The light:dark cycle has dictated biological rhythmicity and physiology influenced by the light/dark cycle

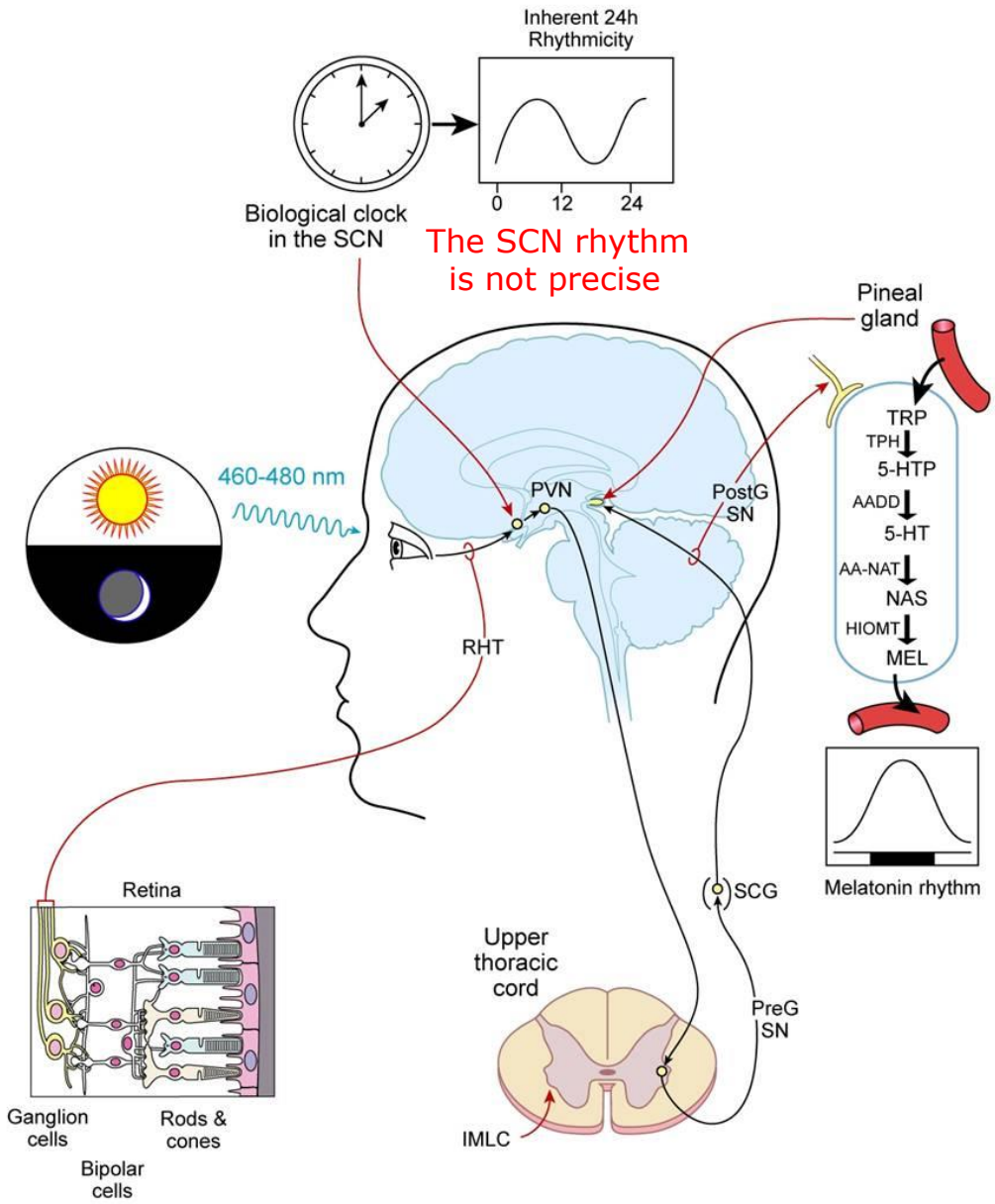


A regular light:dark cycle has existed for millions of years

Vertebrates evolved a biological clock to take advantage of that information

The metabolism of every cell varies over a 24 hour period

Light regulation of the biological clock and of the melatonin rhythm



Humans possess two types of vision:

Visual vision
vs
Circadian vision

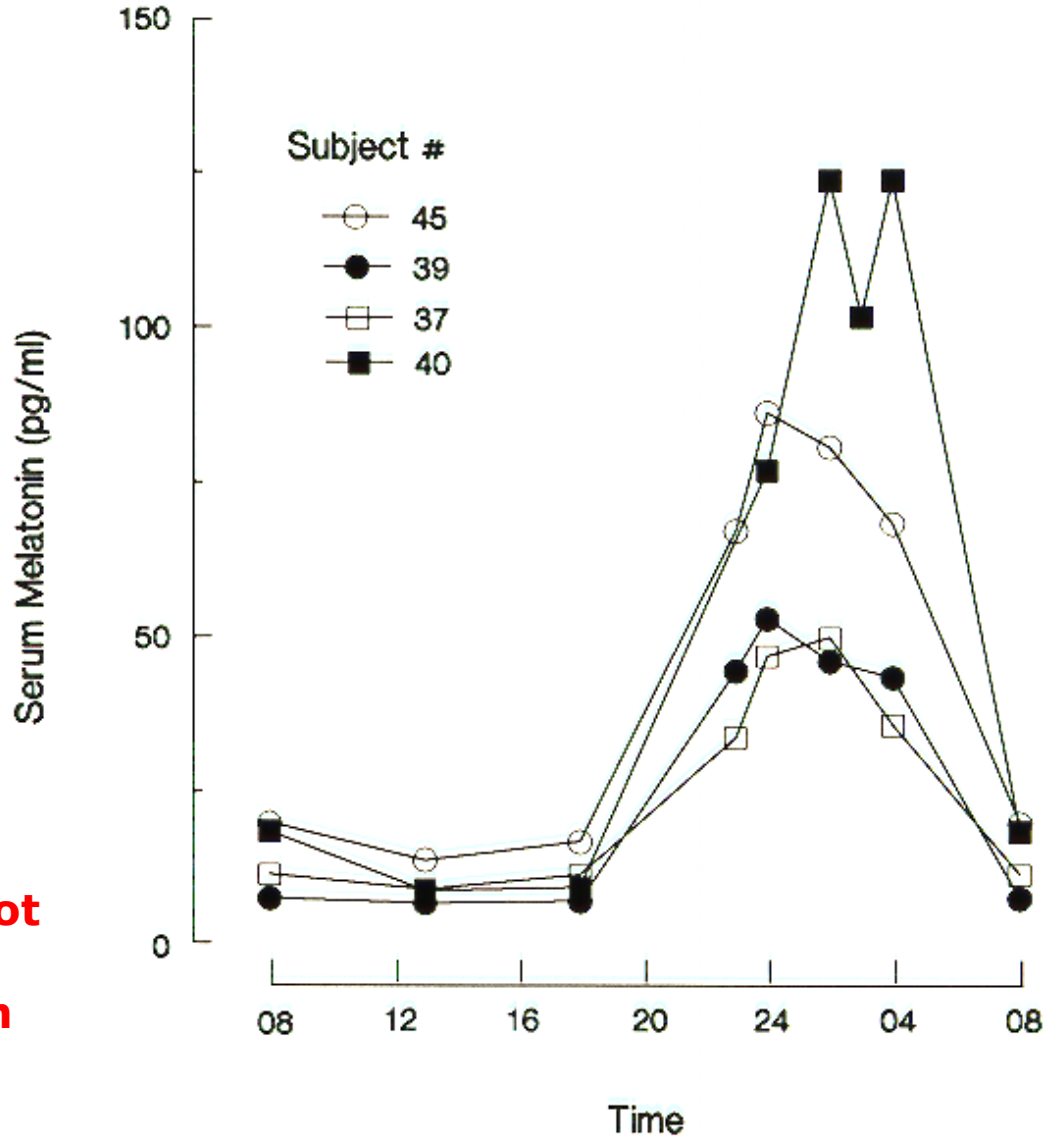
Visual vision requires retinal rods and cones

Circadian vision requires intrinsically-photoreceptive ganglion cells (melanopsin)

Every cell in the body receives information about the light:dark cycle

Reiter et al, 2010

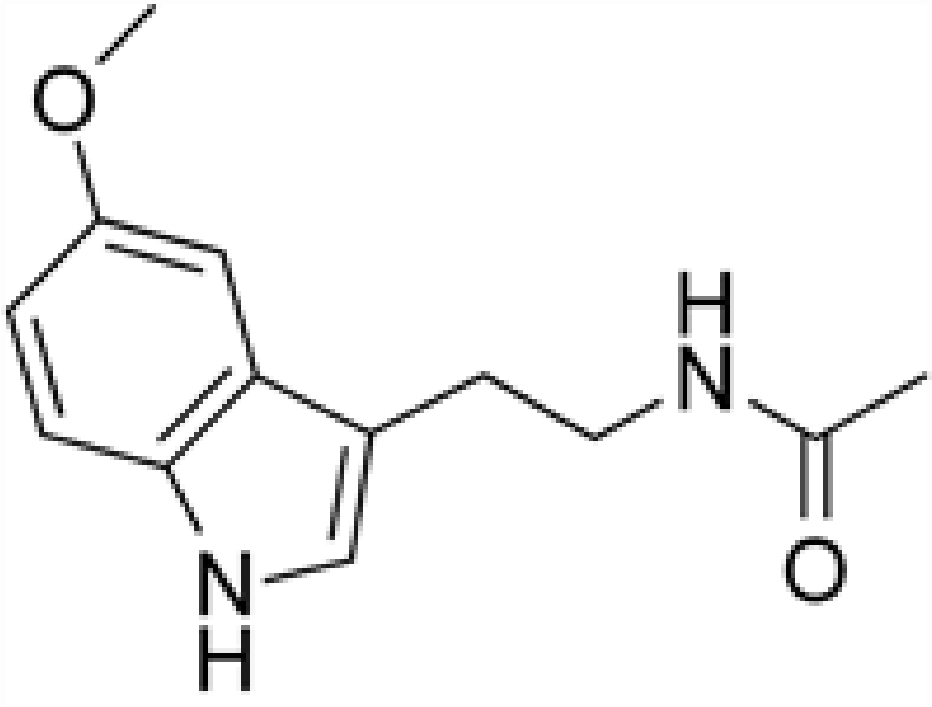
The blood melatonin rhythm is genetically determined

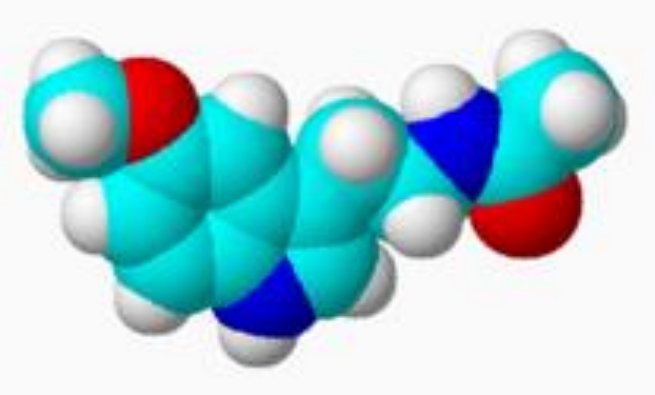


Melatonin is not in equilibrium in an organism

Reiter et al, 2001

N-acetyl-5-methoxytryptamine (melatonin) (an endogenous anti-cancer agent)

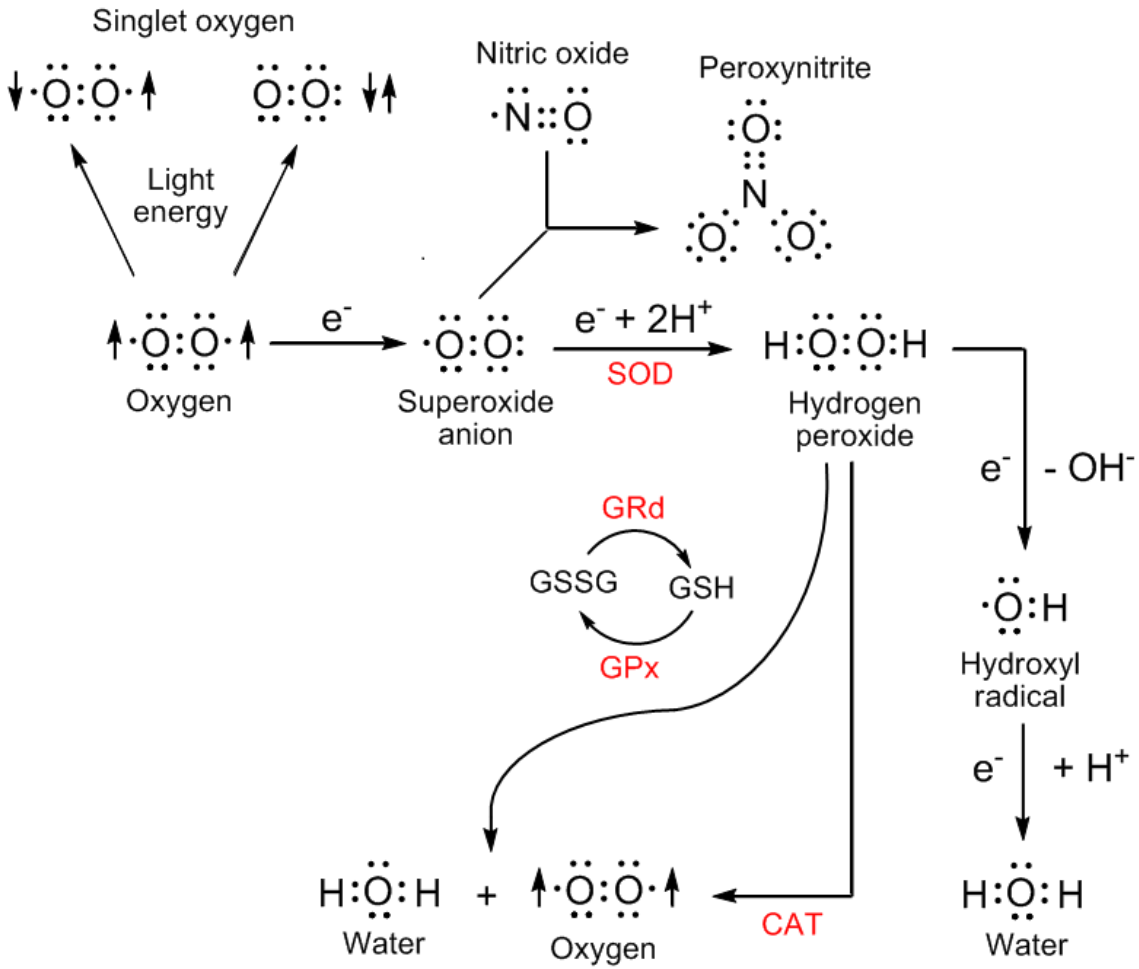




Melatonin evolved 2.5-3.0 billion years ago

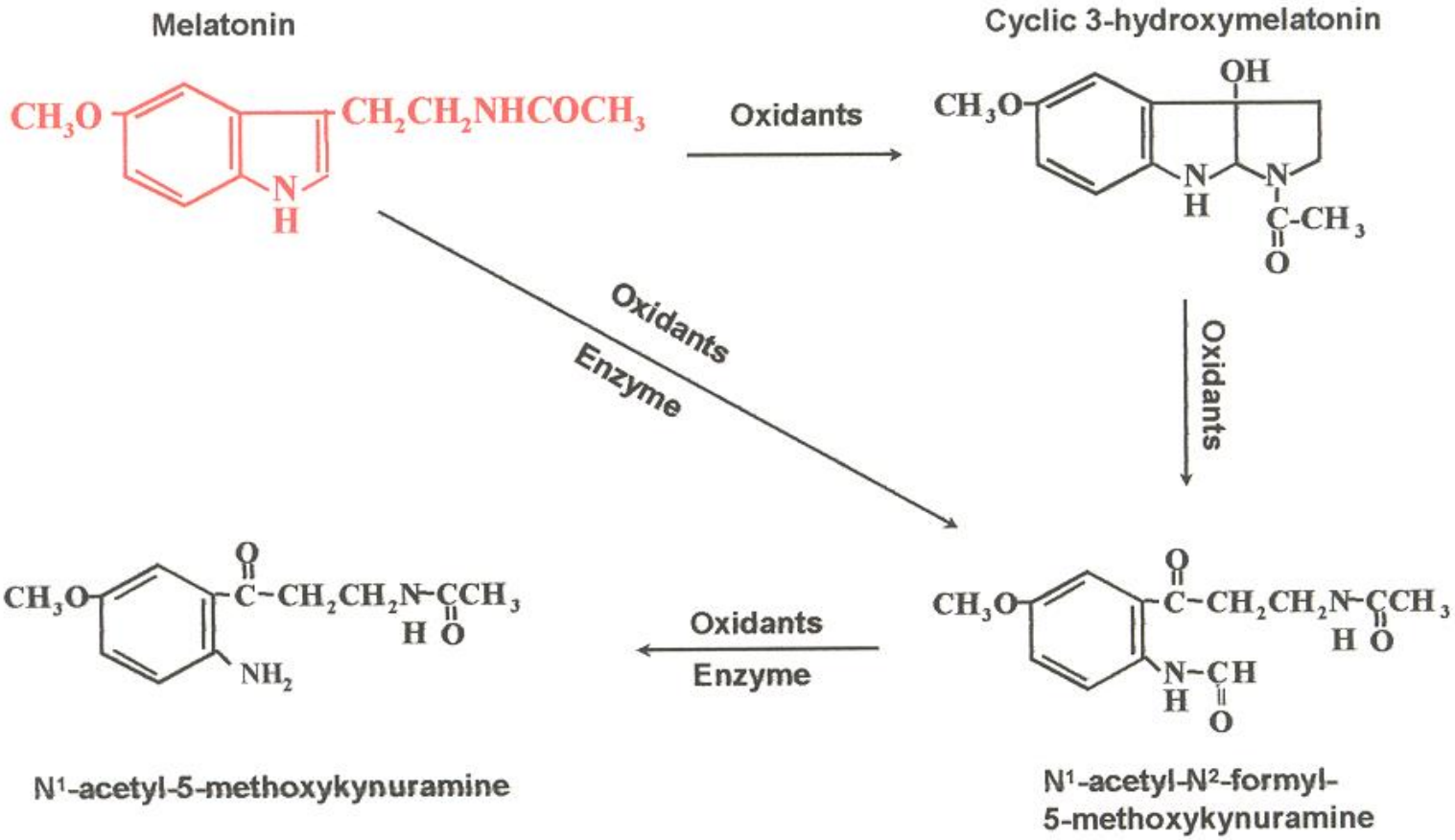
Melatonin is present throughout both the animal and plant kingdoms

Oxygen gives rise to reactive oxygen species which are highly toxic



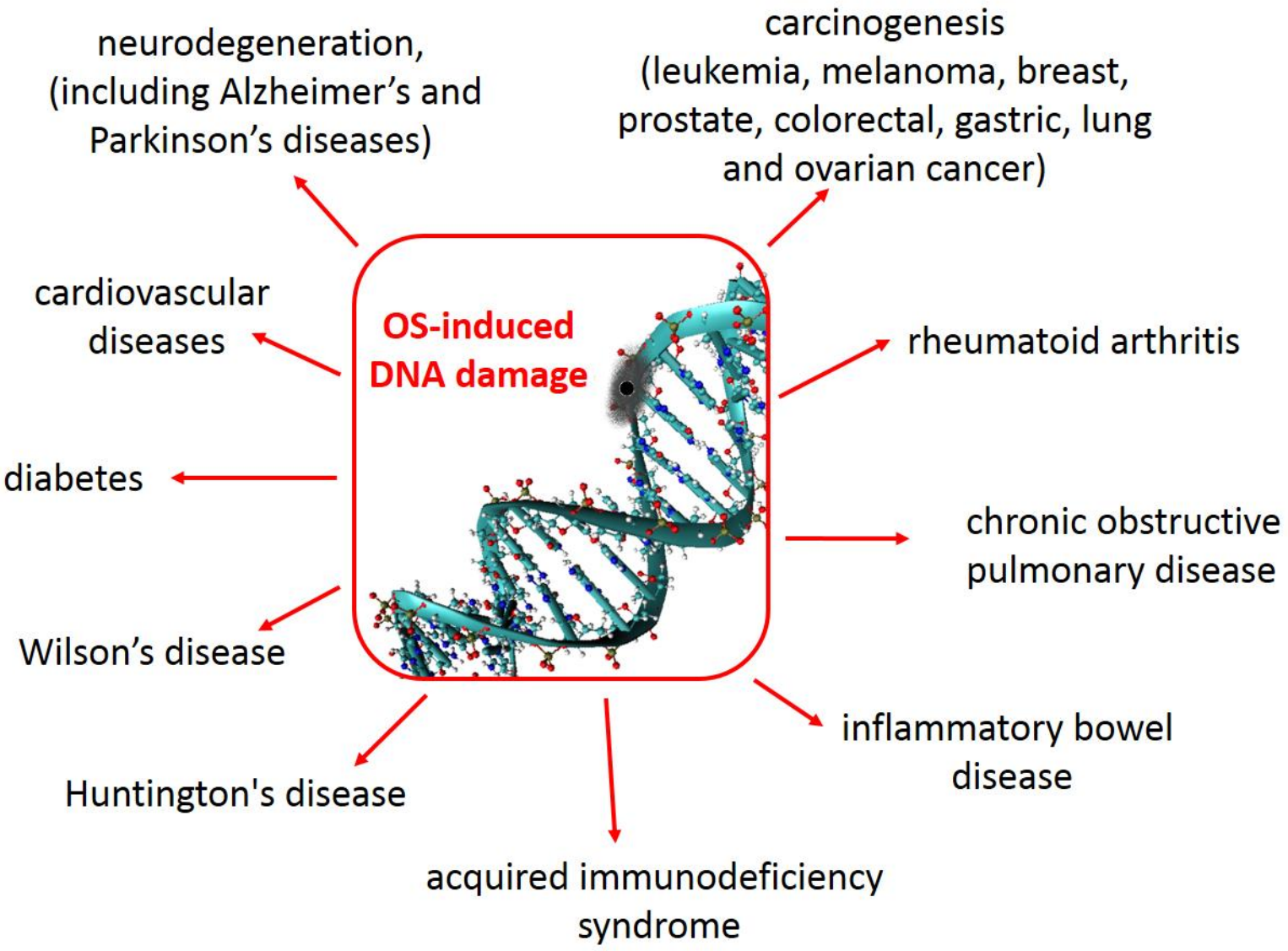
Many reactive oxygen species (free radicals) are produced in mitochondria and chloroplasts

Melatonin as an antioxidant



Melatonin and all of its metabolites are powerful free radical scavengers via the antioxidant cascade

Diseases that involve DNA damage due to oxidative stress



Threats to DNA and mechanisms by which melatonin provides protection

Threats

Free radicals
(OH, NO, RO, ROO)

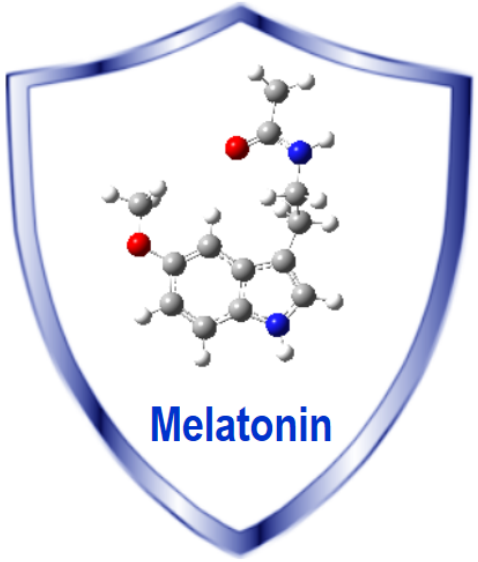
Metals
(Fe, Cu, Cr, Pb, Ni, Co, Hg, As)

Other chemicals
(formaldehyde, 17β-estradiol, MPTP/MPP^+, $KBrO_3$, d-aminolevulinic acid, thioacetamide)

Radiation

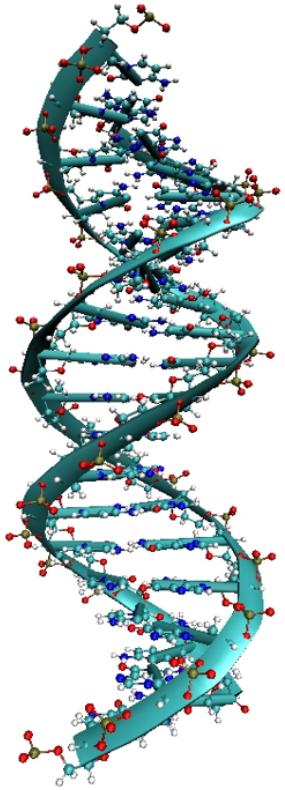
Health disorders

Shield



- ✓ scavenging free radicals
- ✓ inhibiting metal-induced DNA damage;
- ✓ protecting against non-radical chemicals;
- ✓ protecting through its metabolites;
- ✓ activating antioxidative enzymes;
- ✓ inhibiting pro-oxidative enzymes;
- ✓ boosting the DNA repair machinery

Target

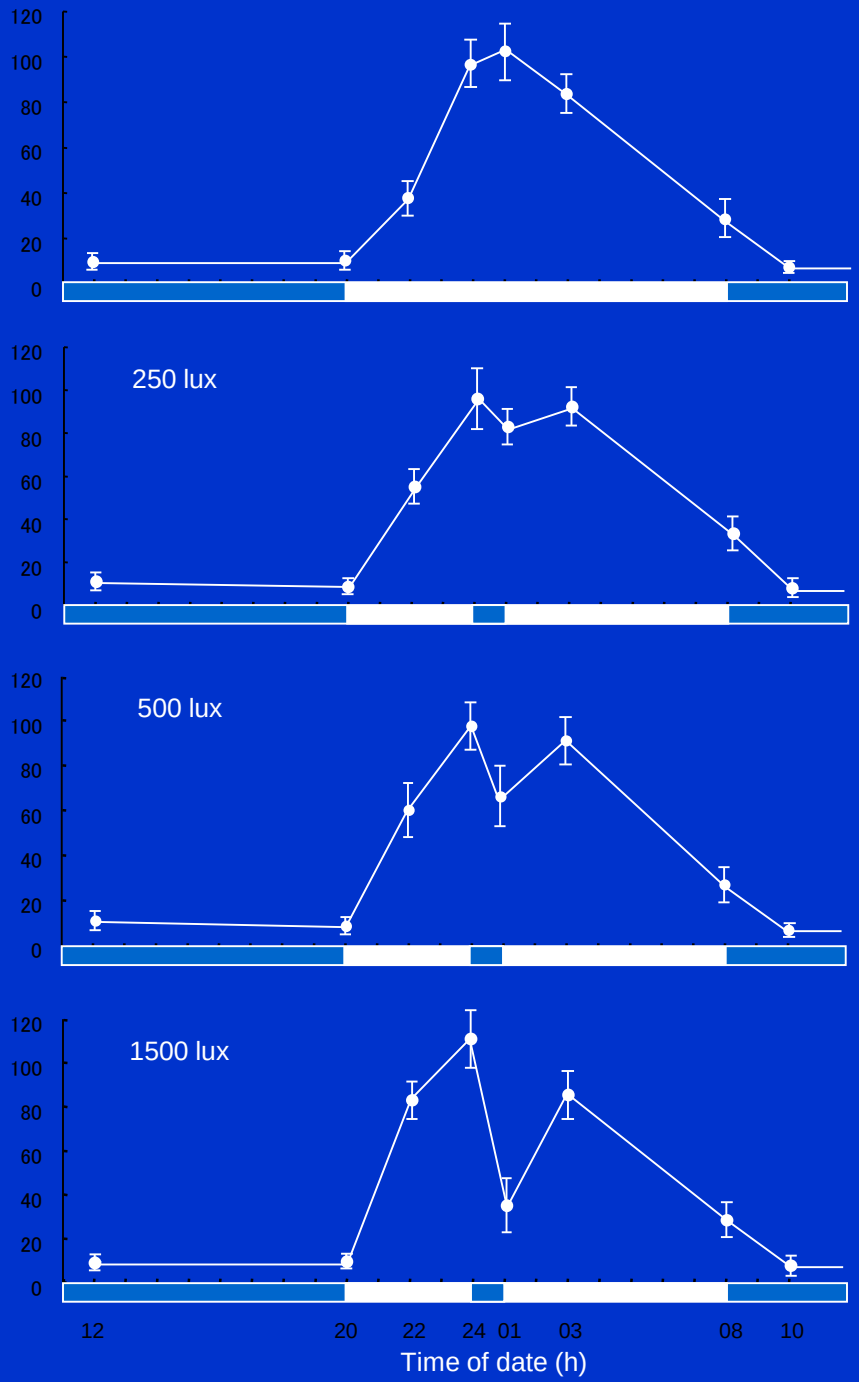


DNA





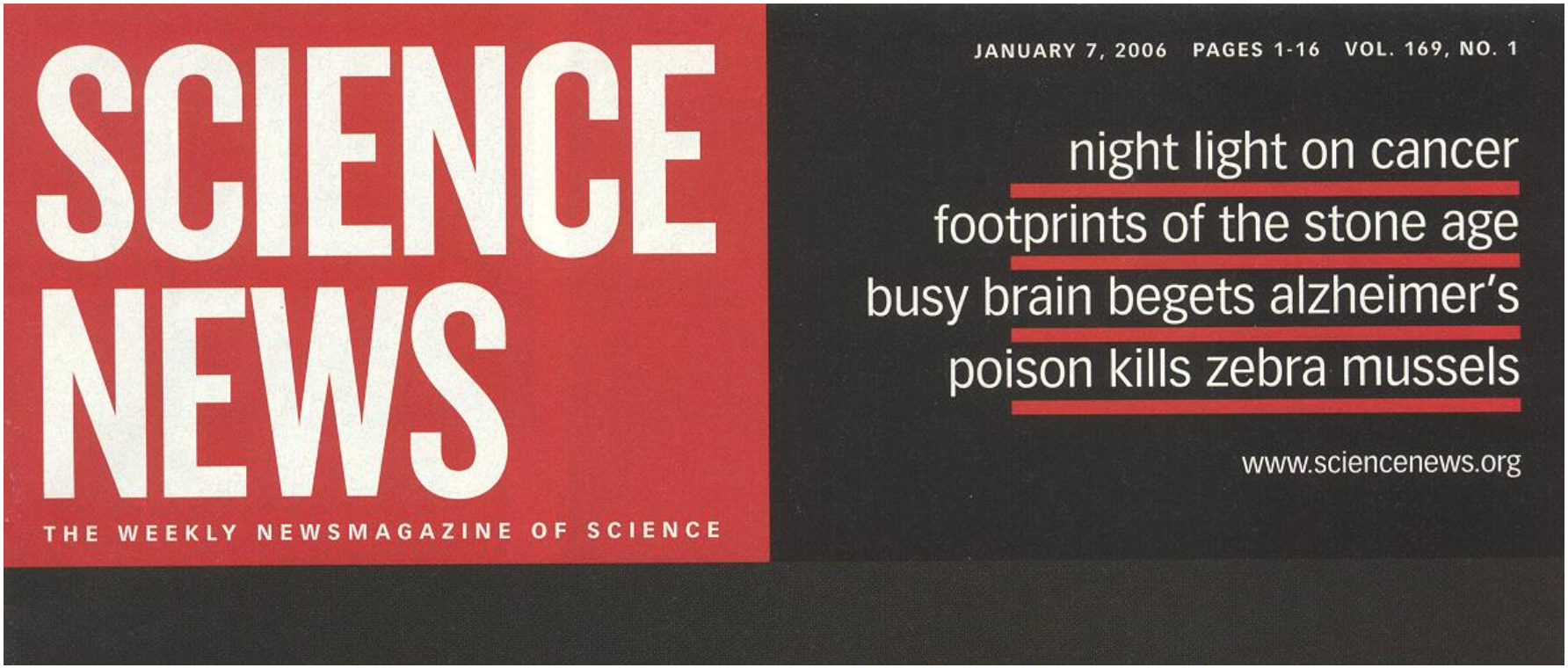




Light at night suppresses melatonin levels proportional to the brightness

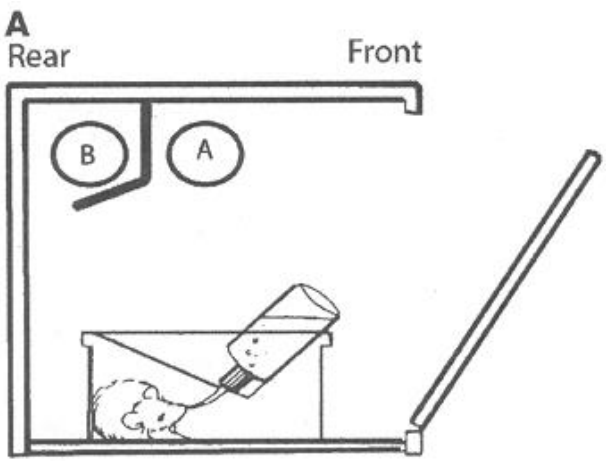
Light is a drug

Epidemiological studies have reported an increased cancer incidence in night shift workers

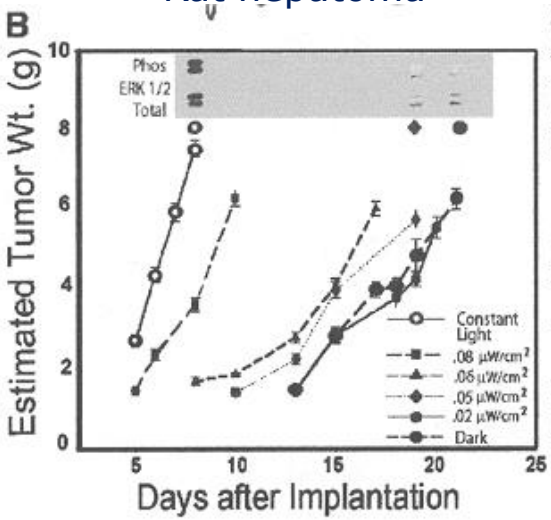


Increasing light intensity at night accelerates growth of human breast cancer xenografts

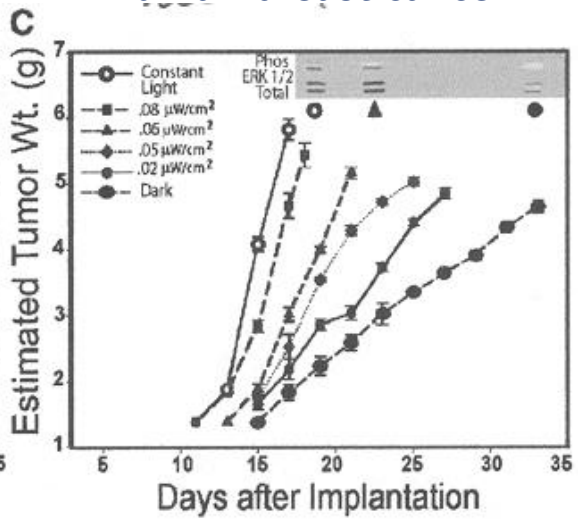
Animal chamber



Rat hepatoma



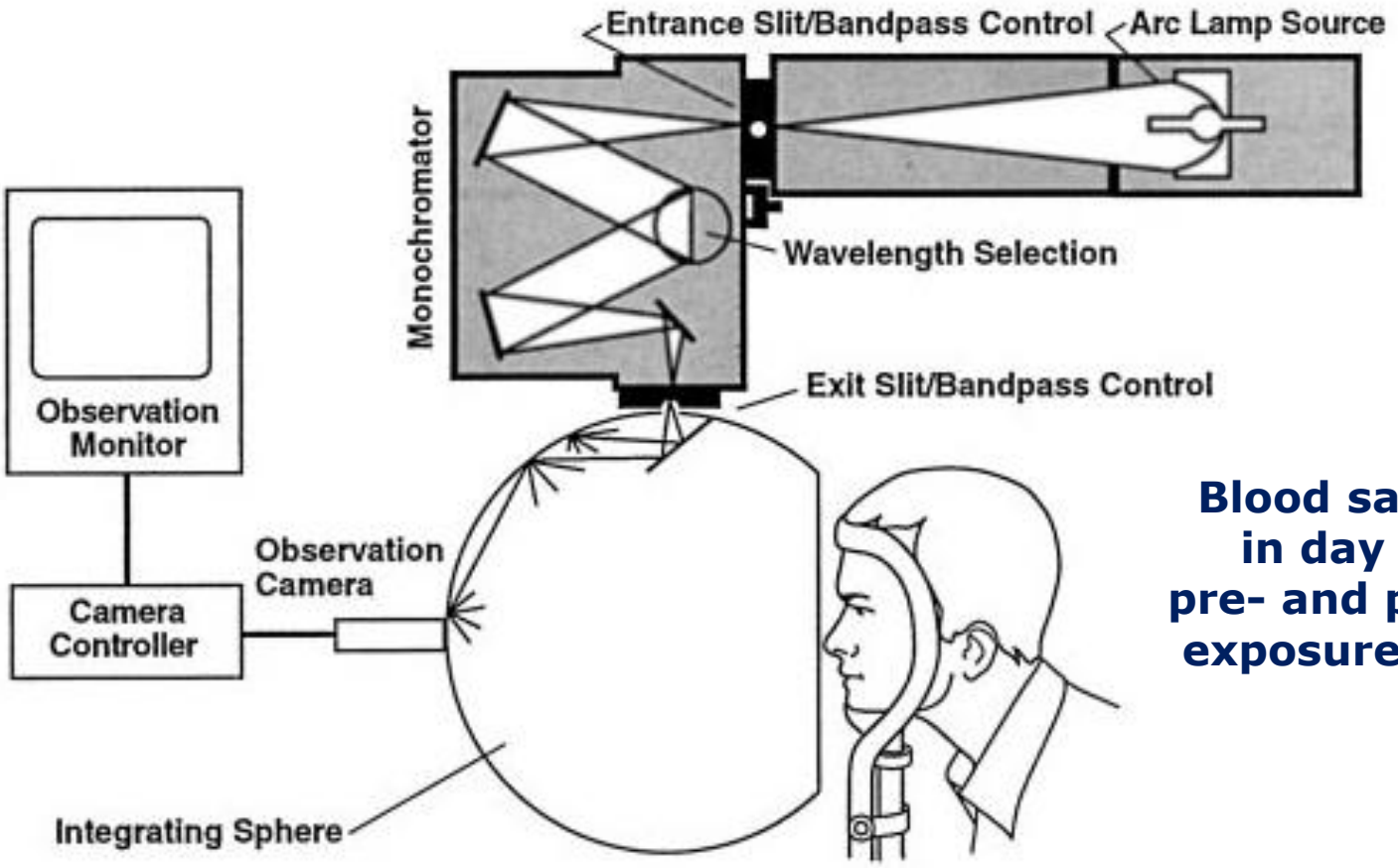
Human breast cancer



These animals are circadian disrupted and nocturnal melatonin levels are depressed

Brainard et al, 2005

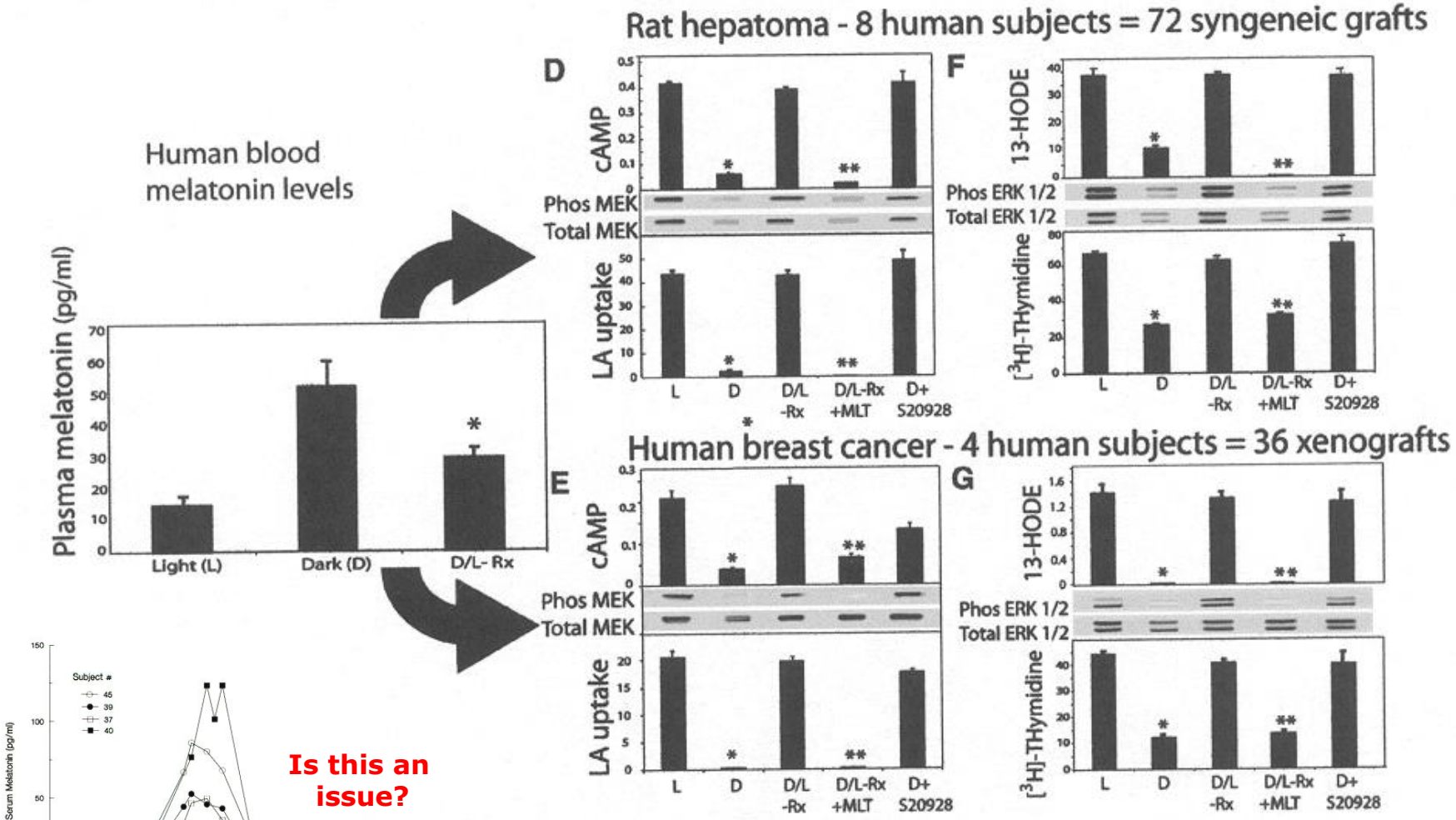
Ganzfeld dome system used to test light intensity and wavelength effects on circadian disruption and melatonin suppression



Blood samples in day and pre- and post-light exposure at night

Brainard et al, 2006

Physiological nighttime levels of melatonin inhibit uptake of growth factors by human breast cancer cells

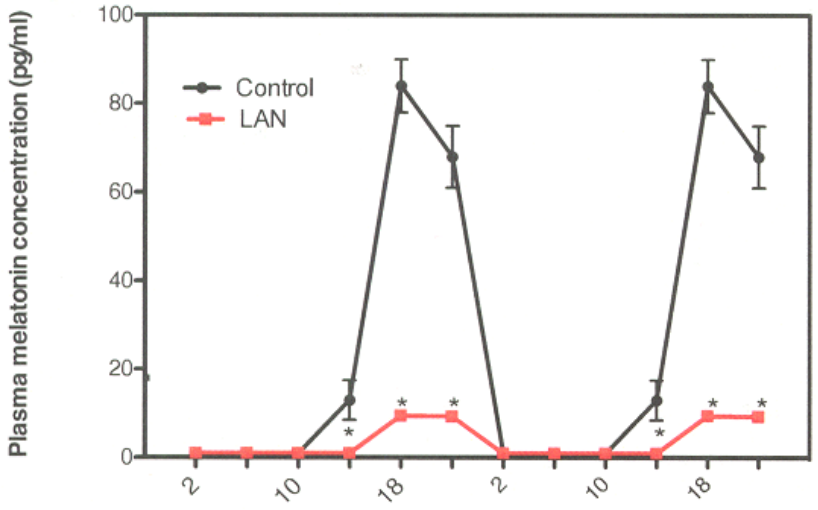


Blask et al, 2006

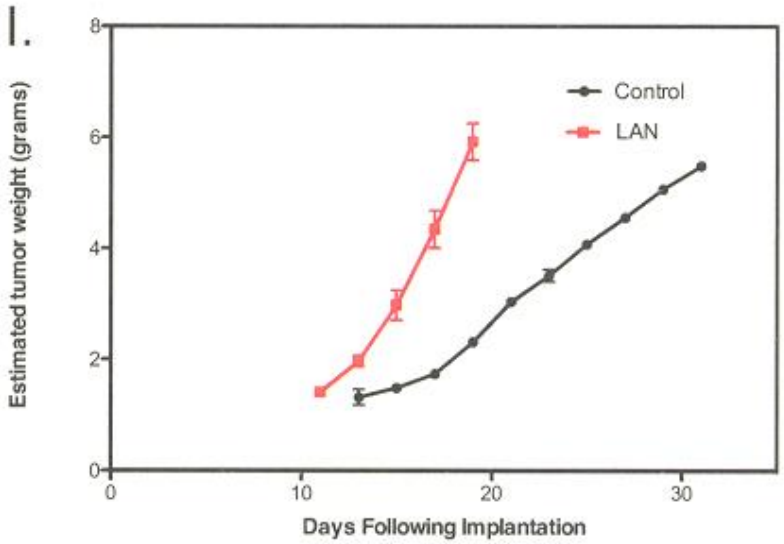
Melatonin suppression and accelerated tumor growth in a light:dark cycle and with dim light at night (LAN)

Day time light = 345 lux (141 μW/cm²); LAN = 0.2 lux (0.08 μW/cm²)

A.



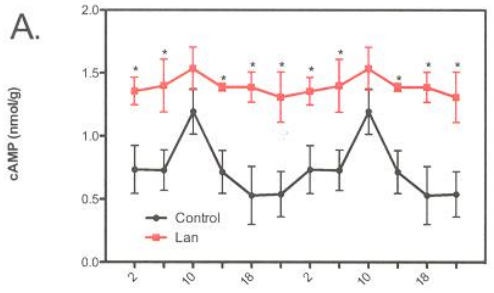
I.



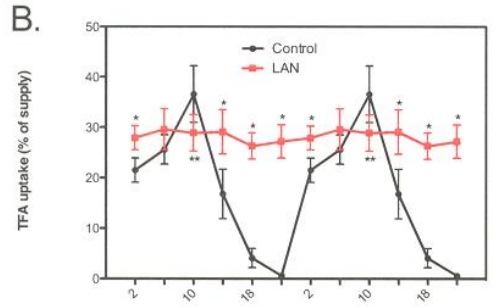
Melatonin rhythm

Tumor growth

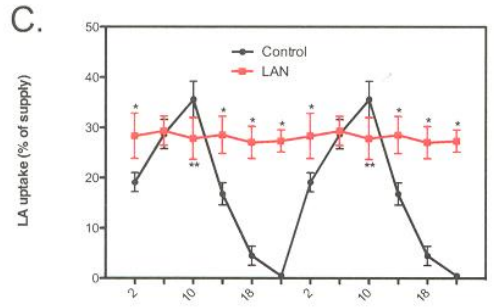
(SR- MCF-7)



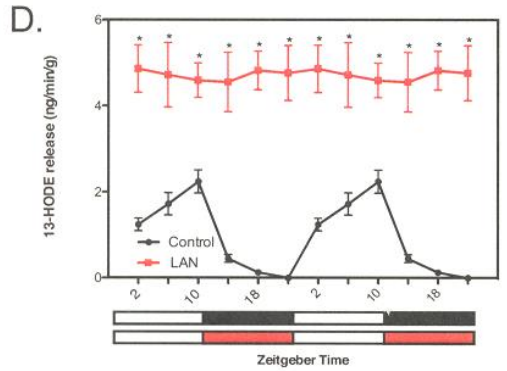
cAMP



Total fatty acid



Linoleic acid



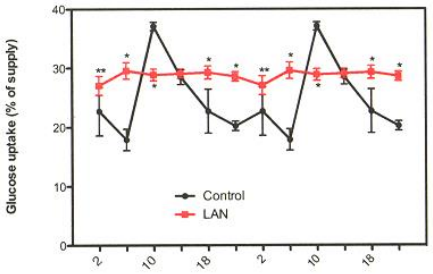
13-HODE

Changes in metabolism and growth factor uptake by tumors as a function of the L:D cycle

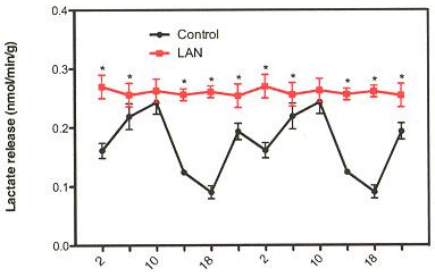
Black line = with melatonin rhythm in L:D cycle

Red line = with melatonin suppression due to LAN

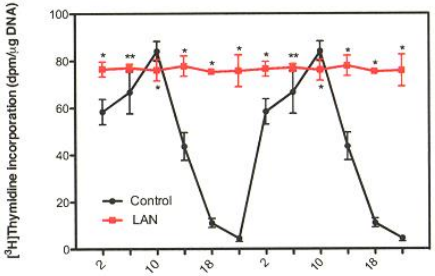
Blask et al, 2013



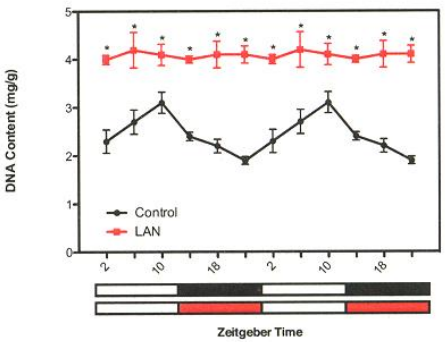
Glucose uptake



Lactate release



3H-thymidine incorporation



DNA content

Features indicative of aerobic glycolysis (Warburg effect)

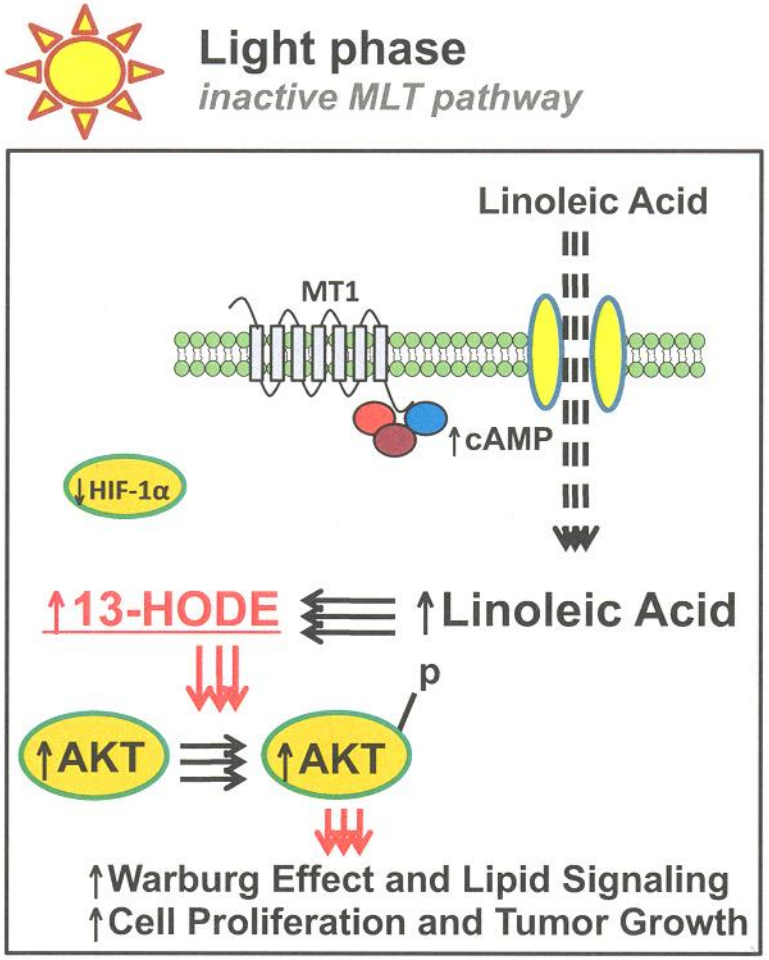
Changes in tumor metabolism as a function of the light:dark cycle

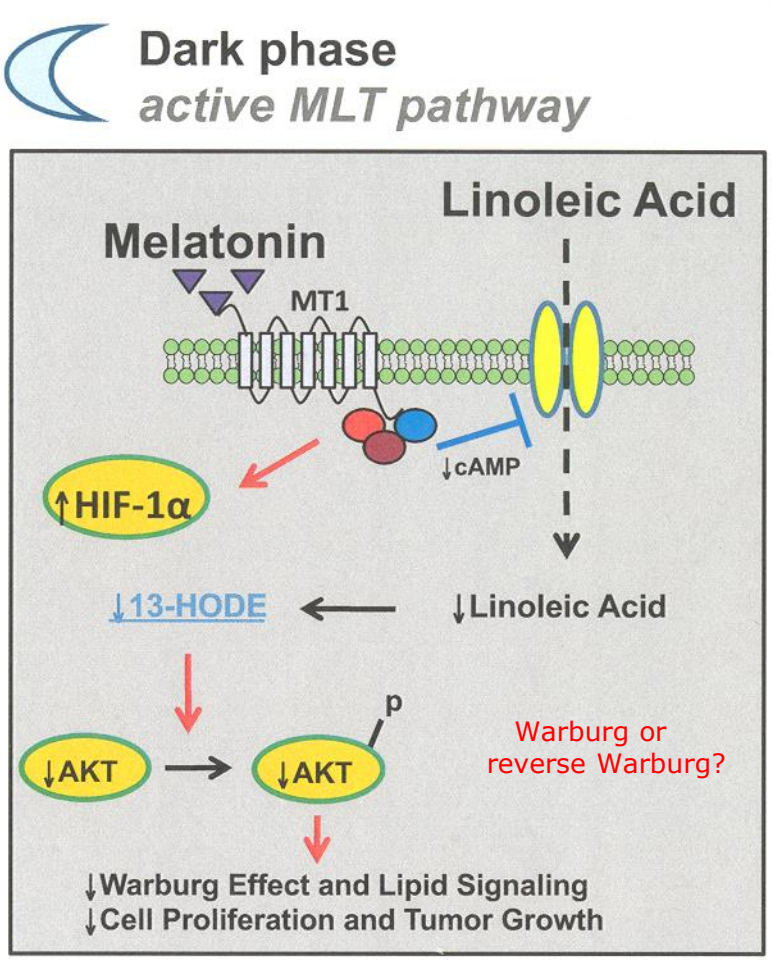
Black line = with melatonin rhythm in L:D cycle

Red line = with melatonin suppression due to LAN

Blask et al, 2013

Provisional scheme of tumor metabolism throughout the light:dark cycle and with LAN





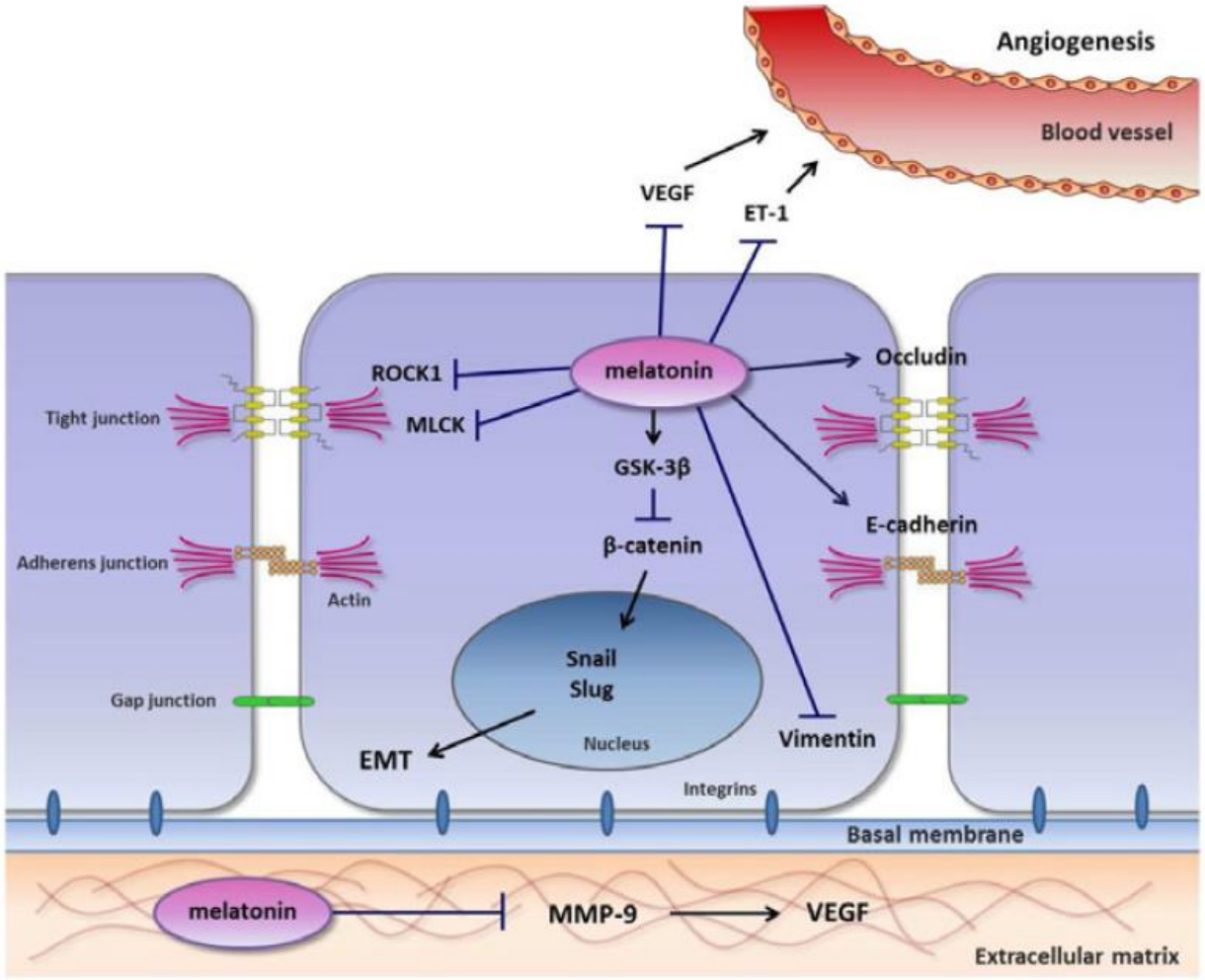
Normally during the light phase or with LAN

Normally during the dark phase

Hill et al, 2013

These actions require only physiological levels of melatonin

Mechanisms by which melatonin reduces cancer metastasis



1. Melatonin upregulates adhesion molecules, occludin, E-cadherin and β1 integrin

2. Melatonin downregulates intermediate filament protein, vimentin

3. Melatonin downregulates major kinases, ROCK1 and MLCK

4. Melatonin activates GSK3β to reduce EMT-associated transcription factors, Snail & Slug

5. Melatonin attenuates expression of pro-angiogenic factors, VEGF and ET-1

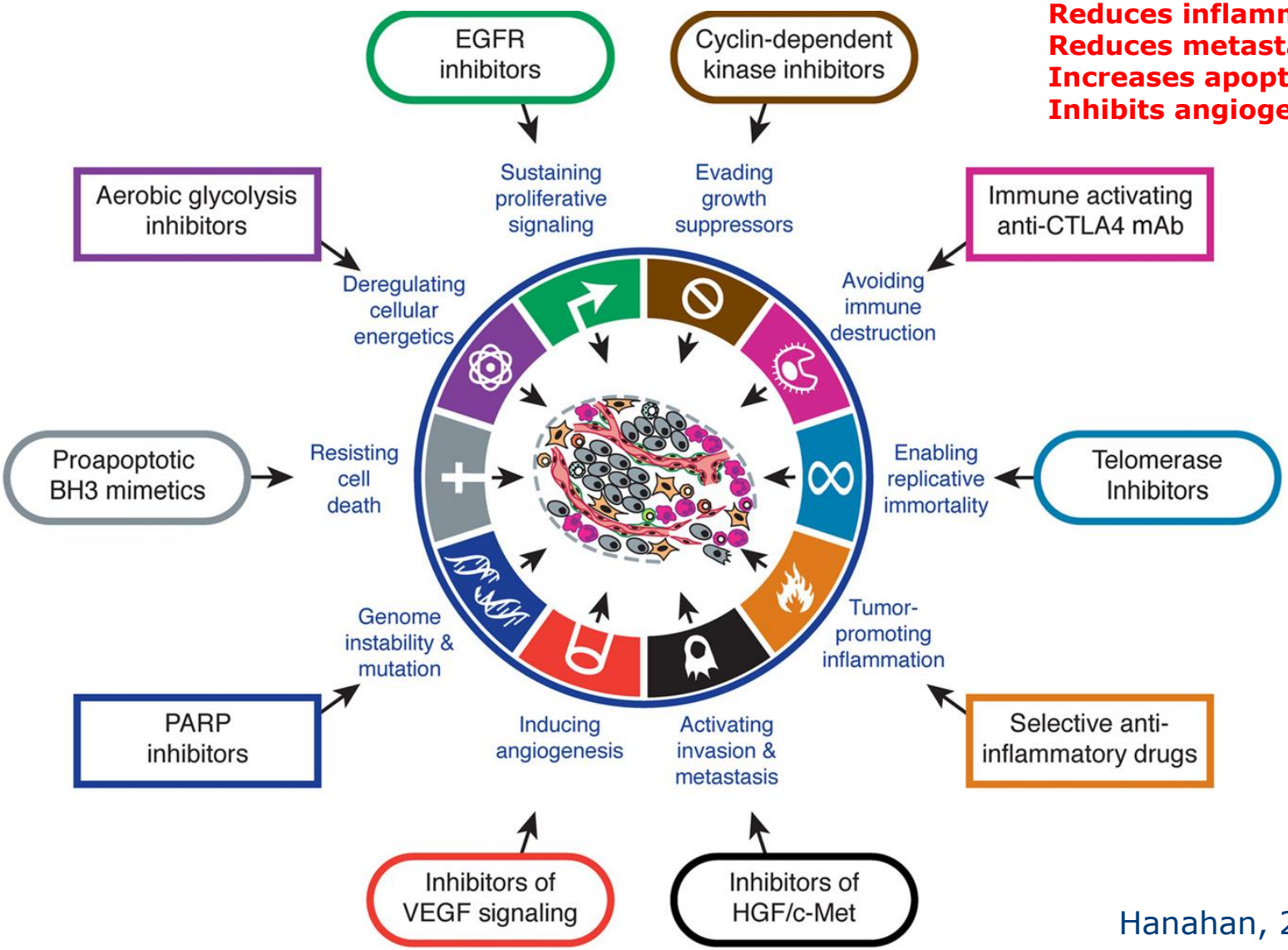
6. Melatonin inhibits MMP-9. reducing ECM breakdown

Su et al, 2017

Melatonin inhibits the hallmarks of cancer cells

Cancer cells control their microenvironment and master their own destiny

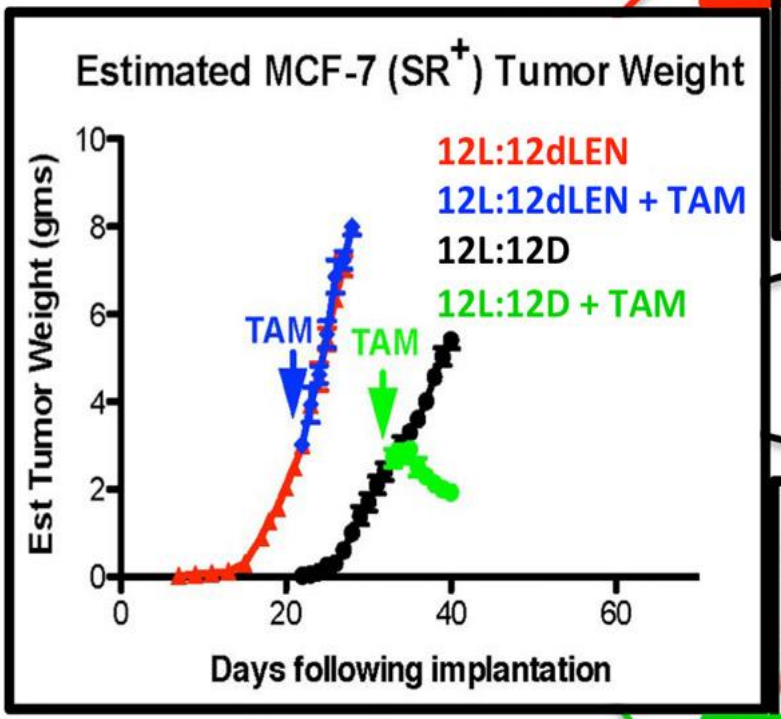
Reduces glucose uptake
Reduces aerobic glycolysis
Reduces cell proliferation
Reduces telomerase activity
Reduces inflammation
Reduces metastasis
Increases apoptosis
Inhibits angiogenesis

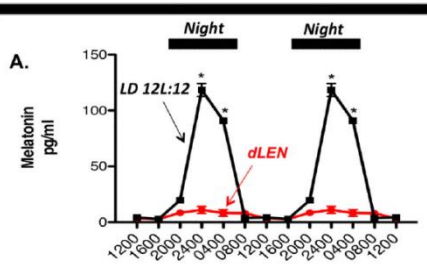


Hanahan, 2011

Melatonin renders treatment resistance cancers sensitive to chemotherapies (tamoxifen)

Study I







dLEN



12L:12D

Day 28



12L:12D + diluent

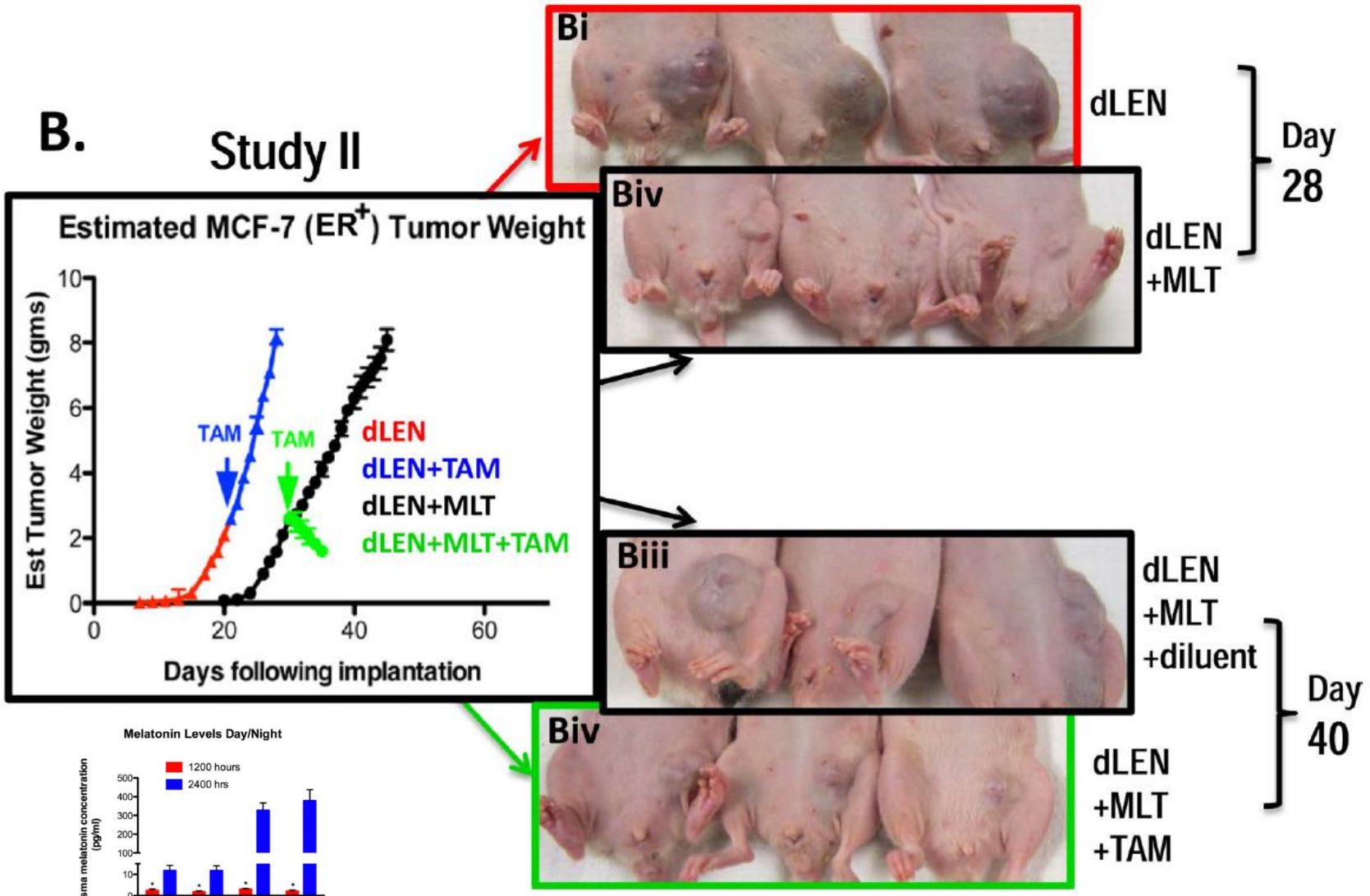


12L:12D + TAM

Day 40

Dauchy et al., 2014

Melatonin renders treatment resistance cancers sensitive to chemotherapies (tamoxifen)



Dauchy et al, 2014

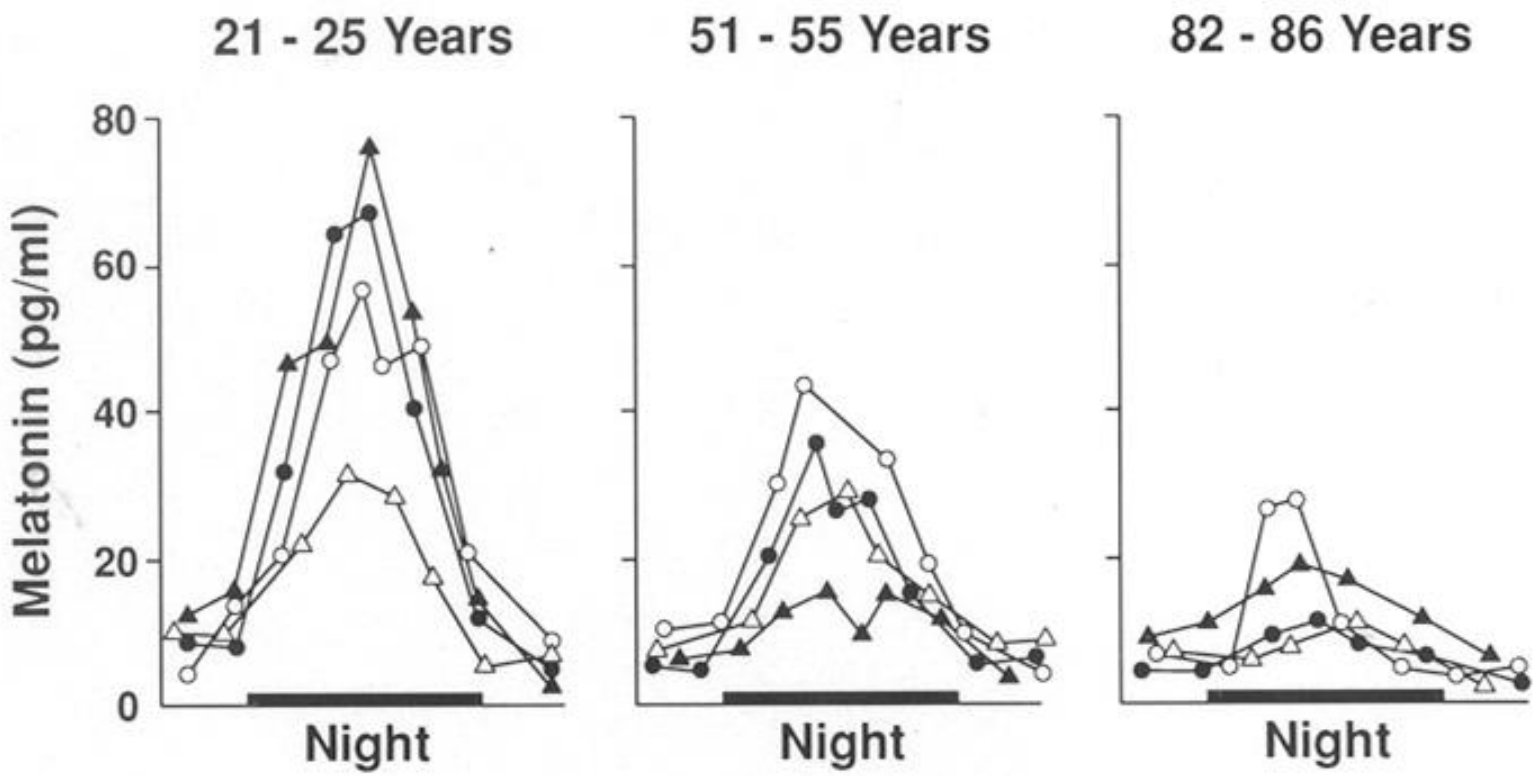
Light pollution worldwide

(This contributes to chronodisruption and melatonin suppression)



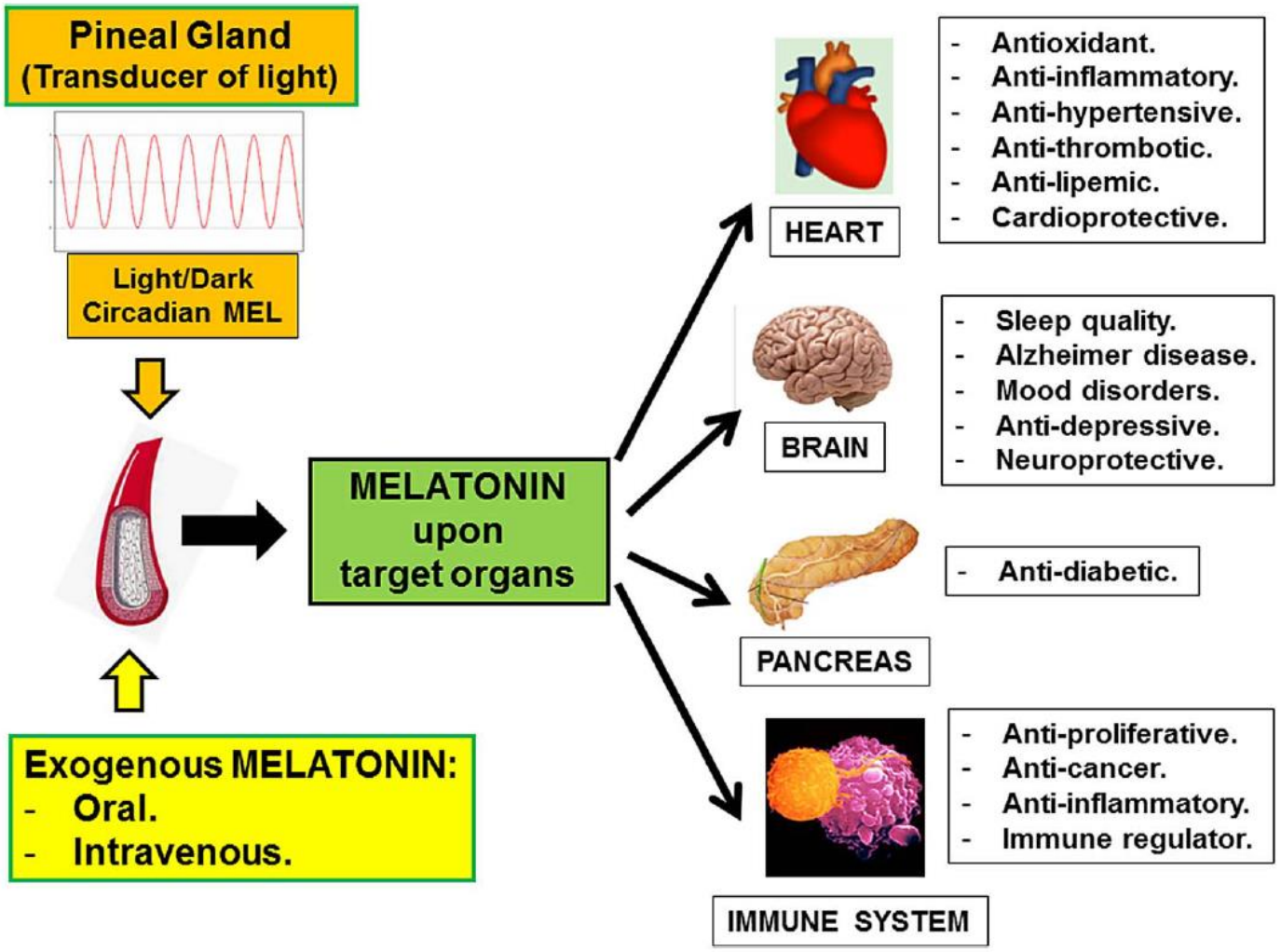
The health consequences may be numerous and grave

Reduction in circulating melatonin during aging



Most cancers occur late in life

Summary of Translational Aspects of Melatonin



Melatonin is also highly beneficial in animals and plants

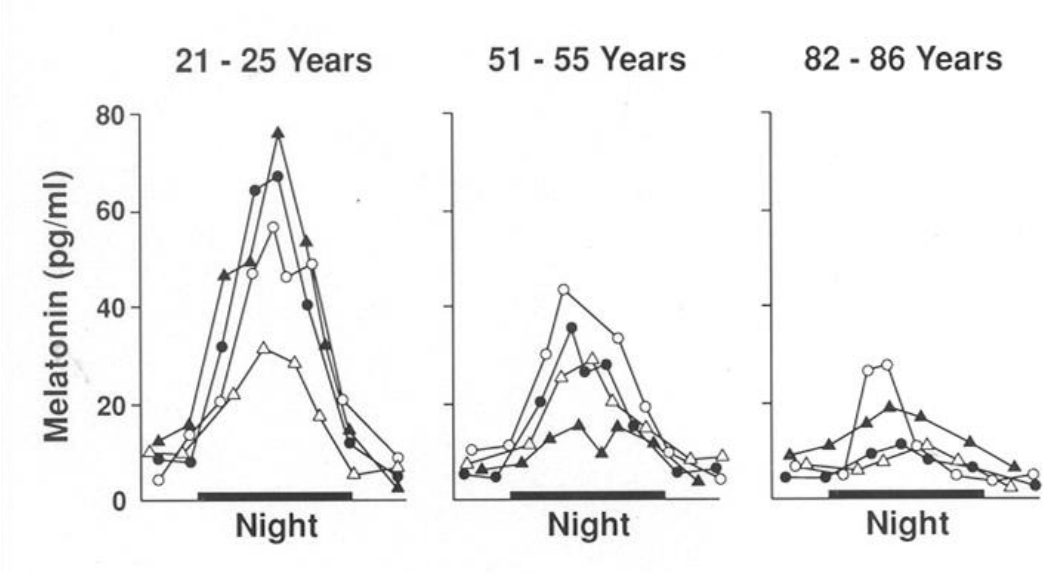
Mitochondrial Free Radical Theory of Aging (MFRTA)



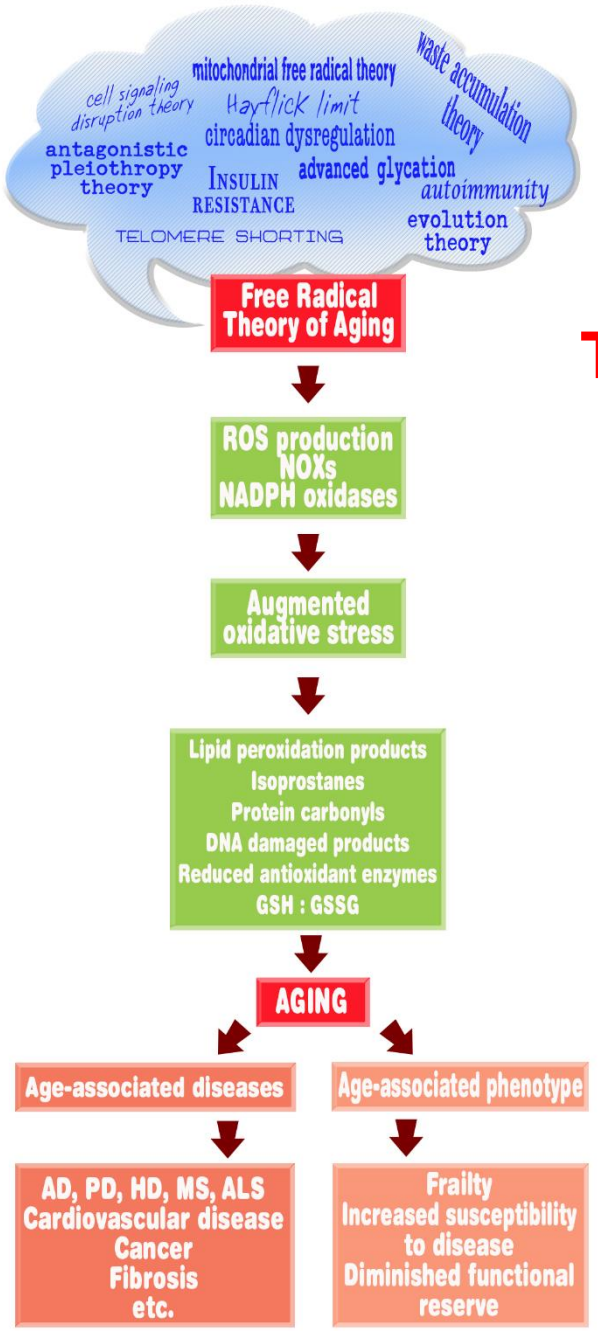
Mitochondrial damage
during aging becomes
a vicious cycle
of functional deterioration

Normal aging is accompanied by

- increased somatic mitochondrial DNA (mtDNA) mutations
- respiratory chain dysfunction (reduced ATP)



Aging is associated with loss of melatonin



Conclusion

The drop in melatonin with age and its suppression by light at night, etc., is likely consequential in aging and age-related diseases

Most theories of aging implicate oxidative stress and mitochondria at the epicenter of age-related pathophysiology

I am Russ Reiter and I approve this message



I have no conflicts of interest

reiter@uthscsa.edu