# Melatonin aging/age-related neurodegeneration

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# AGING DEFINITION

Aging is usually defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality with advancing age.
(Kirkwood et al, 2000)

The old age begins at age 65
and divides into:
young-old: ages 65-74
old-old (or old): ages 75-84
oldest-old: ages 85 and beyond
(Kaplan and Sadock's, 2005)

## WHO

World Health Organization

AGING EPIDEMIOLOGY

WHO ( 2012):
By 2050: two billion people ¼ will be older than 60 years
2030: 65 years, 71.5 million in the year, which is twice the number alive during the year 2000.
(Lister et al., 2009).

## WHO

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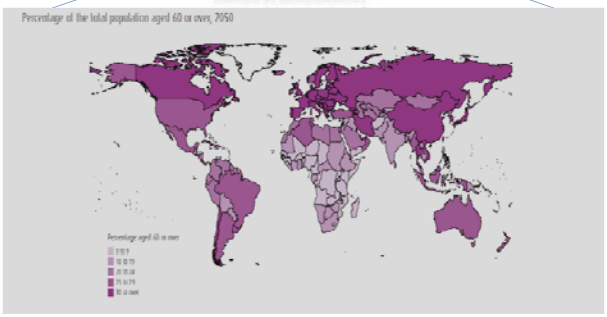
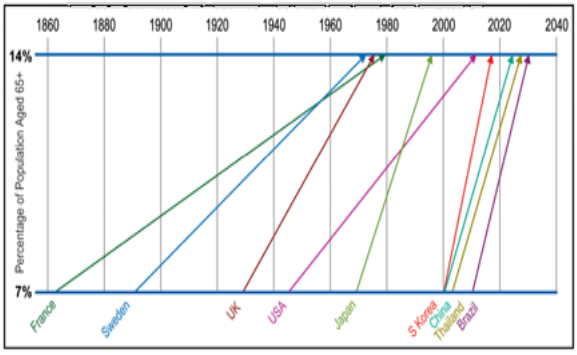
AGING EPIDEMIOLOGY




# AGING IN THAILAND




The speed of population aging (Global brief for World Health Day 2012)

# AGING IN THAILAND

WHO report in 2012, time required or expected for population aged 65 or older to increase from 7% to 14% in Thailand is 20 years

**Thai population > 60 years**
2012: 11%
2015 :14%
2025 :19.8%
2050: 30%

The speed of population aging (Global brief for World Health Day 2012)

## *Why Do We AGE ?*

## Aging process

There are many biological changes with aging such as hair graying (neural crest derived melanocytes), sensory changes resulting in a reduced acuity of vision and impairment in hearing(neural crest derived sensory neurons), constipation(neural crest derived enteric nervous system) and decline in cognition and memory and motor deficits (neural tube derived structures)`(Kaplan and Sadock's, 2005) (Bowen et al., 2004).

## ↑ Age

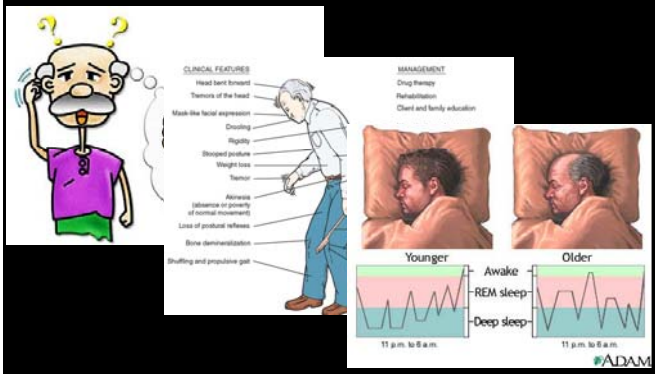
## ↓

## ↑ Incidence of

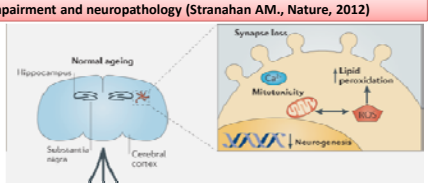
## Neurodegenerative Diseases:

## Alzheimer's, Parkinson, Stroke, etc

## Brain Ageing




**Age-related cognitive impairment and neuropathology (Stranahan AM., Nature, 2012)**




Age-related pathologies such as Alzheimer's disease, Parkinson's disease and Huntington's disease arise from a combination of genetic and environmental factors ageing sets the stage for the onset of pathology. Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; DJ1, Parkinson's disease protein 7; P, phosphorylation site; REST, repressor element 1-silencing transcription factor.

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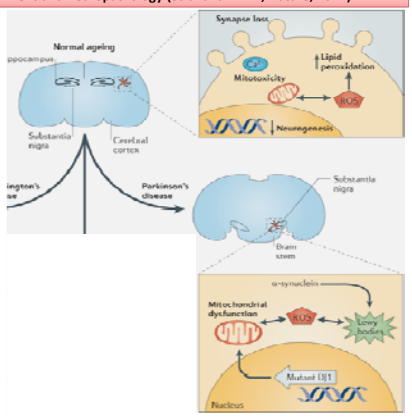


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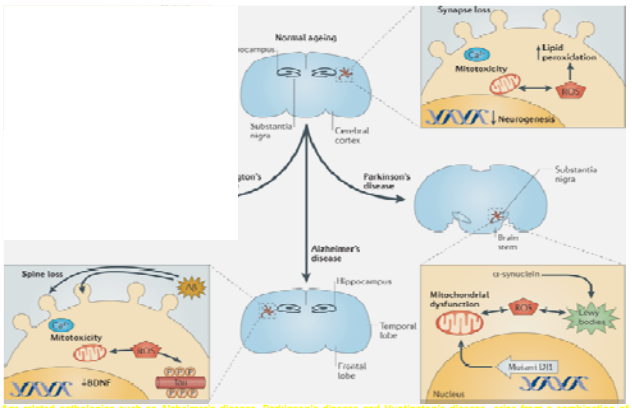


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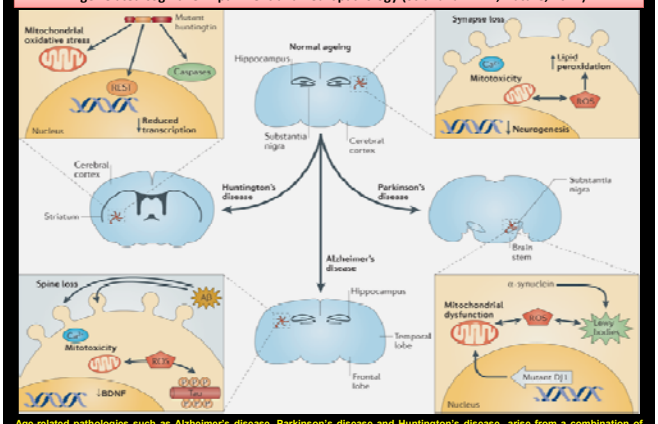


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## Proposed theories to explain aging processes

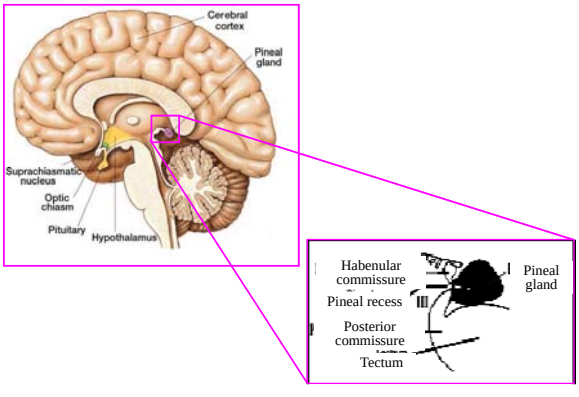
**I. Programmed theory**
1. Programmed longevity (genes)
2. Endocrine : clock gene, hormones
3. Immunological theory
   - Immune dysfunction
   - Inflammation
   - Alzheimer's disease
   - Cancer

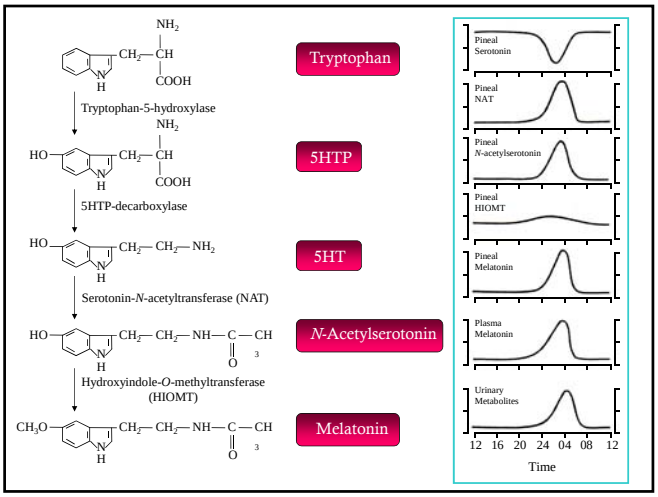
**II. Damage or error theory**
1. Rear & tear theory (cells, tissues)
2. Rate of living theory
   - Cross linking theory
3. Cross linked protein
4. Free radical/Mitochondril theory
5. DNA damage theory

**Others**
- Telomere
- Caloric restriction & sirtuins
- Insulin/IGF (Insulin resistance)
- Epigenetic aging
- Stem cell aging

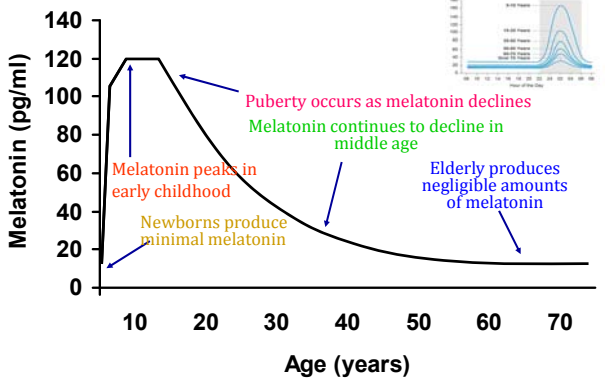
## *Why Do We AGE ?*


## Melatonin is synthesized in pineal

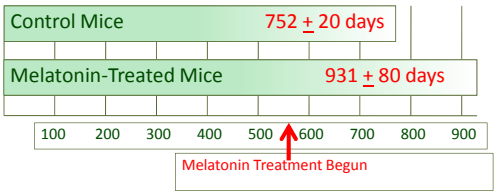


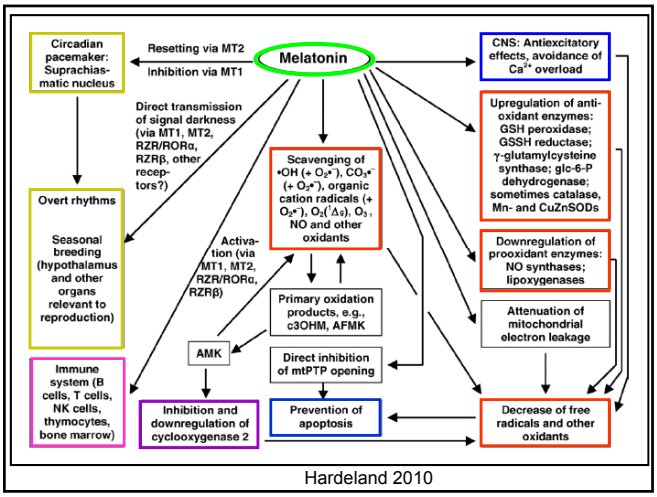
## Nocturnal melatonin levels throughout the life span




## Melatonin Increases Lifespan

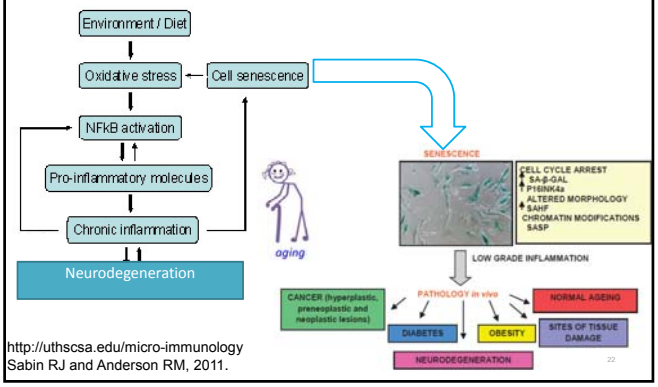



Increased lifespan in mice due to administration of melatonin 10μg/ml in drinking water at night (Maestroni et al., 1988)




Hardeland 2010

## Aging

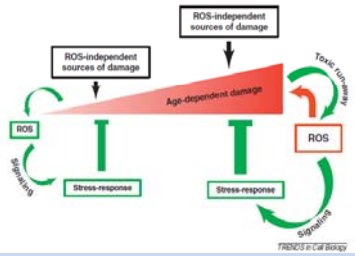



http://uthscsa.edu/micro-immunology
Sabin RJ and Anderson RM, 2011.

## Free radical theory of aging

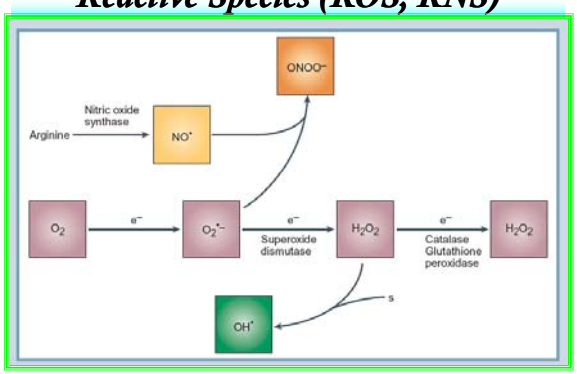
Endogenous oxygen radicals were generated in cells and resulted in a pattern of cumulative damage.

Free radical theory of aging proposed by Harman in 1956




The base of this theory is some observation that there is a strong correlation between chronological age and the level of ROS generation, mitochondrial function decrease during aging and oxidative stress increases in several age-dependent diseases.
(Balaban et al, 2005)

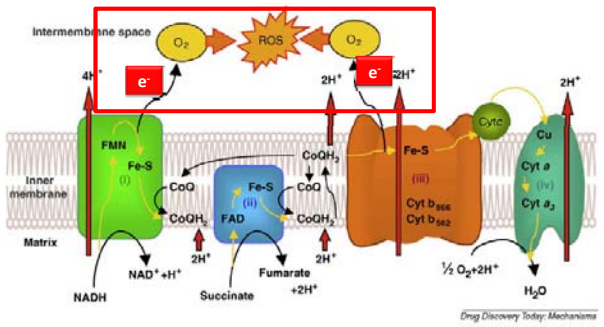
## Reactive Species (ROS, RNS)




Nature Medicine 2004; 10 (7S): S18-

# Free-Radical Theory of Aging

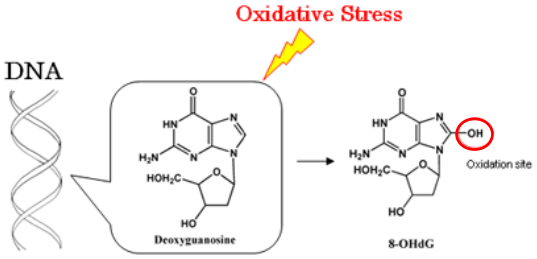
## Mitochondrial dysfunction




Yamashina S et al., 2009.

# Free-Radical Theory of Aging

- Free radicals and DNA damage




http://en.ori-japan.com

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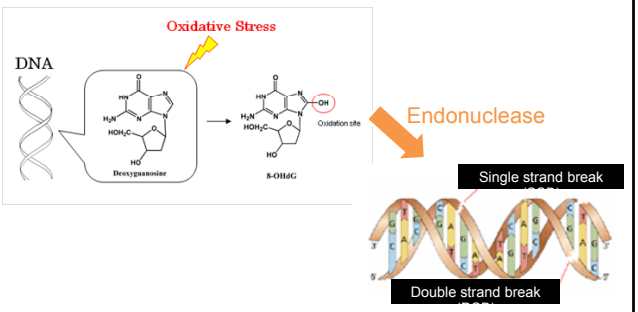
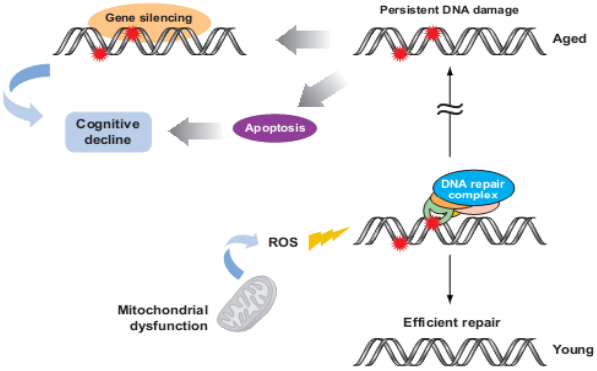
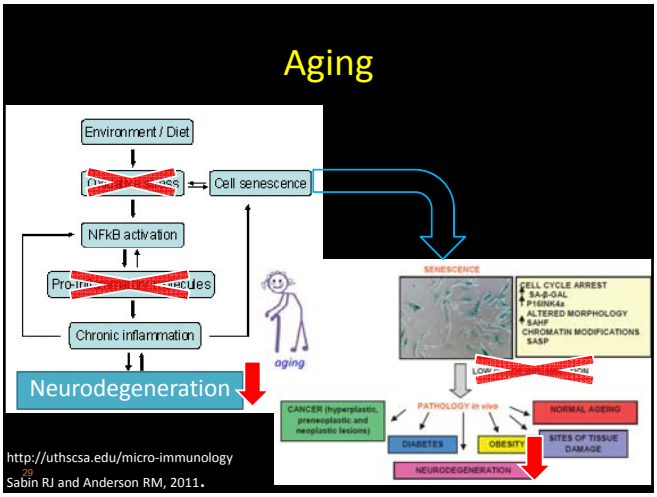



http://en.ori-japan.com, http://vefir.mh.is




# Aging

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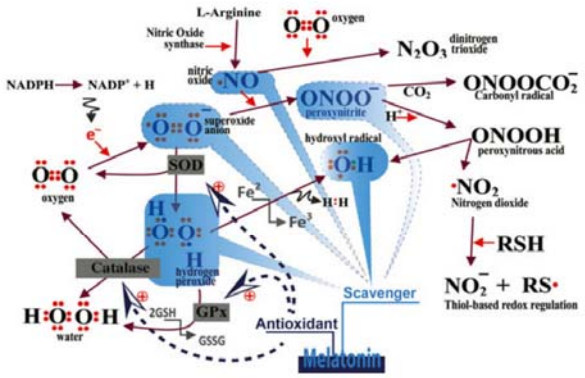



Major oxidative pathways of melatonin via promoting the activity of antioxidant enzymes (dashed blue arrows). Derived from metabolic activity, particularly from mitochondria in aging, melatonin plays an important role as a free radical scavenger (blue balloons).

(Rosales-Corral et al., 2012)

### Immunological Theory

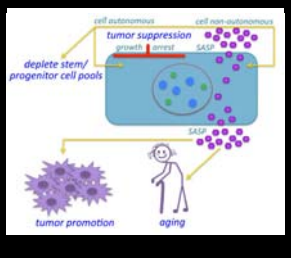
The immune system is programmed to decline over time, which leads to an increased vulnerability to infectious disease and thus aging and death.

Ab lose their effectiveness in old age, and fewer new diseases can be combated effectively by the body. The dysregulated immune response has been linked to cardiovascular disease, inflammation, Alzheimer's disease, and cancer.

Although direct causal relationships have not been established for all these detrimental outcomes, the immune system has been at least indirectly implicated.

## Cellular Senescence

- Senescence-associated secretory phenotype (SASP)




SASP:
Cytokines
Chemokines
Proteases
Growth factors

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## Cellular Senescence

- Senescence-associated secretory phenotype (SASP)

**Table 2.1:** The examples of SASP in the senescent cells (Coppe et al., 2010).

| Types of SASP | SASP factors |
|---|---|
| Interleukins (IL) | IL-1α, IL-1β, IL-6, IL-7, IL-13, IL-15 |
| Chemokines (CXCL, CCL) | IL-8, GRO-α, GRO-β, GRO-γ, MCP-2, MCP-1α, Eotaxin-3 |
| Other inflammatory factors | GM-CSF |
| Growth factors and regulators | EGF, bFGF, HGF, KGF, VEGF, Angiogenin, SCF, SDF-1, IGFBPs |
| Proteases and regulators | MMP-1, MMP-3, MMP-10, MMP-12, MMP-13, MMP-14, CathepsinB |
| Soluble or shed receptors or ligands | ICAM-1, ICAM-3, OPG, sTNF-RI, sTNF-RII, TRAIL-R3, Fas, uPAR, SGP130, EGF-R |
| Nonprotein soluble factors | PGE2, Nitric oxide |

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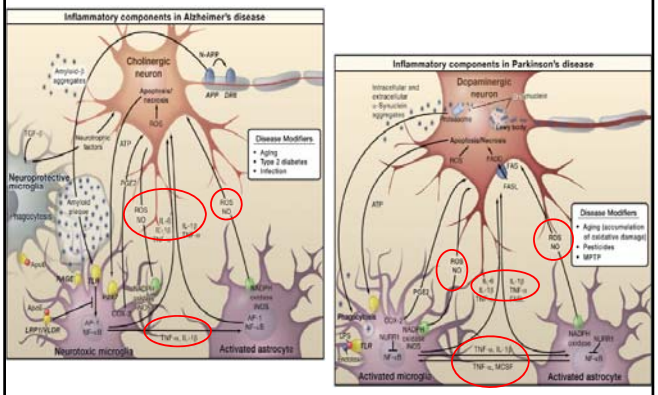
Alzheimer's disease

Parkinson's disease

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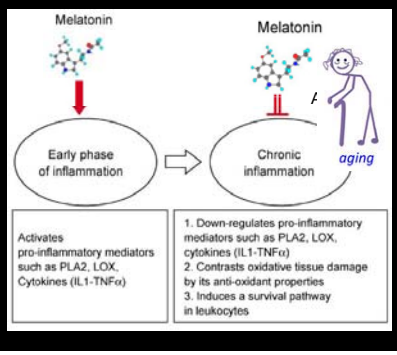
## Melatonin

- Melatonin and Inflammation

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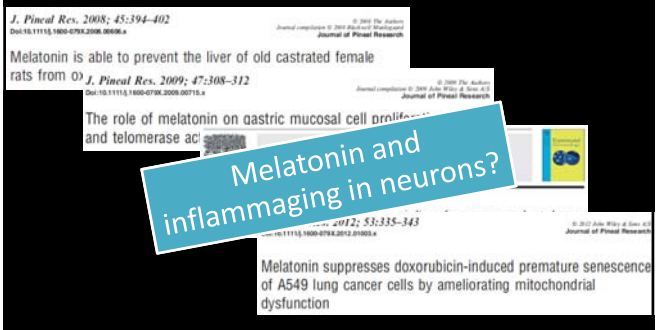
## Objectives

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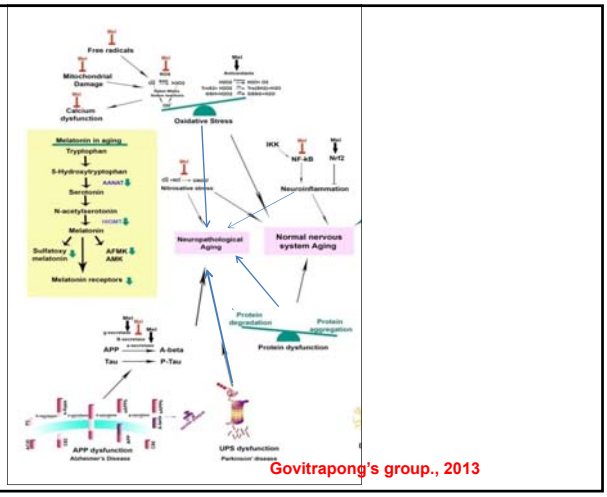
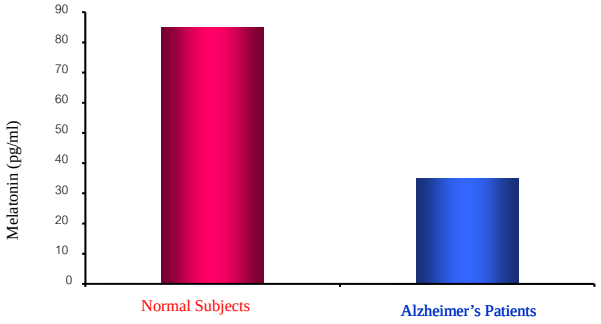



Govitrapong's group., 2013

## *Low Plasma Melatonin Levels in Alzheimer's Patients*




## Low melatonin levels in CSF of AD patients

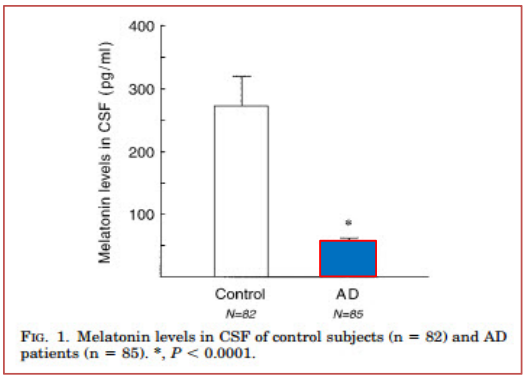
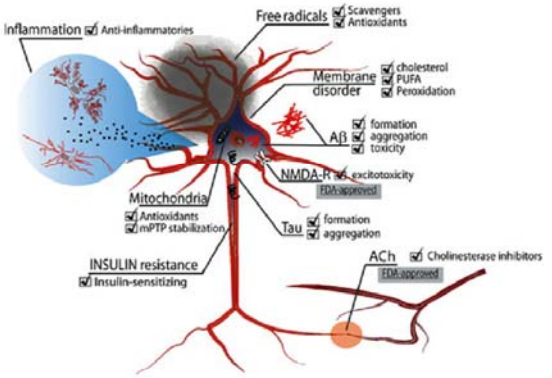



FIG. 1. Melatonin levels in CSF of control subjects (n = 82) and AD patients (n = 85). *, $P < 0.0001$.

Liu RY et al., 1999.

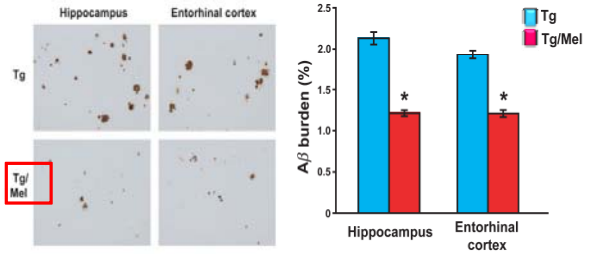
## Major targets for Alzheimer's disease therapy




(Rosales-Corral et al., 2012)

## Melatonin and AD

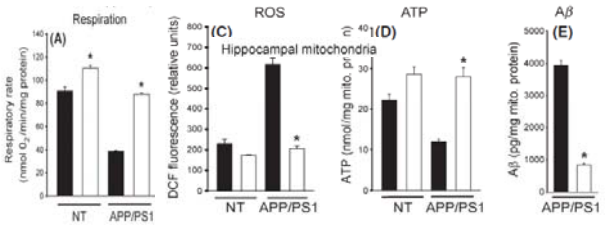
Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of Alzheimer disease




Reductions in Aβ deposition

Olcese et al., 2009

## Melatonin treatment restores mitochondrial function in Alzheimer's mice: a mitochondrial protective role of melatonin membrane receptor signaling




Dragicevic et al,2011

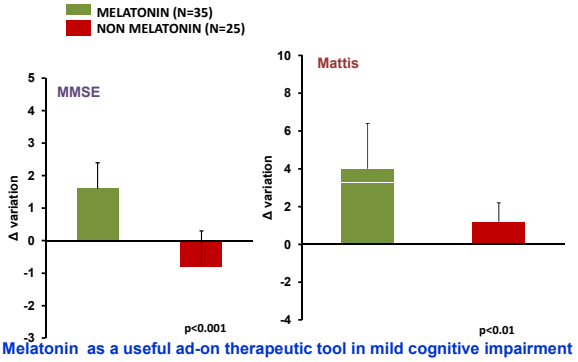
## AD patients treated with melatonin

| Subjects | Treatment | Study duration | Measured | Results | Reference |
|---|---|---|---|---|---|
| 10 demented | 3 mg mel P.O./daily at bedtime | 3 w | Sleep/wake quality | 7/10 better | Fainstein et al 1997 |
| 14 AD | 9 mg mel P.O./daily at bedtime | 22-35 m | Sleep/wake quality, Neuropsychological assessment | 12 pateints better | Brusco et al 2000 |
| Monozygotic twin AD fo SY | 1 treated with 9 mg mel P.O. at bedtime | 36 m | Neuropsychological Neuroimage | - treated Mel get better<br>- cognitive function | Brusco et al 1998 |
| 14 AD | 6 mg mel at bedtime | 4 w | Sleep/wake | better in sleep | Misfrsima 2000 |
| 11 AD | 3 mg | 3 w | Sleep/wake | better in sleep | Cohen-Monsfield 2000 |
| 45 AD | 6-9 mg | 4 m | Sleep/wake, Neuropsychological assessment | better in sleep | Cardinali 2002 |
| 25 AD | 6 mg | 7 w | Actigraphy | sleep | Seslaty et al 2002 |
| 20 AD | 3 mg | 4 w | Actigraphy Neuropsychological | Sleep Cognitive function improve | Krayama 2003 |

## MCI patients treated with melatonin

| Subjects | Treatment | Study duration | Measured | Results | Reference |
|---|---|---|---|---|---|
| 10 MCI | 6 mg | 10 d | Actigraphy Neuropsychological | - improve sleep quality<br>- improve memory<br>-↓ depresed mood | Jean-Louiser 1998 |
| 26 MCI | 1 mg | 4 w | Sleep question air | - improve scan on learnny<br>- improve memory | Peck et al 2004 |
| 50 MCI | 3-9 mg | 9-18 m | Sleep/wake Neuropsychological | improve | Furio 2007 |
| 354 MCI | 2 mg (prolonged release) | 3 w | Neuropsychological | - improve sleep | Wade et al 2007 |
| 189 MCI | | | Neuropsychological | improve memory | Reimersnea-van du Lek 2008 |
| 22 MCI | 5 mg | 2 m | Neuropsychological | improve memory | Garzon et al 2009 |
| 60 MCI | 3-9 mg | 9-24 m | Neuropsychological | - improve better perform | Cardinali 2010 |

## Melatonin increases memory in MCI and Alzheimer's patients

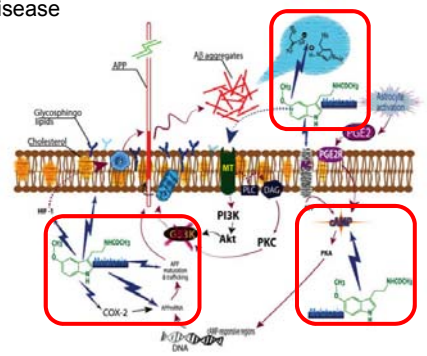



**Melatonin as a useful ad-on therapeutic tool in mild cognitive impairment (MCI) and Alzheimer's Disease (AD)**

***Cardinali et al,Current Neuropharm 2010***

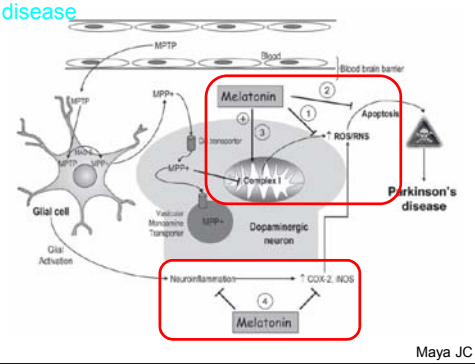
## Melatonin

Alzheimer's disease




## Melatonin

Parkinson's disease




Maya JC et al., 2005.

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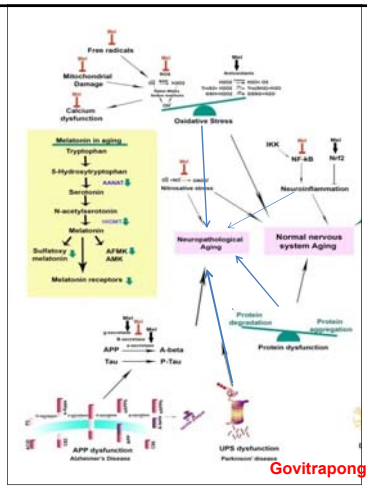
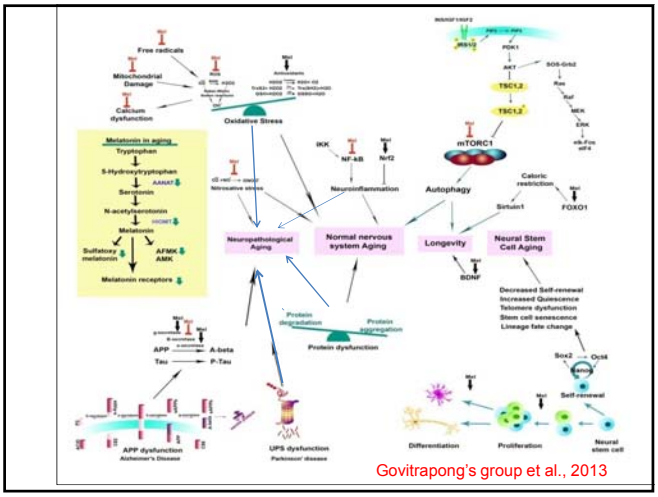
- Autophagy
- Stem cell aging



Govitrapong's group., 2013

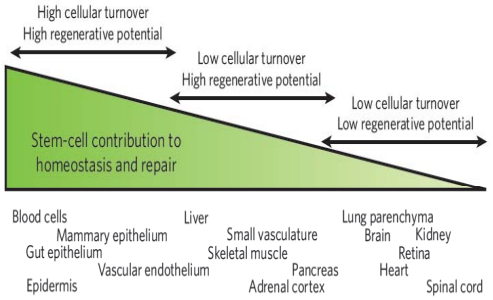


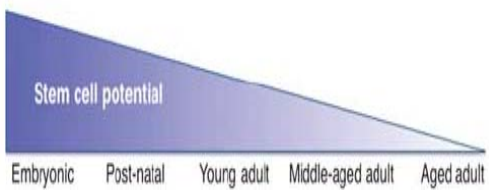
Govitrapong's group et al., 2013

## Aging Theories

**Stem cell theory of Aging**

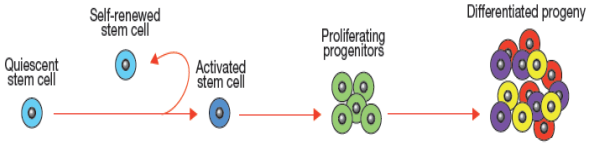
**During aging there is a gradual loss of organ function and tissue homeostasis that can be related to decreased ability of stem cells to replace the tissue with functional differentiated cells (Jones and Rando, 2011)**
**The number of stem cells and their potential to proliferate and differentiate decline with age.**




-numbers of stem cells during ageing
-Functions of stem cells during ageing
the ability to repopulate a tissue after injury,
the ability to proliferate in response to external stimuli
the ability to differentiate into multiple cell types

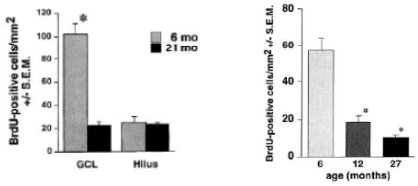
**Stem Cell Aging**




**The balance between self-renewal and commitment of stem cells is important**

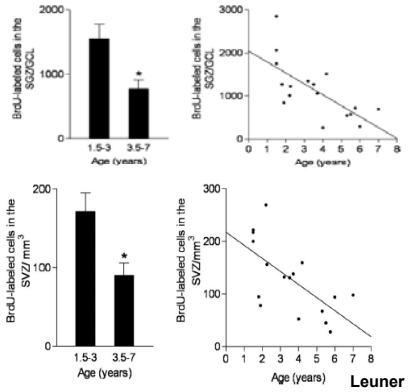
**Decrease proliferation** 1

In aged dentate gyrus Reduced neurogenesis is linked with decreased proliferative activity of neuronal precursor cells, thus by analyzing of newborn cells density by BrdU labeling in rat Kuhn and others showed age related decrease of neuronal progenitor proliferation in dentate gyrus




(Kuhn et al., 1996)

Adult neurogenesis decreases with age. Leuner and his colleagues showed this decline in older macaques linearly .



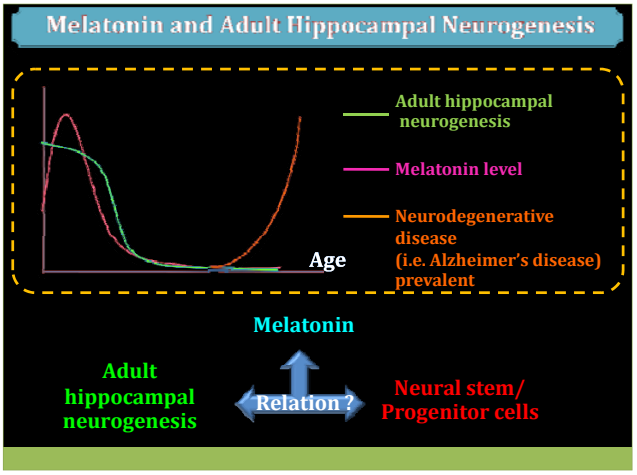

Leuner et al., 2007

Stem Cell Aging:
Decrease the number
Decrease the potential

decrease of proliferation activity in neuronal progenitor cells
inhibited migratory mechanism in newborn cells
newborn cells die before differentiating into granule cells.

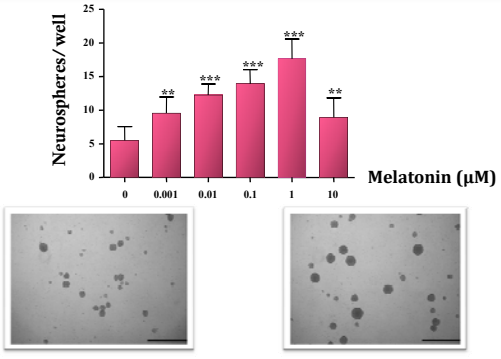
Cellular senescence

## Melatonin and Adult Hippocampal Neurogenesis

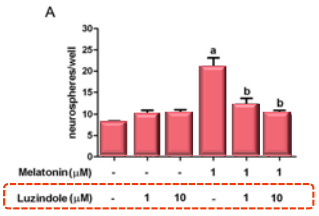



## Does Melatonin affect Neurogenesis?

## Melatonin increases proliferation of progenitor cells from adult mouse SVZ




*Sotthibundhu et al., 2010 J Pineal Res.*

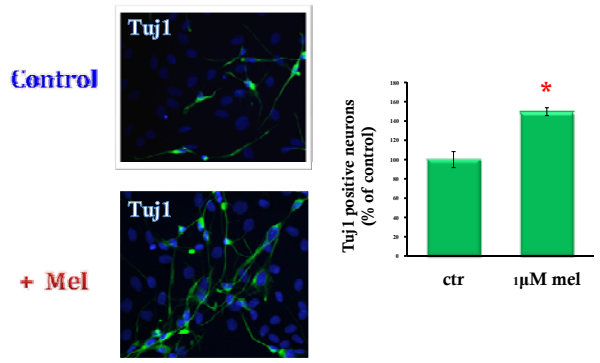



**Luzindole**
(MT1 antagonist)

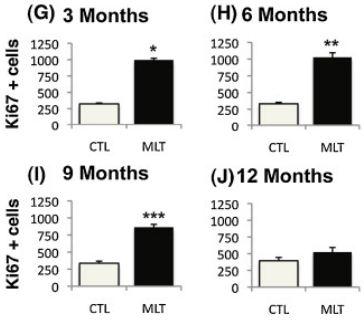
**PTX**
Inhibits
G protein couple

*Sotthibundhu et al., 2010 J Pineal Res.*

## Effect of Melatonin on Neuronal Differentiation in SGZ

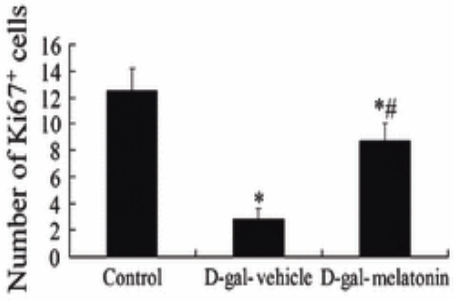



Melatonin supplement delay the decline of adult hippocampal neurogenesis during normal aging of mice

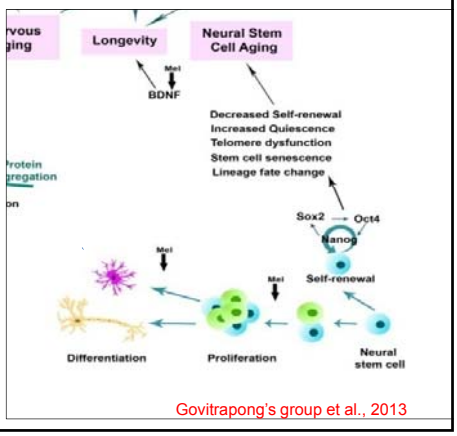



Ramfirez-Rodrfguez et al., Neurosci Lett 2012

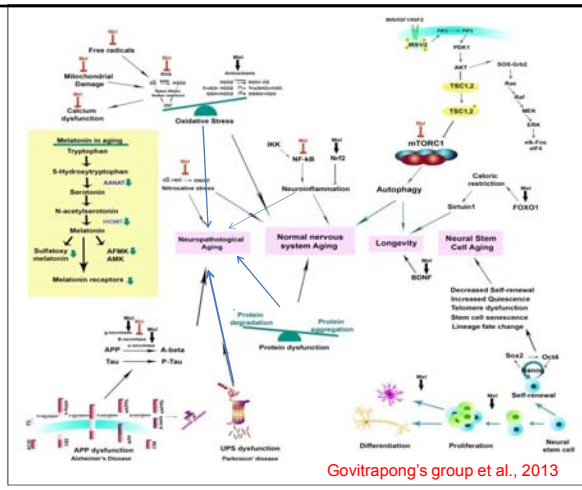
Melatonin improves D-galactose-induced aging effects on behavior, neurogenesis, and lipid peroxidation in the mouse dentate gyrus via increasing pCREB expression



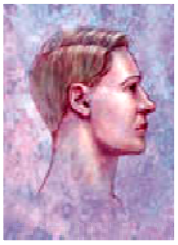

Dae Young Yoo et al., J Pineal Res, 2012




Govitrapong's group et al., 2013



Govitrapong's group et al., 2013



Healthy Brain

Melatonin

(Neuroprotection & Neurogenesis)

Aging Brain

Learning & Memory Impair

↓ Neurogenesis

↓ Number of neuron