# Melatonin‘s Indications

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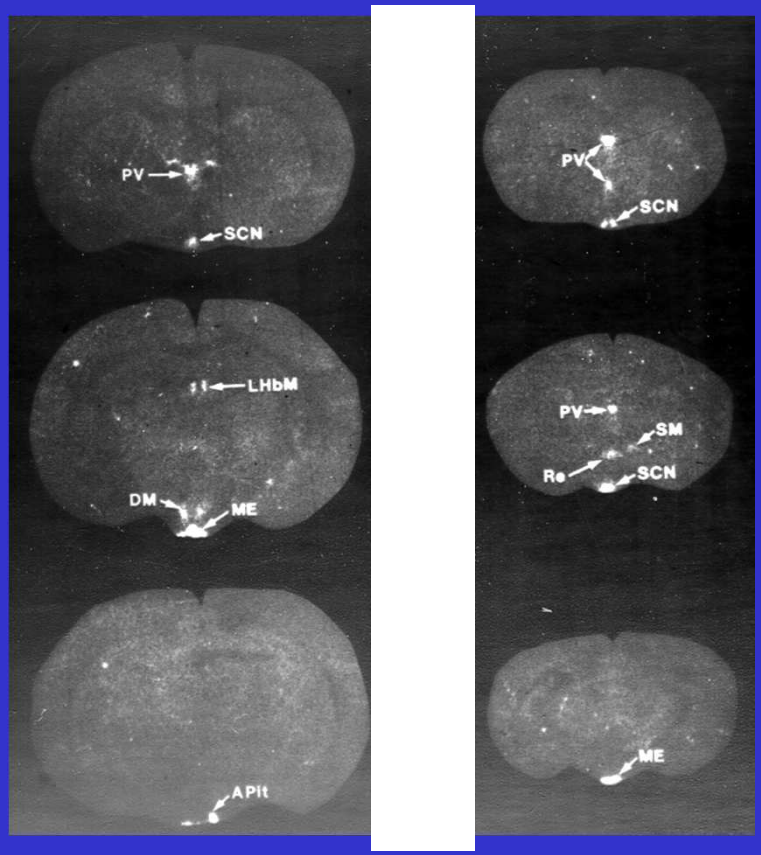
**ea3m GmbH & Co. KG**

**Kalletal**

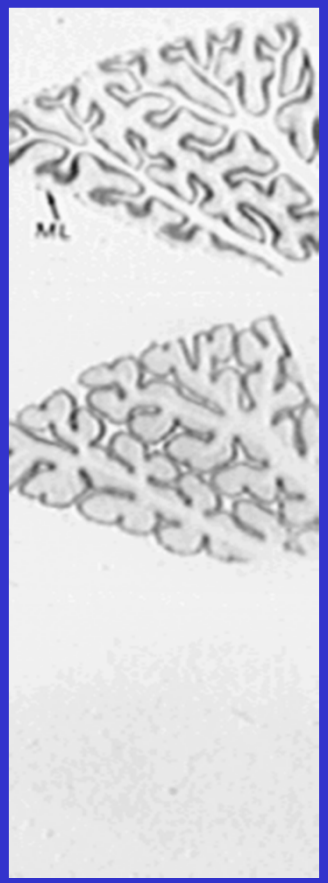
## Melatonin receptor in rodents CNS (Reppert et at.)

**Rat** **Mouse**

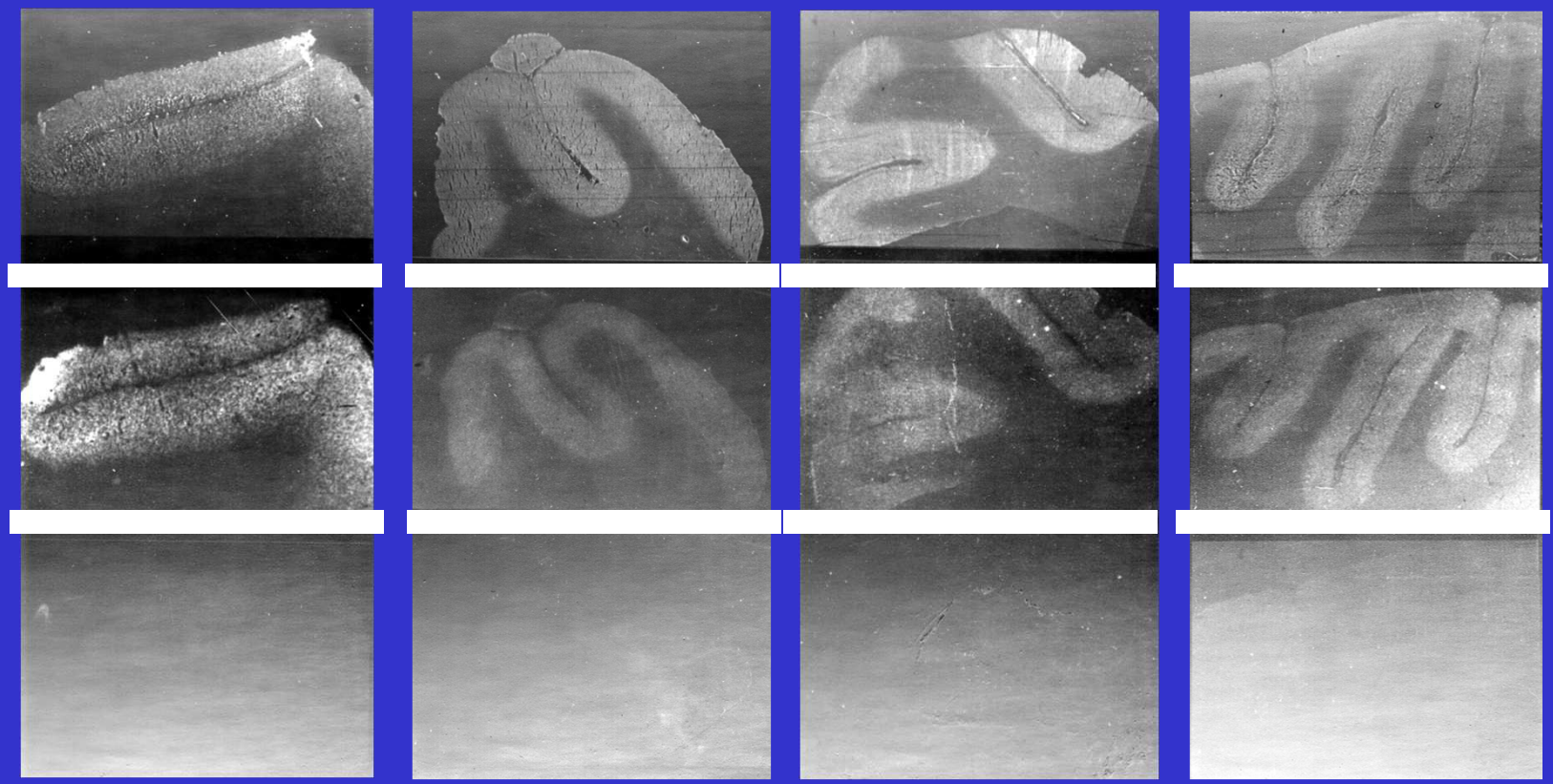


**Human SCN**
**Melatonin receptor**

**Human cerebellum**
**Melatonin receptor**



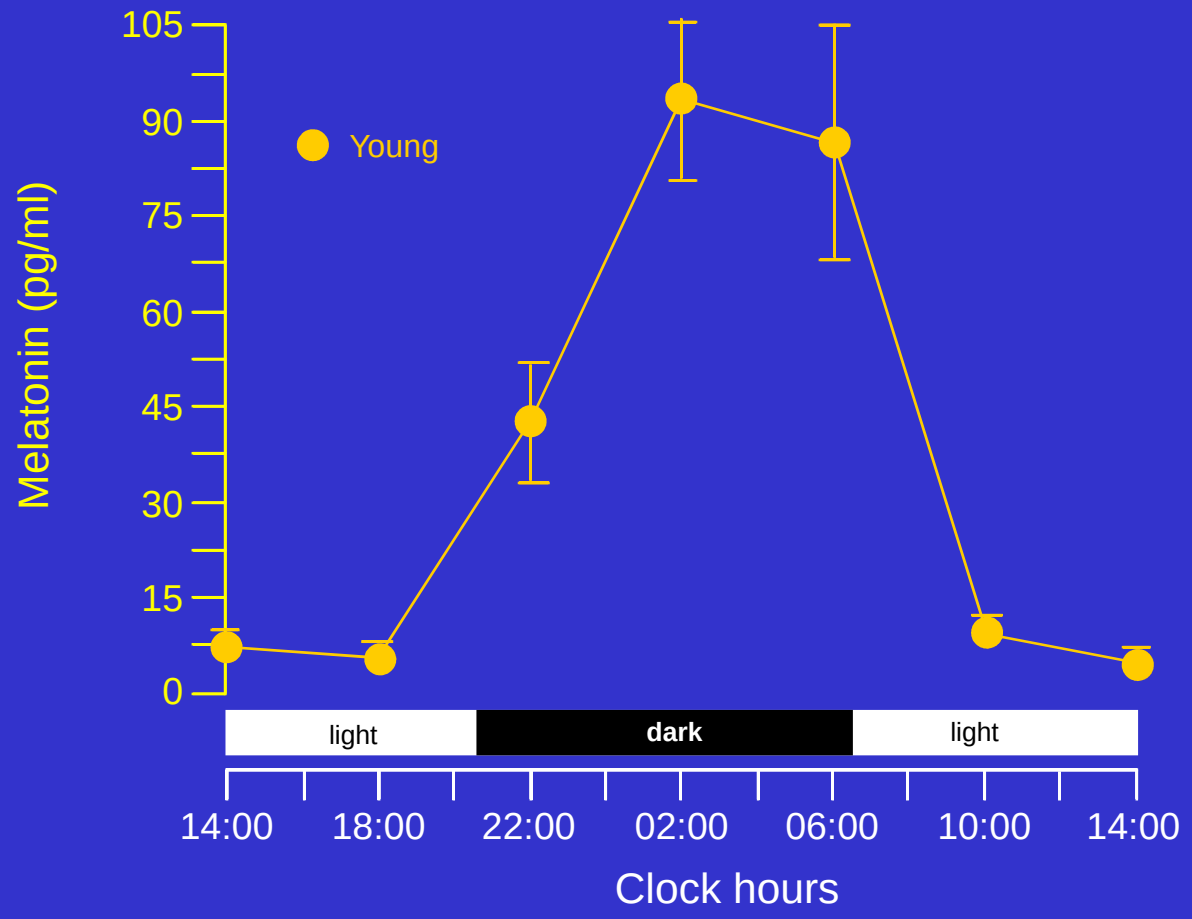
# Melatonin receptor in the human CNS



## Conclusions (I):

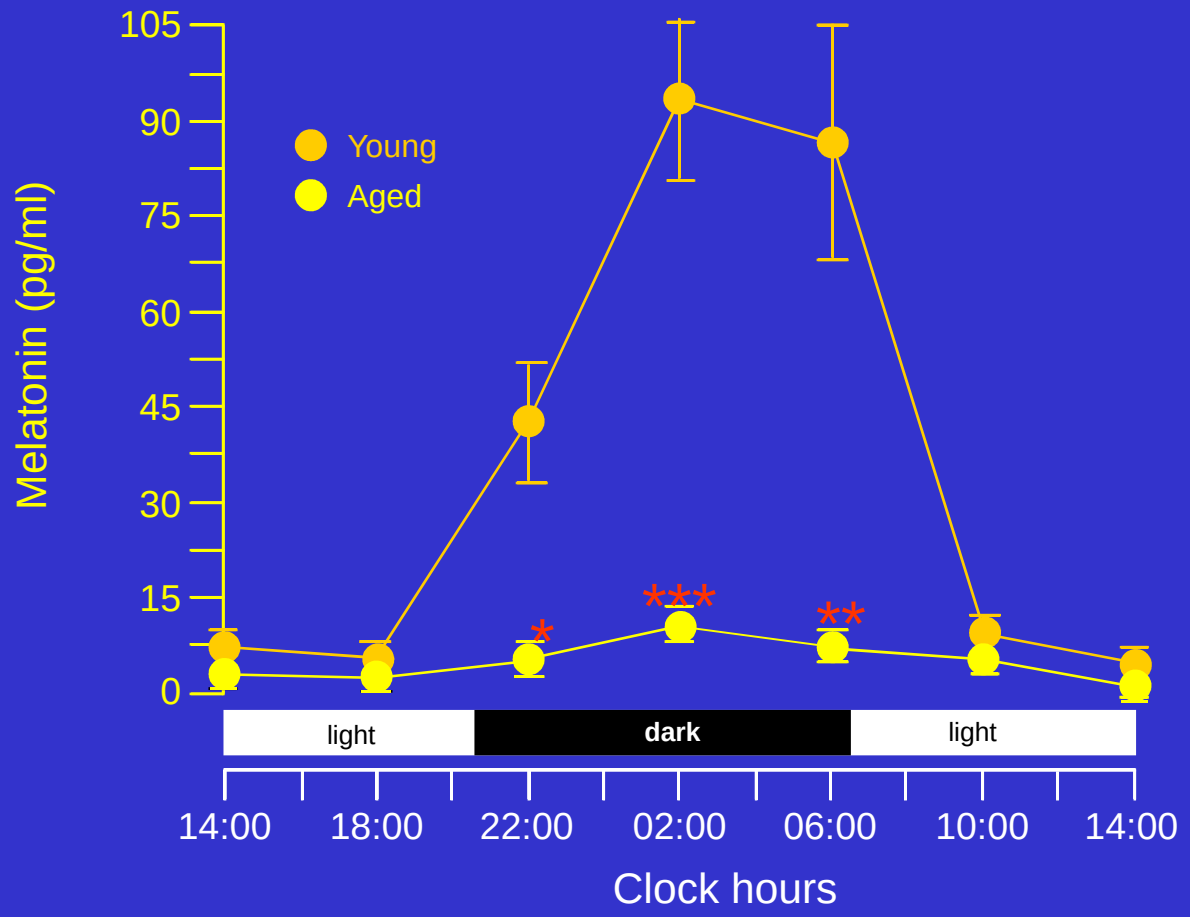
1. Melatonin receptors are mainly located in the CNS.
2. There are significant differences concerning the melatonin receptor distribution between animals and human beings.
3. Animals express receptors mainly in structures, which regulate the seasonal reproductive activity.
4. In human beings, the neocortex, the cerebellum, and the internal biological clock are the main targets for Melatonin action.
5. Therefore, Melatonin shows different effects in human beings rather than in animals.

It has been clearly demonstrated that due to age, the circadian system deteriorates. Melatonin levels drastically decrease and as a consequence there is a significant change in a number of vital body parameters, but most importantly, the sleep-wake cycle is negatively affected.




Melatonin peripheral blood levels in young subjects.

H. Iguchi et al. J of Clin Endocrinol and Metabol 1982 - 55 (1) - 27-29.




Melatonin peripheral blood levels in young and elderly subjects. Note the significant decrease of the melatonin levels in the aged group.

H. Iguchi et al. J of Clin Endocrinol and Metabol 1982 - 55 (1) - 27-29.

The deterioration of the circadian system and the dramatic decrease of the melatonin levels due to age have imposed the necessity of substituting melatonin.

The approach utilised so far has been generic, consisting of administering high doses of either standard or slow-release melatonin formulations.

Both do not satisfy the circadian body requirements, because melatonin has a very short half-life (ß1/2 approx. 30-40 min. in the human beings), but melatonin has to be bioavailable continuously for 5-7 hours, from the beginning to the end of the scotophase.

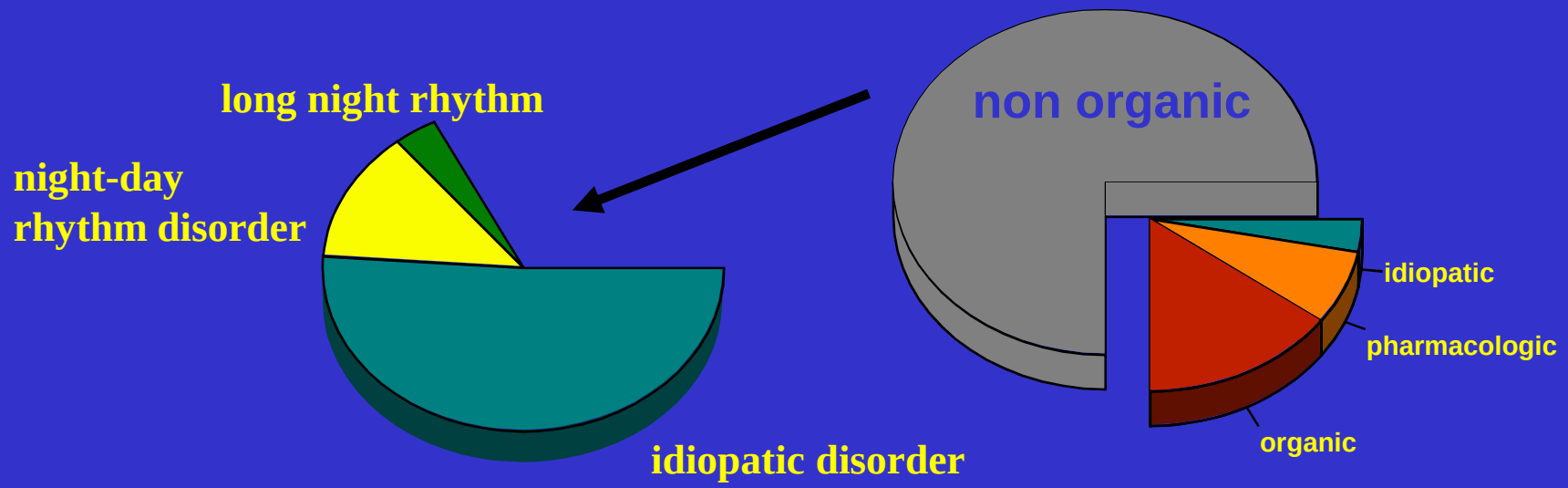
# *Melachron®*

A new formulation for treatment of sleep disorders within the Hormone Replacement Therapy

# Sleep disorders = less than 7 hours sleep per day

| | |
|---|---|
| **Incidence:** | **20% - 30% of total population**<br>**70% - 80% of patients over 65 years** |
| **Medical visit:** | **30% - 35% of all the patients** |
| **Medical use:** | **ca. 70% medical prescription (BZD)**<br>**ca. 30% self medication (Antihistaminic)** |
| **Amount (Euro) 1995:** | **1,5 Mrd (Europe: Hypnotics, Anxiolytics)** |
| **Amount (Euro) 2002:** | **3,2 Mrd (Europe: Hypnotics, Anxiolytics)** |

# Classification of sleep rhythm disorders

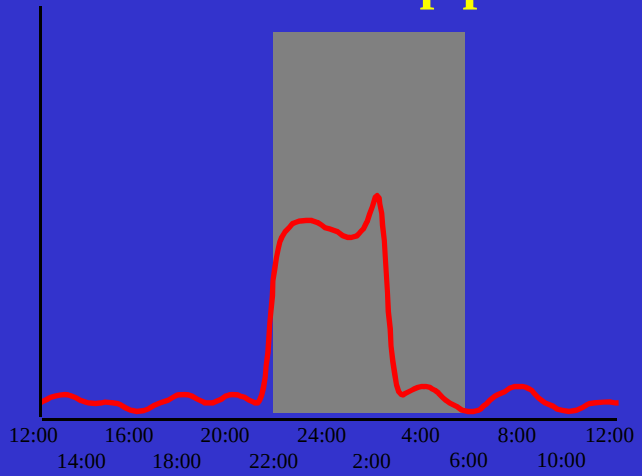



**Therefore, probably about 4 out of 10 people suffer from idiopatic sleep disorder**

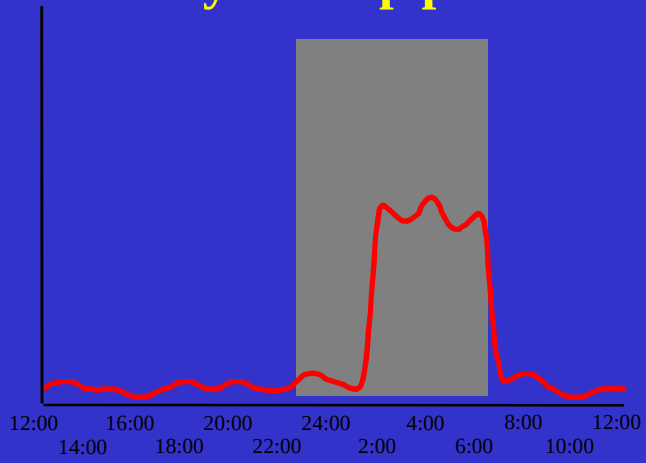
**These patients may strongly benefit from a therapy with Melatonin**

# Melatonin deficits in correlation to sleep disorders

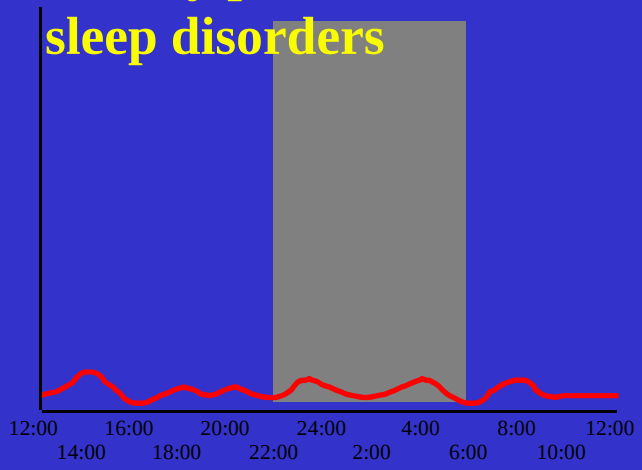
## Advanced sleep phase



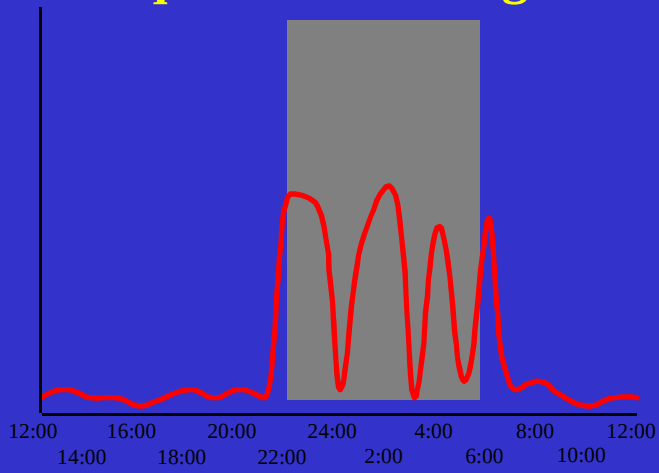

## Delayed sleep phase



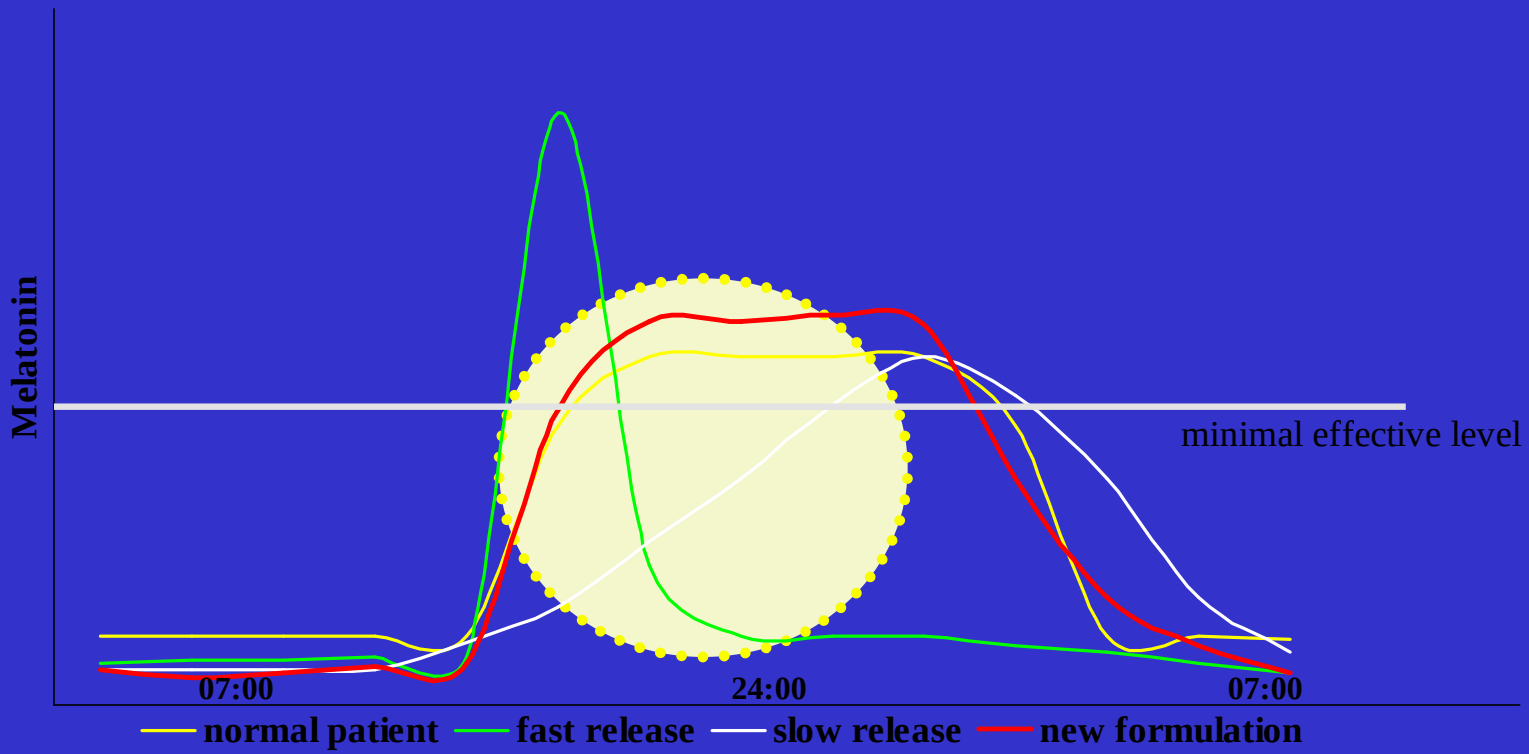

## Elderly patients with sleep disorders



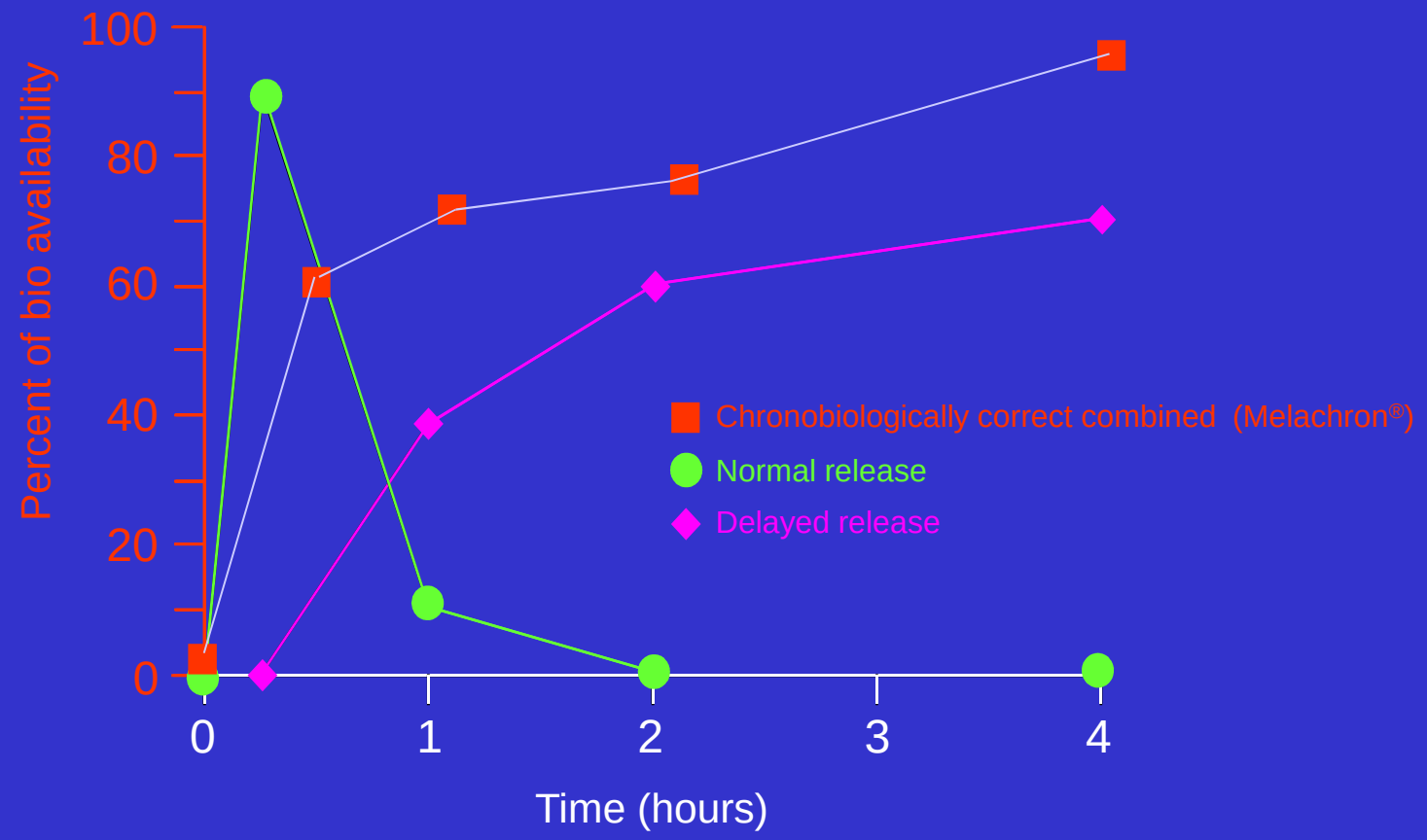

## Frequent awakenings



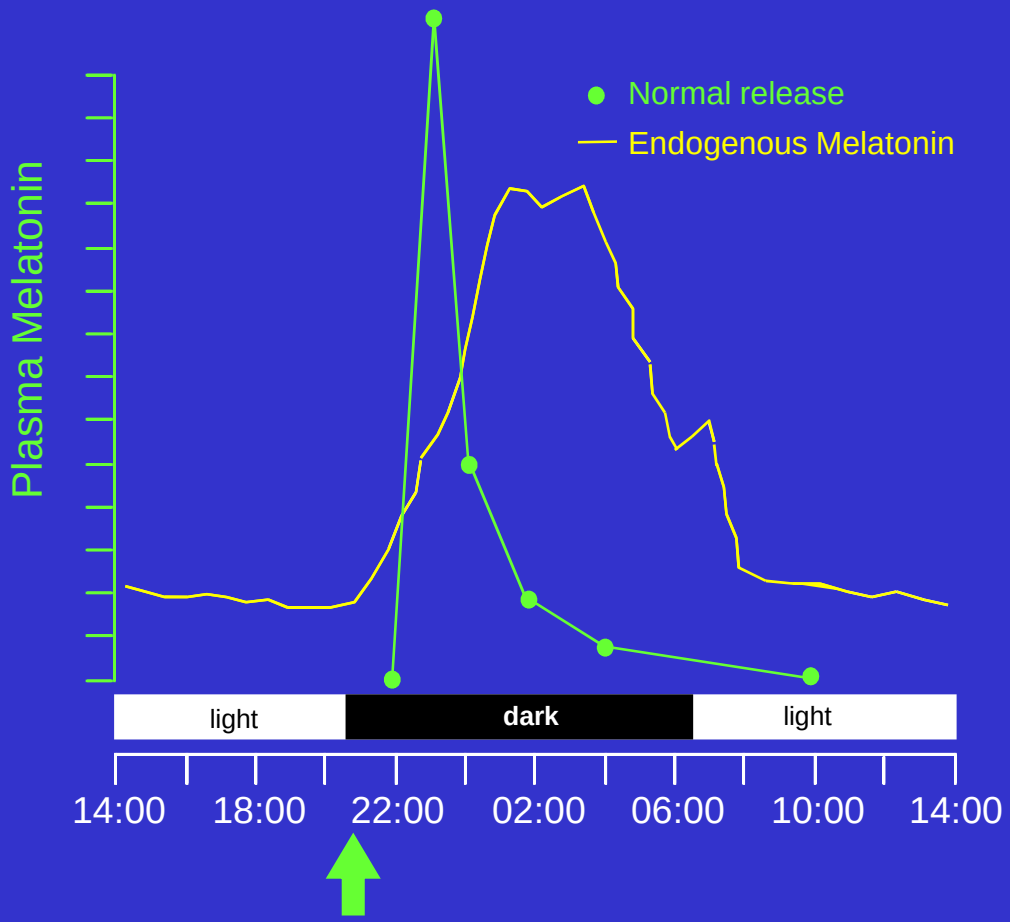
# Theoretical serum levels following Melatonin treatment



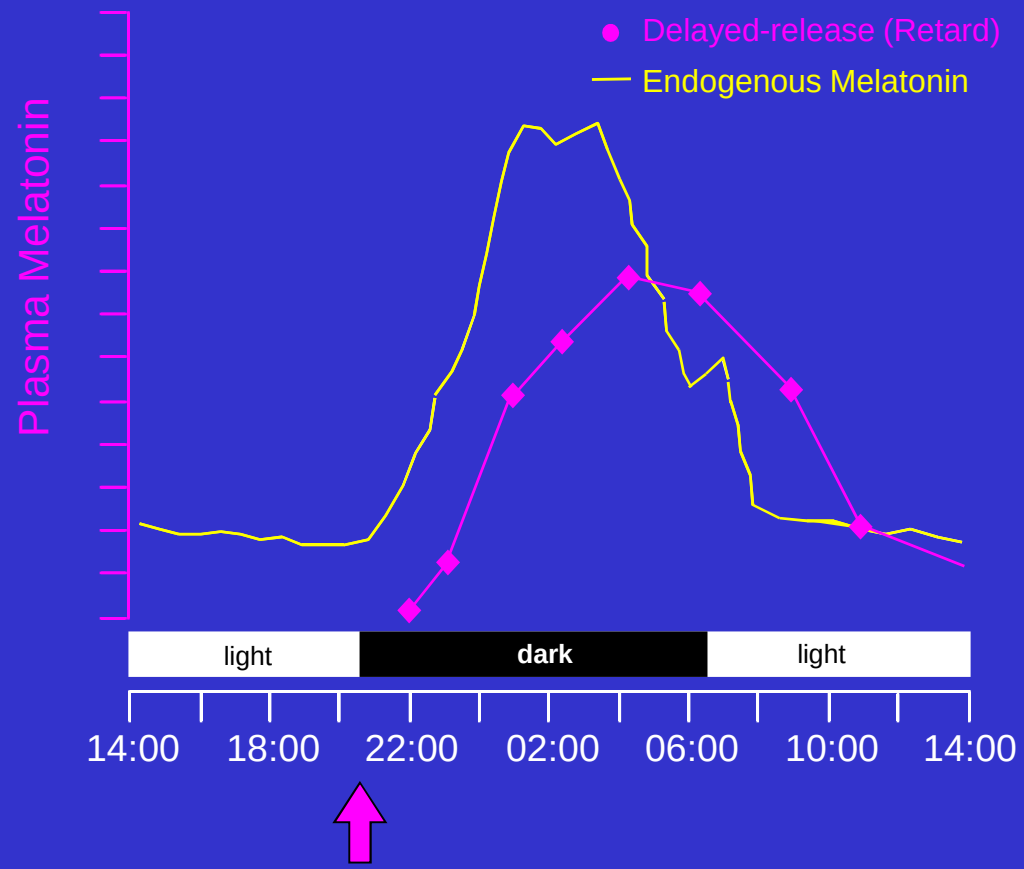
**It has been developed a chronobiologically correct controlled release formulation that gives the possibility of closely reproducing the nocturnal pattern of Melatonin release.**



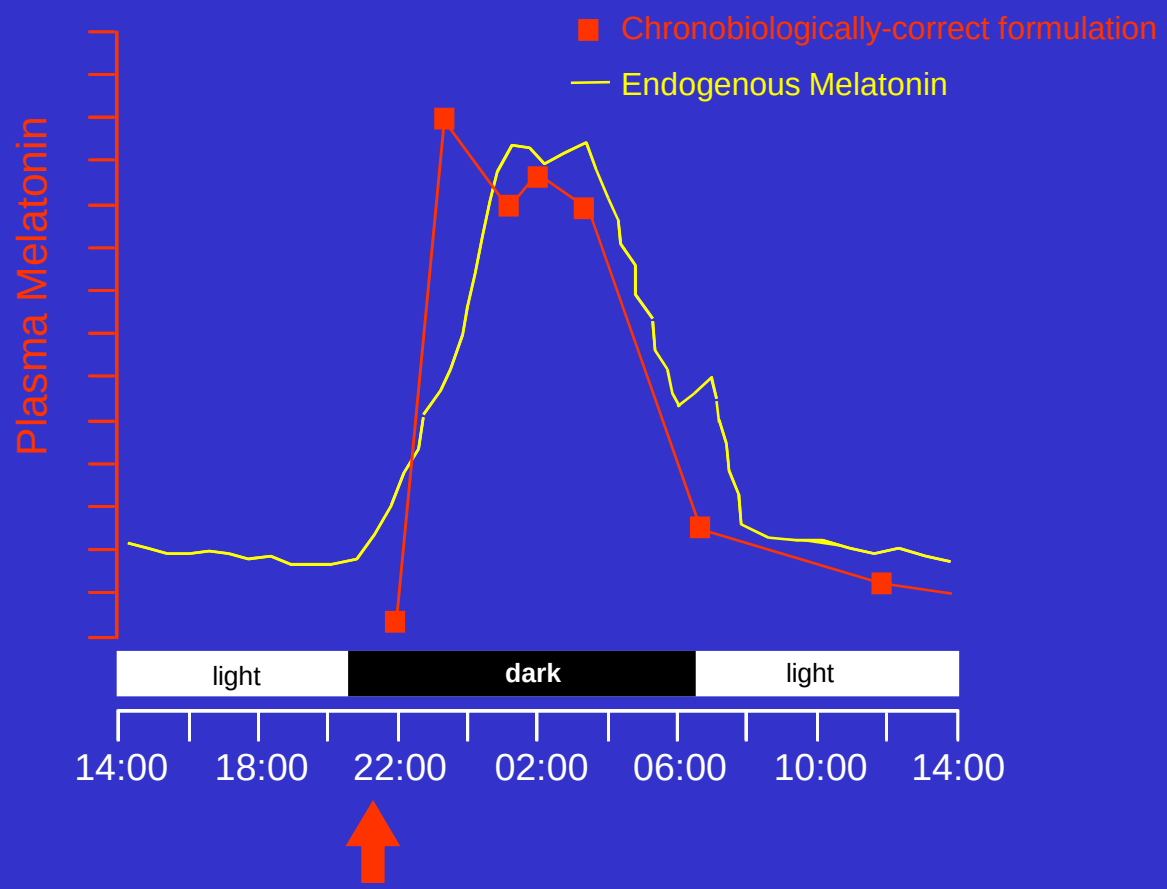

In vitro Melatonin release from different types of formulation.




Comparison among Melatonin levels obtained following administration of various normal-release formulations used in the *in vivo* tests. Clearly, with the normal release formulation, Melatonin is not bioavailable in the second part of the dark period.

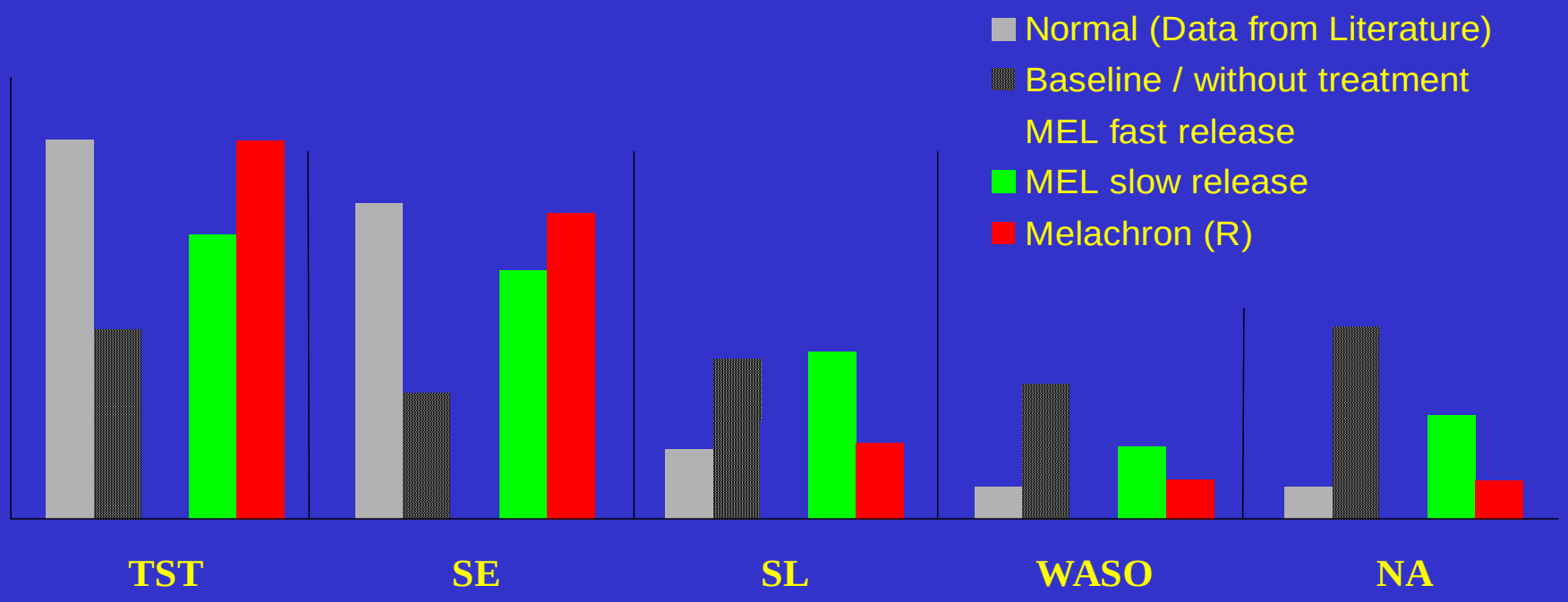



Comparison among Melatonin levels obtained following administration of delayed-release (retard) formulations used in the *in vivo* tests. Melatonin is not available in the first but only in the second part of night.




Comparison among Melatonin levels obtained following administration of controlled-release formulations in humans. Clearly, using the cronobiologically-correct formulation Melachron®, Melatonin is bio-available for the entire dark period.

# Results of a double-blind, crossover study on 15 middle aged people suffering from sleep disorders




TST = total sleep time; SE = sleep efficacy; SL = sleep latency; WASO = wakening after sleep onset; NA = number of awakenings per night

Melachron® is significantly better than the slow release formulation and both are significantly better than fast release preparations.

## Conclusions II:

1. Melatonin is useful in regulating sleep
2. Fast release preparations do not maintain the sleep
3. Timed-release (Retard) preparations do not promote sleep initiation
4. Melachron® a chronobiologically correct combined formulation, able to promote **and** to maintain sleep
5. Therefore it is important to substitute elderly patients with the most-correct galenic formulation, if a HRT is desired.

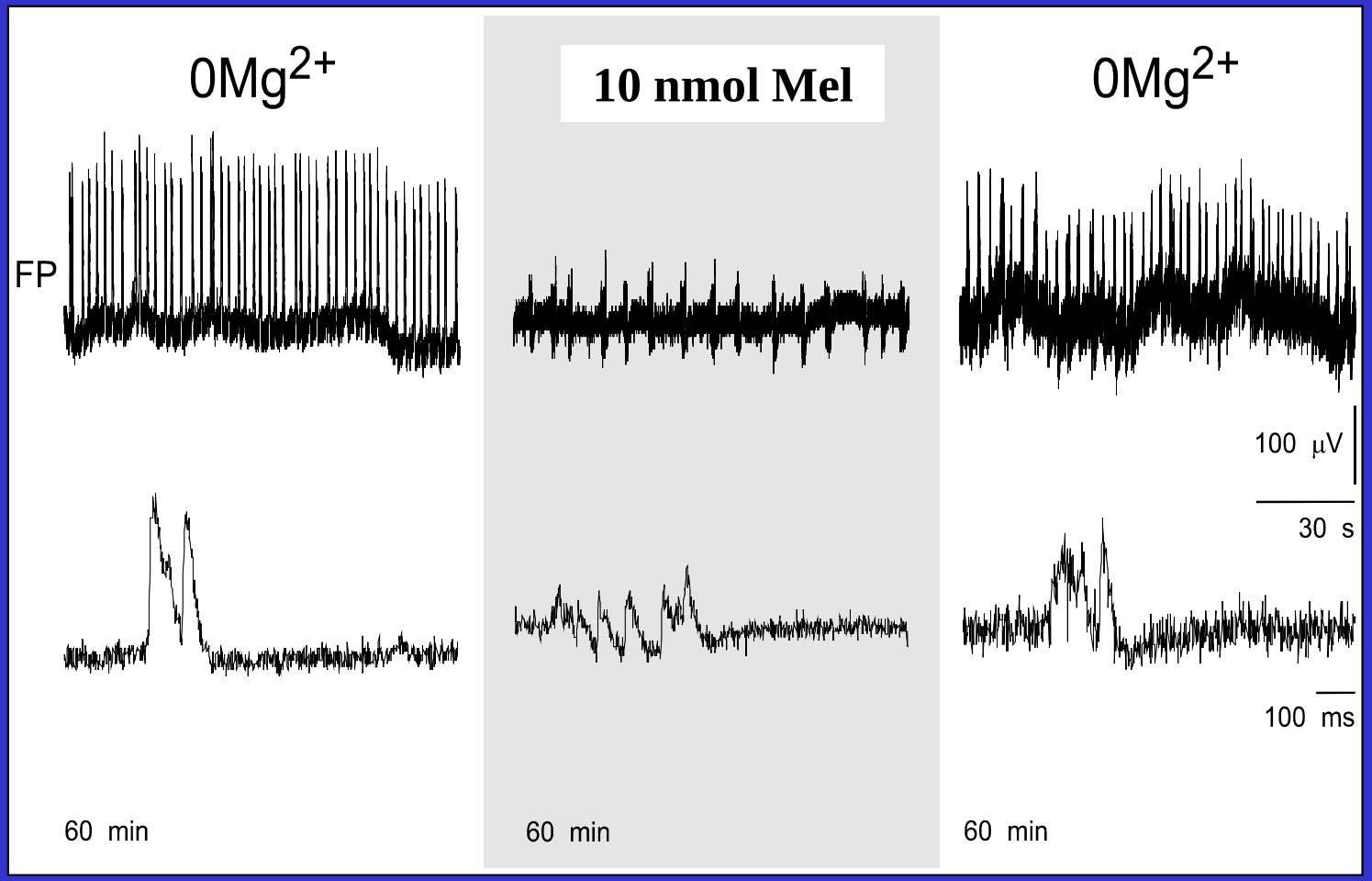
## Cerebellum Cortex:

**Muscle tone in sleep**
**Restless Leg Syndrome**

## Cerebral Cortex:

**Sleep**
**Epilepsy**

# Melatonin‘s effects on in-vitro neuronal activity



# Melatonin‘s effect in children affected by convulsive attacks

# Nucleus suprachiasmaticus:

## Internal Clock

# Hormonal rhythm in blind people without treatment

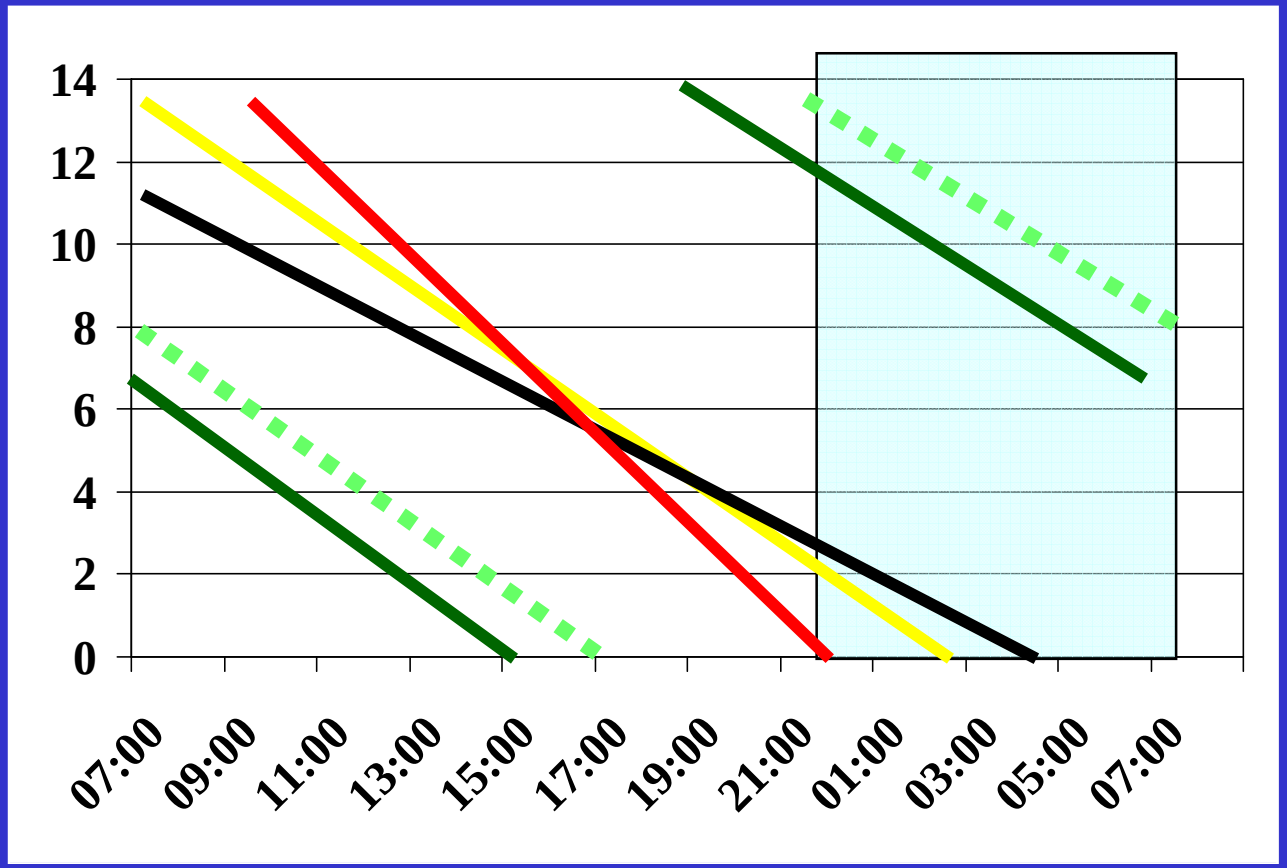
Testosterone

DHEA

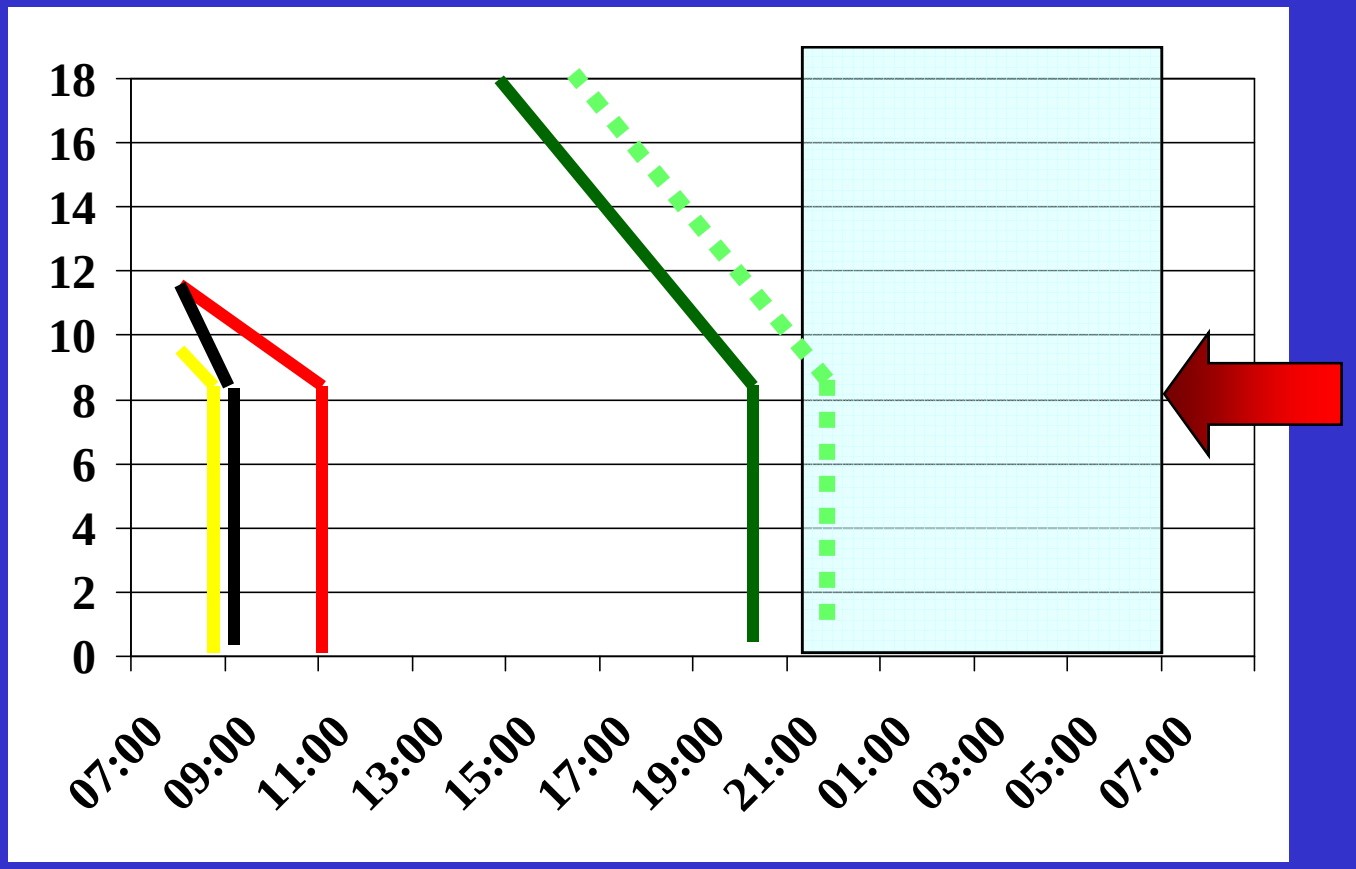
Cortison

GnRH

Melatonin

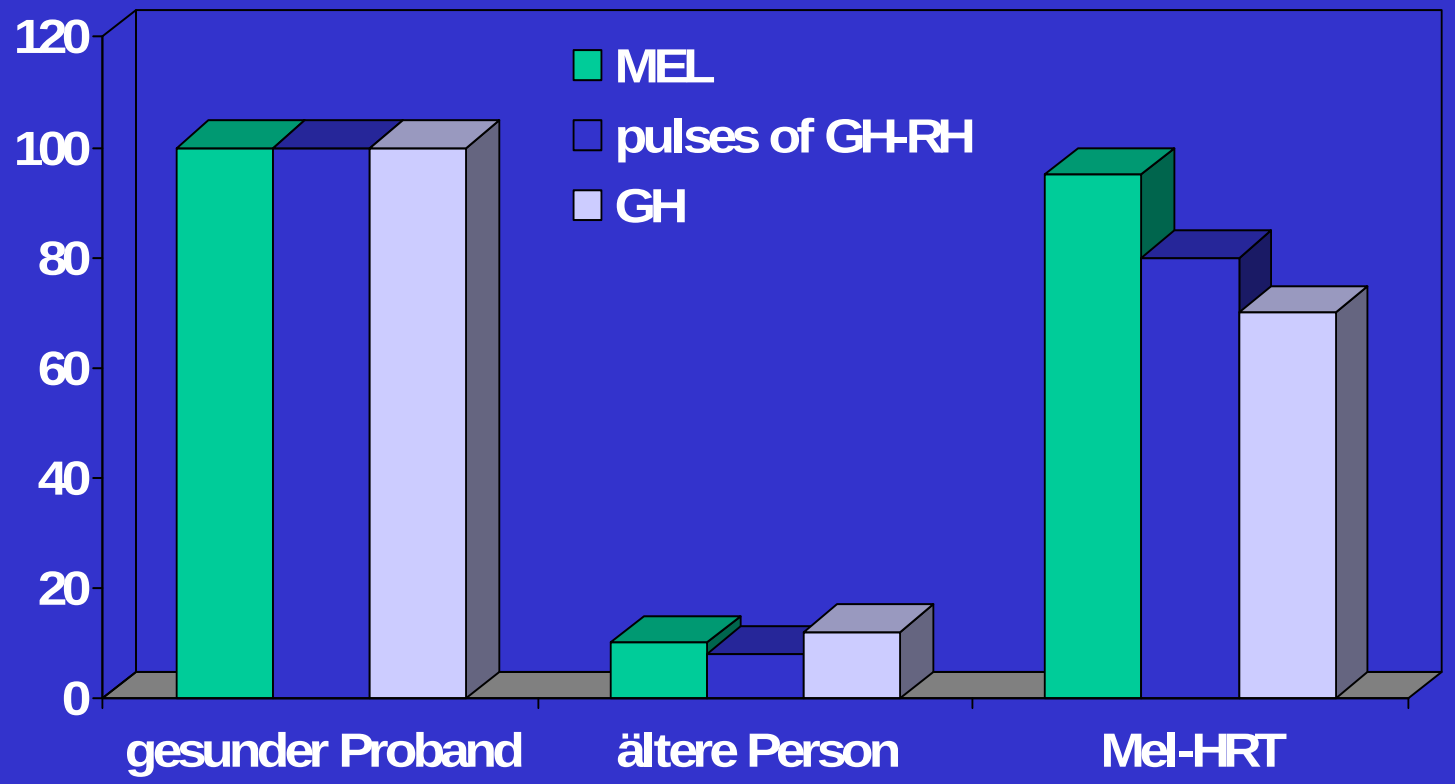


# Hormonal rhythm in blind people after treatment



# Melatonin‘s effects on other circadian systems such as GH

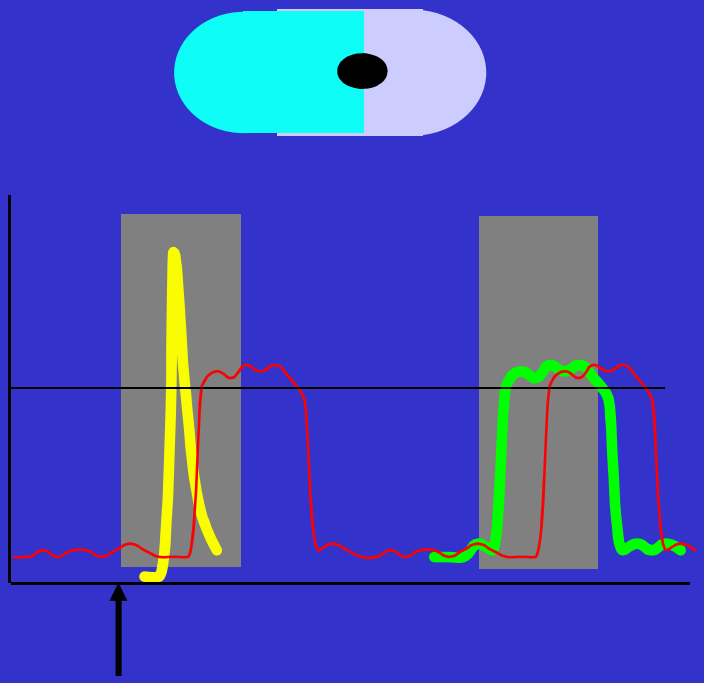
# Melatonin's effects on GH/GH-RH release in elderly people (Lewy et al. 2005)



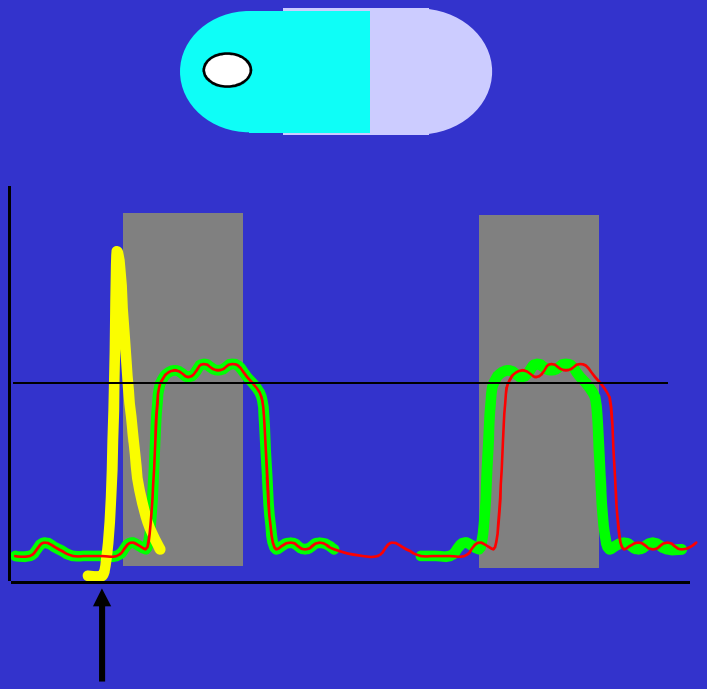
# Melatonin used for CNS disorders
# Example of  Jet leg

# Chrono - Therapy

**day 1 of therapy**



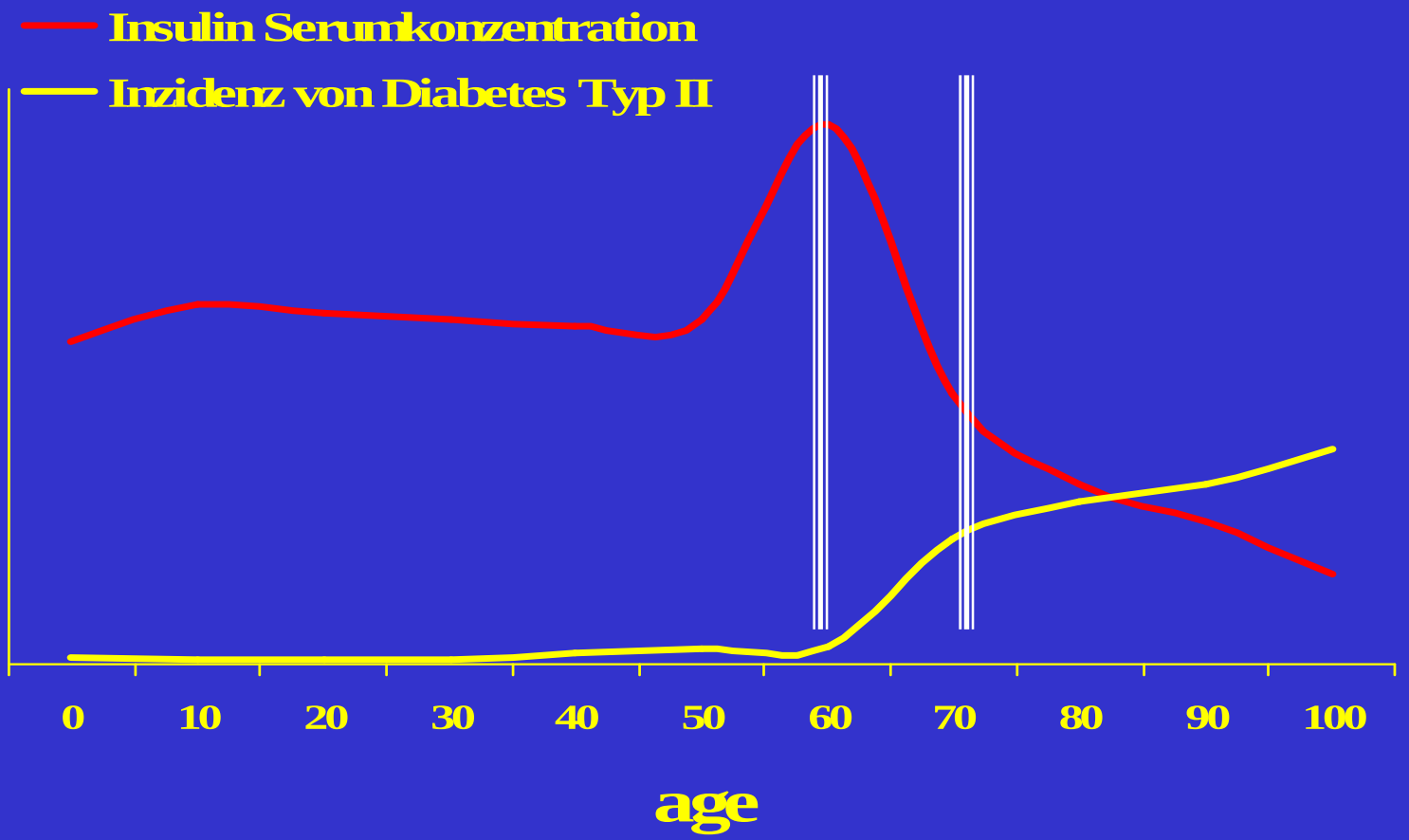
**day 2 of therapy**



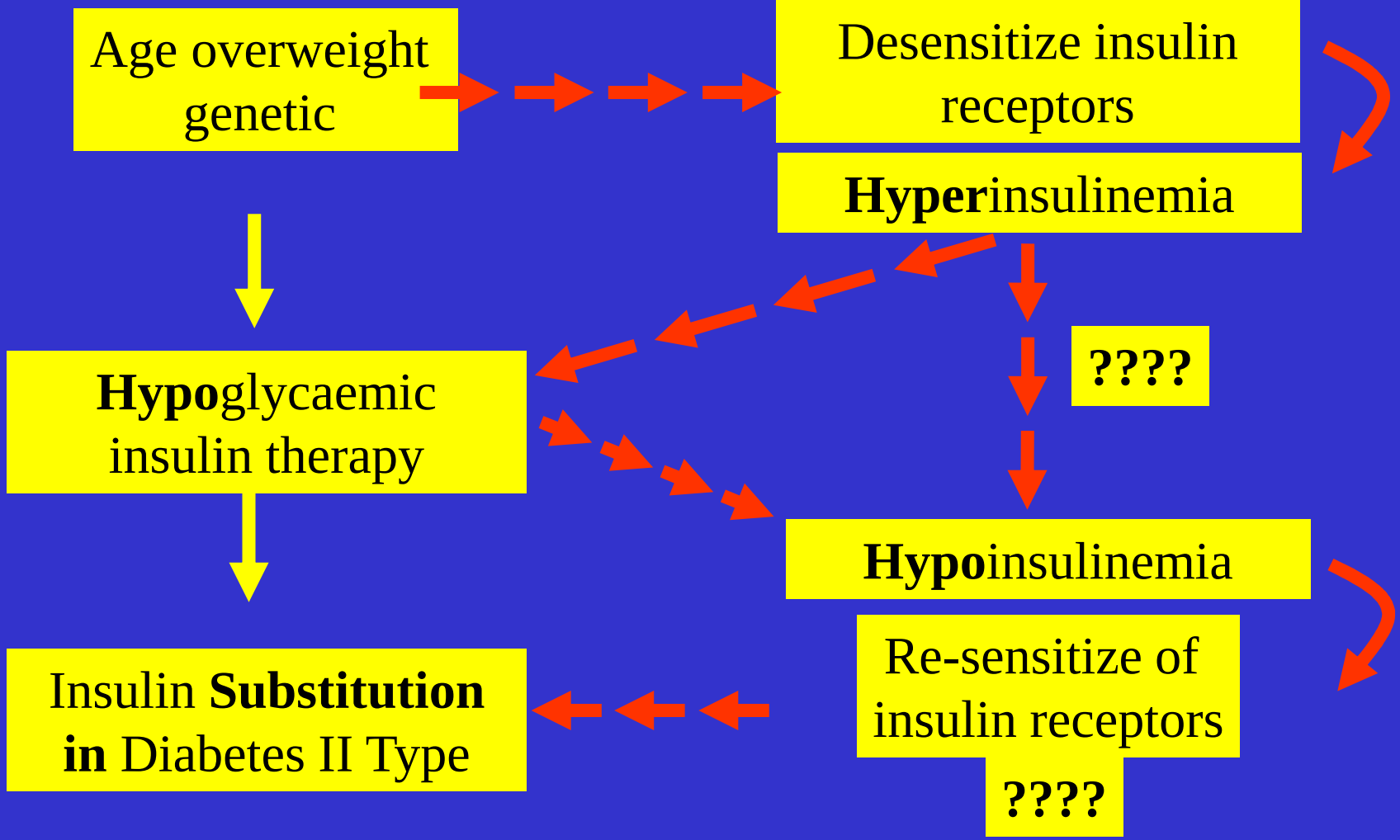
# Diabetes mellitus II Type:

## Do the pathological physiology and the deriving therapy of „Age diabetes“ have to be rewritten?

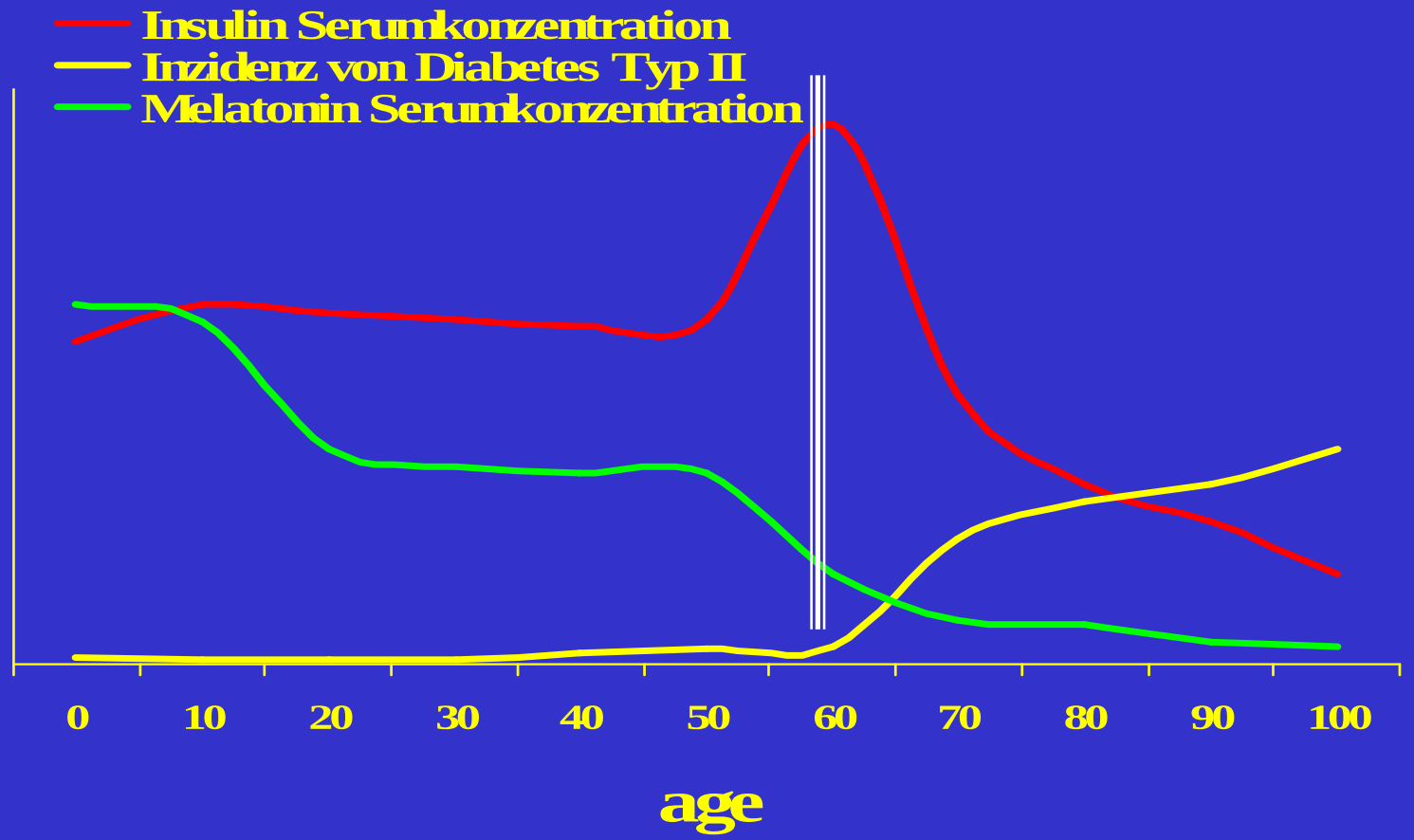
# Epidemiological correlation between insulin serum concentration and Diabetes mellitus II Type behaviour



# Schematic representation of Diabetes mellitus II Type pathological physiology



# Epidemiological correlation between Diabetes mellitus II Type insulin serum concentration and Melatonin‘s deficit



# Physiologic correlation between insulin and melatonin

Is there an insulin receptor in the pineal organ?

**NO →**

There is not any connection between insulin and melatonin release!

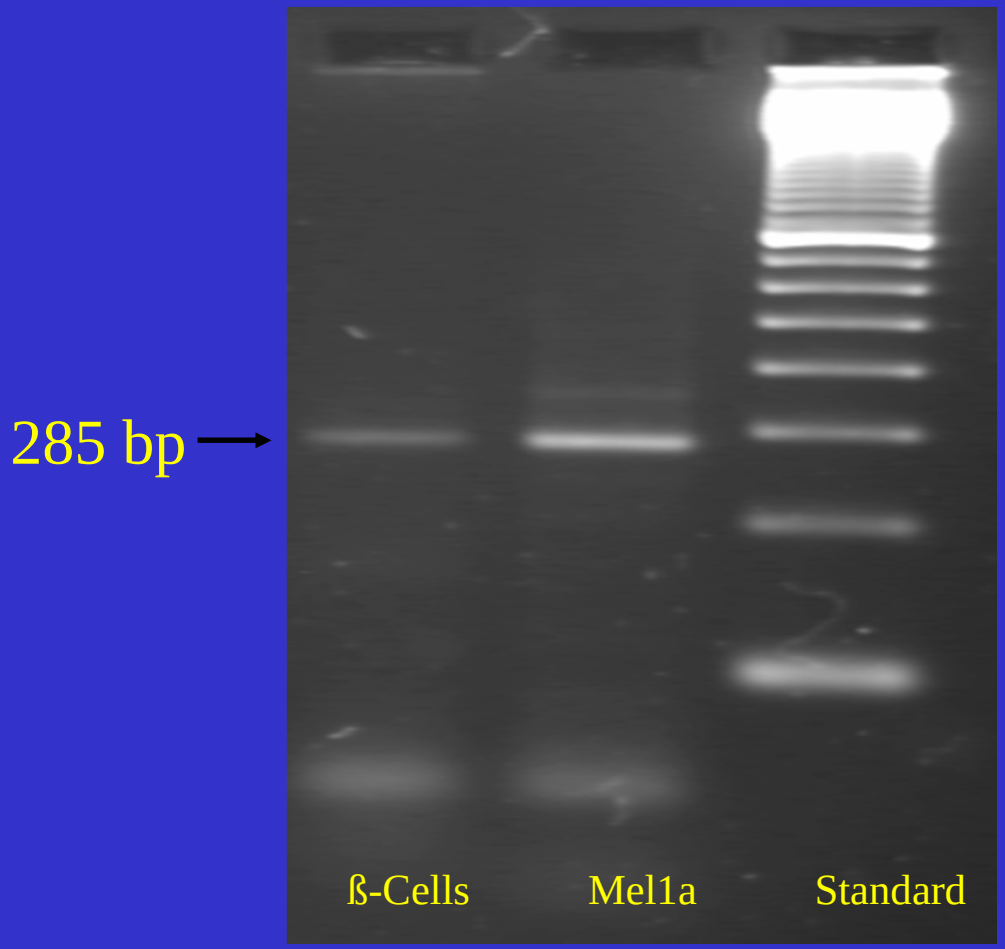
Are there melatonin receptors on the pancreatic ß-cells?

**YES→**

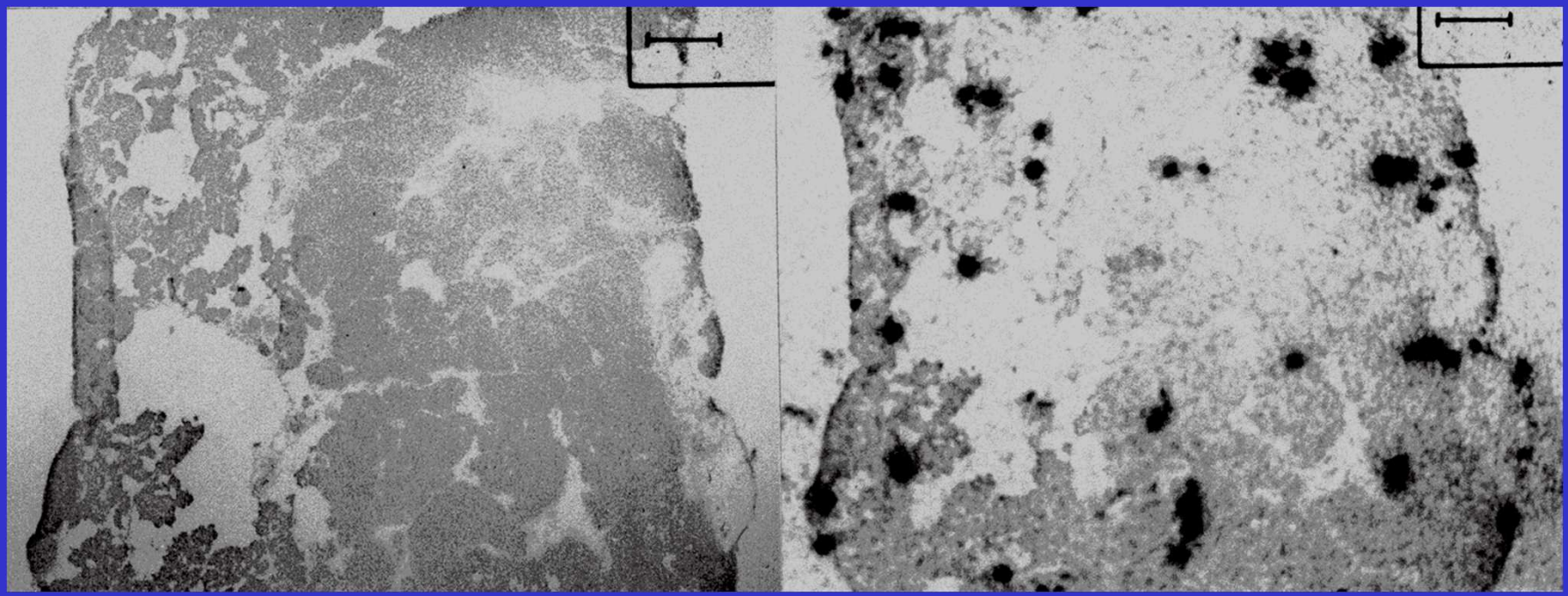
Possible Melatonin‘s effects on insulin release

# In-Vitro Data to the melatonin – insulin release interplay

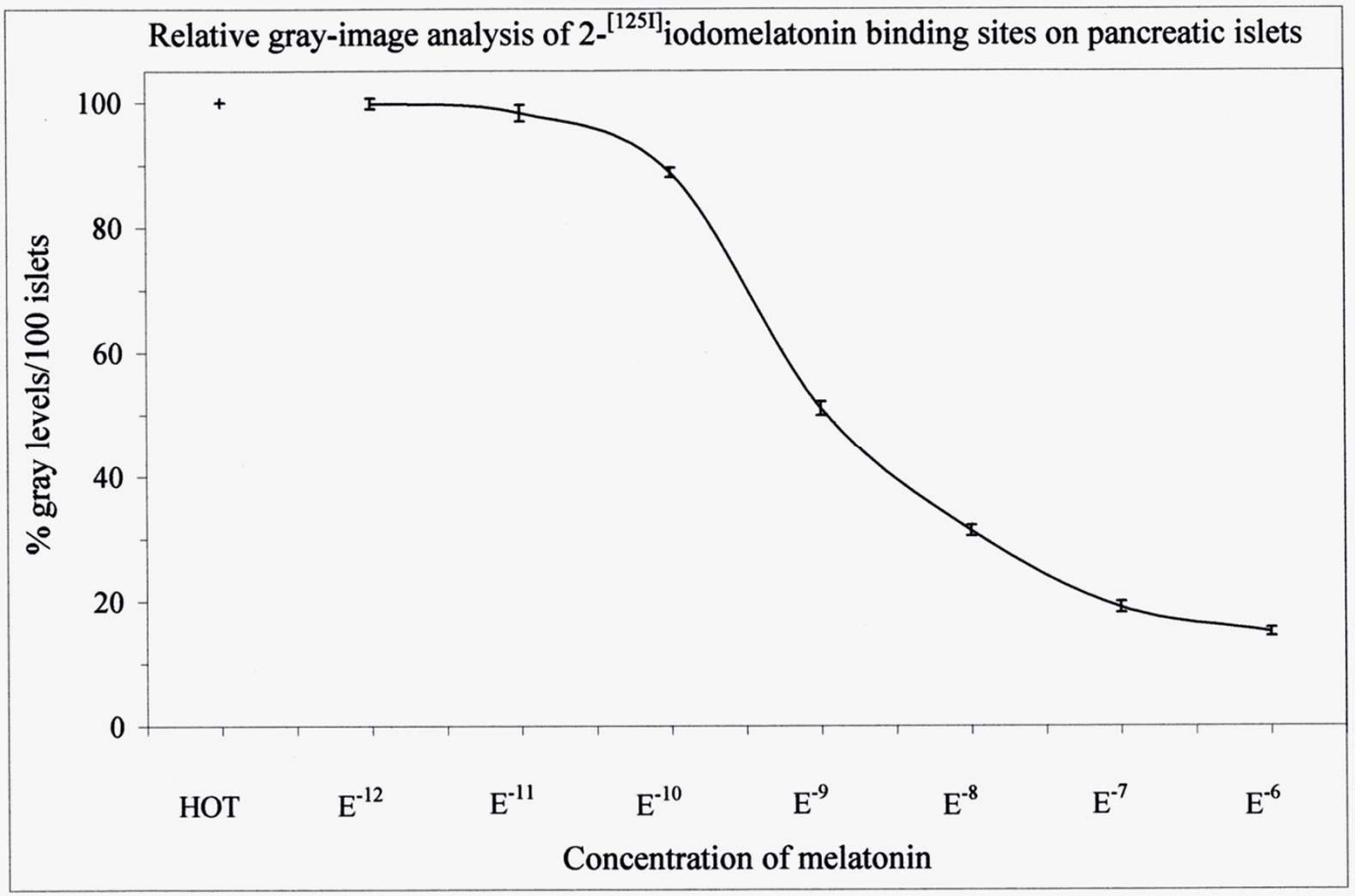
# RNA from ß-cells of the pancreatic islet



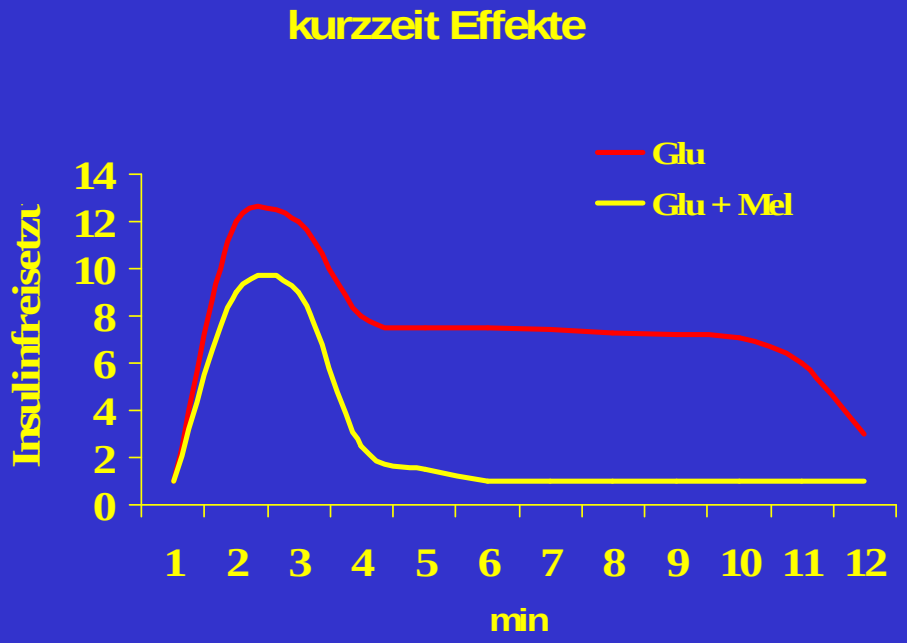
# Autoradiographic representation of Melatonin‘s receptors on the ß-cells of the pancreatic islet



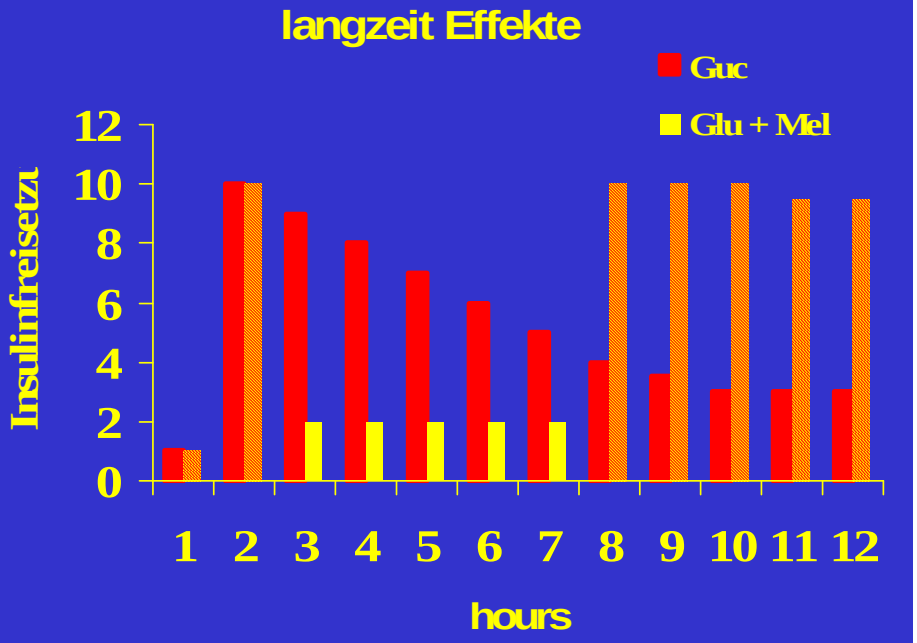
# Melatonin‘s receptors specificity on the ß-cells of the pancreatic islet



# Melatonin effect on the insulin secretion: *in-vitro* experiment on isolated islets




$AUC_{Glu} >> AUC_{Glu + Mel}$

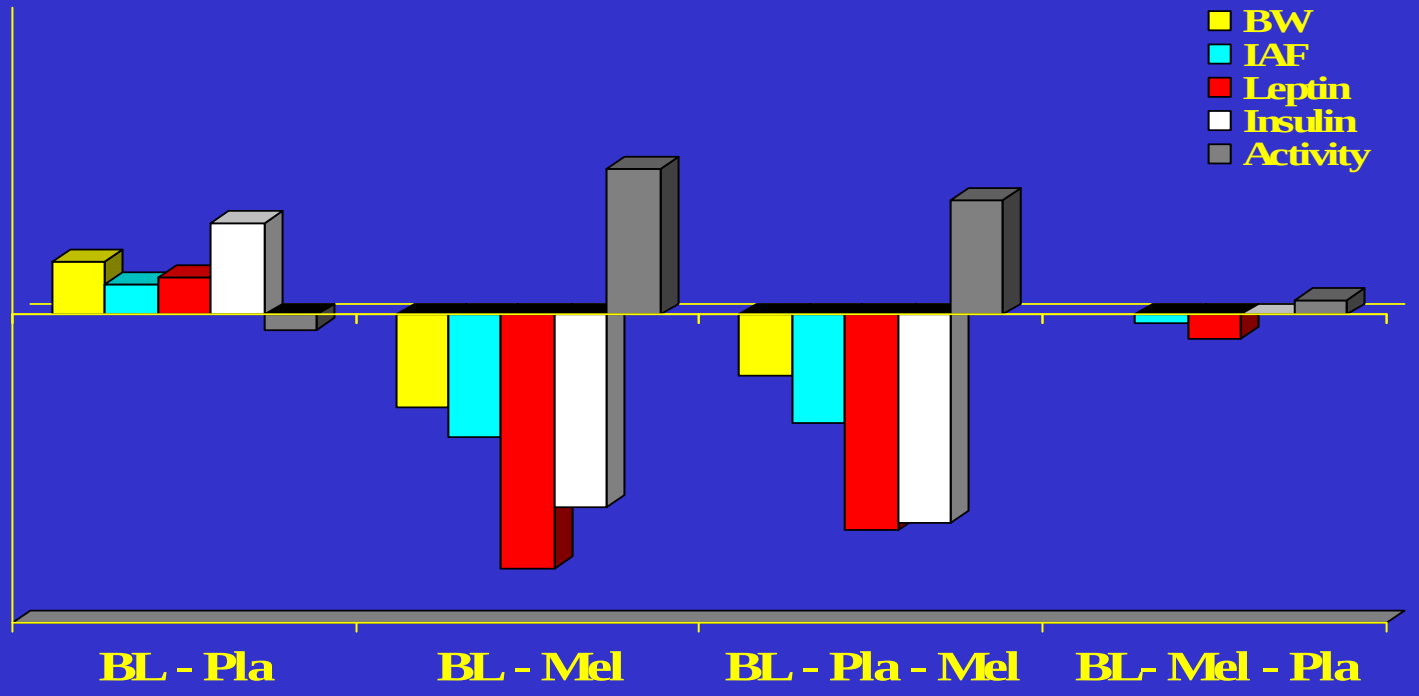



$AUC_{Glu} < AUC_{Glu + Mel}$

# In-Vivo Data to the melatonin – insulin release interplay Study on animals

# BW, intra-abdominal fat, leptin – insulin and serum levels after a 3 weeks therapy with melatonin in rats in cross-over

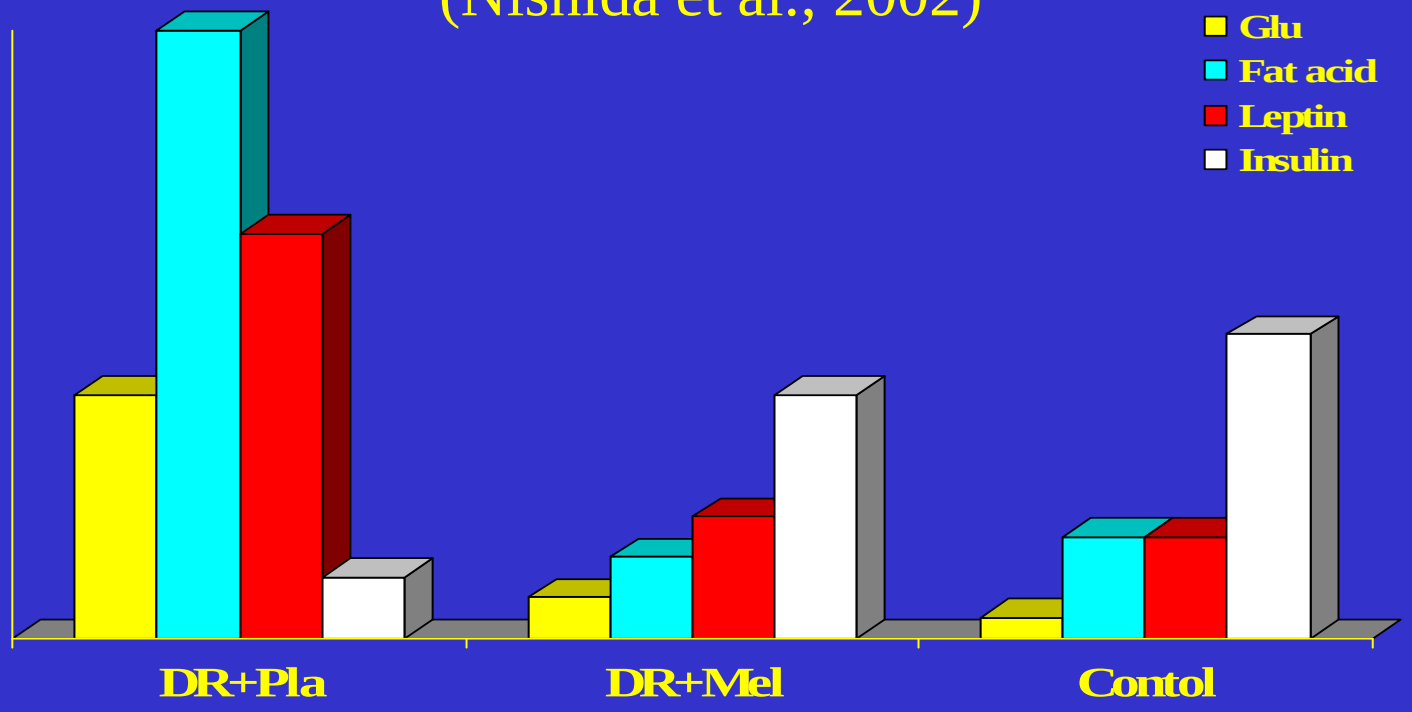
(Alter: middle-aged) (Wolden-Hanson et al.; 2000)




**Note: Melatonin influences significantly the metabolism in older rats**

# Glucose, fat, leptin, insulin and serum levels after a 35 weeks therapy with melatonin or placebo in diabetic rats compared with normal rats

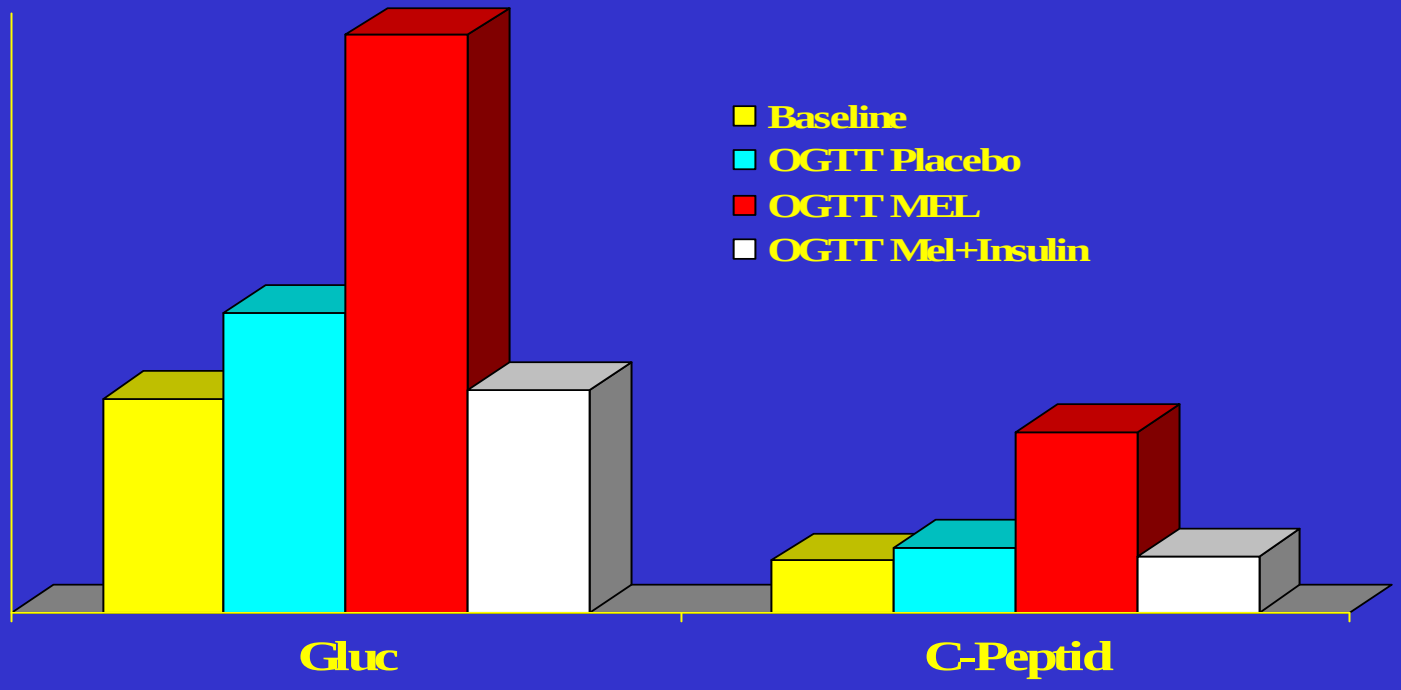
(Nishida et al.; 2002)




**Note: Melatonin normalizes the metabolism in older diabetic rats**

# In-Vivo Data to the melatonin – insulin release interplay Application observations in human beings

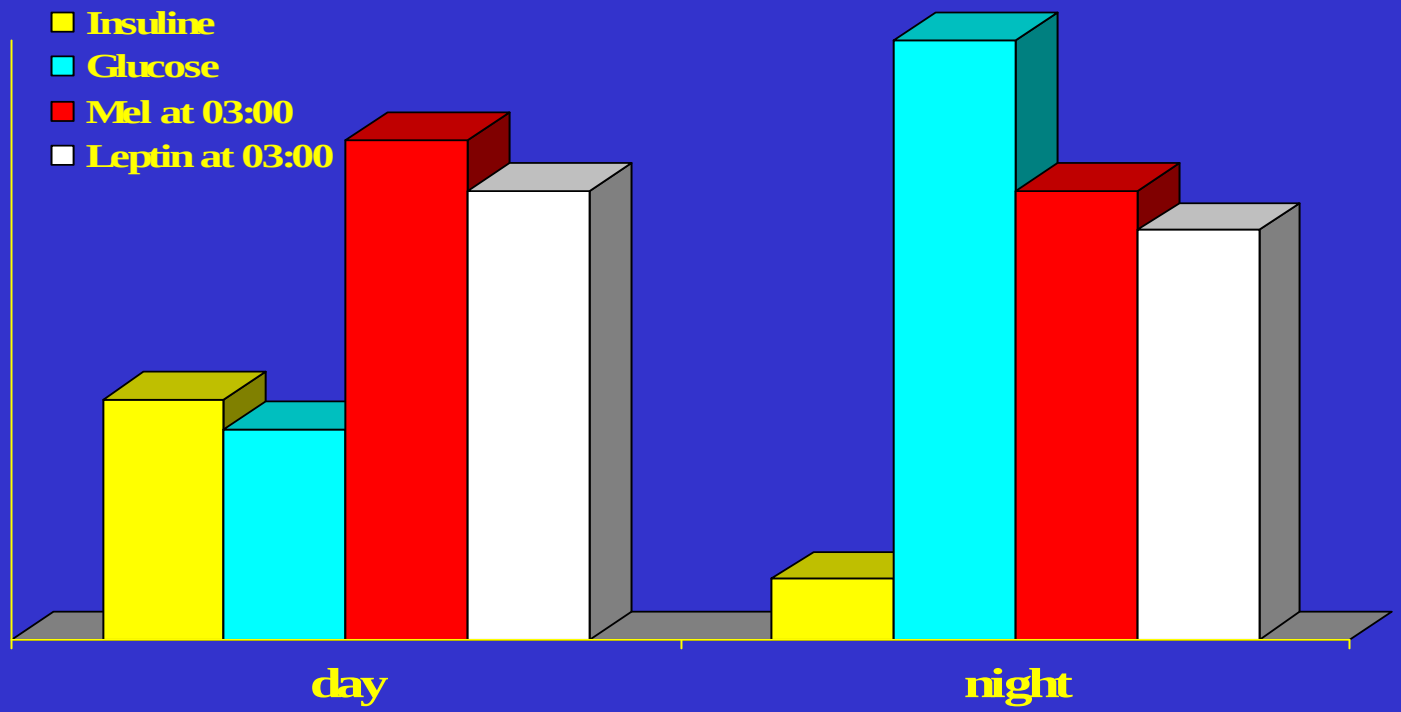
# Oral glucose tolerance in the morning Test in simultaneous administration of placebo or melatonin (Cagnacci et al. 2001)




**Note: Melatonin reduces significantly the GT and insulin effect, if given in the morning**

# Glucose and insulin serum values in the „Day“ or rather „Night“ eaters

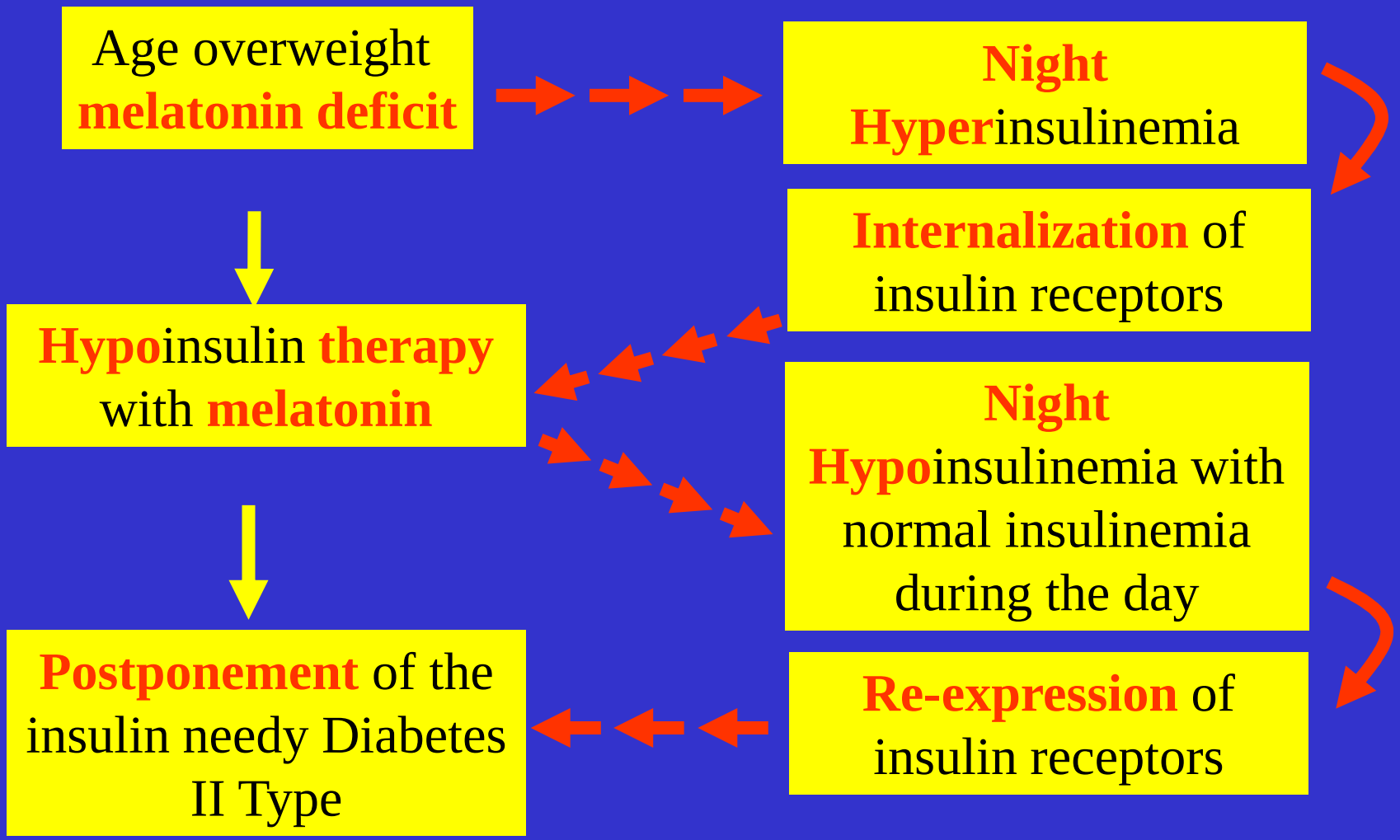
(Schlaf: 0:30 - 08:30)(Qin et al. 2003)




**Note: the night Melatonin reduces the insulin effect and with that increases significantly the glucose levels in the night**

# Postulated correlation between melatonin and the formation or rather the therapy of Diabetes mellitus II Type

# Schematic representation of new therapy approaches of Diabetes mellitus II Type



# Summary

- The insulin release can be put down thanks to melatonin through specific receptors
- A sudden block of the insulin release causes a „re-bound“ effect
- Epidemiologically, the prediabetic patients need frequently a melatonin deficit therapy
- An adequate treatment with i.e. Melachron® could delay the formation of insulin dependent Diabetes if necessary year after year, because transitory Hyperinsulinismus would be causally treated.

# Further Steps…

- Starting from January 2014 opening of a Melachron® application observation in prediabetic patients:
  - In January 2016 an online survey will be available: www.vitabasix.com

# Effects not found by the receptor:

## Antioxidant effects

***IMPORTANT:***

***No difference between human beings and animals***

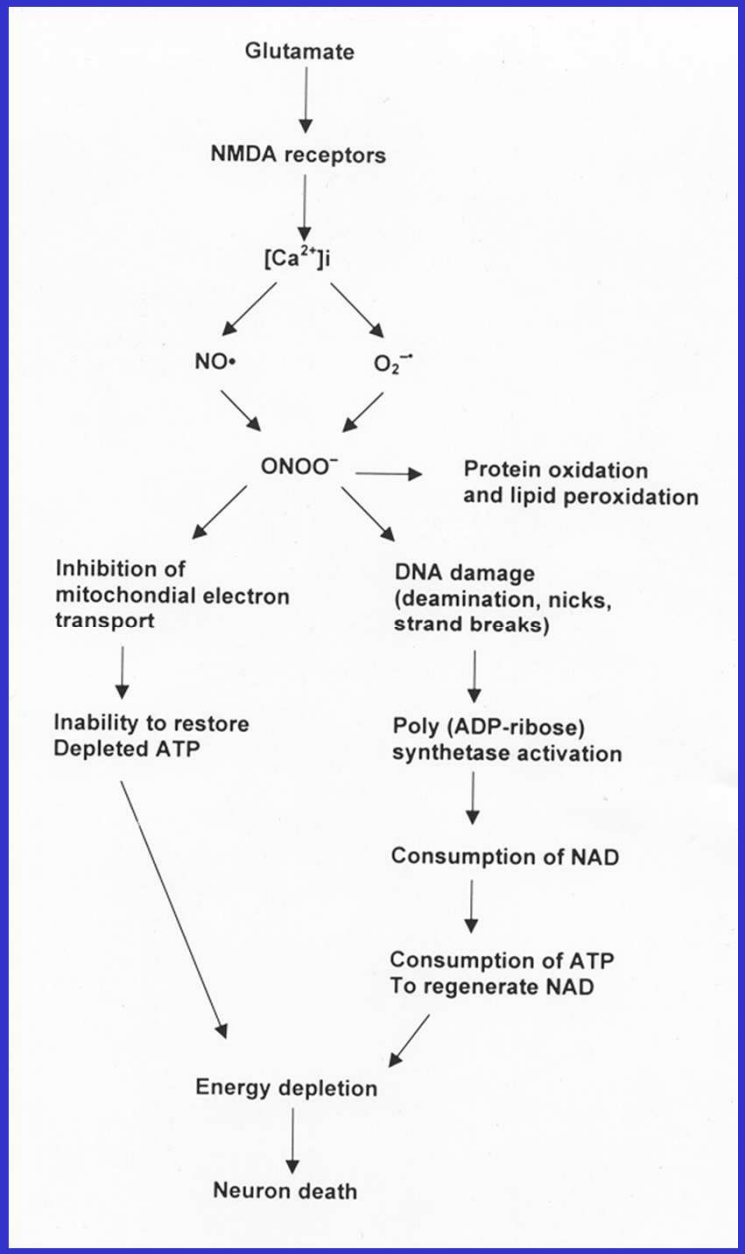
Alzheimer's disease
Amyotrophic lateral sclerosis
Down's syndrome
Head trauma
Epileptic seizures
Hyperbaric hyperoxia
Inflammation
Ischemia/reperfusion
Muscular dystrophies
Myasthenia gravis
Neural ceroid-lipofuscinosis
Neurotoxin exposure
Parkinson's disease
Progeria
Schizophrenia
Spinal cord injury
Tardive dyskinesia
Werdnig-Hoffman disease
Vitamin E deficiency
Xenobiotic-induced nerve injury

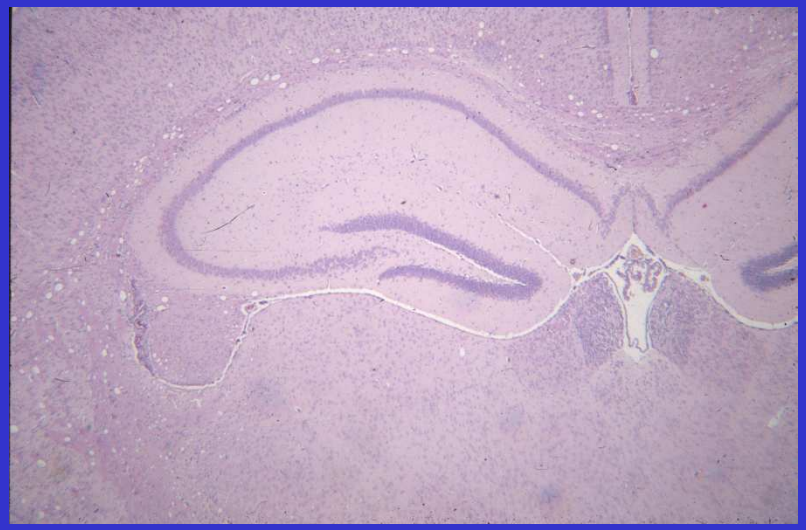
**Protection from neurotoxicological processes:**

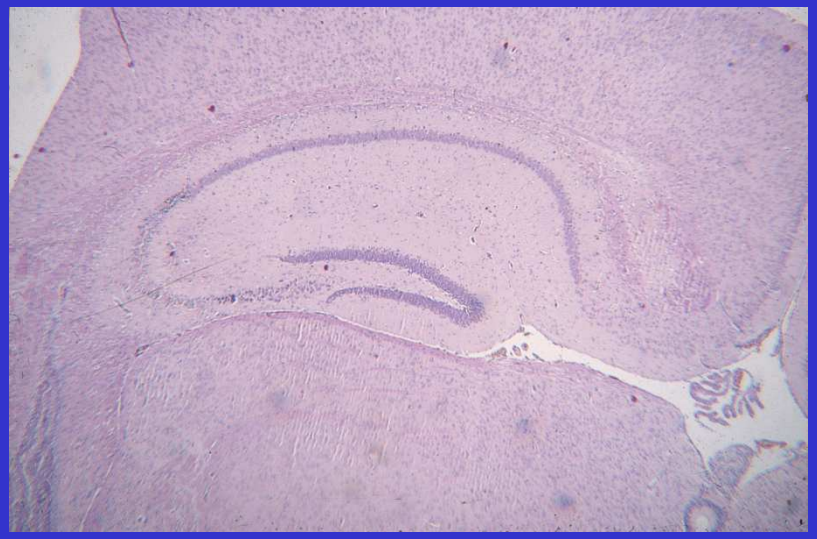
**i.e.**

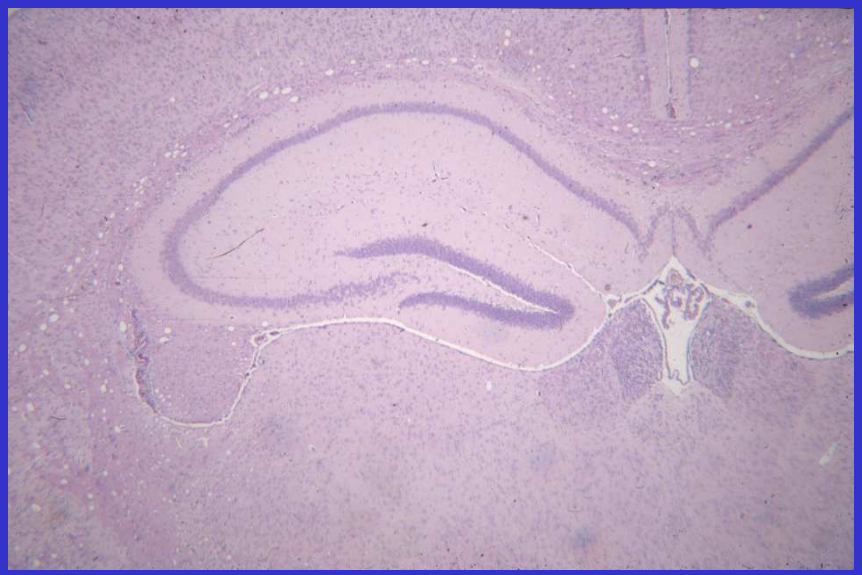
**Dementia**

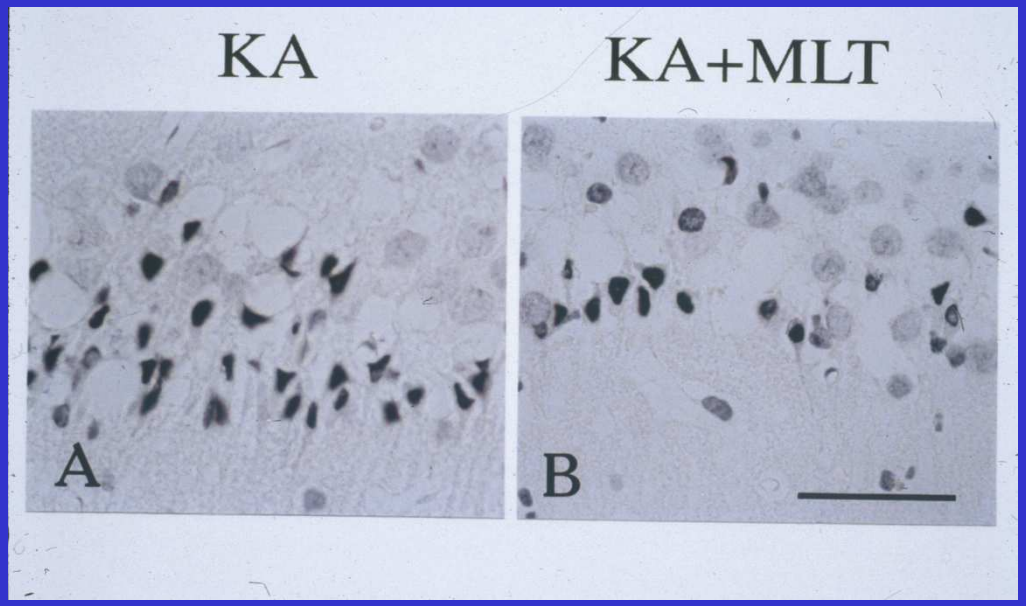
**Epilepsy**

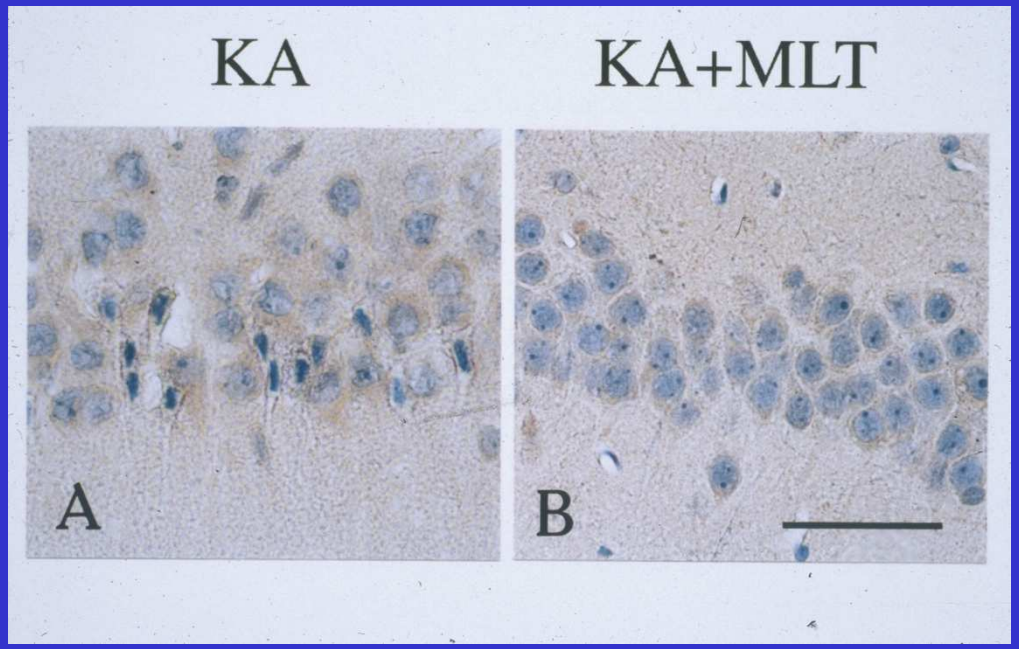

Glutamate
NMDA receptors
[Ca2+]i
NO•
O2−•
ONOO−
Protein oxidation and lipid peroxidation
Inhibition of mitochondial electron transport
DNA damage (deamination, nicks, strand breaks)
Inability to restore Depleted ATP
Poly (ADP-ribose) synthetase activation
Consumption of NAD
Consumption of ATP To regenerate NAD
Energy depletion
Neuron death





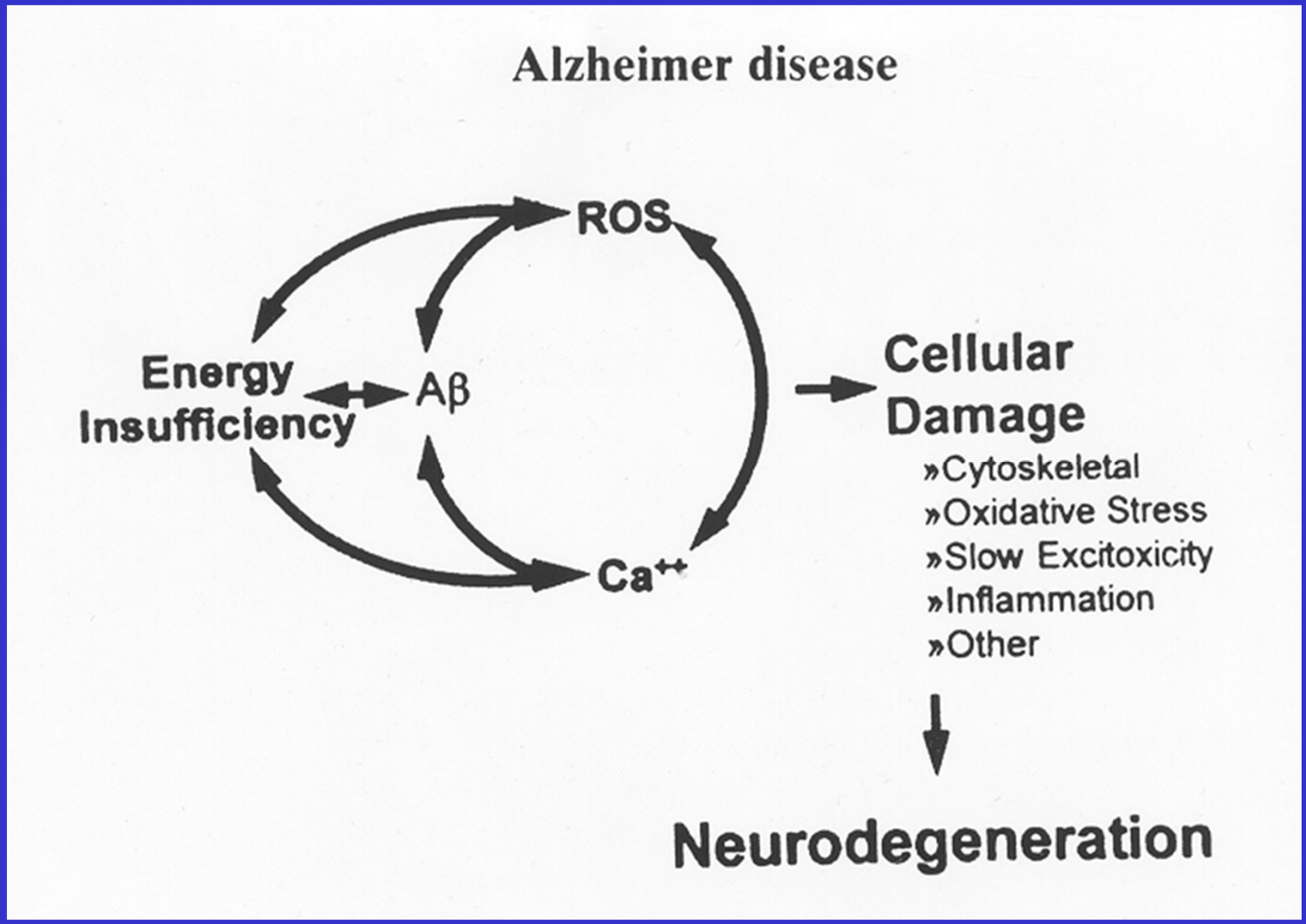


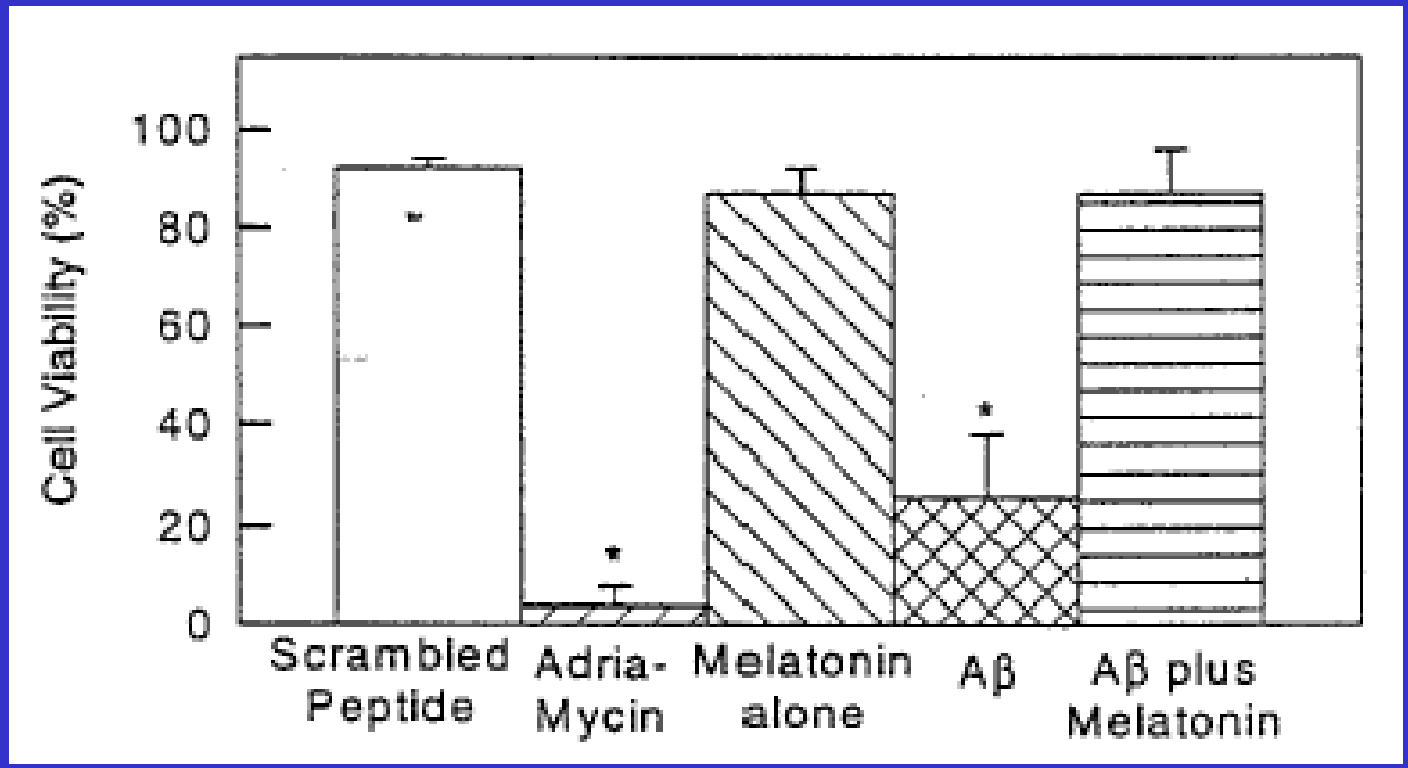

KA
KA+MLT
A
B

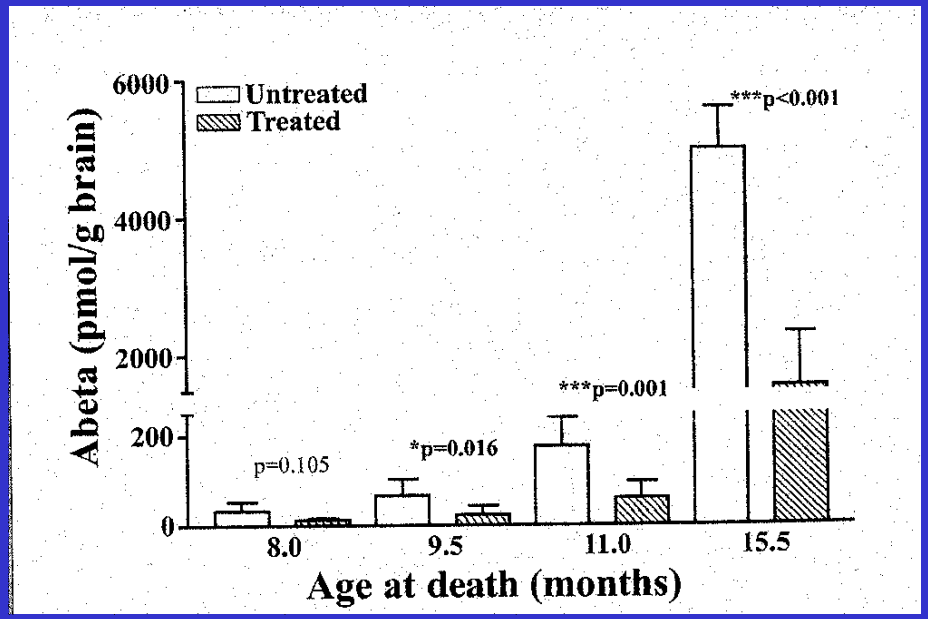

KA
KA+MLT
A
B

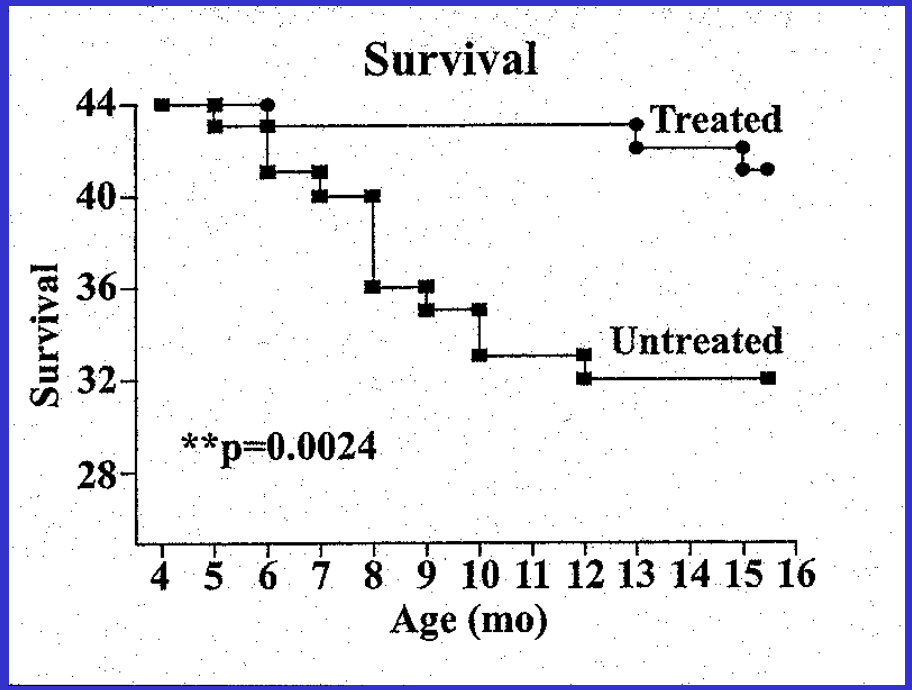
# Protection from diseases caused by old age:

## Alzheimer's Disease


Alzheimer disease
ROS
Energy
Insufficiency
Aβ
Ca++
Cellular
Damage
»Cytoskeletal
»Oxidative Stress
»Slow Excitoxicity
»Inflammation
»Other
Neurodegeneration


Cell Viability (%)
100
80
60
40
20
0
*
*
*
Scrambled Peptide
Adria-Mycin
Melatonin alone
Aβ
Aβ plus Melatonin


Untreated
Treated
Abeta (pmol/g brain)
6000
4000
2000
200
0
p=0.105
*p=0.016
***p=0.001
***p<0.001
8.0
9.5
11.0
15.5
Age at death (months)


Survival
Treated
Untreated
Survival
44
40
36
32
28
**p=0.0024
4 5 6 7 8 9 10 11 12 13 14 15 16
Age (mo)

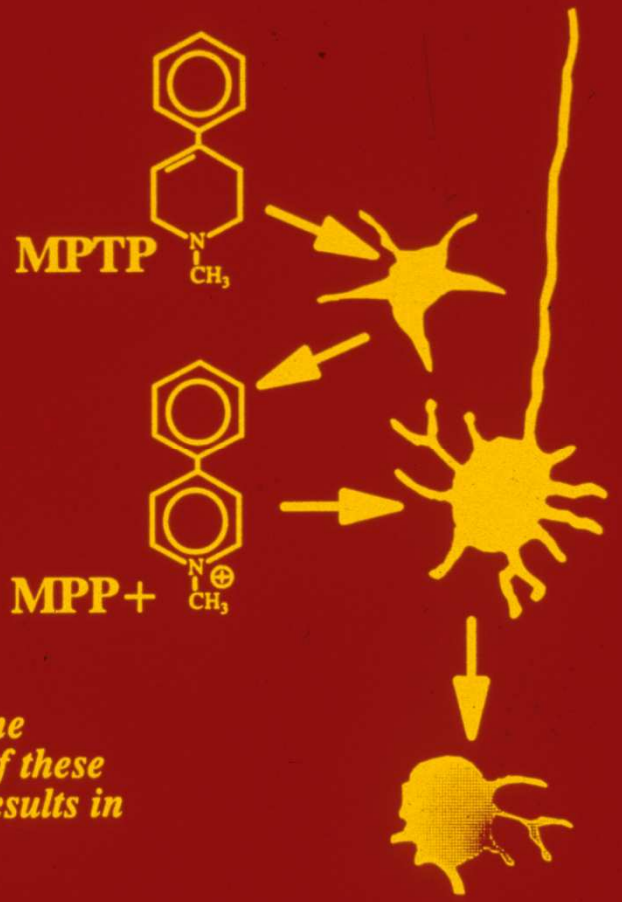
# Protection from progressive diseases:

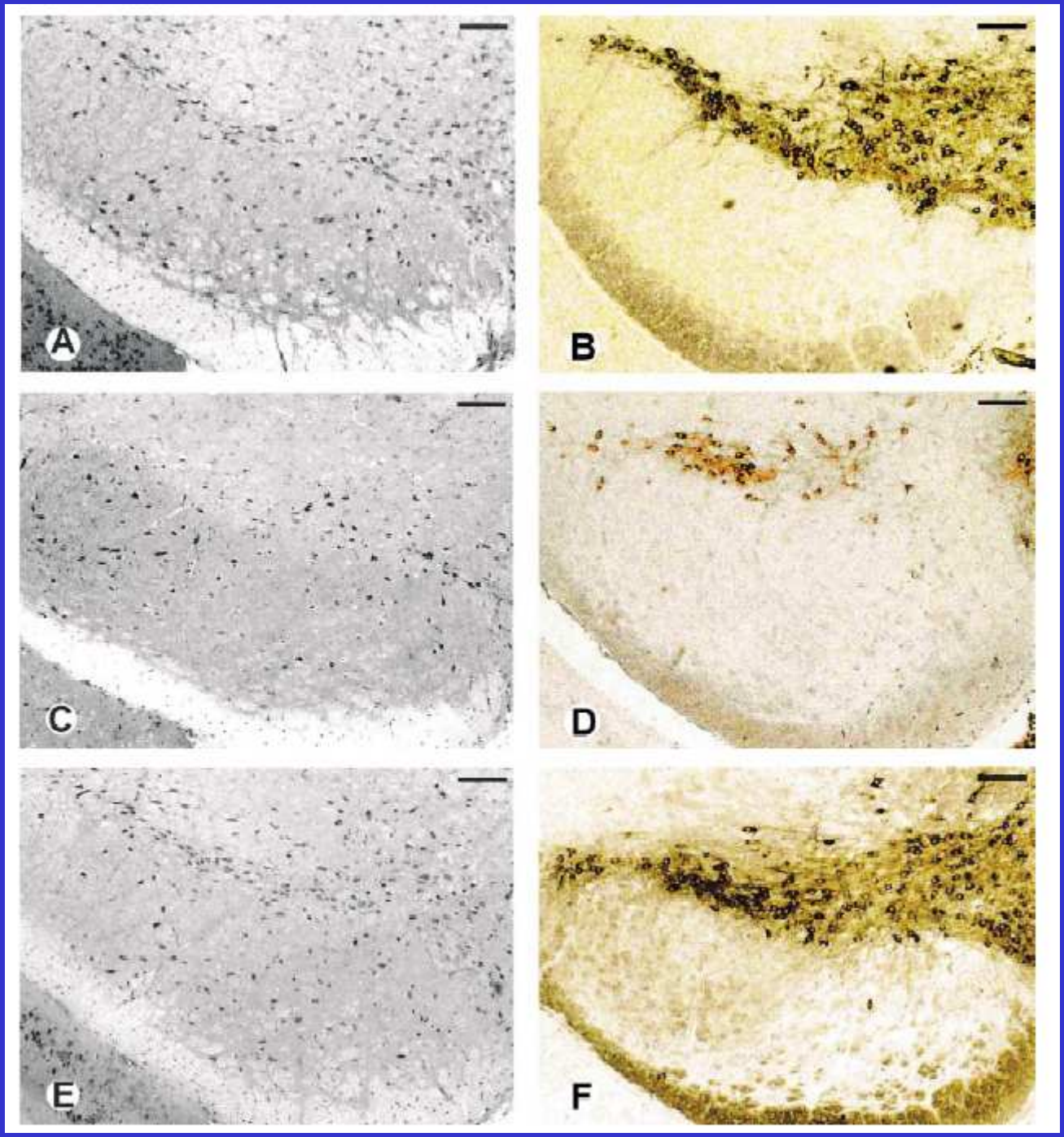
## Parkinson’s disease

*MPTP is taken up by astrocytes in brain. In these glia, it is metabolized to MPP+*

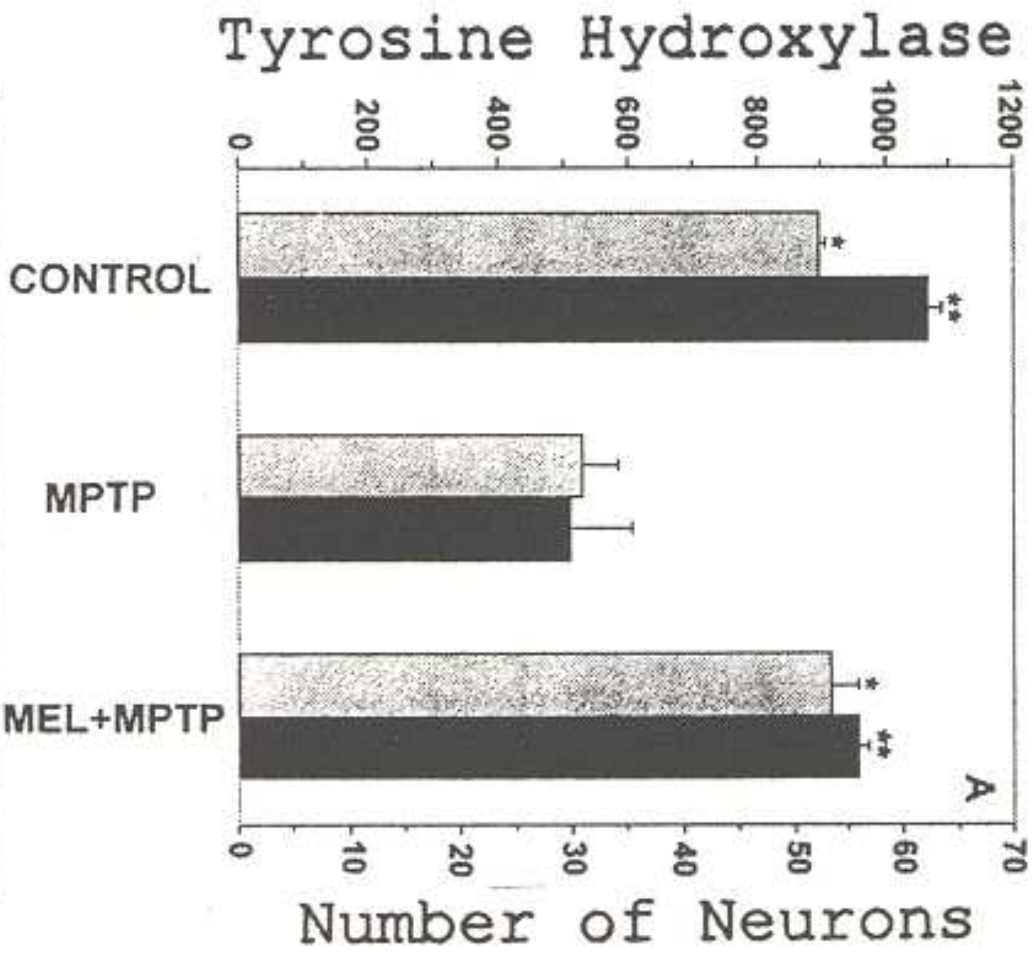
*MPP+ is released by astrocytes and taken up by dopamine neurons via normal dopamine reuptake system.*

*MPP+ kills dopamine neurons; the death of these dopamine neurons results in parkinsonian signs.*



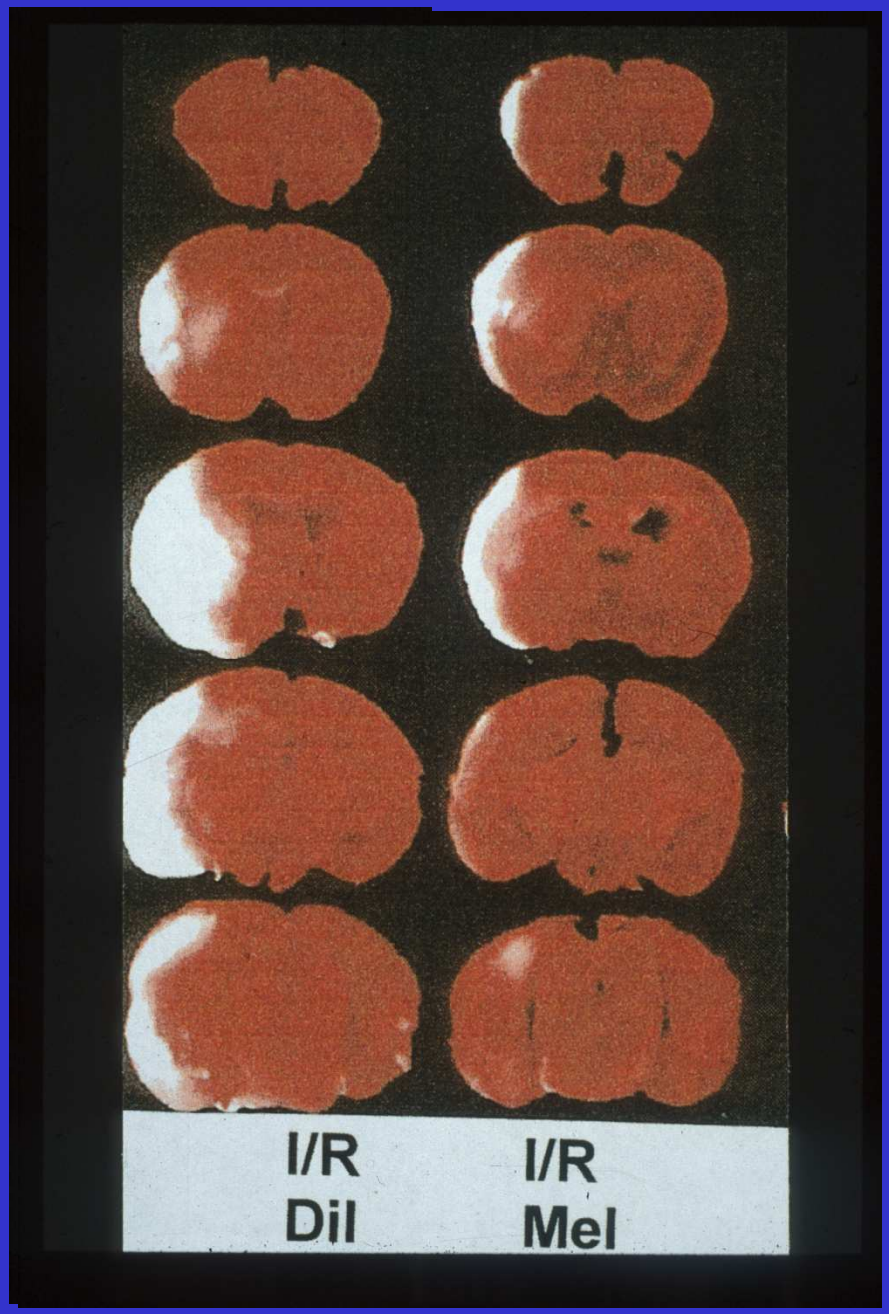

A
B
C
D
E
F

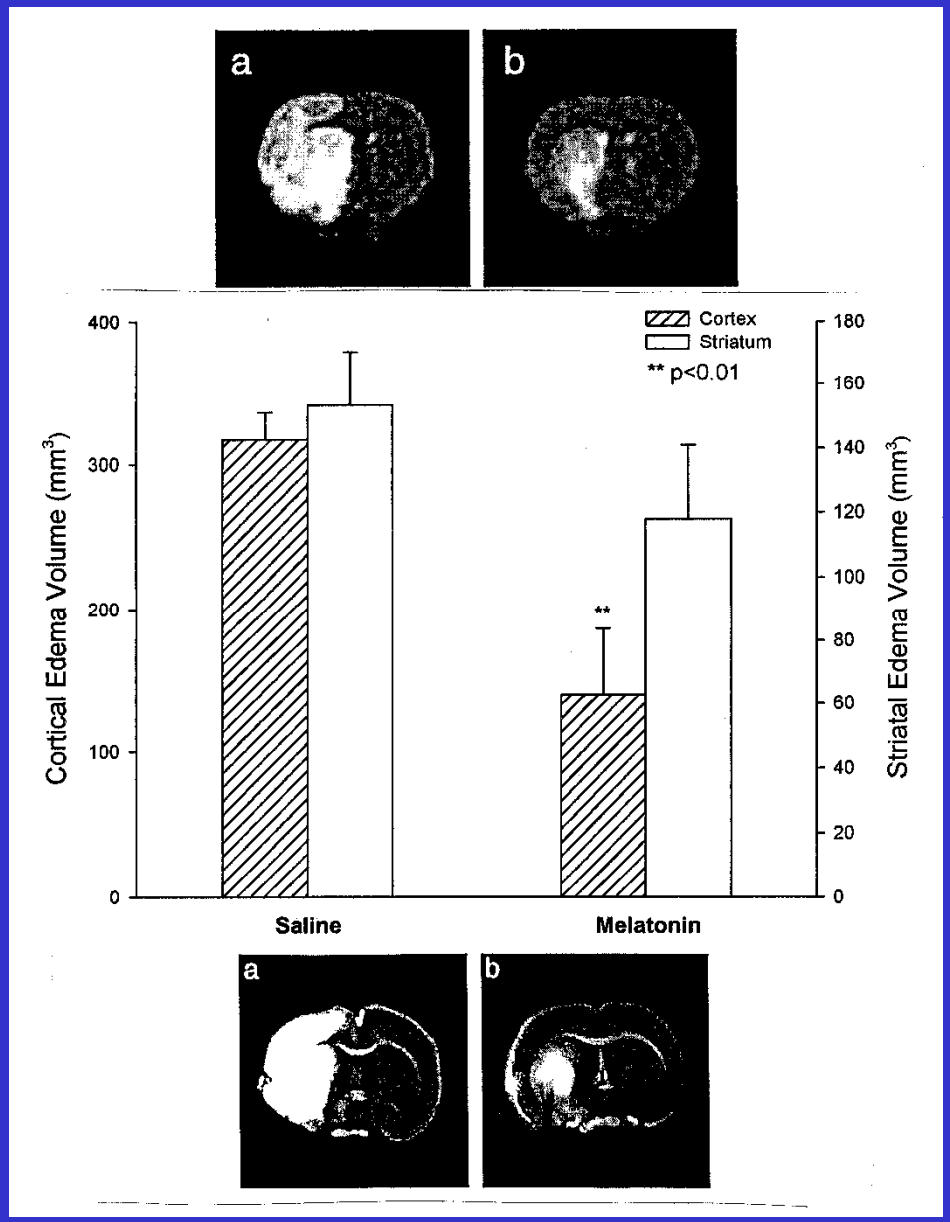

B

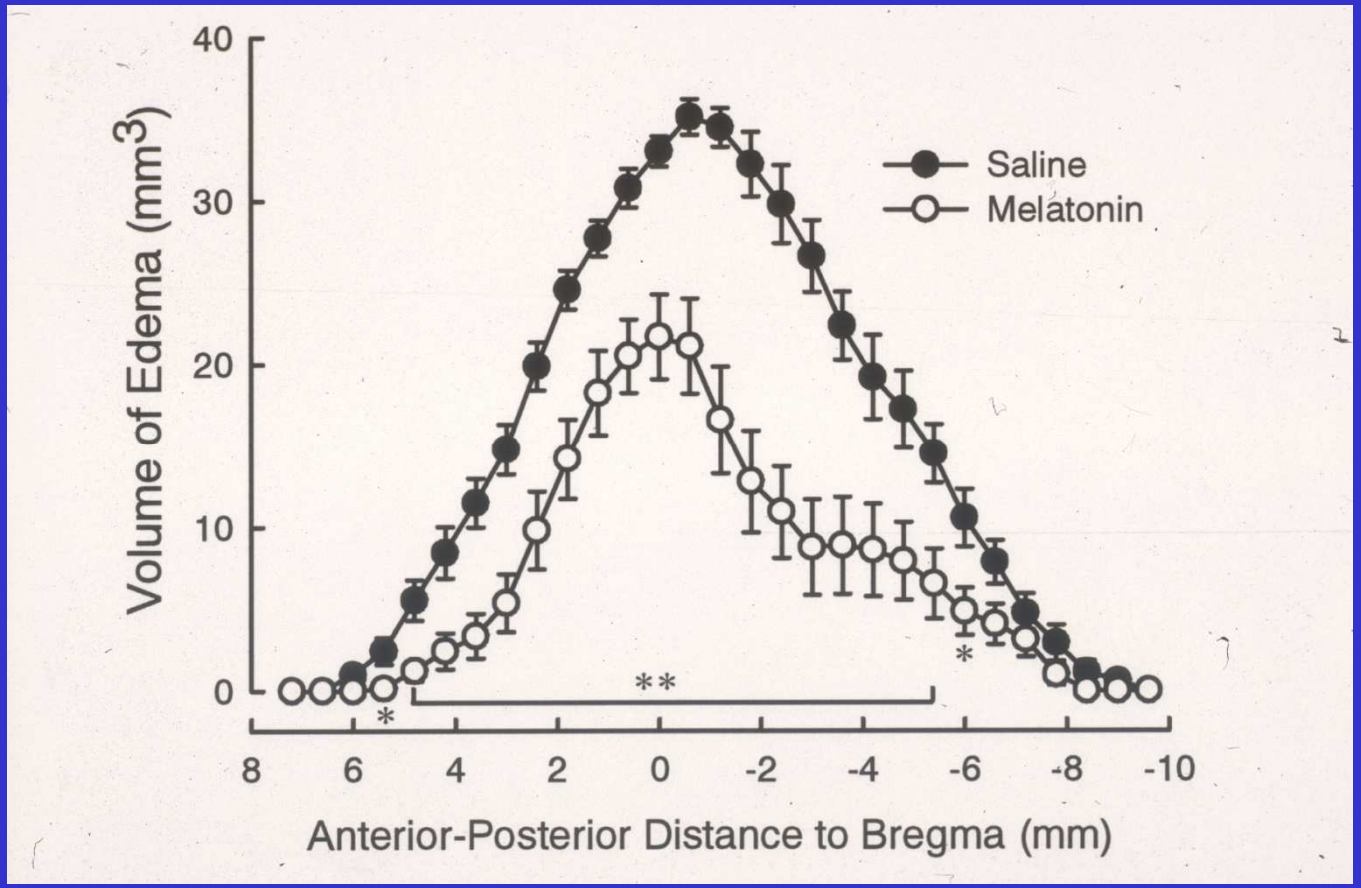

Tyrosine Hydroxylase
0
200
400
600
800
1000
1200
CONTROL
MPTP
MEL+MPTP
*
**
*
**
A
0
10
20
30
40
50
60
70
Number of Neurons

# Protection from consequential damages after embolism:

## Stroke / Heart attack


I/R
Dil
I/R
Mel


a
b
Cortex
Striatum
** p<0.01
Cortical Edema Volume (mm3)
Striatal Edema Volume (mm3)
400
300
200
100
0
180
160
140
120
100
80
60
40
20
0
**
Saline
Melatonin
a
b


Volume of Edema (mm3)
40
30
20
10
0
Saline
Melatonin
*
**
*
8
6
4
2
0
-2
-4
-6
-8
-10
Anterior-Posterior Distance to Bregma (mm)

# Conclusion (I)

- **Melatonin has positive effects through mechanisms not found by receptor on:**
  - **Neurodegeneration (proved in the animal model)**
  - **Alzheimer (proved in the animal model)**
  - **Parkinson (proved in the animal model, the first human beings results are positive)**
  - **Stroke (proved in the animal model, some reports on human beings are positive)**
  - **Heart attack (proved in the animal model, the first clinical study on human beings is positive)**

# Conclusions (II)

- **Melatonin has positive effects through mechanisms found by receptors on:**
  - **Sleep (proved on human beings with Melachron® )**
  - **Epilepsy (proved on human beings with Melachron® )**
  - **Circadian rhythm (proved on human beings with Melachron® )**
  - **Jet-Lag (proved on human beings wih Melachron® )**
  - **Diabetes (Studies with Melachron® are still in progress)**

Partner involved in the arrangement of these outcomes and of the development of ***Melachron®*** and ist effects:

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Prof. B. Stankov (Ambrospharma srl) Milano, Italy
Dr. A. Costa (SIIT srl) Milano, Italy
Dr. J.-D. Fauteck (ea3m GmbH & Co. KG), Germany
Hr. R. Zerga (VITABASIX) Maastricht, Niederlande

And many other people!

A special thanks to all the patients, that have tested ***Melachron® ,*** making this results possible!