adequate amount of antioxidant compounds)
Physical activity
Environmental enrichment (physical and mental activity)

More and healthier longevity

*Higher oxidative stress (immune and other cells)
*Worse function of immune cells
*Worse behavioral response
*Lower longevity

*Improve redox state of immune and other cells
*Improve immune cell functions
*Improve behavior response

Improved homeostasis

Under the influence of oxidative stress and inflammatory stress, the nervous system, endocrine system, and immune system are impaired, leading to morbidity and mortality.

Aging is a complex process influenced by various factors, including oxidative stress and inflammation. Strategies for improving NIM in aging include nutrition, physical activity, and environmental enrichment, which can lead to healthier longevity.
Gender-Specific Neuroimmunoendocrine Aging in a Triple-Transgenic 3×Tg-AD Mouse Model for Alzheimer’s Disease and Its Relation with Longevity

Lydia Giménez-Urtó, Lorena Arranz, Iainre Mate, Mónica De la Fuente

*Department of Psychiatry and Forensic Medicine, Institute of Neuroscience, Autonomous University of Barcelona, Bellaterra, and \(^b\)Department of Physiology (Animal Physiology II), Faculty of Biology, Complutense University of Madrid, Madrid, Spain
Gender-Specific Neuroimmunoendocrine Aging in a Triple-Transgenic 3×Tg-AD Mouse Model for Alzheimer's Disease and Its Relation with Longevity

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Department of Molecular and Clinical Neuroscience, University Hospital of Parc de Salut Mar, Barcelona, Spain
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Key Words
Transgenic mouse, 3×Tg-AD model, Neuroimmunoendocrine aging, Amyloid beta (Aβ), Neuroinflammation, Longevity

Abstract
In the present work, we briefly review the evidence on the role of neuroimmunoendocrine aging in the development of Alzheimer's disease (AD) and provide new behavioral, immune, and endocrinological data obtained in old male and female triple-transgenic 3×Tg-AD mice. The results indicate that several aspects of the neuroimmune network are more robust in female mice than in male mice in this triple-transgenic model. This supports the hypothesis of a sex difference in the regulation of the hypothalamus-pituitary-adrenal (HPA) axis and in the immune system in AD. The results also suggest that female mice have a lower incidence of amyloid deposition and inflammation in the brain than male mice. These findings provide new insights into the role of sex hormones in the pathogenesis of AD and support the idea that sex may influence the progression of the disease.

Introduction
The neurobiology of aging has been one of the most rapidly expanding areas of scientific endeavor over the past 2 decades. Several factors have been suggested to contribute to the development of AD, including environmental factors, lifestyle, and genetic factors. The interaction between these factors and the age-related changes in the brain plays a crucial role in the development of AD. In this regard, sex differences in the progression of AD have been studied extensively, and recent studies have suggested that sex hormones may play a critical role in the development of AD.

KARGER
Crosstalk between Behavior and Immune System in AD
Giménez-Llort et al., Current Pharmaceutical Design, 2014

Peripheral immune system and neuroimmune communication impairment in a mouse model of Alzheimer’s disease
Lycia Giménez-Llort,1 Irene Moté,2 Rafaela Marasora,2 Carmen Viñas,2 and Monica De la Fuente2
1Research Unit for Brain-Body Interactions (INIBIDI), Department of Neurosciences, Fundación Jiménez Díaz, Madrid, Spain
2Department of Neuroimmunology, Instituto de Investigación Sanitaria Gregorio Marañon, Madrid, Spain

HEALTH — HOMEOSTASIS — Alzheimer’s DISEASE

LIFE STYLE STRATEGIES
Healthy Nutrition
Physical exercise
Environmental enrichment
Social enrichment
Early postnatal handling

 Chronological age

 Biological age

 Age

 Time

 Horizontal activity HA
 Vertical activity VA

 a. NEOPHOBIA
 Total time of running

 b. ANXIETY LIKE-BEHAVIOR
 Horizontal activity HA
 Vertical activity VA

 c. PERIPHERAL IMMUNOLOGICAL SYSTEM
 Neutrophils, % body weight
 Thrombocytes, % body weight
 Neutrophils, % body weight
### Table 2. Several functional parameters in immune cells from young to old 3×Tg-AD versus NTg female mice

<table>
<thead>
<tr>
<th>Parameters (function)</th>
<th>2.5 months</th>
<th>4 months</th>
<th>9 months</th>
<th>15 months</th>
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<tbody>
<tr>
<td>Chemotaxis</td>
<td>=</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Proliferation</td>
<td>=</td>
<td>↓↓</td>
<td>↓↓</td>
<td>=</td>
</tr>
<tr>
<td>NK</td>
<td>=</td>
<td>=</td>
<td>=(↓)</td>
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</tr>
<tr>
<td>IL-2 secretion</td>
<td>n.a.</td>
<td>↓</td>
<td>=</td>
<td>↑</td>
</tr>
</tbody>
</table>

### Table 3. Oxidative stress parameters (antioxidants and oxidants) in the spleen of young and adult 3×Tg-AD versus NTg mice

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3×Tg-AD vs. NTg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>GPx</td>
<td>↓↓</td>
</tr>
<tr>
<td>GR</td>
<td>↓</td>
</tr>
<tr>
<td>Oxidant</td>
<td></td>
</tr>
<tr>
<td>XO</td>
<td>↑↑</td>
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</tbody>
</table>
Effect of Huprine X on β-Amyloid, Synaptophysin and α7 Neuronal Nicotinic Acetylcholine Receptors in the Brain of 3xTg-AD and APPswe Transgenic Mice

Monika M. Fiedberg1, M. Victoria Cos5, Martins Rauce2, Daniel Gonzalez1, Christen Ursll Lehner1, Perseo Camps5, Diego Moncada Orriol2, Albert Bada2, Lydia Gomez-Llor1, Amaia Novero1

1Repsilab, Instituto de Neurociencia de Castilla y Leon, CIBERneurona, and Instituto de Fisiología; 2Instituto de Fisiología y Farmacología; 3Neurológia, Facultad de Medicina; 4Neurológia, Hospital de San Pedro, Universidad de Castilla-León; 5Facultad de Medicina, Universidad de Castilla-La Mancha, Ciudad Real, Spain.

Keywords: Neurodegenerative disease - β-Amyloid - Alzheimer's disease - Presenilin-1 - Synaptophysin - Neuronal nicotinic acetylcholine receptors - Transmission of neurons.

Abstract

Background: Several studies have assessed the effects of Huprine X (HX) on β-Amyloid in the brain of 3xTg-AD mice, showing a reduction in β-Amyloid plaque burden. The aim of the present study was to assess the effects of HX on the levels of synaptophysin in the cortex of 3xTg-AD and APPswe transgenic mice. Methods: Male 3xTg-AD mice aged 6 months were treated with either saline (sal) or HX (2 mg/kg) for 21 days. The levels of synaptophysin in the cortex were measured using Western blot analysis. Results: The levels of synaptophysin in the cortex of 3xTg-AD mice treated with HX were significantly increased compared to those treated with saline. Conclusion: The results suggest that HX treatment may have a positive effect on synaptophysin levels in the brain of 3xTg-AD and APPswe transgenic mice.
single-chain variable fragment scFv-h3D6, which has been shown to be capable of avoiding the in vitro toxicity induced by the Aβ peptide in neuroblastoma cell-cultures by withdrawing Aβ oligomers from the amyloid pathway.
Biological bases of environmental stimulation in NDD

Handling (PND1-PND21)

Enrichment (PND21-6m)

Strategies

Preventive Control
Handling EE

Therapeutical Control EE

Learning and Memory deficits
Morris Water maze (trials of 60 seconds, spaced 15 min apart)
Efectos de los tratamientos de handling (H), enriquecimiento ambiental (E) y su combinación (HE) en la morfología neuronal de la región CA1 en ratas RLA

Enriquecimiento (PND21-6m)

C: ratas viejas no tratadas
Y: ratas jóvenes no tratadas

Fernández-Teruel et al., Behav. Genetics, 1997
Enriquecimiento (PND21-6m)

- BDNF, exon I
- Zif268/Krox-24/NGFIA
- Synaptotagmin 5
- Clathrin-associated protein 17 (AP17)
- Cyclooxygenase isoform COX-2
- Integrin β5 subunit
- Neuronal activity-regulated pentraxin
- Vasoinactive intestinal polypeptide (VIP) receptor
- Syndecan
- Vessel
- VGF
- Bcl-2 β
- Neuronal death protein
- Major hsp70-like protein hsc73
- Klotho

- Mitochondrial cytochrome oxidase subunits I, II, III
- Cytochrome P450 arachidonic acid epoxygenase
- Protein processing
- Transcription regulation

Plasticity (37%)
Metabolic (24%)
Anti-aging (15%)
Immune (21%)
Other (10%)

- Complement protein C1q beta chain
- Cyclooxygenase isoform COX-2
- Natural killer cell protein group 2-A (NKG2A)
- Major acute phase α-1 protein (MAP)
- MHC class I cell surface antigen
- Anti-idiotypic immunoglobulin M heavy chain
- Mismatch repair protein MSH2

(a) Environmental stimuli

Hippocampus

- BDNF
- Multiple genes promoting synaptic plasticity

Encoding, resistance to insult

Exercise primes encoding mechanisms

(b) Medial septum (ACh/GABA)

Hippocampus

- BDNF
- Other plasticity genes

Genomic regulation
- Structural change
  - vascular
  - neuronal
  - neurogenesis
- Increased neuronal health

Exercise

Estrogen
Glucocorticoids
IGF-1
Blood–brain barrier
Peripheral factors

Locus coerulescens (NE)
Raphe (5-HT)
Effect of Environmental Enrichment on the Immunoendocrine Aging of Male and Female Triple-Transgenic 3xTg-AD Mice for Alzheimer's Disease

Lorena Amancio*, Pilar M. de Castro*, Isabel Barría, Lydia Giménez-Llort* and Mónica de la Fuente
"Department of Physiology and Polypharmacy, Faculty of Medicine, Complutense University of Madrid (UCM), Madrid, Spain

Table 1
Effect of environmental enrichment on the mortality ratio in 3xTgAD mice from early (6 month-old) to advanced (15 month-old) stages of the disease

<table>
<thead>
<tr>
<th></th>
<th>NTg</th>
<th>3xTgAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Male (n = 9) 0%</td>
<td>Male (n = 9) 33%</td>
</tr>
<tr>
<td></td>
<td>Female (n = 10) 0%</td>
<td>Female (n = 10) 10%</td>
</tr>
<tr>
<td>Environmental</td>
<td>Male (n = 8) 0%</td>
<td>Male (n = 11) 45%</td>
</tr>
<tr>
<td>enrichment</td>
<td>Female (n = 12) 0%</td>
<td>Female (n = 9) 11%</td>
</tr>
</tbody>
</table>

Cognitive and emotional profiles of aged Alzheimer's disease (3 x TgAD) mice: Effects of environmental enrichment and sexual dimorphism

Gloria Blázquez*, Toni Callejo, Adolf Tobeña, Lydia Giménez-Llort, Alberto Fernández-Teruel
Medical Physiology Unit, Department of Psychiatry and Neurosciences, Institute of Neuroscience, Autonomous University of Barcelona, 08193 Bellaterra, Spain

HIGHLIGHTS
* Aged 3 x TgAD mice show deficits in spatial learning, short-term and working memory.
* 3 x TgAD mice show signs of increased anxiety and reduced immunocompetence.
* Sexual dimorphism is reflected by increased behavioral in males.
* Environmental enrichment induces beneficial effects on working memory.

Figure 1: Splenic and thymic lymphocyte chemotaxis and plasma corticosterone levels in NTg and 3xTgAD mice under control and environmental enrichment conditions.
Effects of exercise

Increases cerebral function
Protects from neurodegeneration
Improves cognition and emotions (Depr)

Oxidative stress
Atenuates ROS production
Increases antioxidant capacity

Growth factors
BDNF, VEGF, FGF-2, NGF, IGF-1
Gens for synaptic plasticity, L&M
Neurogenesis & Angiogenesis

Beta-amloid neuropathology
Increases proteasoma degradation

MAPK, PI3K, PI/Akt signalling
pCREB transcription factor
NMDA (NR2A NR2B)
Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

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<th>Ex</th>
<th>ME</th>
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<tbody>
<tr>
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<tr>
<td>BAT involution</td>
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<td>Sensorimotor tasks (coordination)</td>
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<tr>
<td>BPSD (CT, OF, HB)</td>
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<td>L&amp;M (PT acquisition)</td>
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<td>Sing</td>
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<td>L&amp;M (RM)</td>
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Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

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<td>Tau (AT8)</td>
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<td>Redox status Cx</td>
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<tr>
<td>CoQ9 and Respiratory chain complex</td>
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<tr>
<td>mtDNA/nDNA</td>
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![Graphs and images showing data analysis results](image)
Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse

Yosvies Garcia-Mesa, Lydia Gimenez-Llort, Luis C. Lopez, Carmen Vazquez, Rosa Cristino, German EsCanes, Darío Azara-Camargo, Carlos Sanz

1. Introduction

Healthy lifestyle options such as physical exercise, cognitive training, and a diet rich in unsaturated food increase physical reserve and delay symptoms of aging and hence may protect against age-related disease (Emslie, 2018; Joseph et al., 2004; Melton and Yaffe, 2006). The health-promoting lifestyle intervention known as the most effective is daily aerobic exercise.

Abstract

Alzheimer’s disease (AD) is a devastating age-related neurodegenerative disorder that has been suggested as having a multifactorial pathogenesis. Vigorous physical exercise and other cognitive training interventions have been proposed as effective treatments for AD. However, these strategies have not yet been shown to be effective in the majority of AD patients. In this study, we investigated the effect of a combined treatment of melatonin plus physical exercise on behavioral and physiological parameters in a murine model of AD. The results showed that melatonin plus physical exercise significantly reduced the number of abnormal behaviors and improved cognitive function in the Tg-AD mouse model. These findings suggest that melatonin plus physical exercise may represent a promising therapeutic approach for AD.
Short Communication

Neophobia, NQO1 and SIRT1 as premorbid and prodromal indicators of AD in 3xTg-AD mice

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1 Departamento de Farmacología, Facultad de Medicina, Universidad Autónoma de Barcelona, Barcelona, Spain
2 Institute of Pharmaceutical Biology, Swedish University of Agricultural Sciences, Umeå, Sweden
3 Department of Pharmacology, Faculty of Medicine, Universidad Autónoma de Barcelona, Barcelona, Spain
4 Centre for Experimental Imaging in Neuroscience, Umeå University, Umeå, Sweden
5 Department of Experimental Medicine, Faculty of Medicine, Umeå University, Umeå, Sweden
6 Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

Highlights

- Neophobia was the first behavioral indicator of preclinical AD in 3xTg-AD mice.
- Premorbid AD was clearly defined by cognitive deficits at 6 months of age.
- High levels of cortical and hippocampal NQO1 were a robust indicator of preclinical AD.
- SOD2 was changed only in hippocampus at 4 months of age before preclinical AD.
- SIRT1 levels had opposite regional and temporal profiles of prodromal patterns.