A4M | MEDICINE REDEFINED

CLINICAL WEIGHT MANAGEMENT

Certification Program

IPS THE PREMIER EDUCATIONAL RESOURCE FOR SAFE & ADVANCED PEPTIDE THERAPY

EDUCATIONALLY PARTNERED WITH A4M

Sleep and the Reprogramming of the Master Clock

By Marisol Duque MD

“No actual or potential conflict of interest in relation to this program/presentation”.

- Understanding the Circadian Rhythm
- Circadian Desynchrony
- The importance of a good sleep cycle
- Circadian Rhythm Synchronization

Circadian Rhythm

Is a biological process that regulates various physiological and behavioral processes in living organisms, including humans.

It is an internal biological clock that operates on a 24-hour cycle and is influenced by external cues such as light and temperature

Circadian Rhythm

Circadian rhythms allow us to anticipate regular environmental changes that happen every single day as a consequence of the earth rotating about its axis, our body knows is 8:45am

Behavior Biology Align to the 24-hour solar day in every living organisms

Circadian Rhythm

EVERY CELL IN OUR BODY IS DESIGN TO BE IN SYNCRONY WITH OTHER CELLS, AND THEN IN SYNCRONY WITH OUR PLANET

Circadian rhythms influence our lives and health

Behavior

Sleep cycle

Appetite

Cognitive performance

Physiology

Metabolism

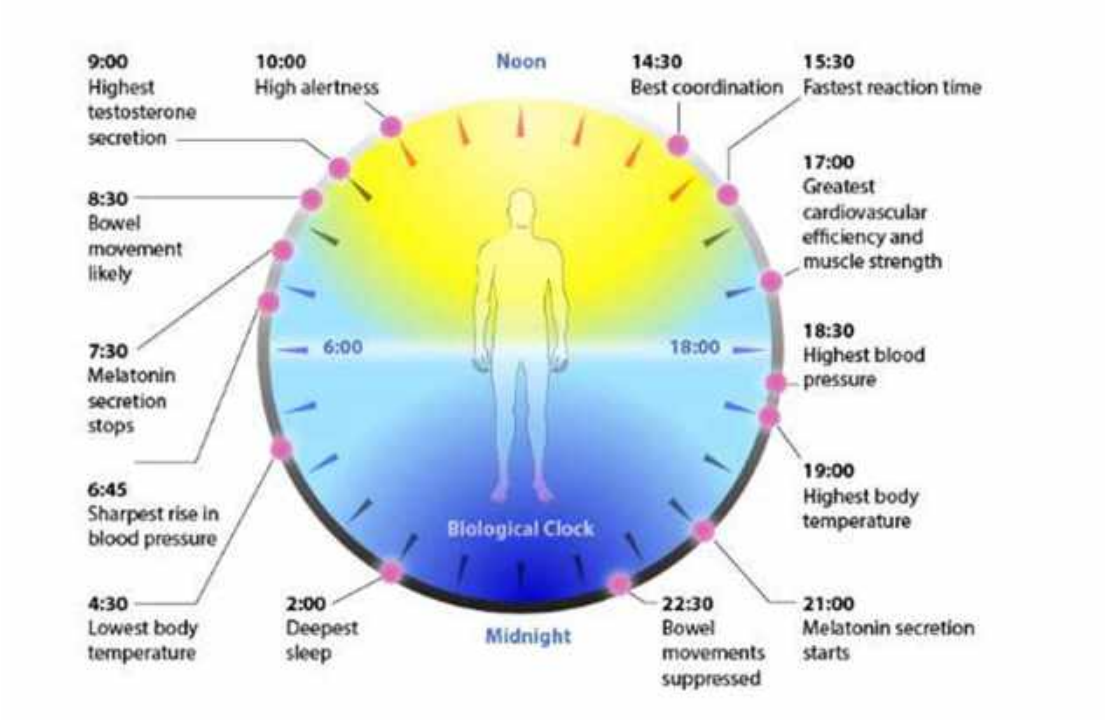
Hormone production

Cardiovascular function

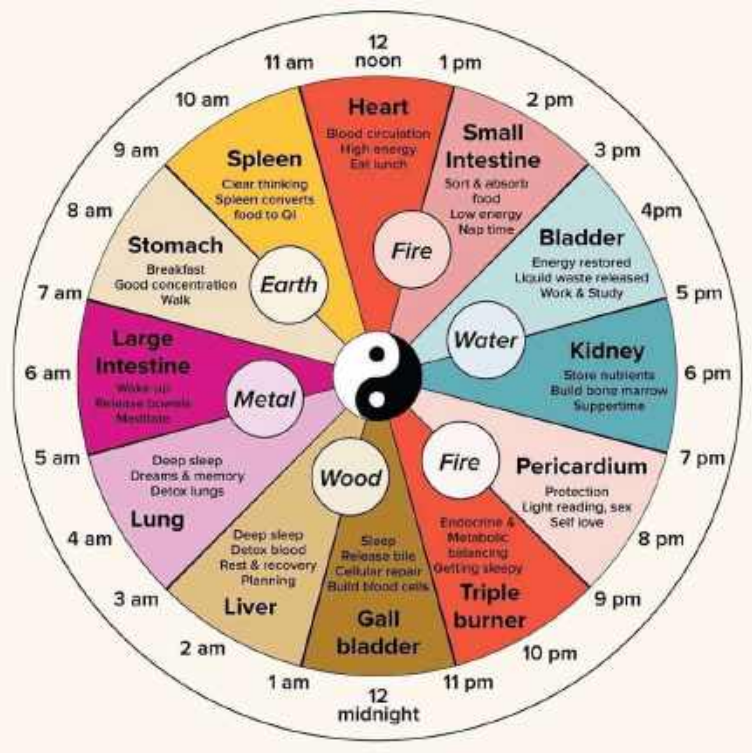
Cell Division

The circadian clock

Our Circadian Clock dictates the best time for everything we do

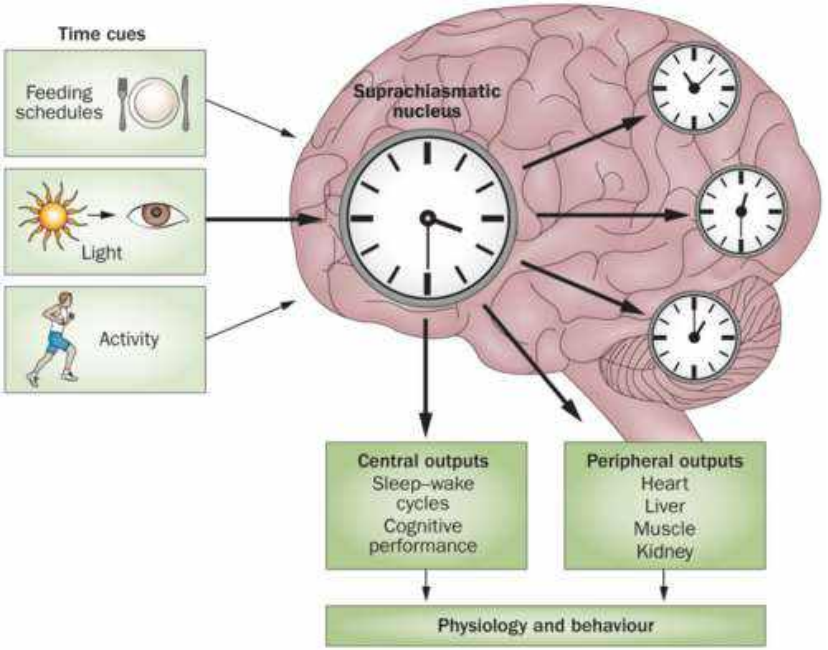


Circadian Clock in Chinese medicine



Biological Clock in humans

- Our biological clock is situated in the suprachiasmatic nucleus, and what's keeping it in check is primarily light dark cycles
- Feeding times, activity times
- This clock is design to have a proper hour for everything that happens in our body
- Synchronizes the other clocks that we have in our body

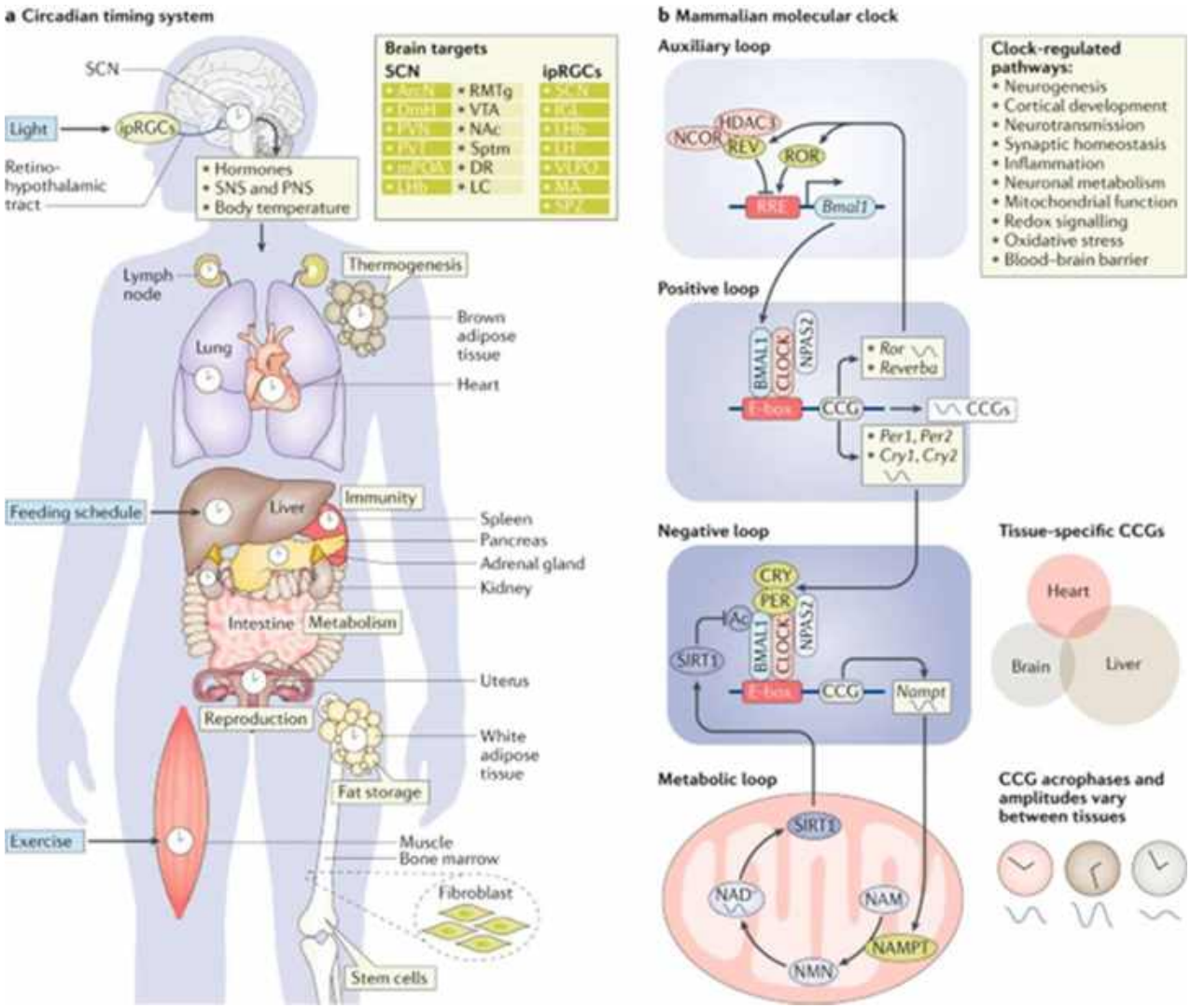


Circadian Rhythm and Genes

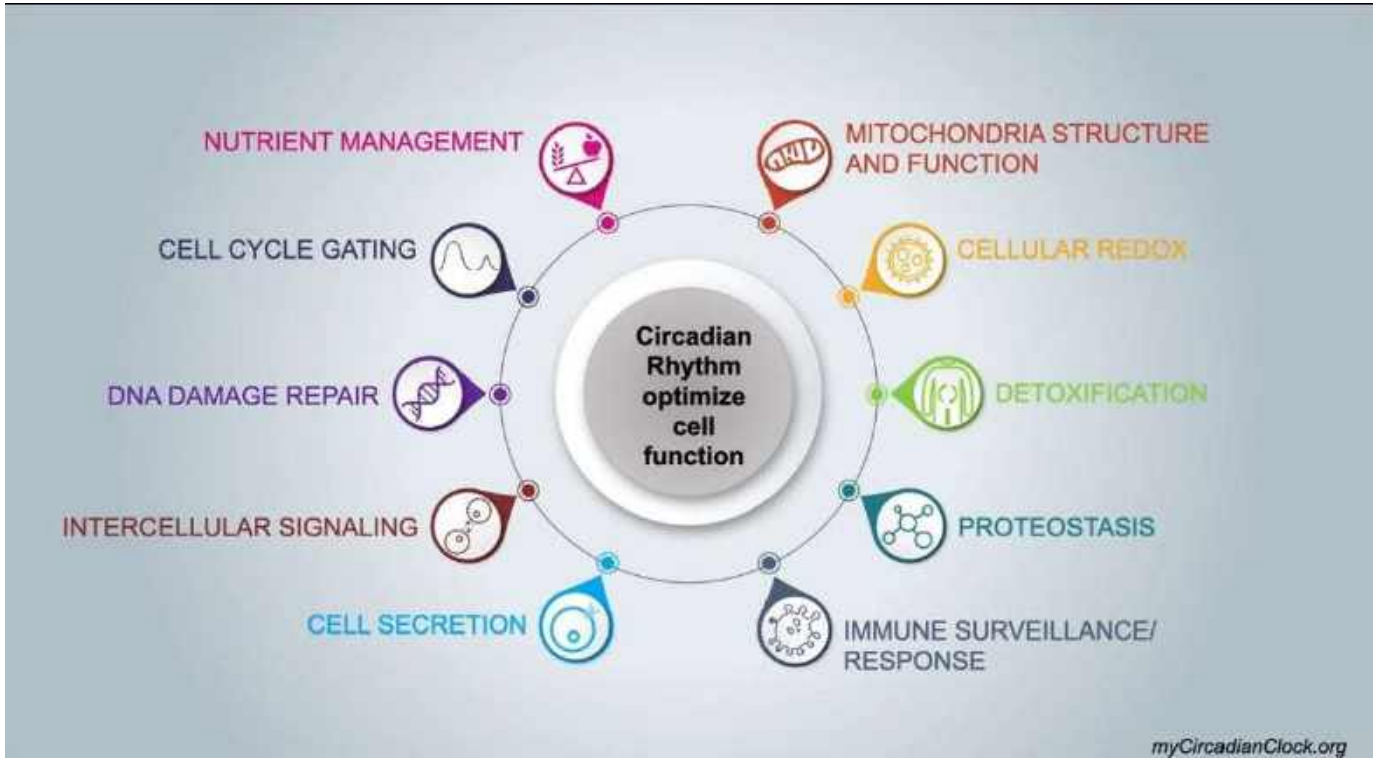
- Clocks in cells are run by genes, the proteins CLOCK and BMAL1 act as activators, and members of the periods (PER) and cryptochrome (CRY) families are repressors
- Receptors in the retina receive light cues, which are carried through the hypothalamic optic tract and transmitted to the SCN, resulting in its SYNCHRONIZATION
- Clocks in organs and tissues (peripheral clocks) can be changed by feeding rhythms, exercise, social activity, temperature, humidity

Circadian Rhythm in medicine

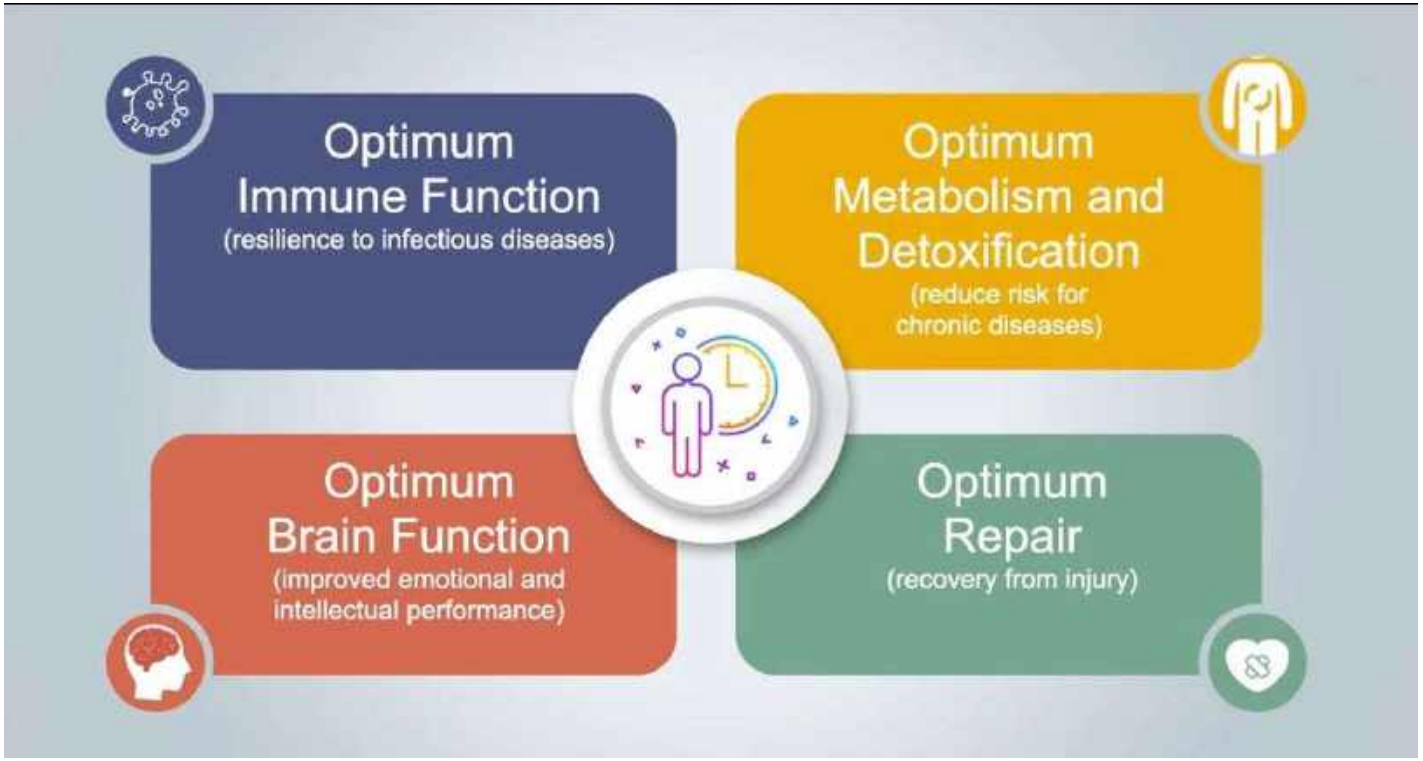
Circadian rhythms are near-24-hour oscillations found in essentially every physiological process in the human brain and body . The suprachiasmatic nucleus (SCN) in the hypothalamus serves as the master pacemaker that sets the timing of rhythms by regulating neuronal activity, body temperature and hormonal signals. The circadian timing system synchronizes clocks across the entire body to adapt and optimize physiology to changes in our environment.



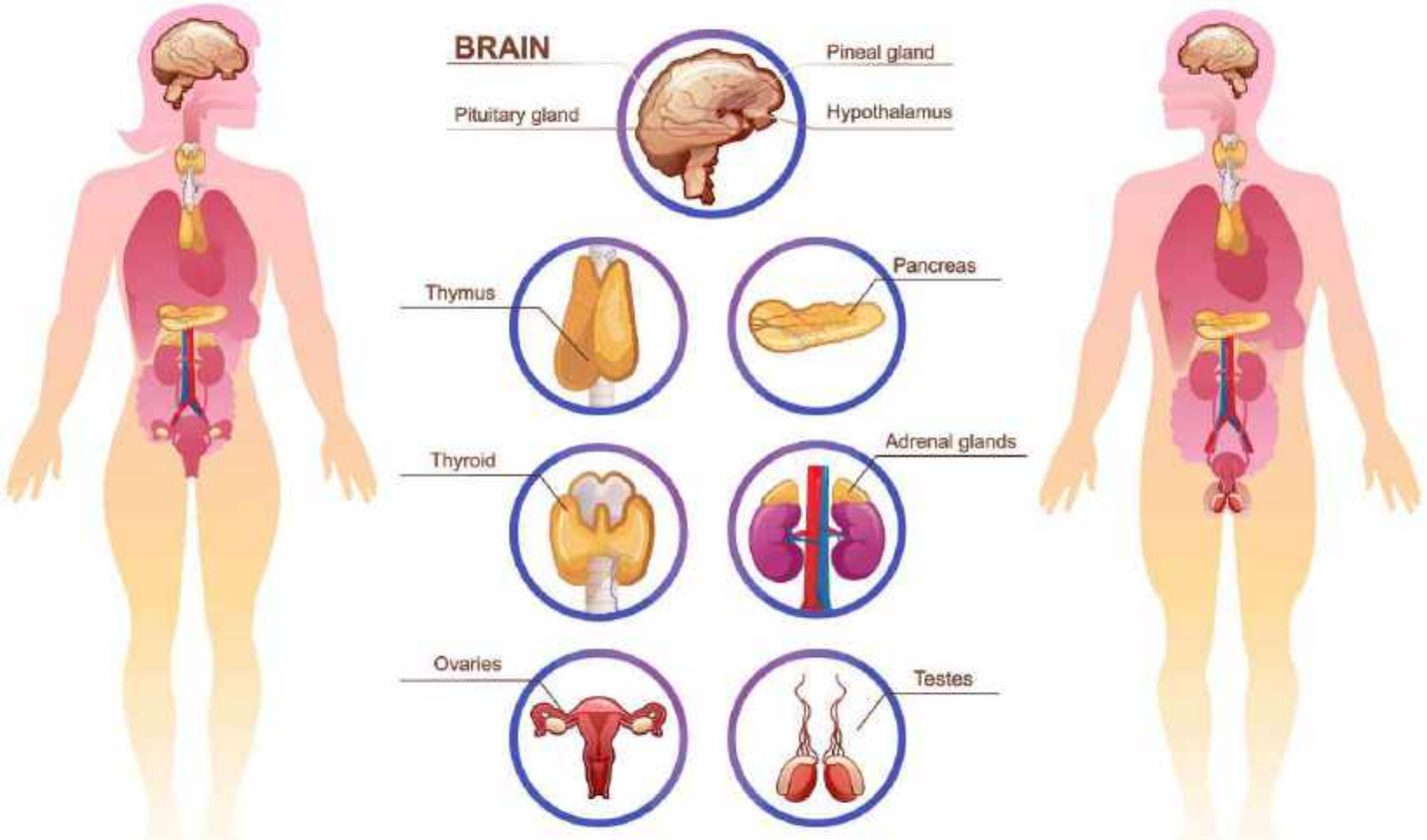
Circadian Rhythm Optimize Cell Function



Circadian Rhythm Optimize Cell Function

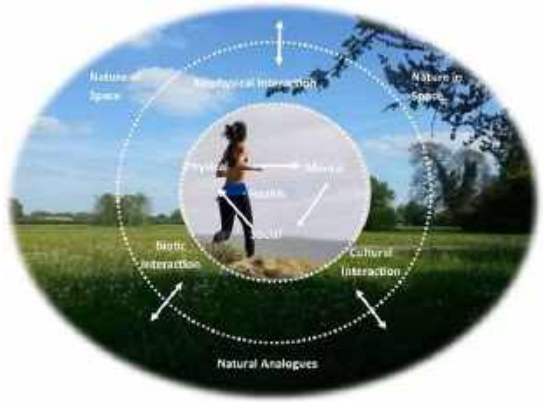


ENDOCRINE SYSTEM



Circadian Rhythm and synchrony with nature

- Disharmony and disturbance with the circadian clock will lead us to disease
- Lifestyle, shift work at night, sleep cycle, food habits
- Mutation in circadian genes
- Metabolic obesity, cardiovascular disease, phycological behavioral



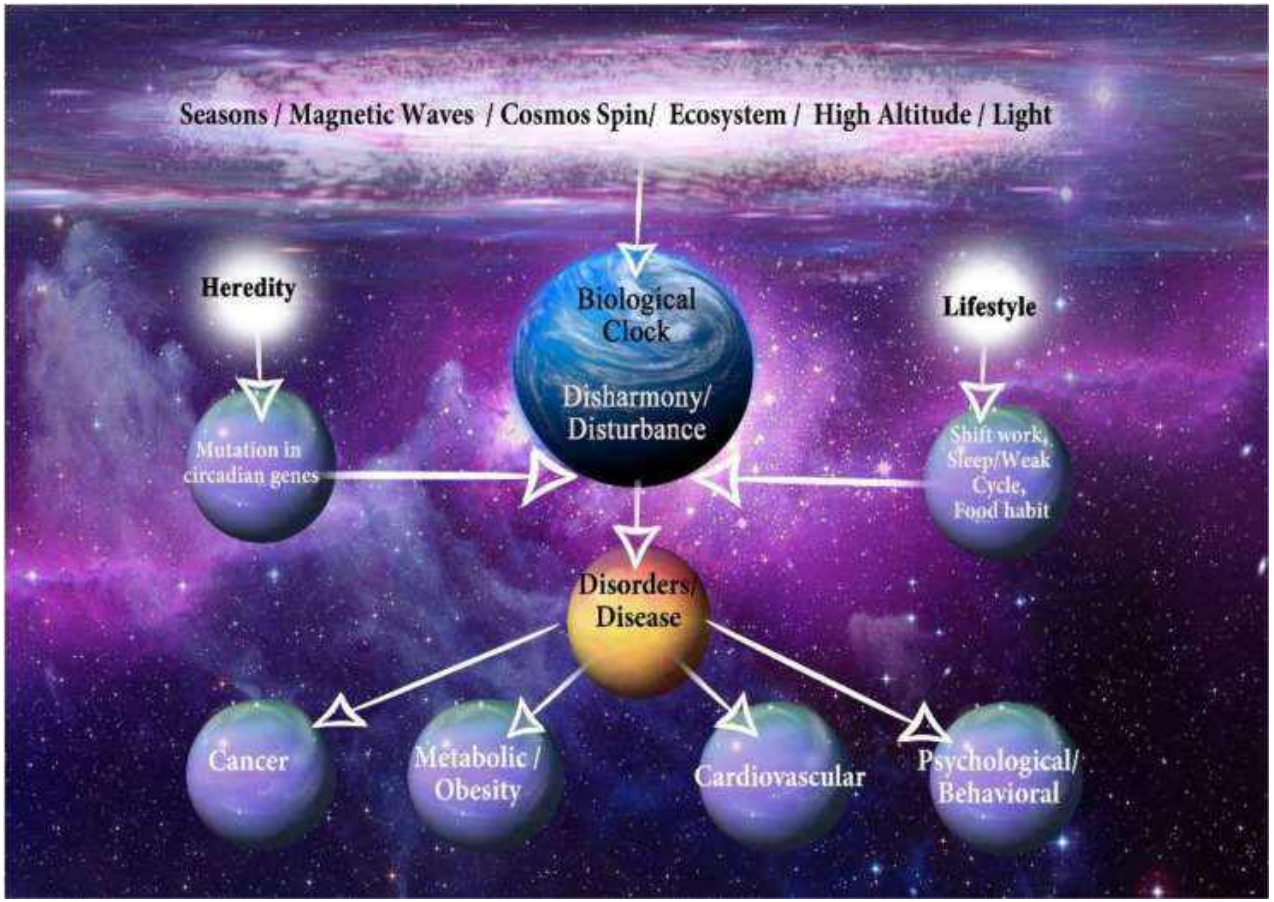
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632990/

Why can’t we live a long healthy life?

Collective diseases that we have

- High blood pressure (50% of all adults)
- Prediabetes or diabetes (50 % of all adults)
- Liver disease (30% metabolic disease)
- Cancer (40% in their lifetime)
- Depression or anxiety (50% of adults)
- Digestive issues (50% of adults)
- Injuries (by age 60 , 50%)

Circadian Desynchrony

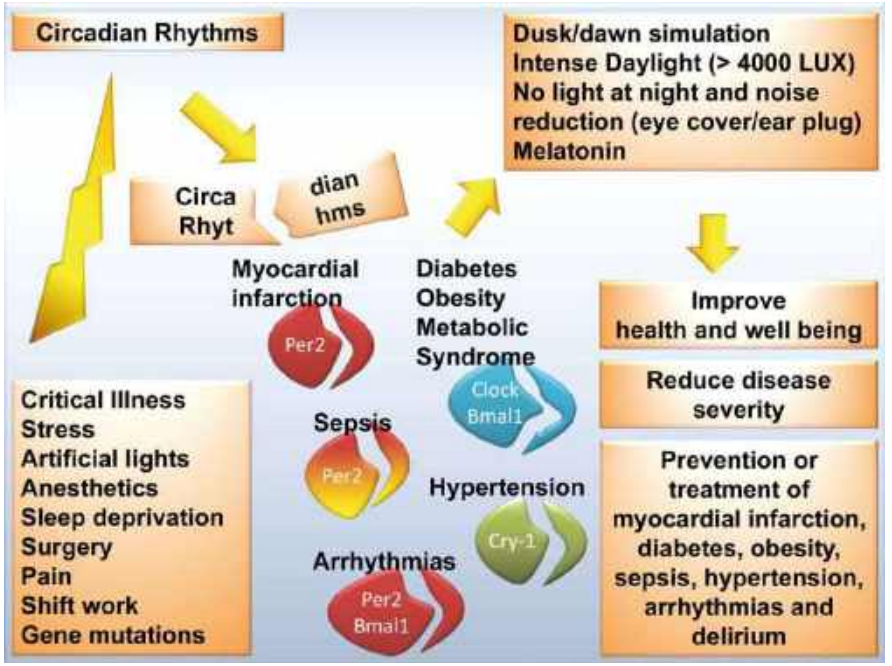


Circadian Desynchrony

- CNS: depression
- Pancreas: Hyperinsulinemia, insulin resistance
- Muscle: Sarcopenia
- Adrenals: Chronic Fatigue
- Hematopoietic: Autoimmunity
- Vasculature: thromboembolic events
- Intestine: Dysbiosis
- Adipose: obesity
- Liver: dyslipidemia

Disruption of the circadian Rhythms

- When the circadian rhythms gets broken, dysregulation of the circadian genes PER,CRY,BMAL1
- Our epigenome starts changing
- The health of our organs, and whether we will develop a particular illness or something else, depends on which genes we have and how they are expressed

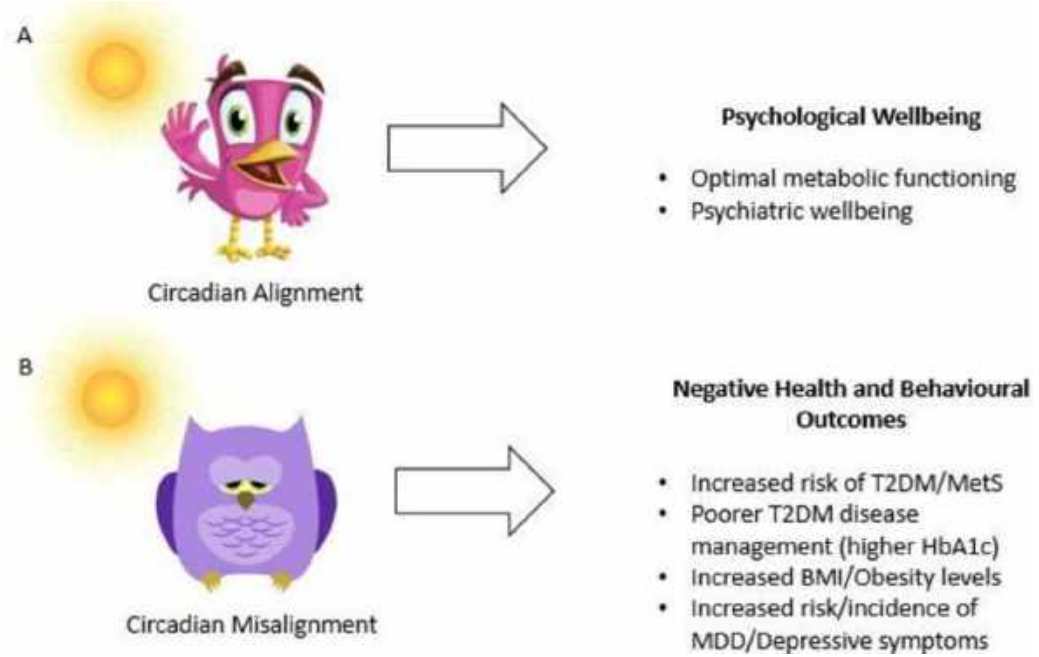


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632990/

Circadian Rhythm

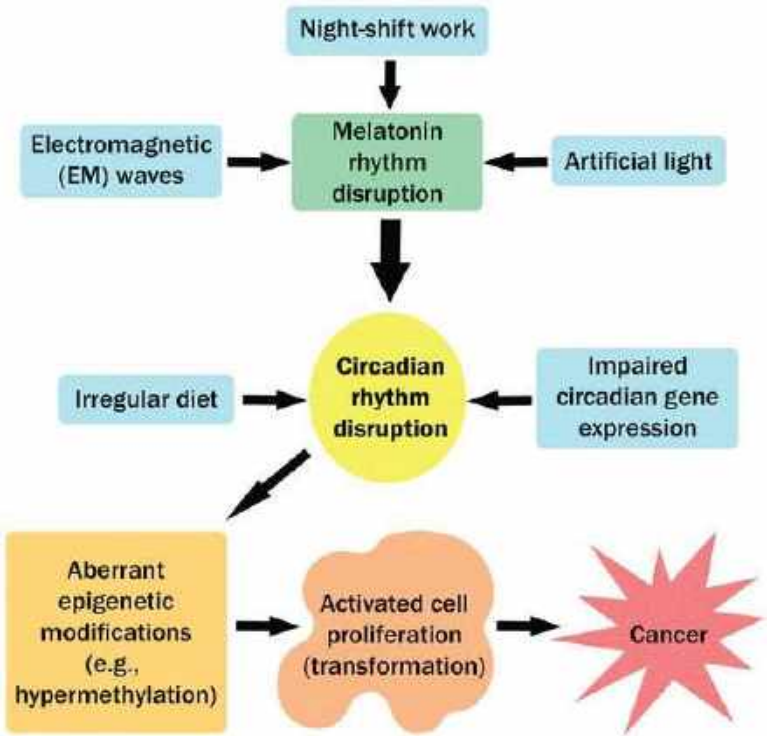
Circadian alignment: brain and all of the peripheral clocks are in alignment, system is working well

circadian misalignment will lead to negative health and behavioral outcomes



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632990/

Circadian Rhythms and cancer



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632990/

Sleep

SLEEP IS NOT ONLY THE ART OF CLOSING THE EYES AND THINK THAT WE ARE RESTING, BUT UNDERSTANDING THE BEAUTIFUL BIOLOGY THAT HAPPENS IN IT

What happens when we sleep

Sleep

- Most individuals should obtain at least 7-8 hours of quality sleep a night
  (Centers for Disease Control, CDC, 2011).
  Centers for Disease Control (CDC). www.cdc.gov.
- 67% of Americans experience frequent problems sleeping
- 43% say lack of sleep interferes with their daily activities.
- Between 9-12% of the population are clinically diagnosed with insomnia

Insomnia or disrupted sleep

- Disruption of the circadian rhythm
- Alters Growth Hormone release
- Increases TNF alpha, IL-6
- Increases insulin resistance
- Contributes to weight gain
- Alters Digestive health

Sleep support

Melatonin (sleep regulator)

- natural hormone supports sleep cycles
- Antioxidant
- decreases w/ age
- Used for sleep problems
- 3-20mg 1 hr before bedtime
- Watch for paradoxical effects

Melatonin Depleted by

- Beta-blockers
- Calcium channel blockers
- Benzodiazepines
- Estrogen-containing medications
- Hydralazine
- Loop diuretics
- Theophylline
- Antidepressants, including SSRI (Selective serotonin reuptake inhibitors)
- NSAIDs (Non-steroidal anti-inflammatory drugs)

Melatonin and Pancreas

Review > Diabetologia. 2009 Jul;52(7):1240-9. doi: 10.1007/s00125-009-1359-y.
Epub 2009 Apr 18.

Melatonin receptors in pancreatic islets: good morning to a novel type 2 diabetes gene

H Mulder [1], C L F Nagorny, V Lyssenko, L Groop

Affiliations + expand

PMID: 19377888 DOI: 10.1007/s00125-009-1359-y

Abstract

Melatonin is a circulating hormone that is primarily released from the pineal gland. It is best known as a regulator of seasonal and circadian rhythms; its levels are high during the night and low during the

Sleep Support

GLYCINE

Stress Reduction:

1. Glycine has been suggested to have an anxiolytic (anti-anxiety) effect, potentially reducing stress and promoting a calm state conducive to sleep.
2. By modulating neurotransmitter activity, glycine may help individuals unwind and relax before bedtime, leading to improved sleep outcomes.

Sleep Disorders:

- Glycine supplementation has shown promise in certain sleep disorders. For example, studies have explored its potential benefits in individuals with insomnia, sleep apnea, and restless leg syndrome.

Sleep Support

Magnesium citrate:

- Improved insulin sensitivity
- Enhanced metabolism
- Regulation of blood sugar levels
- Reduced stress and anxiety
- Improved sleep quality

Nutrients. 2021 Feb; 13(2): 320.
Published online 2021 Jan 22. doi: 10.3390/nu13020320
PMCID: PMC7912442
PMID: 33499378

Magnesium in Obesity, Metabolic Syndrome, and Type 2 Diabetes

Gabriele Piuri,[1,†] Monica Zocchi,[1,†] Matteo Della Porta,[1] Valentina Ficara,[1] Michele Manoni,[2] Gian Vincenzo Zuccotti,[1,3] Luciano Pinotti,[2] Jeanette A. Maier,[1] and Roberta Cazzola[1,*]

Mario Barbagallo, Academic Editor

Sleep habits

Circadian Rhythm Synchronization

Intermittent fasting

- Stimulates growth hormone Improved cognition
- Decreased neurodegeneration
- Stimulates brain derived neurotrophic factor (BDNF)
- Weight loss
- Improved blood pressure
- Cancer protective
- Improved insulin sensitivity
- Increased PGC1 alpha
- Decreased inflammation
- Reduces oxidative stress
- Rids body of excess fluid
- Improves adaptive responses

Circadian Rhythm Synchronization

- 3 week alternate - day fasting
  - Improved fat oxidation
  - Improved weight loss
  - Improved insulin sensitivity
  - Improved HDL
  - Triglycerides decreased
  - Improved adiponectin (37%)

NUTRITION

QUALITY

FOOD SYNCHRONISES OUR LIVER WITH THE OUTSIDE WORLD

QUANTITY

TIME (TRE window)

8 habits for Circadian Rhythm Synchronization

1. Time sleeping
   8 hours

2. Avoid eating, at least for 1 hr after waking up (only water)

3. Intermittent fasting or TRE
   8 hr TRE
   10 hr TRE
   11 hr TRE
   12 hr TRE

4. GO OUTDOORS
   >30 min of daylight

5. DAILY EXERCISE
   > 30 min of activity preferably in the afternoon

6. 2-3 H BEFORE BEDTIME
   No bright light
   No calories

7. Meditate
   15 min AM
   15 min PM

8. CONSISTENCY

ECM and Homotoxicology

Homotoxicology is the study of the influence of homotoxins on the human organism.

Represents a unique synthesis of healing disciplines designed to strengthen the organs of detoxification and secretion to remove the toxins accumulated in the extracellular matrix, to stimulate and modulate the immune system.

Extracellular Matrix and Homotoxicology

- According to Reckeweg, homotoxins are divided in two groups :

1. Exogenous homotoxins

substances that originate outside the body, in the environment and have a direct toxic effect on tissues, organs or regulation mechanisms.

2. Endogenous homotoxins

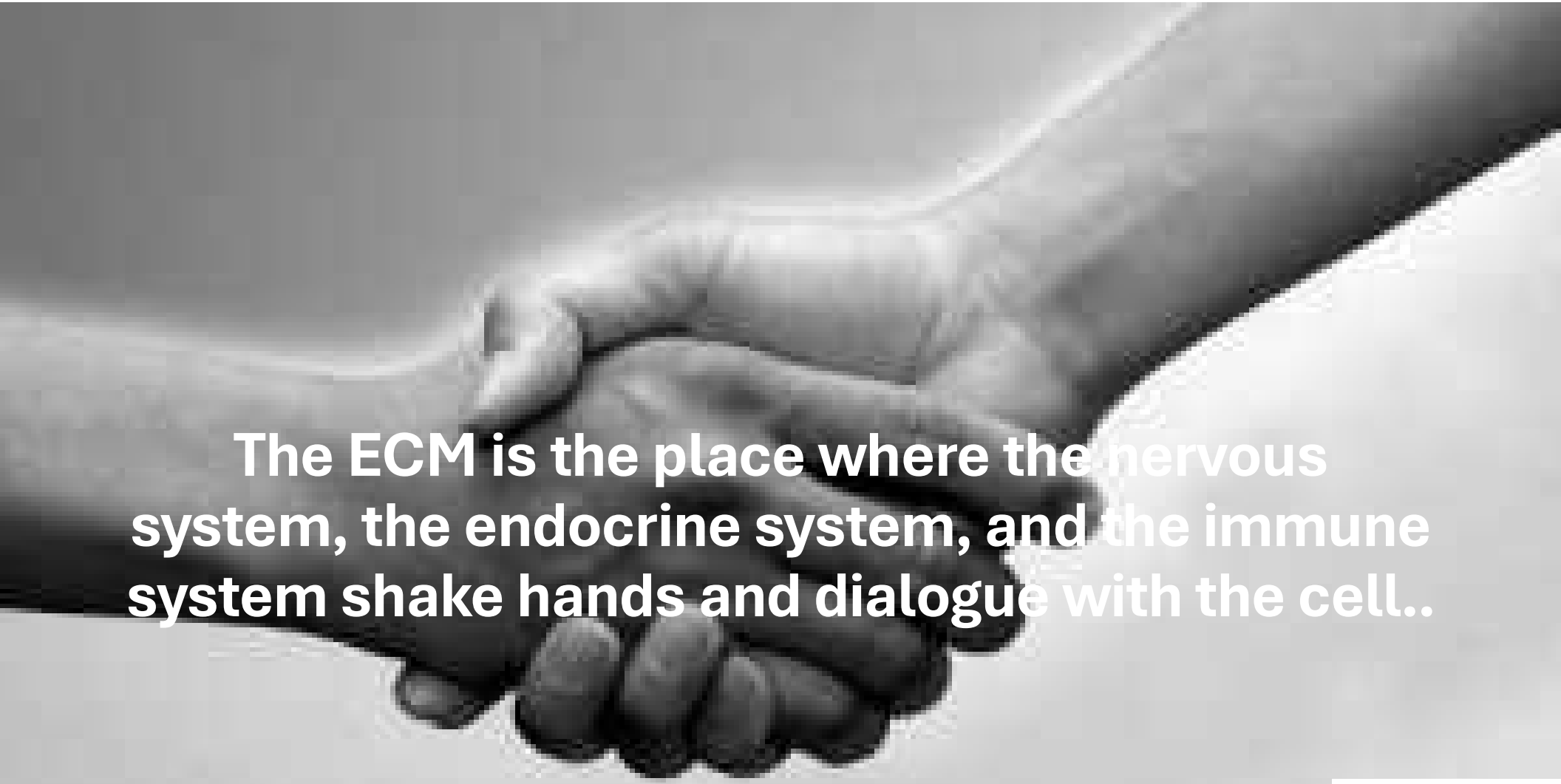
Substances created by the body itself. These are mostly metabolic intermediary or end products such as acids and free radicals.

Extracellular Matrix

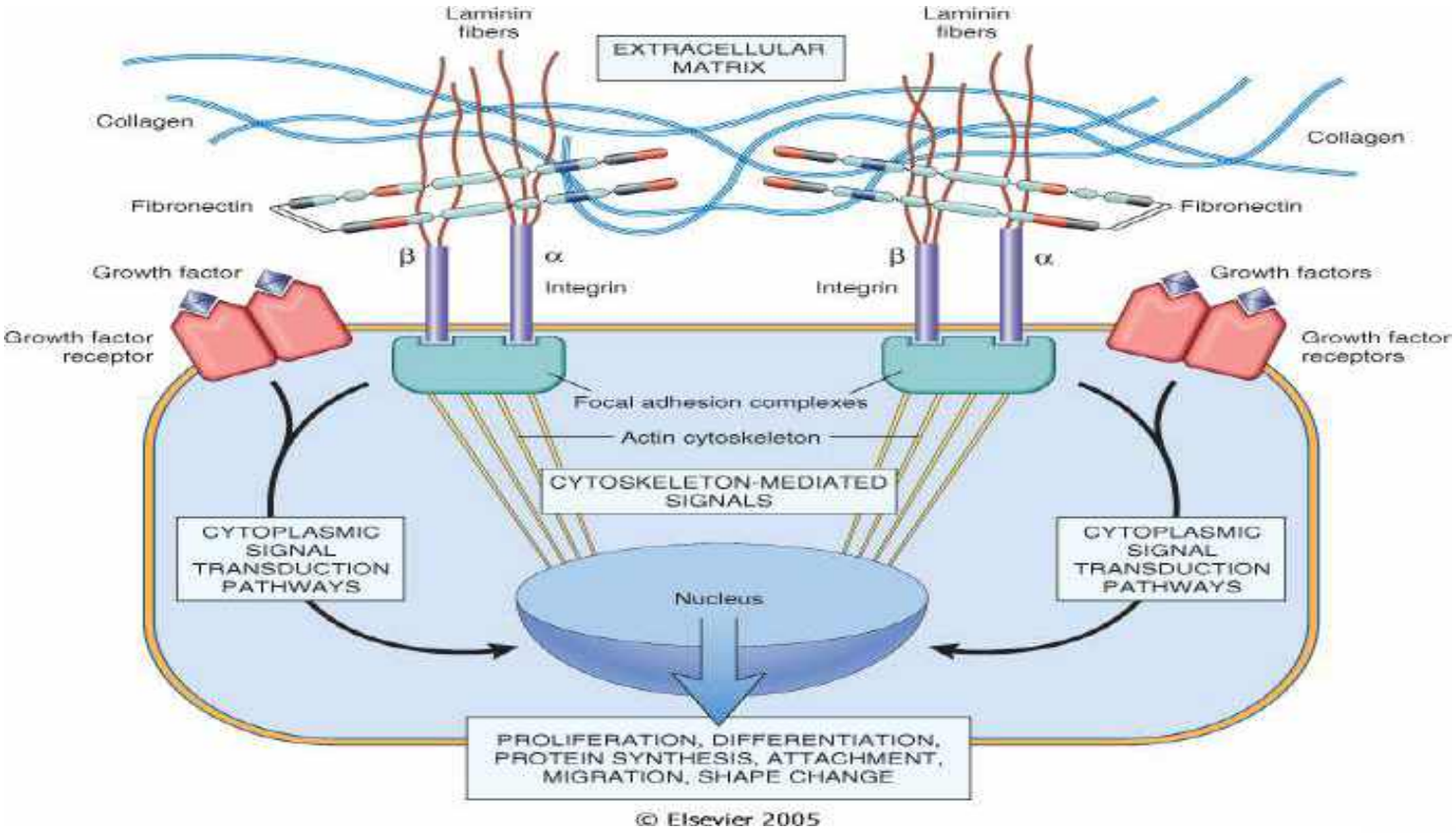
- The extracellular matrix is a supportive network comprised of connective tissue, collagen fibers, water, lymphatic vessels, and all the tributaries in the lymphatic system that creates the environment between and around cells.
- It is not just for the physical support of the cells, but also is integral to the function and behavior of the cells in many different ways.
- It controls the life cycle of the cells.
- Modulates and influences how growth factors are utilized; 15 - 20 growth factors are regulated in the ECM such as glycoproteins.

Extra Cellular Matrix

- The ECM is a three-dimensional network that contains all the organs, tissues, and cells of the body, playing a fundamental role in protection, nutrition and cell innervation; it is the substrate where the response of the immune system takes place, angiogenesis, fibrosis, and tissue regeneration occur.
- Receives Innervation from the free endings of the ANS fibers, which behave as a ***synapse*** with the cells of the matrix and parenchyma.
- The alteration of the ECM will lead to a loss of its function, affecting a correct immune response to infectious, tumor and toxic agents.



Naranjo A.T, Noguera-Salvá R, Fariñas Guerrero. ***Extracellular matrix: morphology, function and*** **biotensegrity** F*Rev Esp Patol 2009; Vol 42, n.º 4: 249-261*


Laminin fibers
EXTRACELLULAR MATRIX
Laminin fibers
Collagen
Collagen
Fibronectin
Fibronectin
β
α
Integrin
β
α
Integrin
Growth factor
Growth factors
Growth factor receptor
Growth factor receptors
Focal adhesion complexes
Actin cytoskeleton
CYTOSKELETON-MEDIATED SIGNALS
CYTOPLASMIC SIGNAL TRANSDUCTION PATHWAYS
CYTOPLASMIC SIGNAL TRANSDUCTION PATHWAYS
Nucleus
PROLIFERATION, DIFFERENTIATION, PROTEIN SYNTHESIS, ATTACHMENT, MIGRATION, SHAPE CHANGE
© Elsevier 2005

Definition of Neural therapy

- Injections of local anesthetic in low concentrations in specific points of the nervous system with therapeutic and diagnostic purposes

- Specific points based on the patient's clinical history

- The main objective is to eliminate irritations of the nervous system, primarily of the autonomic nervous system to restore its regulatory function.

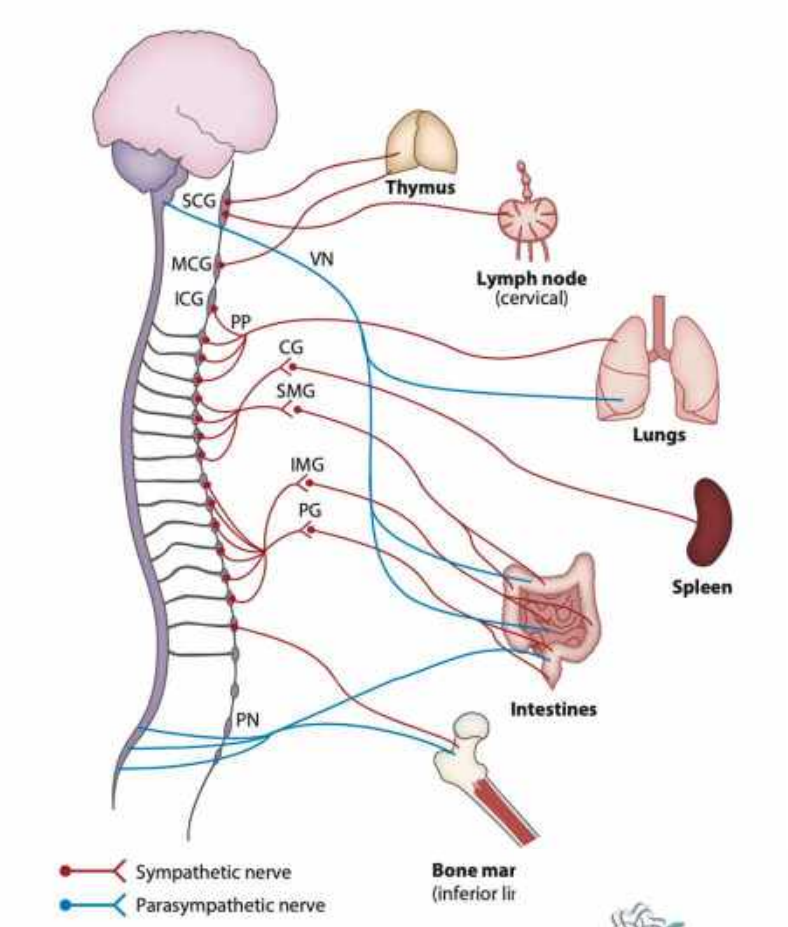
(Dosch, 1986; Huneke, 1989; Barop, 2018; Fischer, 2019, Payán, 2016)

Our body communicates through electricity, Neural therapy is a way to make sure the correct energy is going to all the correct places in your body, the nerves in our bodies ultimately control everything from blood flow, to muscle movement to all aspects of digestion and healing.

Neural Therapy Is not based on the treatment of nerves, but rather based on the premise that illness may result from a nervous system that has become unregulated or temporarily damage

ANS

Homeostasis is carried out by balancing the sympathetic and parasympathetic branches, working as a functional unit and regulating vital functions such as the vascular function, the respiratory, cardiac, digestive, hormonal, metabolism, reproduction, body temperature, glandular secretion, among others.



(Jänig W. Auton Neurosci. 2014;182:1–3)

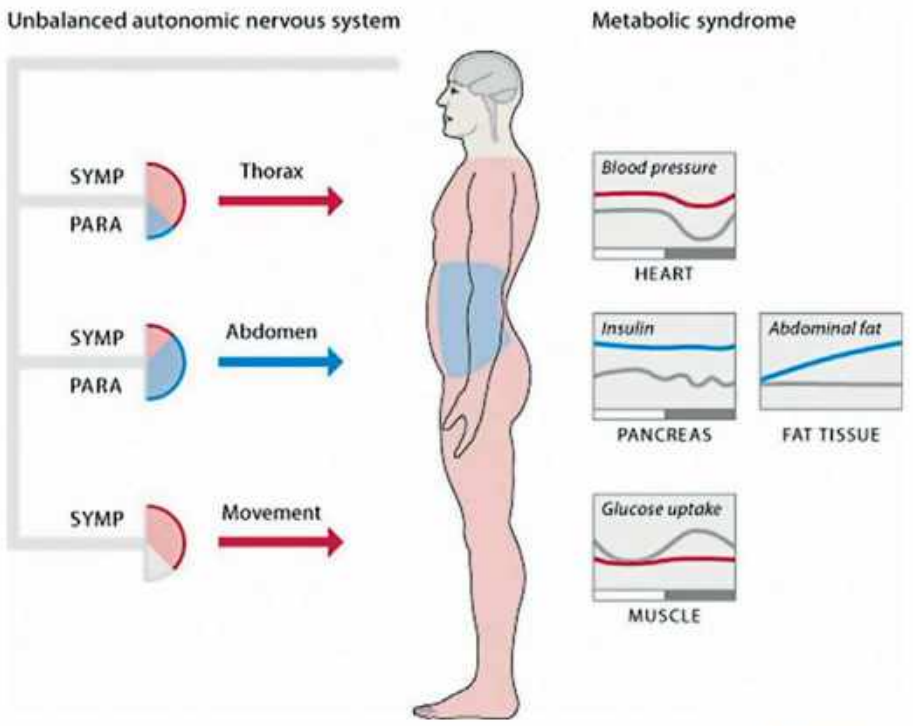
Model of the Metabolic Syndrome caused by desynchronization

The disturbed output resulting from lifestyle changes and excessive food intake affects the balance of the **ANS**.

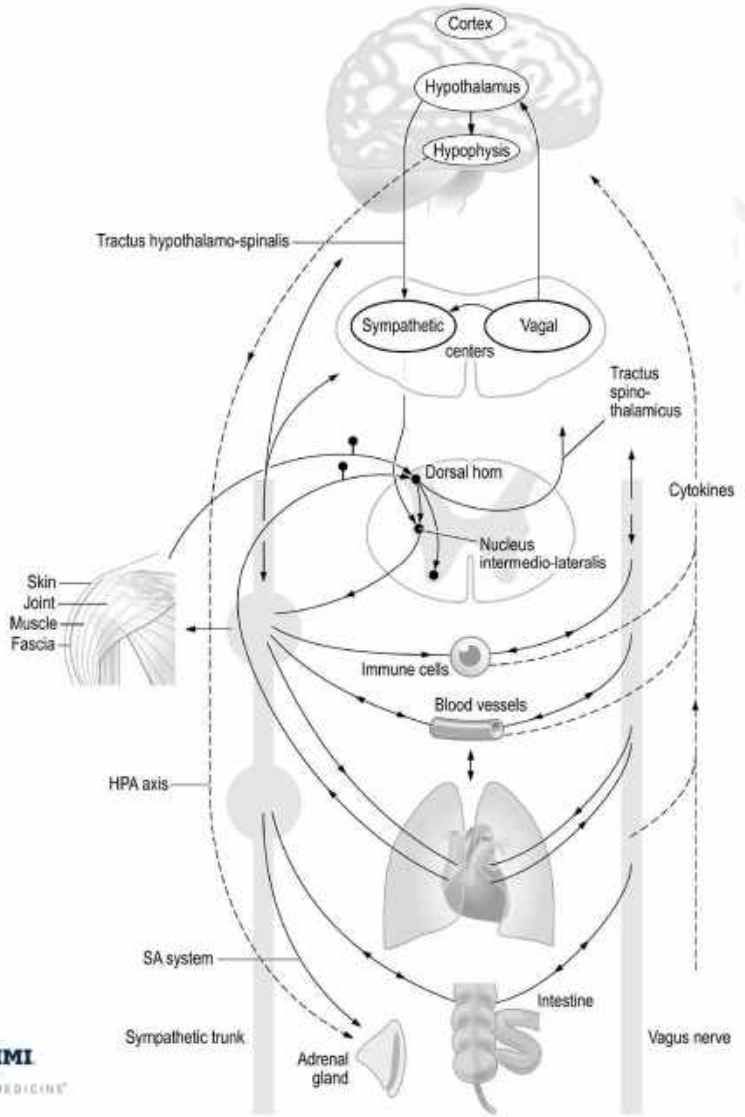
In intra-abdominal compartment, prevails the **PS** branch (**blue**), increasing insulin secretion and growth of intra-abdominal fat tissue compared with normal values (**gray**).

In thorax and movement compartment, the **S** branch (**red**) prevails, increasing blood pressure and impairing glucose uptake by the muscle.

In this model, the symptoms of the metabolic syndrome are the result and not the cause of the disease.



Reproduced from Kreier et al, 2003, in Buijs RM. The autonomic nervous system: A balancing act. Handb Clin Neurol. 2013;117:1-11



Review > Complement Med Res. 2022 Feb 3. doi: 10.1159/000522391. Online ahead of print.

The Influence of Modern Neurophysiology on the Previous Definitions of "Segment" and "Interference Field" in Neural Therapy

Raphaela Engel, Hans Barop, Jürgen Giebel, Sabina Maria Ludin, Lorenz Fischer

PMID: 35114664 DOI: 10.1159/000522391

Free article

Procaine

Neural Therapy technique primarily involves the injection of local anesthetic called Procaine (Novocain) into scars, trigger points, tendon and ligament insertions, peripheral nerves, autonomic ganglia, and different tissues

It is hydrolytically broken down within a few minutes by plasma cholinesterase.

It is used in the form of Procaine Hydrochloride diluted to 0.5% or 1%, without excipients and without mixing

Vasodilation , anti inflammatory, anti rheumatic, improves coronary perfusion, negative inotrope, antiarrhythmic, antimicrobial anti cancer

Neural Therapeutic Effect

- Procaine briefly interrupts the irritative stimulus allowing early neuro-regulation of the area.
- Local anesthetic stabilizes the basement membrane of nerve cells and causes hyperemia due to vasodilation

Neural Therapy

› Horm Metab Res. 1990 Jan;22(1):25-8. doi: 10.1055/s-2007-1004841.

Procaine and lidocaine stimulate corticotropin-releasing hormone secretion by explanted rat hypothalami through a sodium conductance-independent mechanism

A E Calogero [1] M A Kling W T Gallucci R Bernardini G P Chrousos P W Gold

Affiliations

PMID: 1968

Anti-inflammatory properties of local anesthetics and their present and potential clinical implications

J. CASSUTO, R. SINCLAIR and M. BONDEROVIC

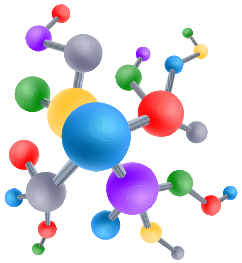
Department of Anesthesiology and Intensive Care and Institution of Surgical Specialties, Sahlgrenska University Hospital, Mölndal, Sweden

Type of Amino acid chains

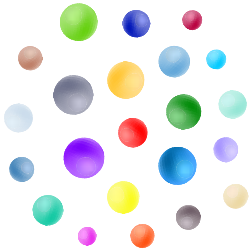
Amino Acids 1

Peptides 2-50

Structure Proteins >50



Peptides



Amino Acids

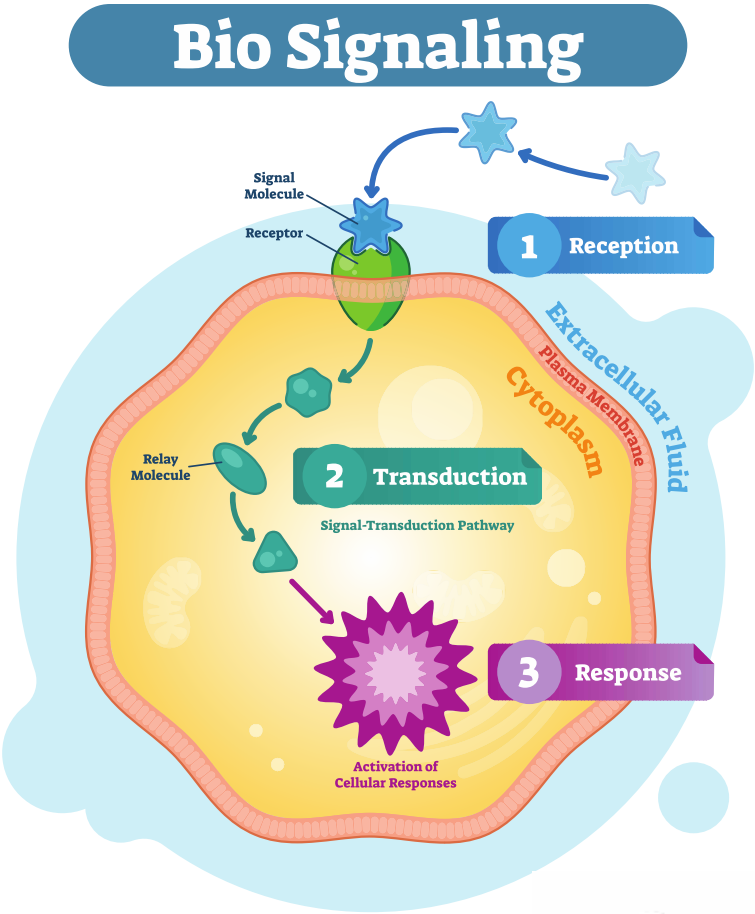
Structure of proteins

What is a peptide

- Short chains of amino acids that act as natural bioregulators, each of which has a very specific function.
- They act as messenger (signaling) molecules within the body.
- Over 7000 have been discovered.
- Very short half life.
- Essencial to life.
- SAFE

How do peptides work

They bind to extracellular receptors located in the cell wall and deliver a message that starts a series of events and then disappear.



Glutathione

- Is a tripeptide of gamma-Glutamyl-cysteinylglycine and the predominant intracellular antioxidant in many organisms including humans.
- Protector and Detoxifier of the cell
- Promotes Longevity, Antiaging Effects
- Increased Energy
- Decreased Inflammation
- Reduce joint discomfort
- Strengthened Immune system, Improved Sleep

VIP

- The twenty-eight amino acid peptide is structurally related to the secretin/glucagon family of peptide hormones, sharing 70% sequence identity with the neuropeptide pituitary adenylate cyclase-activating polypeptide
- VIP is produced by neurons, endocrine and immune cells, and is present in most organs including the CNS, heart, lung, thyroid, kidney, urinary and gastrointestinal tracts, genital organs and the immune system.

VIP Peptide

nature communications

Article | Open access | Published: 02 September 2020

Suprachiasmatic VIP neurons are required for normal circadian rhythmicity and comprised of molecularly distinct subpopulations

William D. Todd, Anne Venner, Christelle Anaclet, Rebecca Y. Broadhurst, Roberto De Luca, Sathyajit S. Bandaru, Lindsay Issokson, Lauren M. Hablitz, Olga Cravetchi, Elda Arrigoni, John N. Campbell, Charles N. Allen, David P. Olson & Patrick M. Fuller ✉

Central Nervous System
VIP

- Regulates Circadian rhythms
- Noncholinergic relaxation of vascular and nonvascular smooth muscle
- Increases neuronal survival and regulates glycogen metabolism in the cerebral cortex
- Promotion of embryonic growth and brain development
- has neurotrophic effects and regulates bone metabolism

Endocrine System
VIP

- Increases insulin and glucagon secretion
- Increases blood flow in thyroid but has no effect on hormone levels
- Promotes the release of prolactin, luteinizing hormone, and growth hormone from the pituitary gland, and regulates insulin and glucagon release

Circulatory System
VIP

- Regulates cardiac contractility
- Coronary and systemic vasodilatation
- Increases glycogenolysis and lowers arterial blood pressure
- Increases cardiac output

Respiratory System
VIP

- Relaxes airway and pulmonary vascular smooth muscle
- Inhibits airway and pulmonary vascular smooth muscle proliferation
- Bronchodilatation

Immune System
VIP

- Macrophage- deactivating factor
- Regulates the differentiation of CD4+ t cells
- Anti-Inflammatory
- Defense mechanism against septic shock

Digestive System
VIP

- Increases the secretion and inhibits the absorption of intestinal luminal fluid
- Relaxes smooth muscle and mediates distension-induced reflexes
- Decreases intestinal paracellular permeability
- Increases epithelial cell proliferation
- Releases pancreatic enzymes

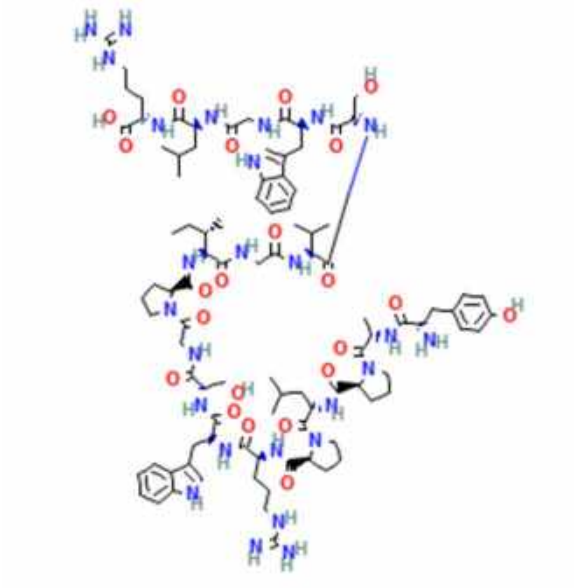
PE -22-28 peptide

PE-22-28

- Is a synthetic derivative of the naturally occurring peptide spadin. Spadin is a secreted peptide derived from sortilin.
- Antagonist of the TREK-1 (TWIK- related-potassium channel) receptor two-pore potassium channel identified as a potential target in the treatment of depression and as a possible neurogenic regulator.
- PE-22-28 is the representative peptide for this group of synthetic spadin analogs
- Has been shown to be more stable and have improved antidepressant activity and neurogenic properties over the naturally occurring spadin

PE -22-28 peptide

- PE-22-28 has been shown to induce neurogenesis after 4 days, which is substantially faster than any known antidepressant.
- Useful in other applications such as learning, stroke recovery and neurodegenerative diseases



TREK-1

- Is the receptor that spadin and PE-22-28 primarily bind to
- Is found in regions of the brain controlling mood, memory, and learning, these areas include the prefrontal cortex, the amygdala, and the hippocampus.
- Helps to protect against excitotoxicity.

Front Pharmacol. 2017; 8: 643.
Published online 2017 Sep 12. doi: 10.3389/fphar.2017.00643
PMCID: PMC5601071
PMID: 28955242

Shortened Spadin Analogs Display Better TREK-1 Inhibition, *In Vivo* Stability and Antidepressant Activity

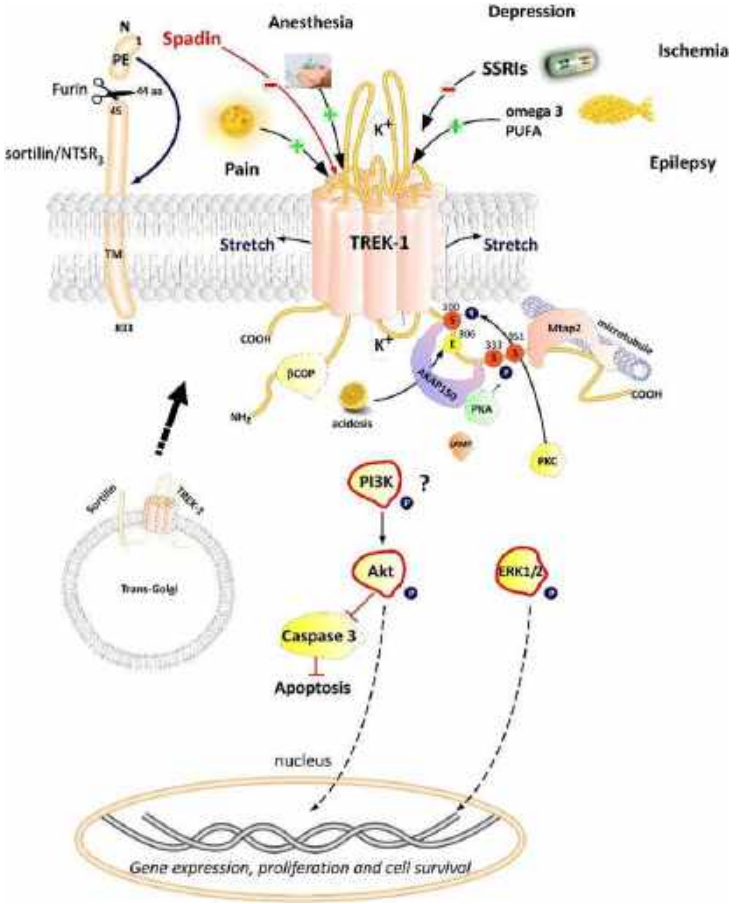
Alaeddine Djillani,† Mariel Pietri,† Sébastien Moreno, Catherine Heurteaux, Jean Mazella, and Marc Borsotto*

TREK-1 PE-22-28

- Depression

PE-22-28 has been shown to relieve depression in just 4 days without producing any side effects on other functions that are controlled by the TREK-1 channel

TREK-1 receptor has been implicated in pain sensitivity, seizure activity, and cardiac ischemia. Research in mice, however, shows none that none of these side effects are observed in the use of PE-22-28



PE-22-28

Neurogenesis

- Research with PE-22-28 shows that this peptide can upregulate neurogenesis, but in shorter duration of time, than regular antidepressants
- studies show that PE-22-28 increases both neurogenesis and synaptogenesis after just 4 days.
- In the case of synaptogenesis PE-22-28 appears to double the rate of synapse formation

Thank you and wish you a happy circadian day