

# *THE GUT-BRAIN AXIS IS RELEVANT TO SKIN AGING*



**21-23  
NOVEMBER**  
BANGKOK  
CONVENTION CENTRE  
AT CENTRALWORLD

**ICAD**  
2019  
INTERNATIONAL CONGRESS OF AESTHETIC DERMATOLOGY

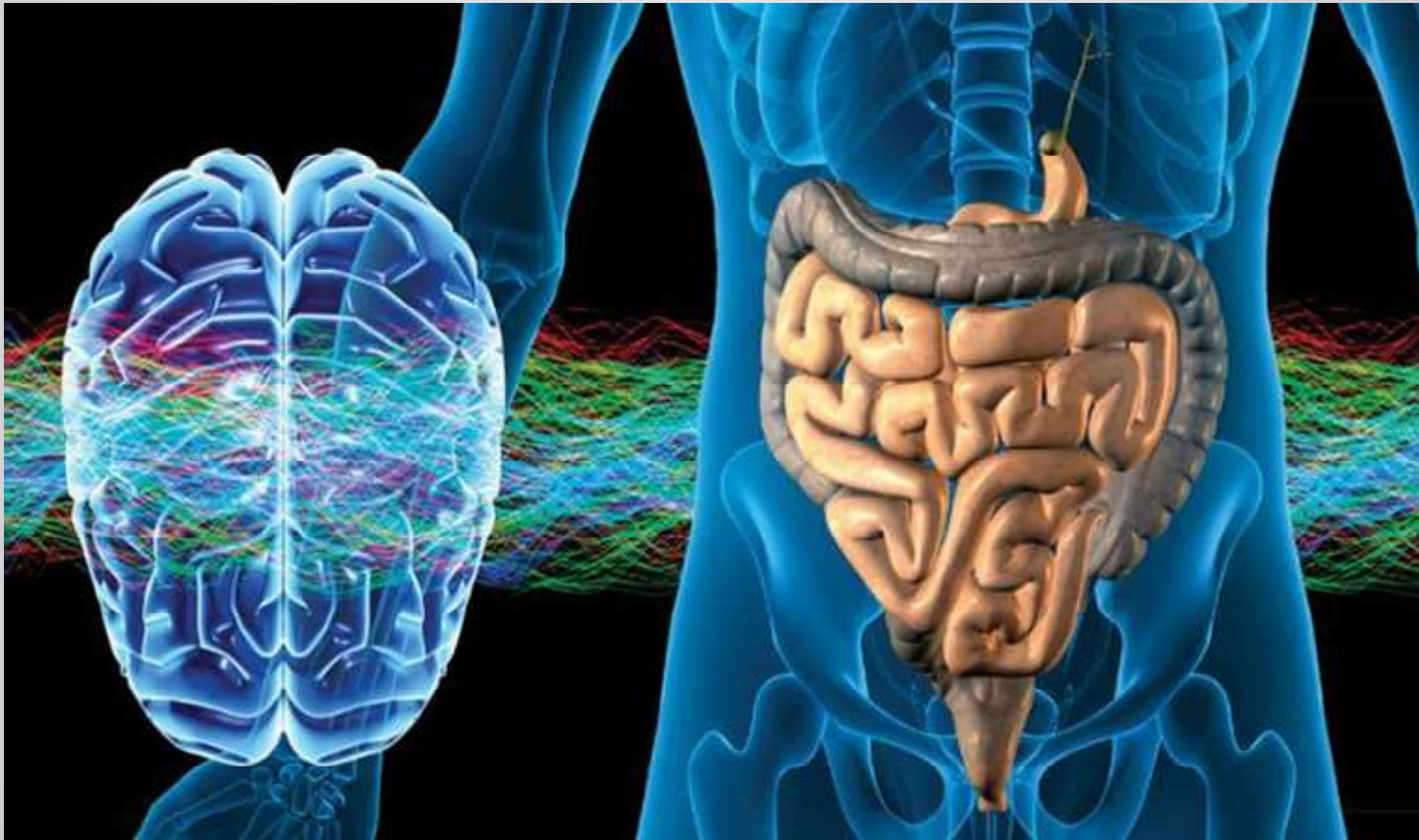
 ORGANIZED IN COOPERATION WITH  
THE OFFICIAL DST  
DERMATOLOGICAL SOCIETY OF THAILAND

PATRIZIA A D'ALESSIO MD PHD

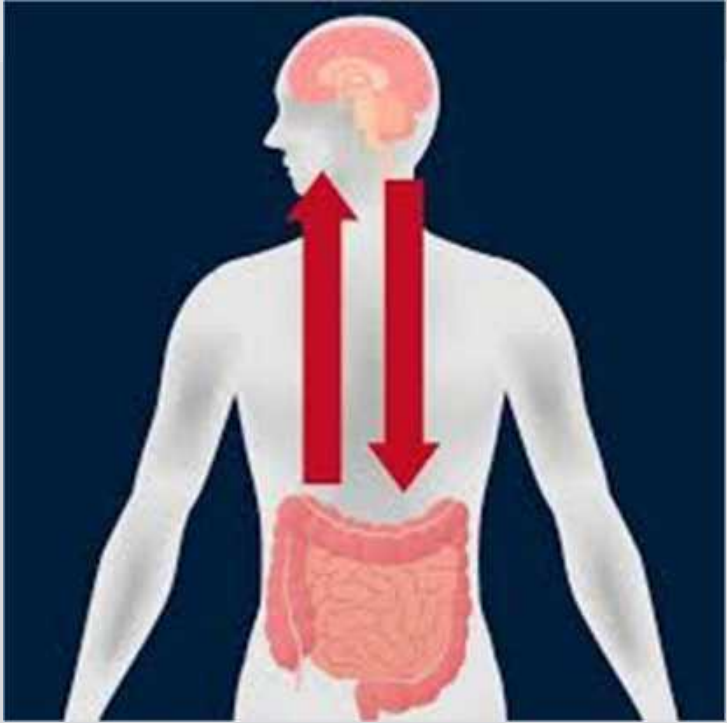
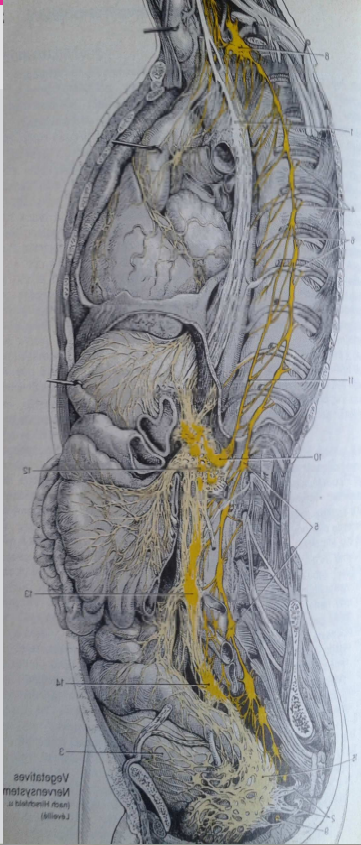
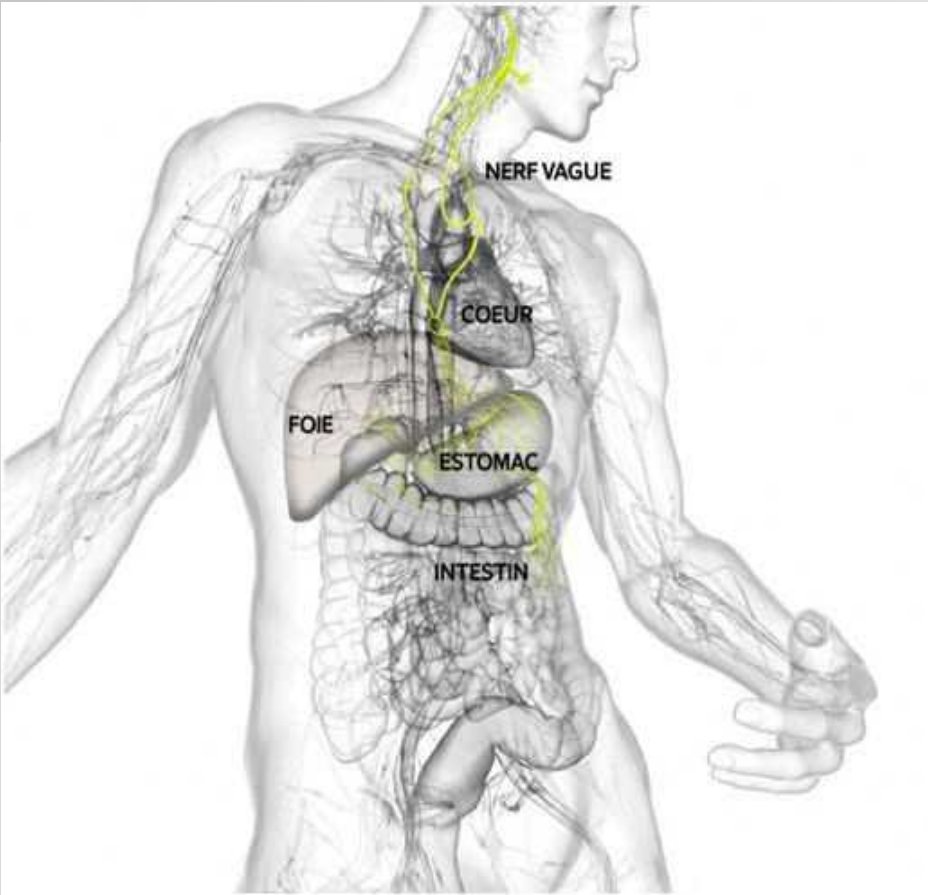
© copyright 2019 by Patrizia A d'Alessio  
Pr Dr University Paris Sud-11 and Genopole d'Evry France

What will we be talking about ?



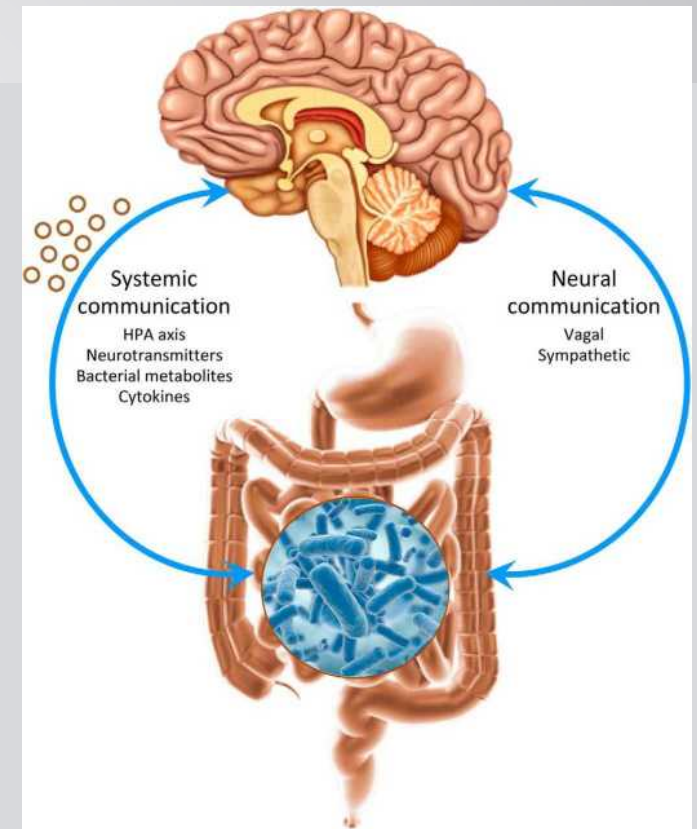


# ANATOMICAL GUT-BRAIN LINK : THE VAGUS NERVE



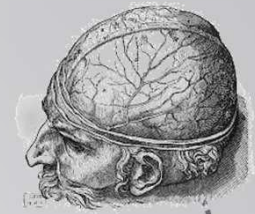
# FUNCTIONAL GUT – BRAIN LINK : THE MICROBIOTA

- ◆ Bidirectional communication channels between the gut microbiome, the gut, and the brain.
- ◆ Endocrine-, neurocrine- and inflammation-related signals generated by the gut microbiota and specialized cells within the gut affect the brain.
- ◆ In turn, **the brain can influence the microbial composition** and function via endocrine and neural mechanisms
- ◆ Dopamine, serotonin, leptin, adiponectin...



# CHARACTERIZATION OF THE GUT-BRAIN CONNEXION

---

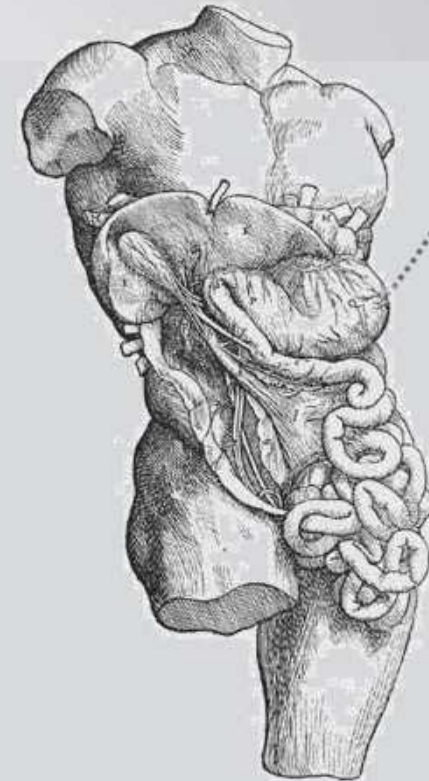


➤ **Food intake and micronutrient signalling**

➤ **Stress management**

- Role of the brain
- Role of the gut barrier immune system

➤ **Relevance to skin health and beauty**

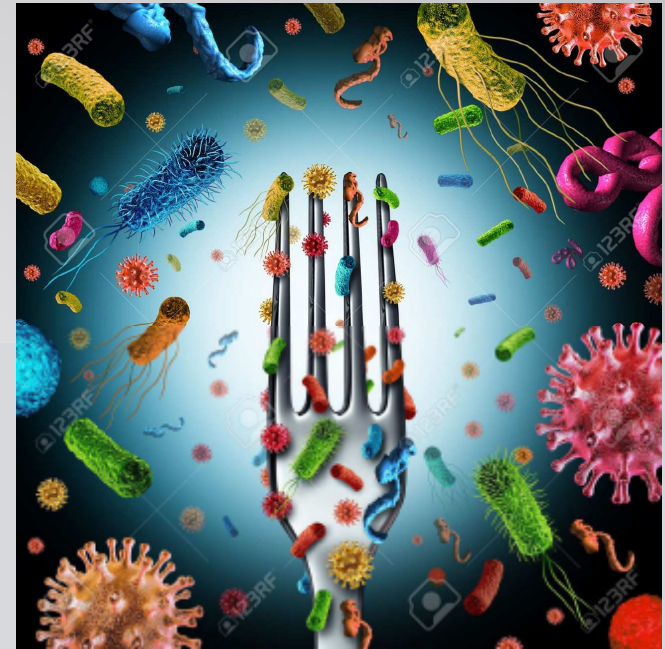




# 1. FOOD INTAKE

---

## MICRONUTRIENT SIGNALLING

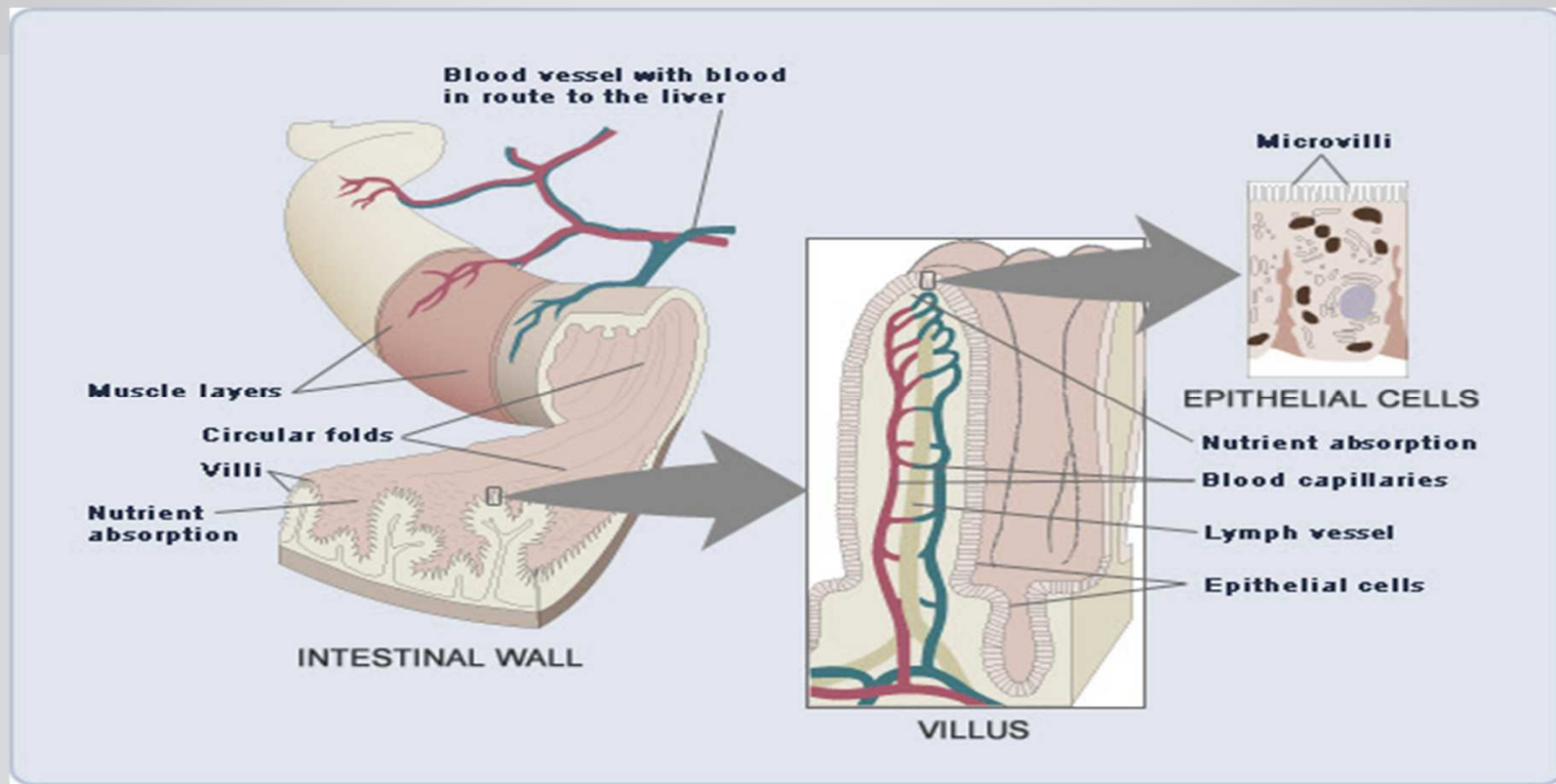


# GUT THE STARTING POINT

---



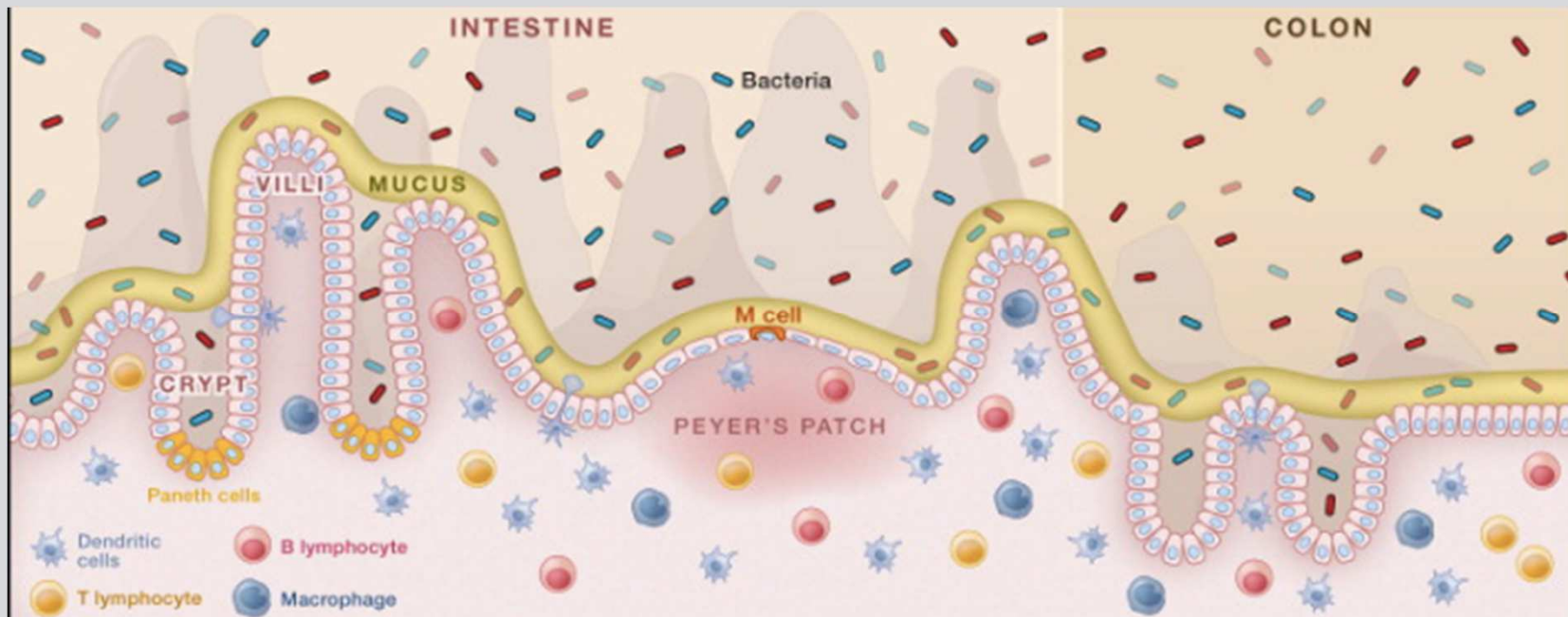
# OUR GUT





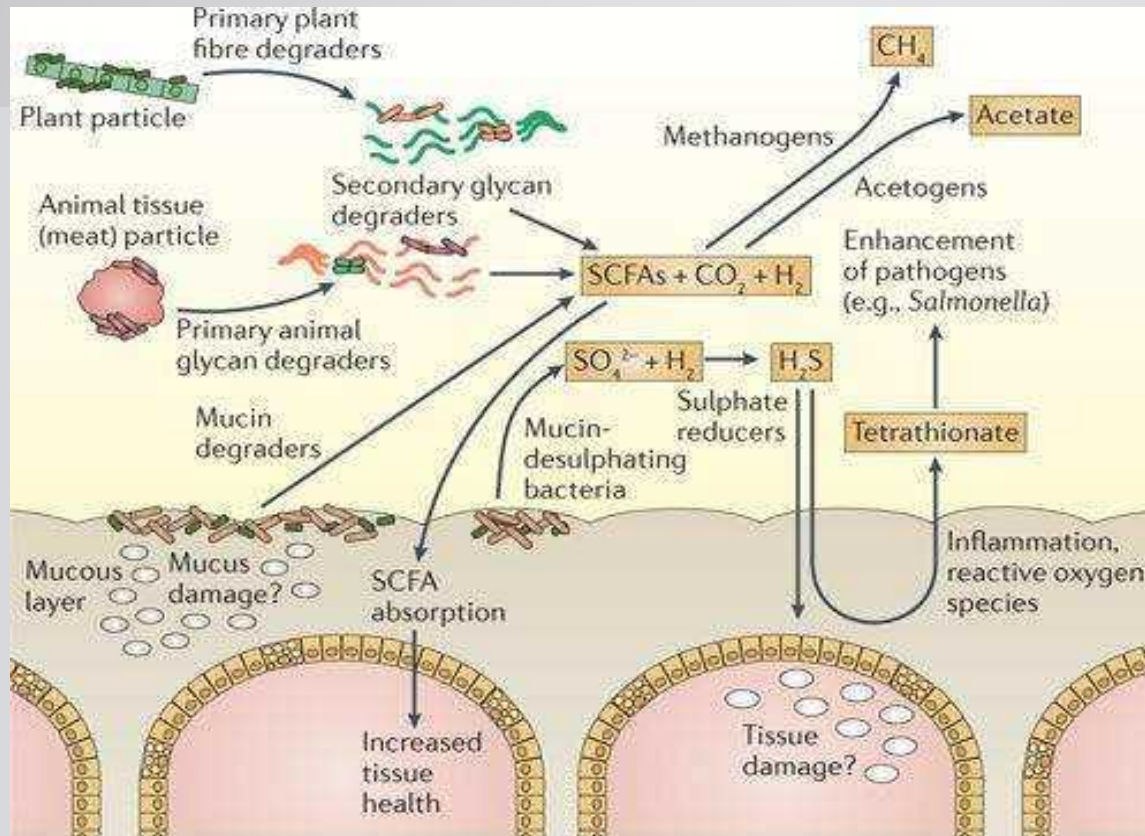
# THE GUT LANDSCAPE : A CONTINUOUSLY PERFUSED AND PERISTALTIC BIOREACTOR FACING A FUNCTIONAL ANTI-INFLAMMATORY BARRIER

**Mucus** builds a barrier between **Microbiota** and the **Mucosa**, while allowing microbiota secretions to reach down and releasing **sIgA** upwards for immune exclusion



Cell 2010;140:859-870

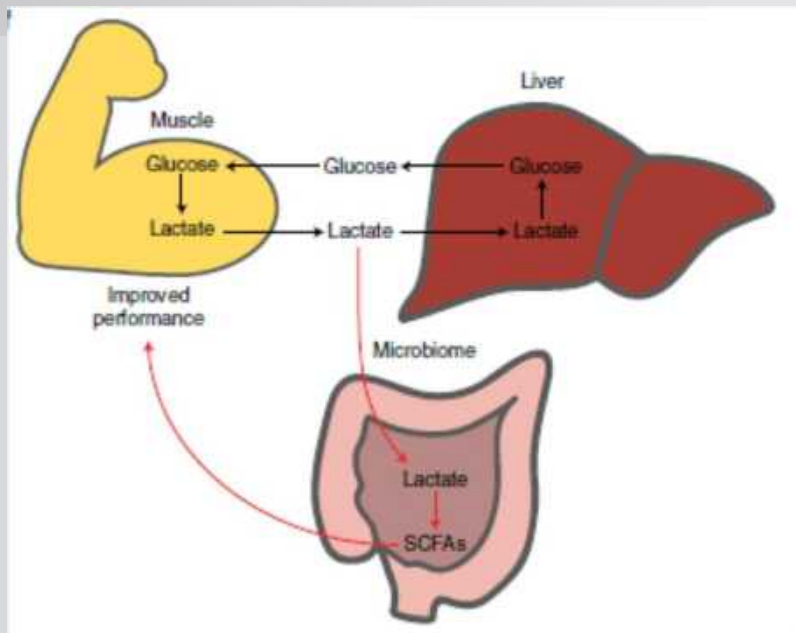
# MICROBIOTA METABOLITES SUSTAIN LIFE



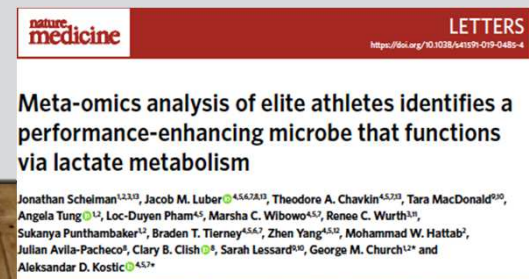
Butyrate, Folate,  
Propionate produced by:

- Bifidobacteria*
- Clostridii*
- Enterobacterium*
- Enterococcus*
- Ruminococcus*
- Roseburia*

# LIVER & MUSCLE : MICROBIOME-SOURCED SCFAs IMPROVE PERFORMANCE

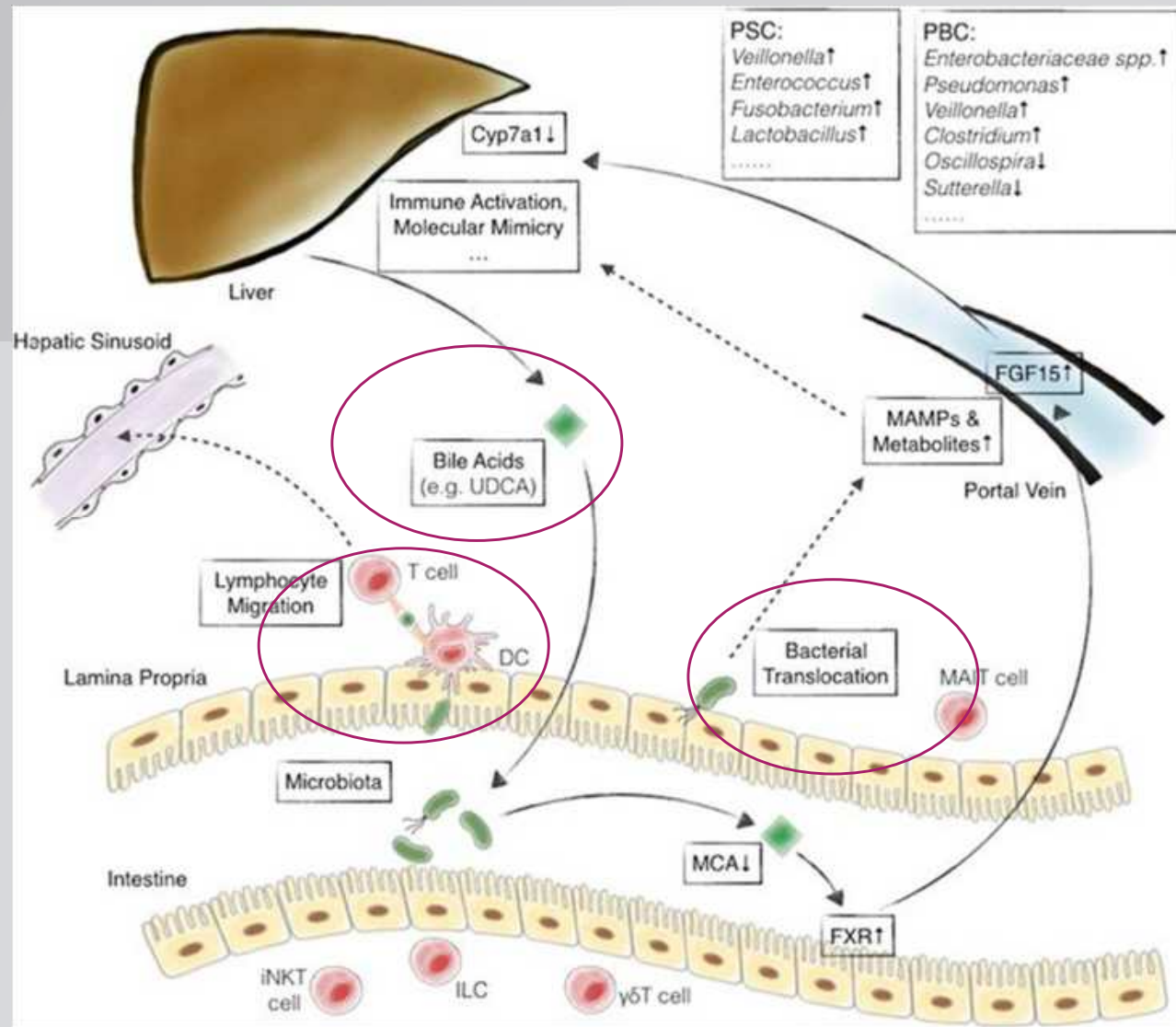


- ◆ Lactate produced in the muscle enters the intestinal lumen via the blood circulation.
- ◆ Here, it selects *Veillonella*, causing the production of SCFA byproducts (propionate).





# THE GUT-LIVER AXIS INFLUENCES THE BRAIN



OPEN

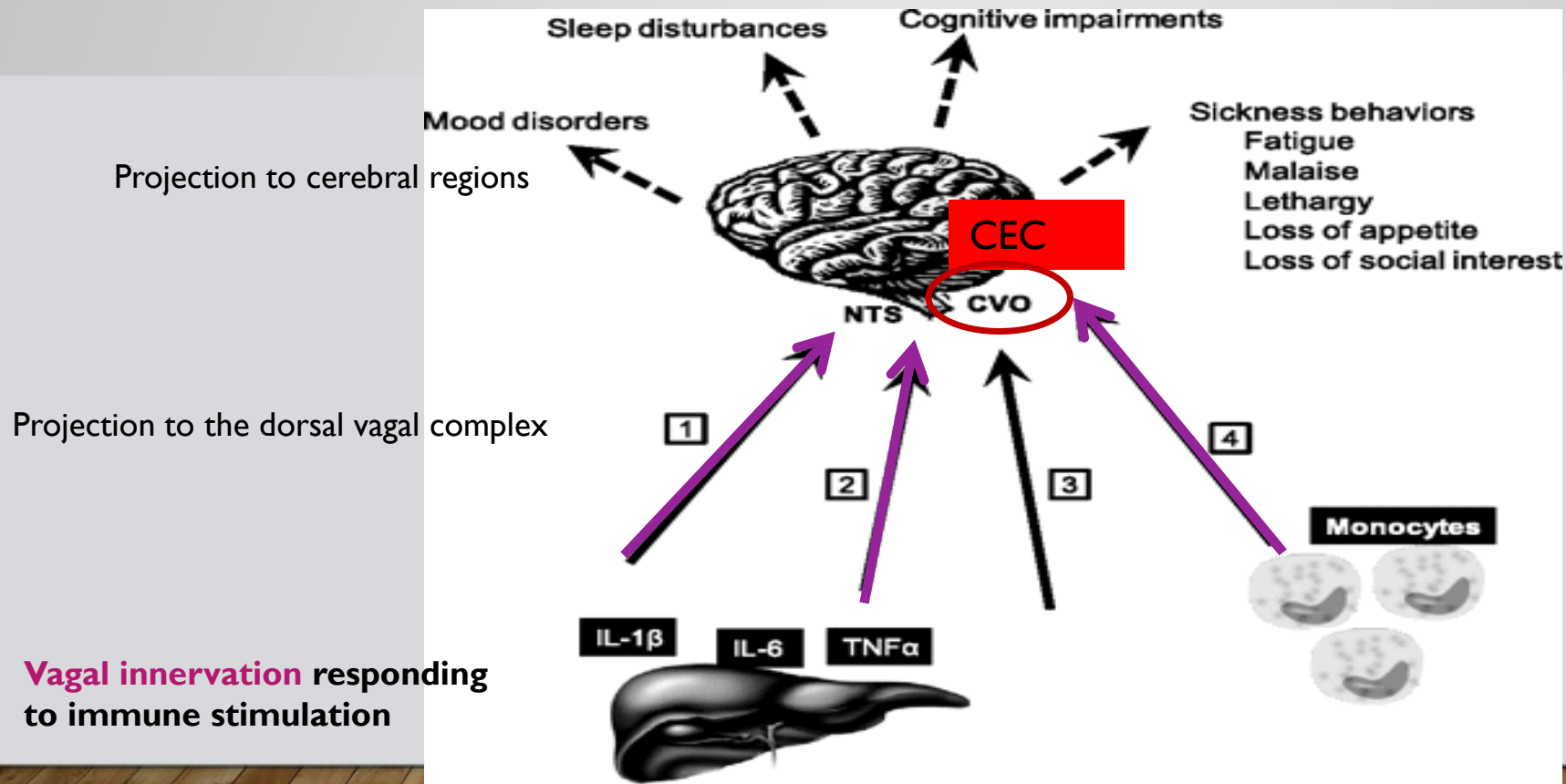
Cellular and Molecular Immunology (2018) 15, 1–15  
[www.nature.com/cmi](http://www.nature.com/cmi)

REVIEW ARTICLE

The microbiome and autoimmunity: a paradigm from the gut–liver axis

Bo Li<sup>1</sup>, Carlo Selmi<sup>2,3</sup>, Ruqi Tang<sup>1</sup>, ME Gershwin<sup>4</sup> and Xiong Ma<sup>1</sup>

# THE LIVER ESTABLISHES THE LINK BETWEEN THE IMMUNE SYSTEM AND THE BRAIN

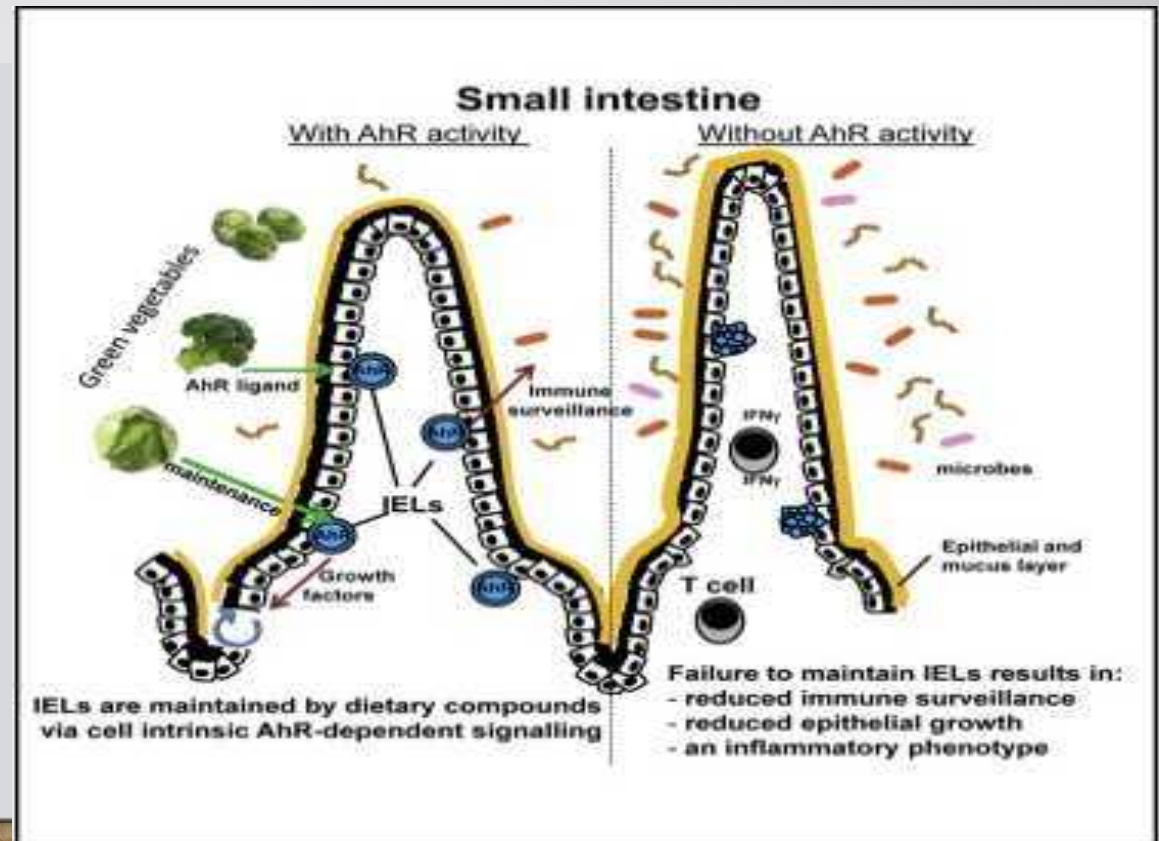


# CONTROL BY INTRA-EPITHELIAL LYMPHOCYTES (IELS) AND AHR RECEPTORS

The epithelial barrier is organized, waterproof, flexible, capable of rapid repair.

The Aromatic hydrocarbon Receptor (AhR) is an important regulator of immune surveillance.

In its absence, IELs disappear and epithelial growth decreases, favoring inflammation.





# ANCIENT TIMES

---



**Dr George Cheyne  
(1671-1743)**

Since the 17th century and during the 18th century, vegetarianism became a treatment for obesity and gout for rich people consuming a lot of meat.

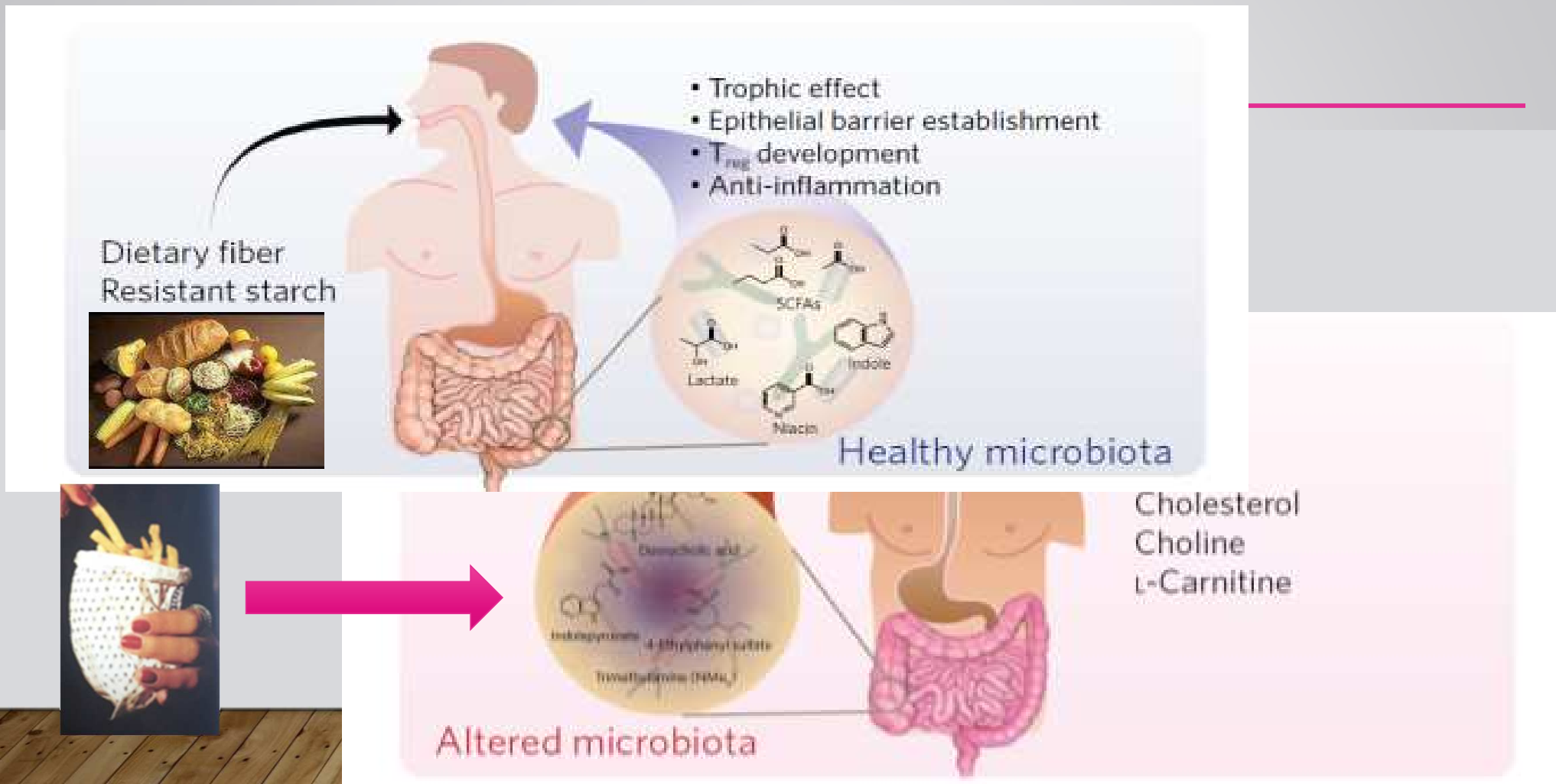
But vegetarianism was also beginning to be considered as a solution to avoid wrinkles and lack of radiance in the skin.

---

# NEW PARADIGMS NOWADAYS

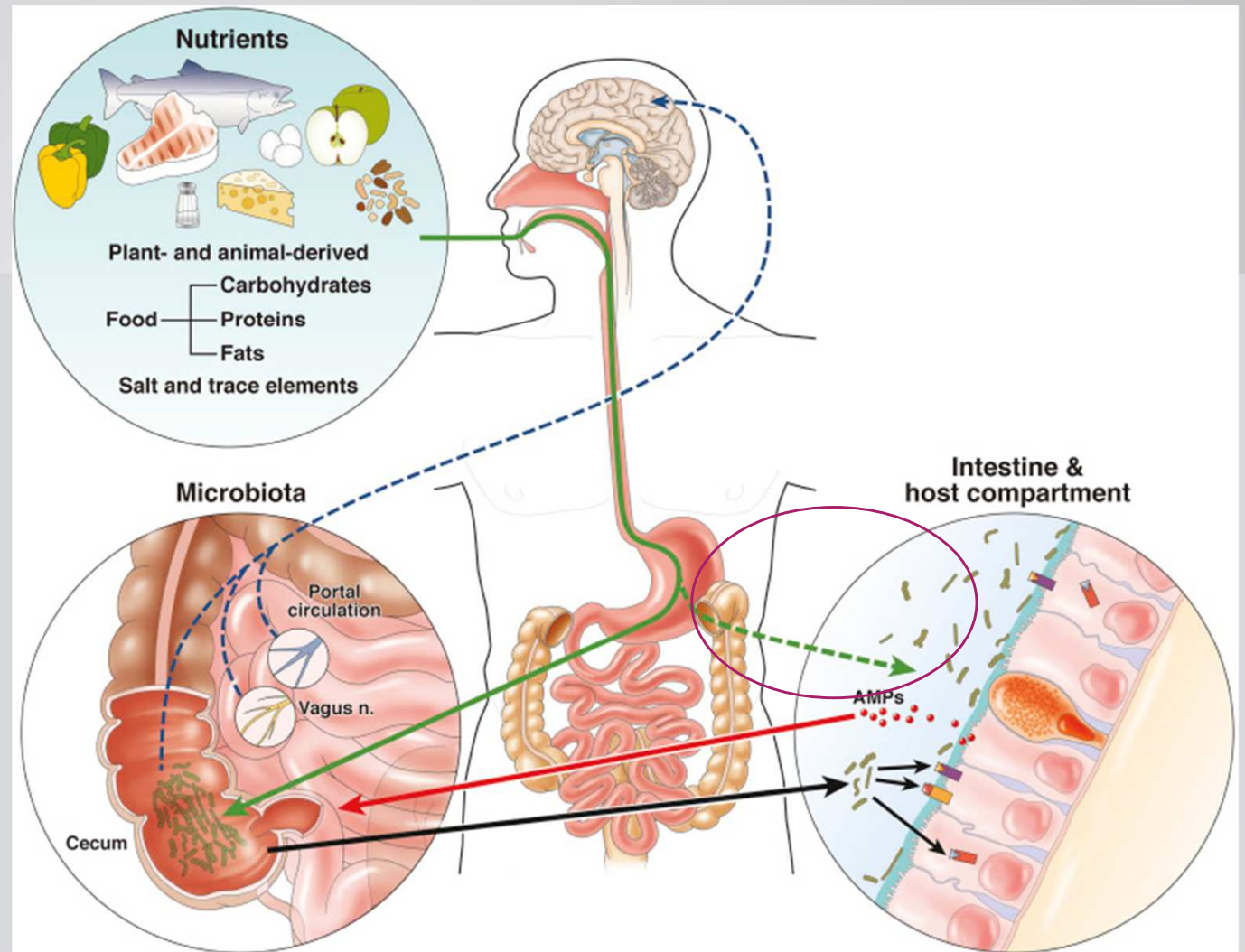


# FOOD IS INITIATING GUT –BRAIN COMMUNICATION





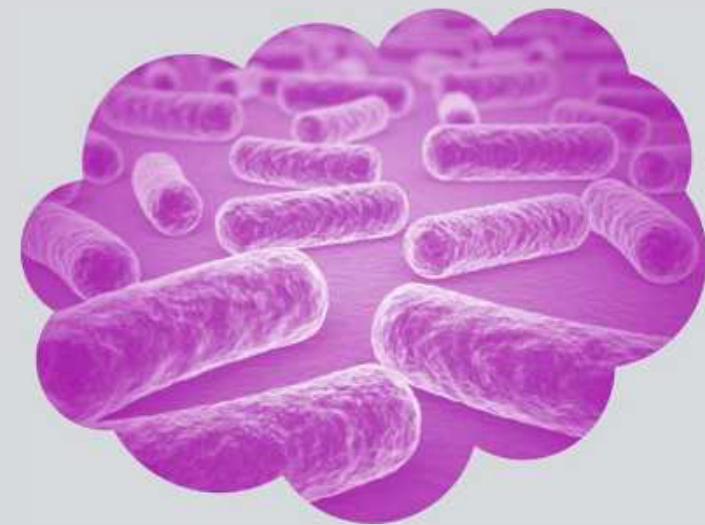
The vagus nerve  
forwards  
the gut – brain  
signalling initiated by  
food intake



# A WINNING ASSOCIATION BETTER AND BETTER UNDERSTOOD...

---

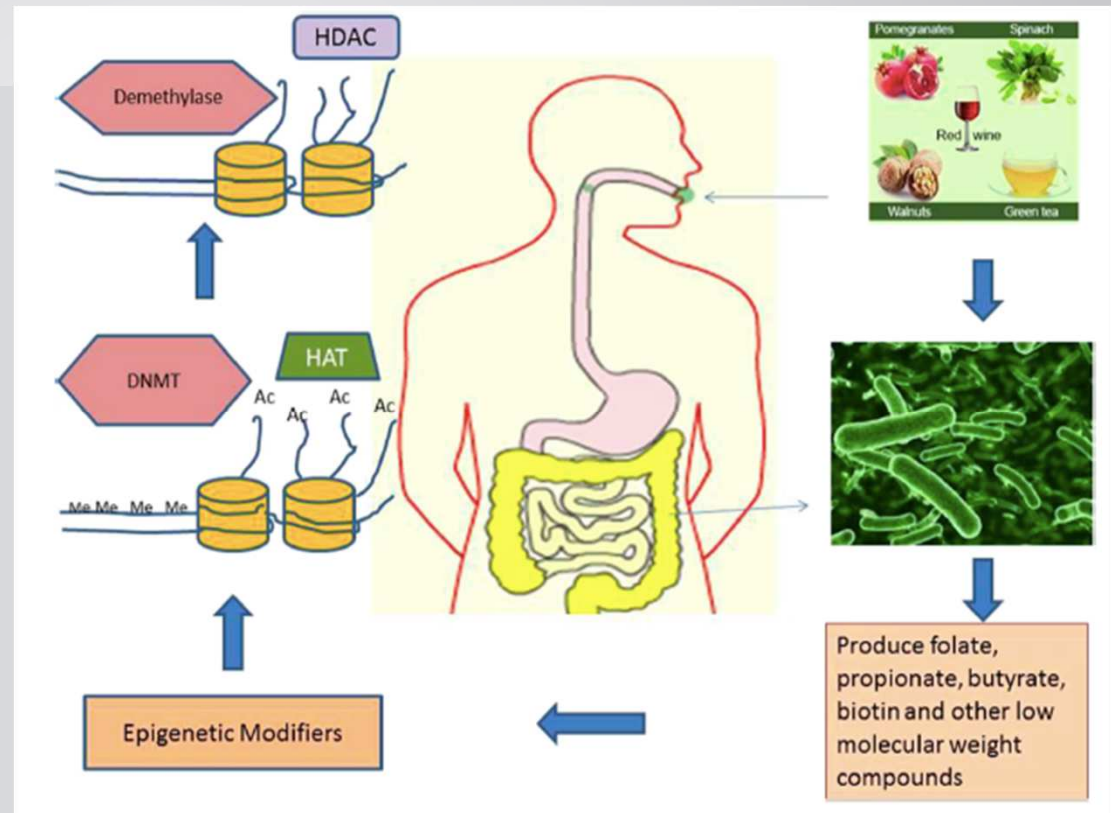
Food...



... and microbiota

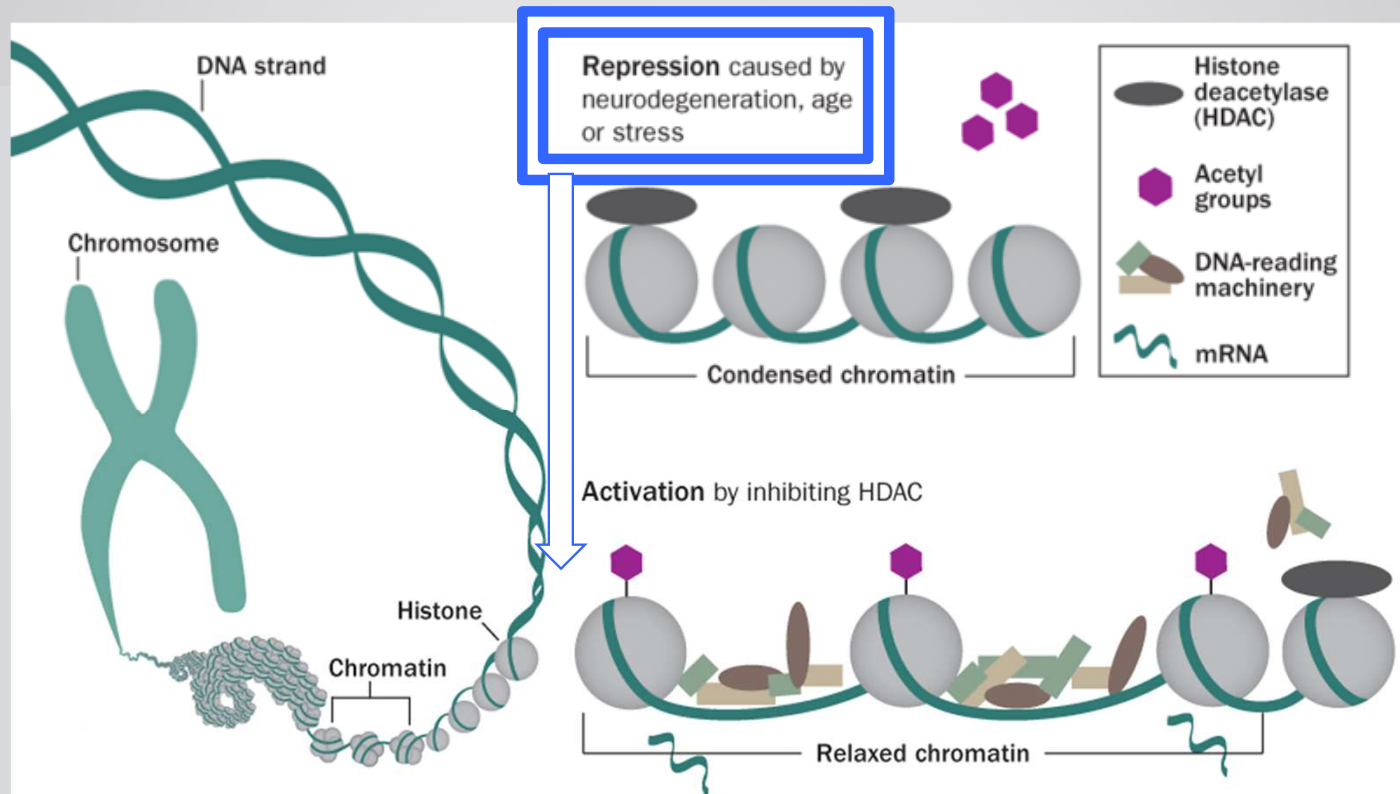
# BACTERIAL METABOLISM OF DIETARY FIBERS IMPACTS EPIGENETICS

Acetate, **butyrate**, propionate (SCFA) and folates, produced following dietary intake of phytochemicals, are epigenetic modifiers.





# HAT add acetyl groups and displace HDAC HDAC inhibitors have the same effect

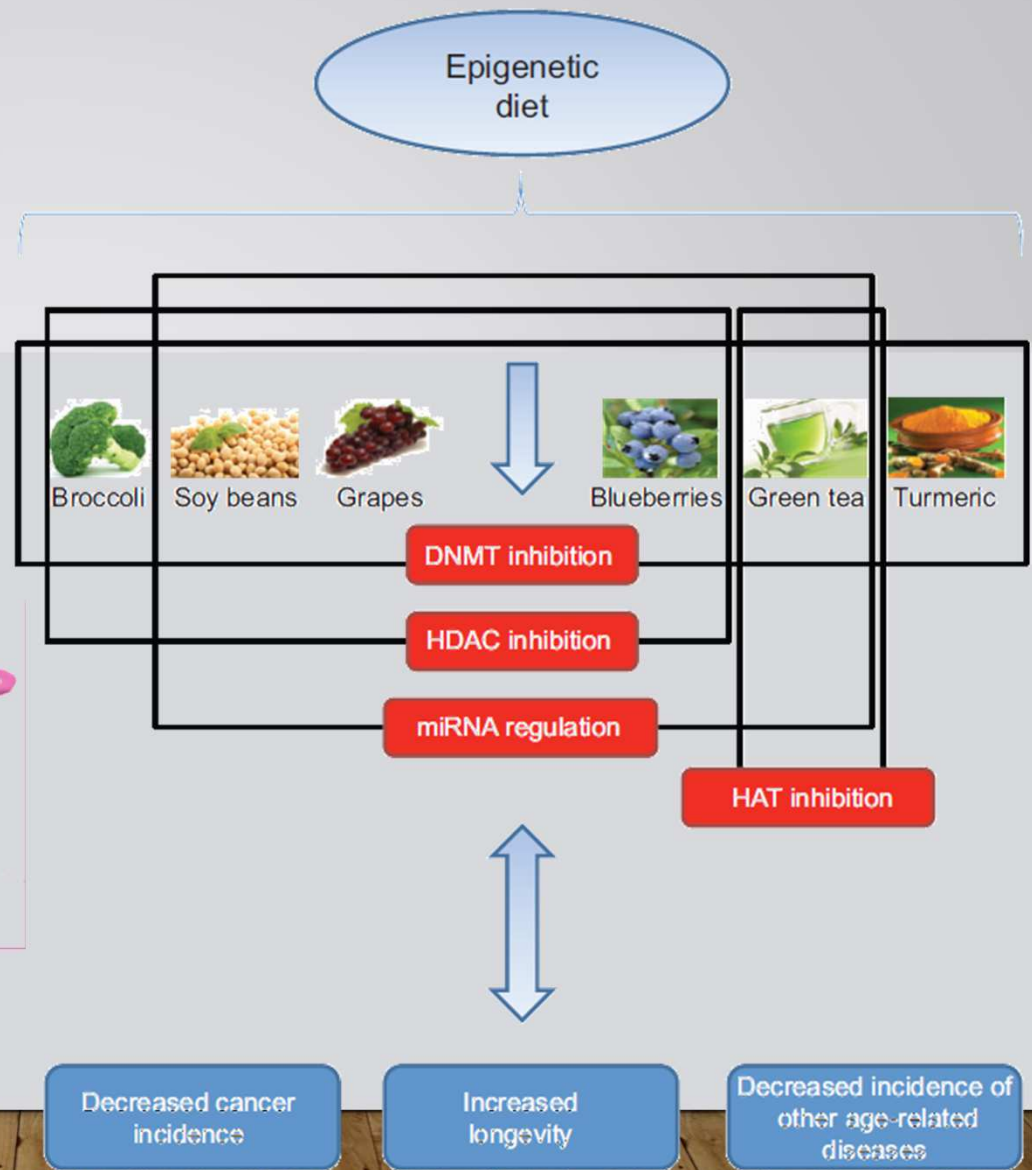


HAT : Histone Acetyl Transferases

HDAC : Histone Deacetylases Acetylation blocks DNA transcription

COULD THE  
MICROBIOTA  
INDUCE  
EPIGENETIC  
MODIFICATIONS  
ASSOCIATED TO  
AGING ?

GLOBAL HYPO-  
METHYLATION AND  
LOCAL HYPER-  
METHYLATIONS



# READING PROCESSES OF OUR DNA DEPEND ON THE QUALITY OF OUR FOOD INTAKE

Acetylated histones



DNA reading



No DNA methylation



# CONCLUSION...

---



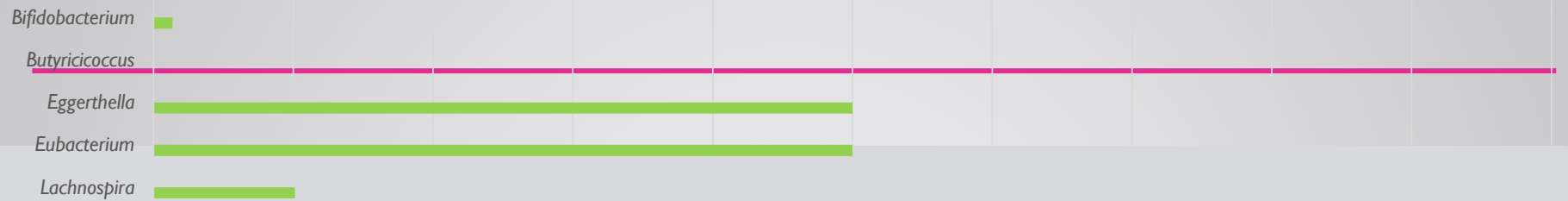
With inflammation at the gut level, the barrier function is altered.

Microbiota has been documented to be linked to healthspan extension.

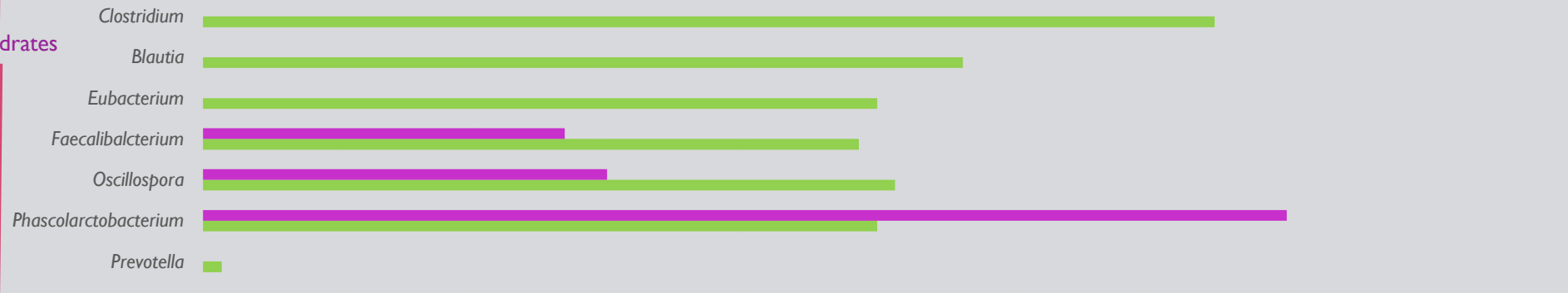
# DEEPER TOWARDS MICROBIOTA SPECIALIZED STRAINS



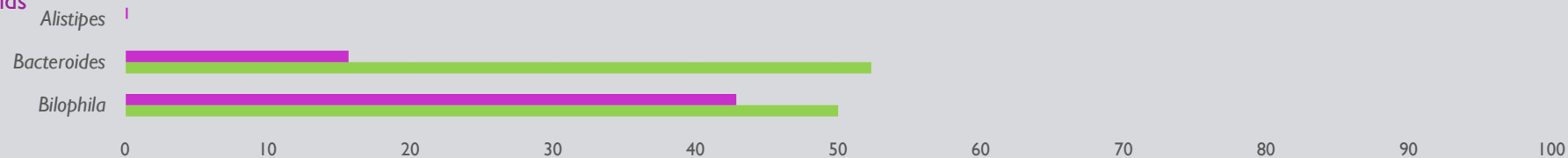
Fibers



Carbohydrates



Proteins / fatty acids





## 2. STRESS MANAGEMENT

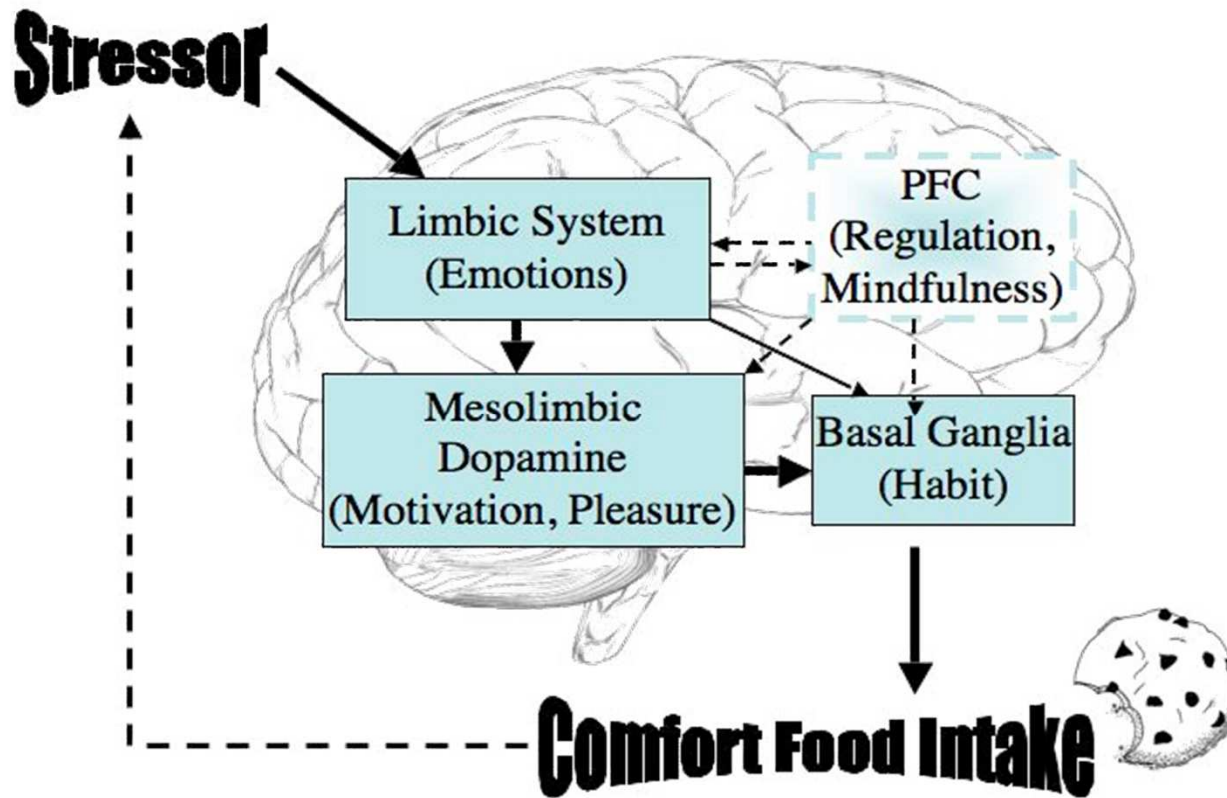
---

### ROLE OF THE BRAIN

- ◆ Role of the gut barrier
- ◆ Immune system



# STRESS-COPING MECHANISMS OF THE BRAIN



STRESS



Thanks to **cortisol**,  
normally you don't realize  
you are under stress



# ACUTE STRESS IS REVERSIBLE

Nerve fibers  
Neuropeptides  
Mast cells  
Kinins  
Prostaglandins

Histamin  
Serotonin  
Leucotriens  
PAF acether

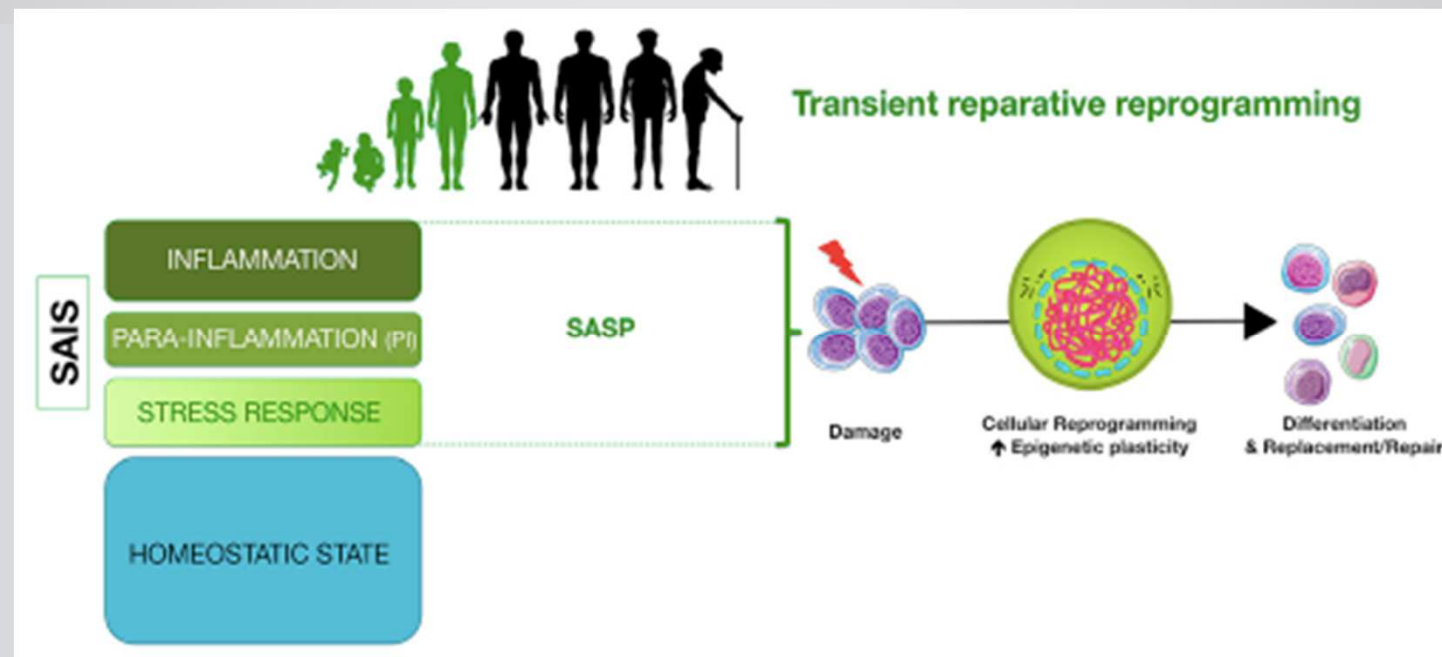
Pyrogenic cytokines : IL-1, TNF- $\alpha$ , IL-6, IFN- $\gamma$   
Natural cryogens: arginine vasopressin,  
 $\alpha$ -MSH, glucocorticoids, NPY, bombesin,  
thyroliberin, IL-1Ra



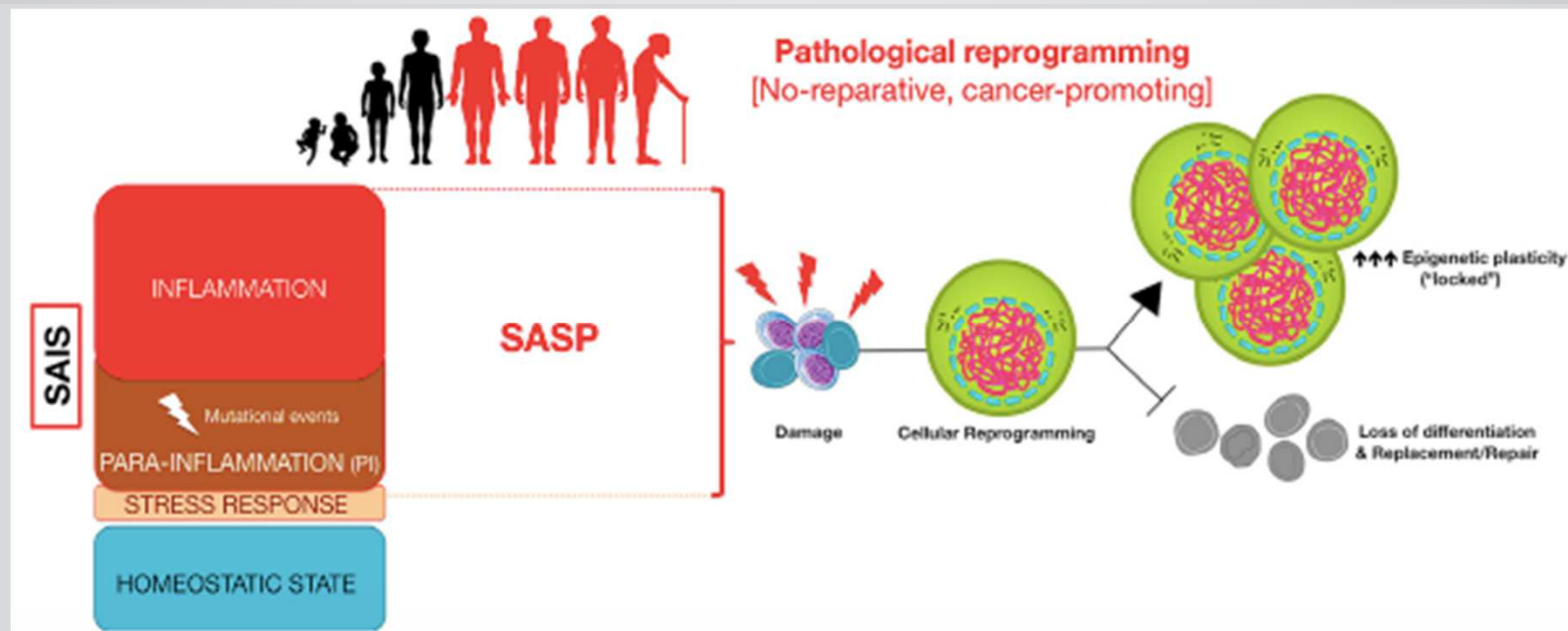
**Inflammation is our first adapting  
tool to the environment.**



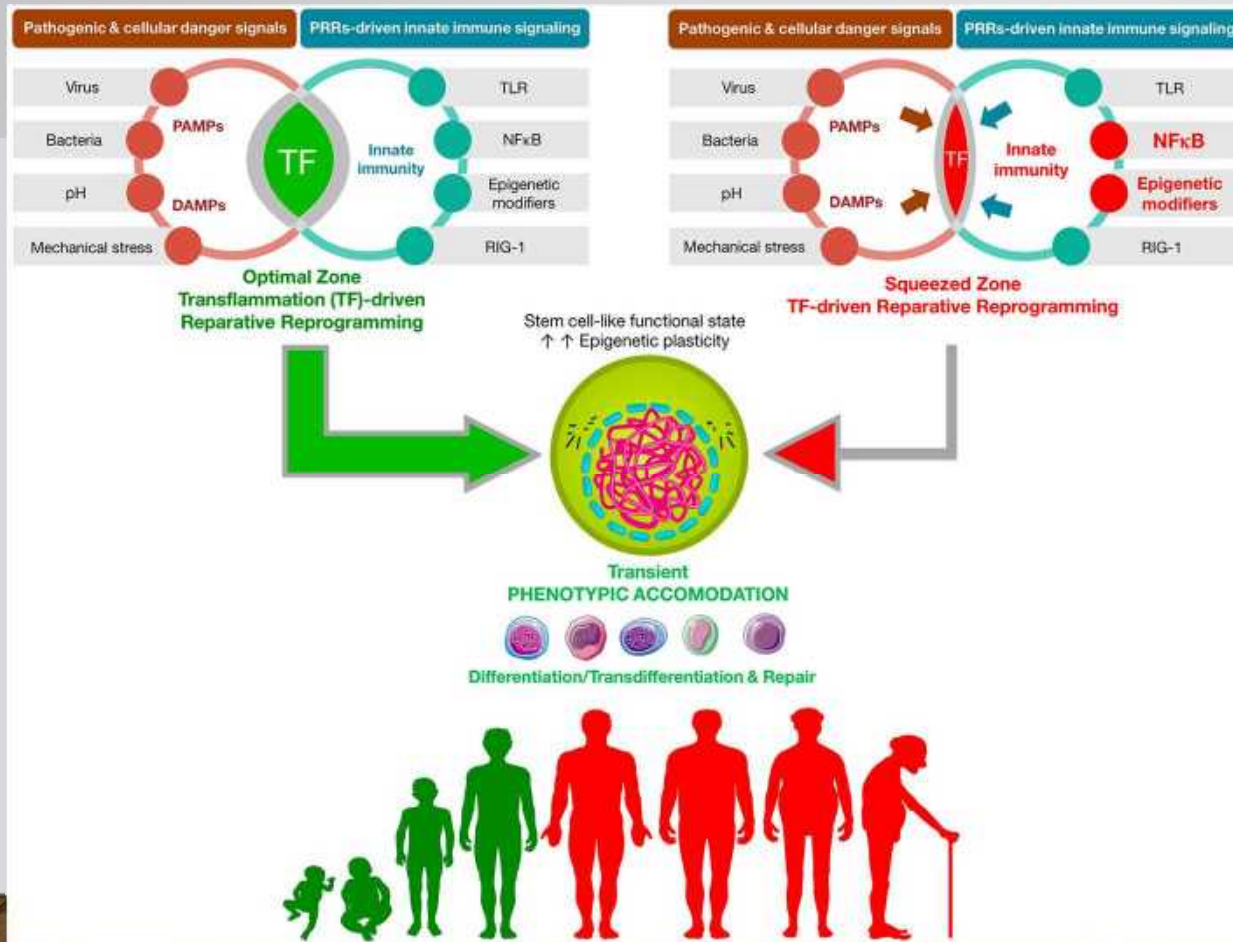
# ACUTE INFLAMMATION SOLVES THE PROBLEM OF THE INABILITY TO GENERATE TISSUE SELF REPAIR VIA FUNCTIONAL STEM-CELL-LIKE CELLS



# ARCHETYPAL INFLAMMATORY PATHWAYS (NF- $\kappa$ B), PROMOTE AN OPEN CONFIGURATION OF THE CHROMATIN, FOR GREATER EPIGENETIC PLASTICITY.



# TRANSFLAMMATION-driven epigenetic plasticity



## TF hallmarks:

- ◆ Increased epigenetic flexibility
  - ◆ Phenotypic malleability
- To adapt responses to stress, injury and disease



# CONTEMPORARY SOCIETY

---



characterized by less acute stress  
chronic stress becomes the rule

## IN A FASCINATING WAY

---



... the same mechanisms that try to respond to traumatic or infectious stress are at work during emotional or psychological stress.

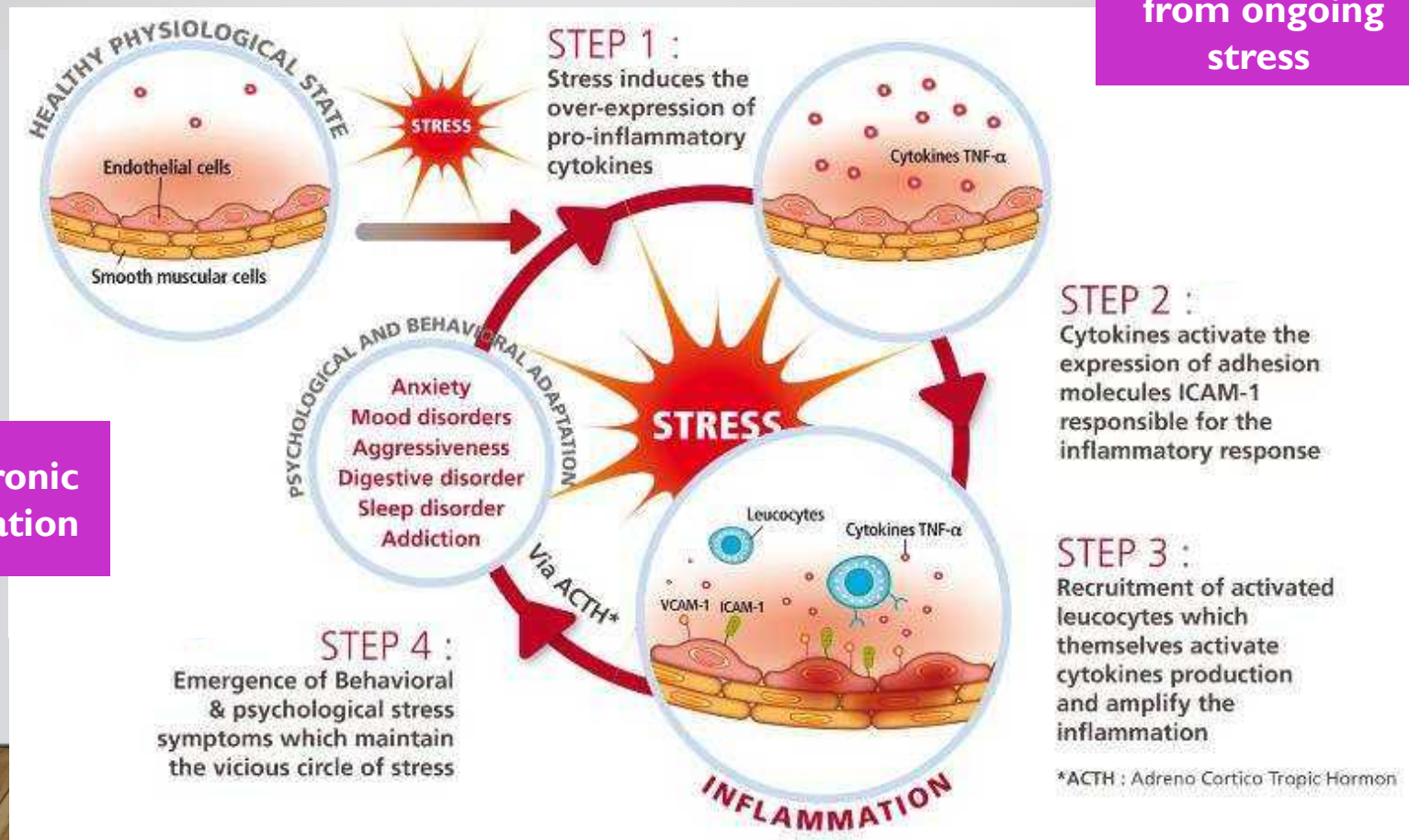
But only long lasting, insidious stress, obsessive thoughts, great psychological pain such as mourning, maintain a really vicious circle...



# BUT AS SOON AS STRESS BECOMES CHRONIC CHRONIC INFLAMMATION IS STARTED

from ongoing stress

...to chronic inflammation





# SIGNS OF CHRONIC INFLAMMATION

Quality of **sleep**  
with difficulty  
falling asleep

Quality of **mood** negative  
or obsessive  
thoughts

Difficulty **concentrating**  
appearance **pain** without  
identifiable pathology

**Reluctance** to  
meet others,  
asociality, isolation

**Inflammation is not any longer our first  
tool to adapt to the environment.**



# Even more insidiously

According to the WHO, “Mental Illness in the Workplace” with disability, absenteeism, sickness benefits and Major Depressive Disease (MDD), will be the concern in major governmental institutions or international enterprises, as a result of a rude and disrespectful line of management exercising unsustainable **pressure** for employees.



In 2030 the second cause of death worldwide is foreseen not to be :

infectious diseases  
cardiovascular disorders  
nor cancer....



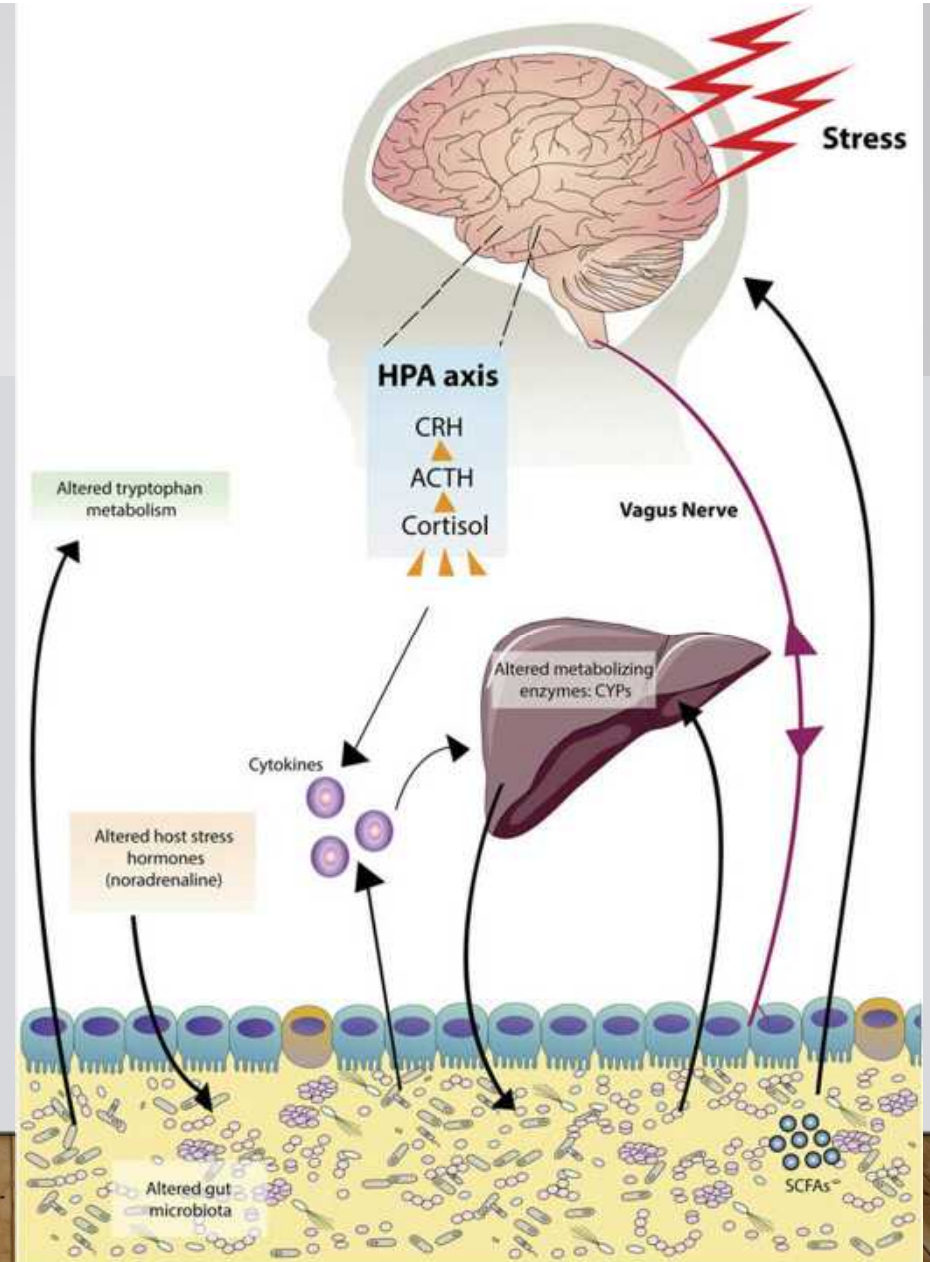
...but premature death due to overdosage  
of legal analgics such as codeine...

...regularly prescribed by physicians!





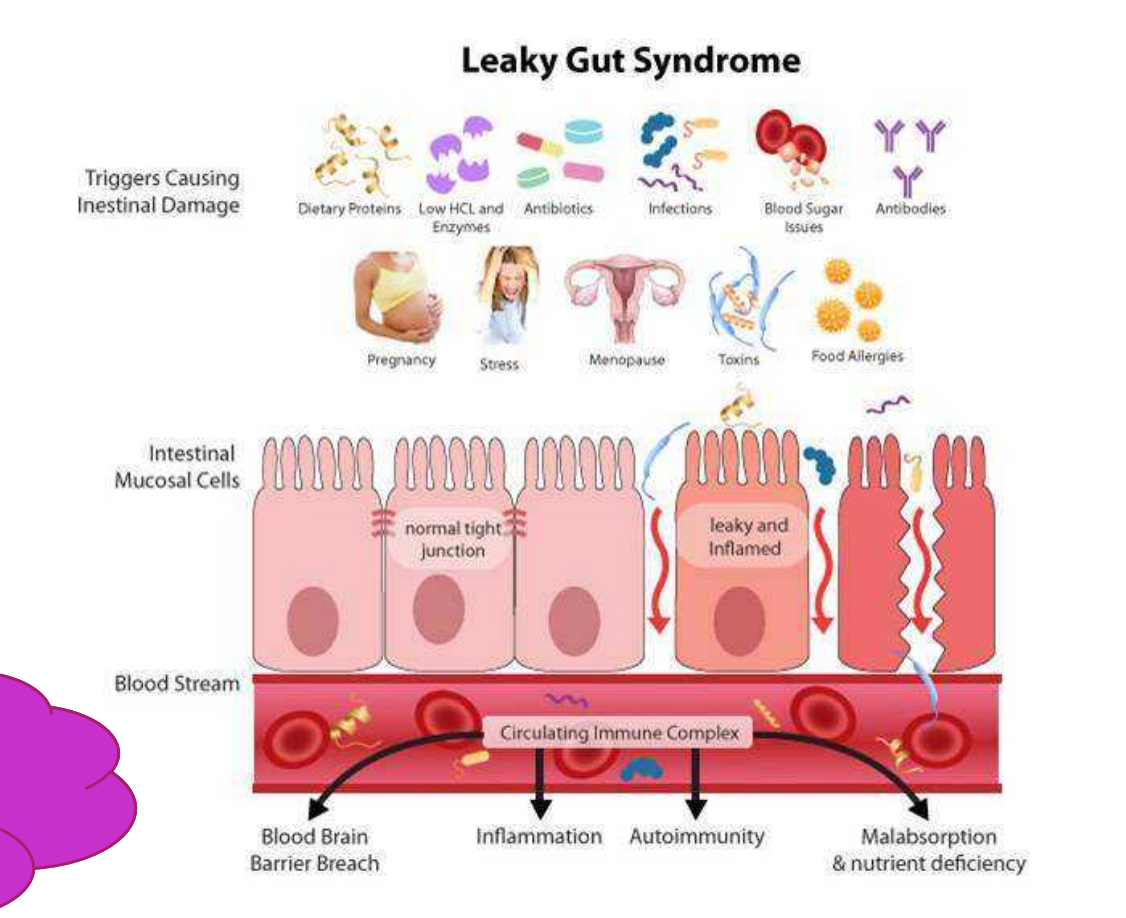
STRESS COPING  
MECHANISMS (CORTISOL)  
GENERATE  
GENERALIZED  
INFLAMMATION



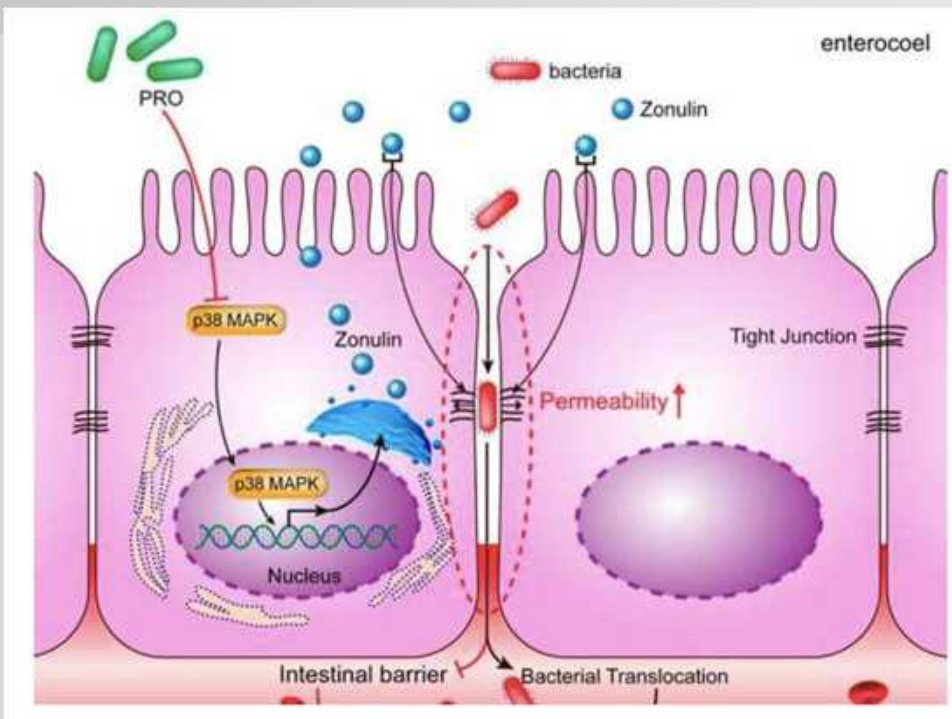
# BARRIER DYSFUNCTION = LEAKY GUT SYNDROME = DYSBIOSIS

Cortisol

Mood



# HOW TO MEASURE A LEAKY GUT ?



**Zonuline**, the only physiologic modulator of intercellular tight junctions.

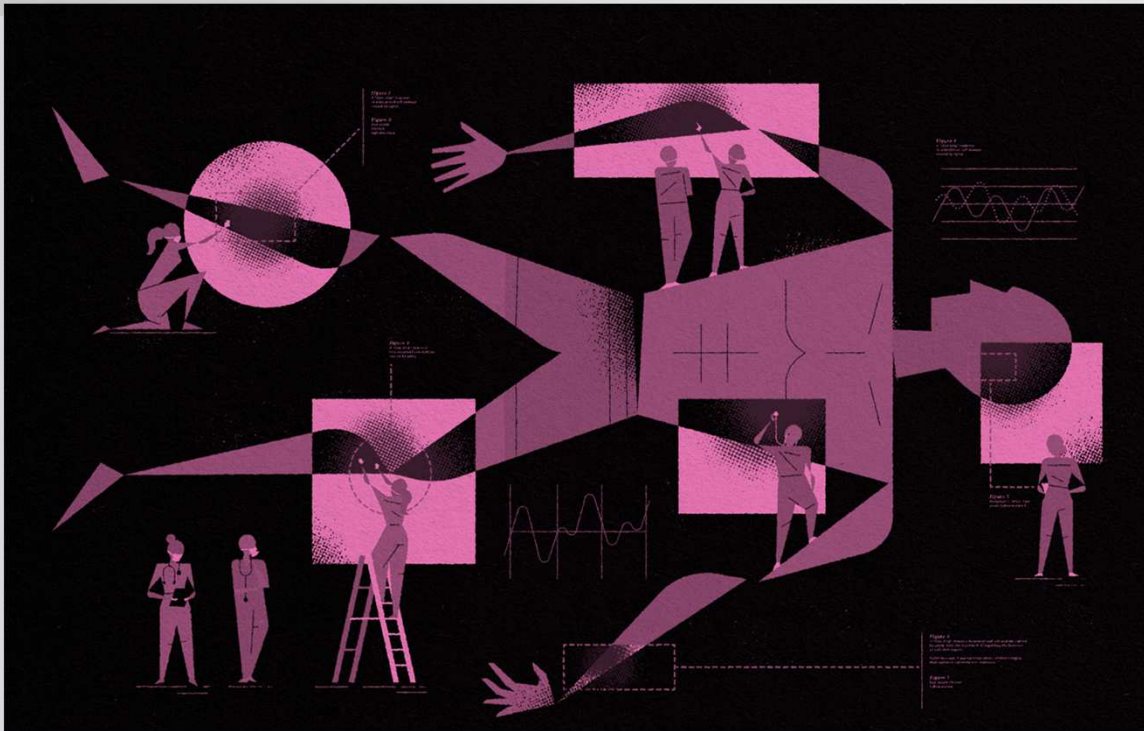
Faeces >78 ng/mL

Serum > 48 ng/mL



# BARRIER DYSFUNCTION AND « SICKNESS DISEASE »

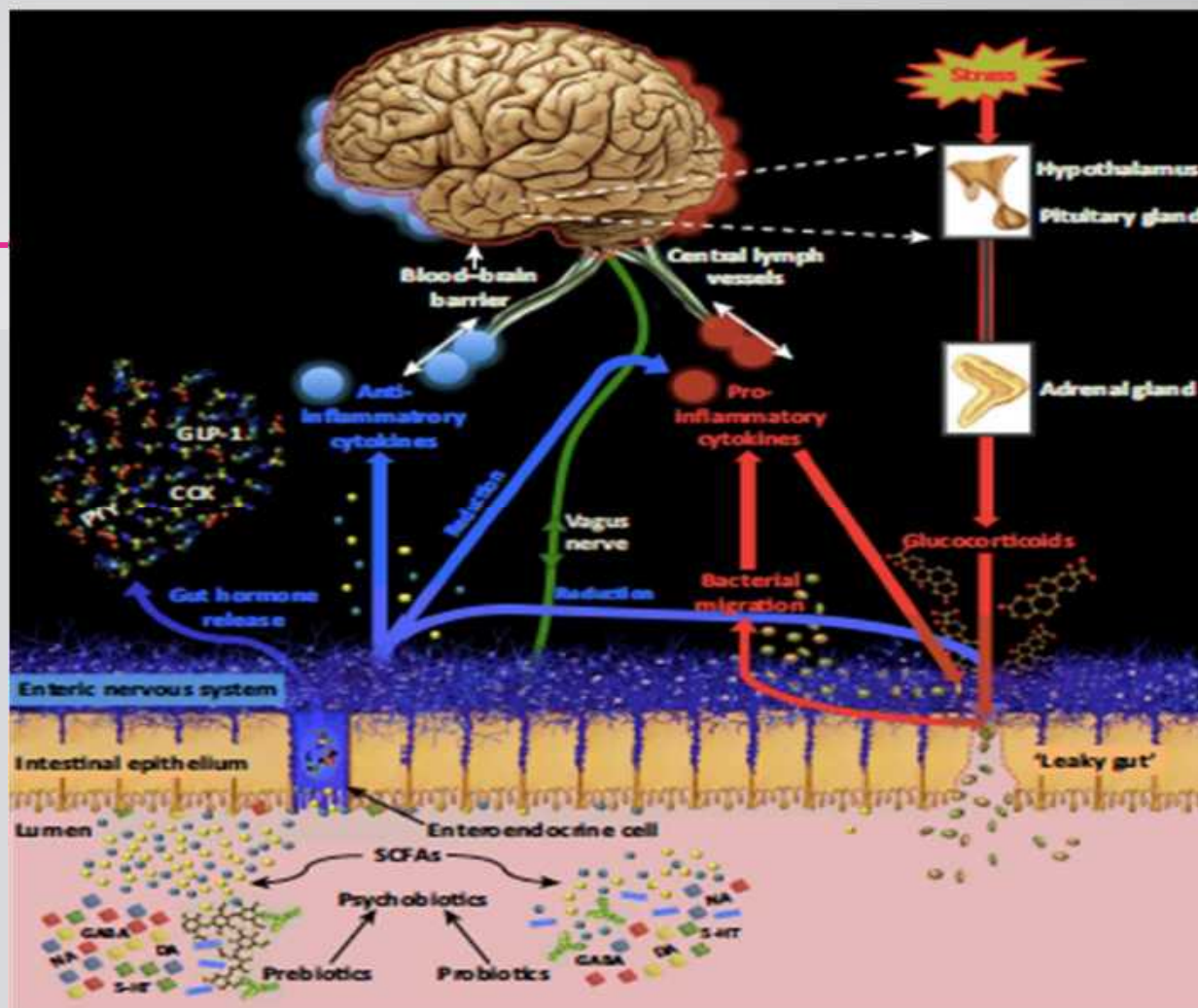
---



loss of memory,  
anxiety,  
refusal to meet social events,  
obsessional thoughts,  
difficulty to concentrate,  
depression,  
chronic fatigue syndrome,  
sleeplessness,  
loss of interest,  
obsessional neurosis

## « PSYCHO-BIOTA »

Our food choices have an influence on the **de-inflammation** of our gut by selecting the beneficial bacterial strains of our microbiota



# NEUROACTIVE POTENTIAL OF MICROBIOTA

---

- ◆ *Faecalibacterium* and *Coprococcus*, producers of propiobutyrate, are regularly associated with indicators of good **quality of life (QoL)**
- ◆ Together with *Dialister*, *Coprococcus spp.* are decreased in case of depression, even after correction for the confounding effects of antidepressants.





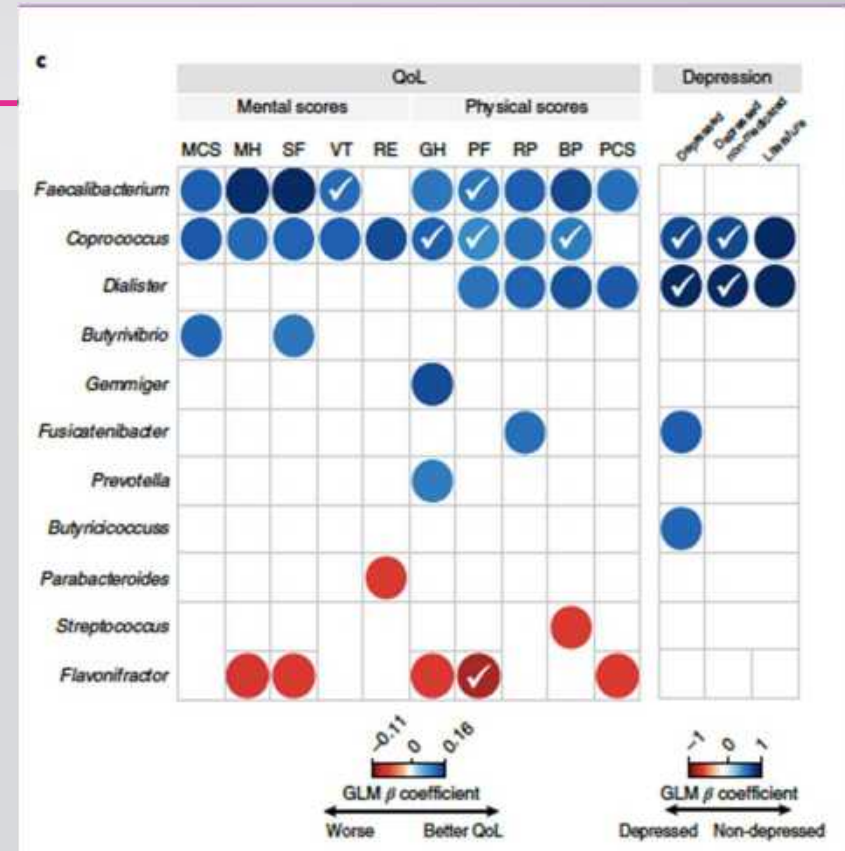
# QUALITY OF LIFE (QOL) IS AN AFFAIR OF BACTERIAL STRAINS

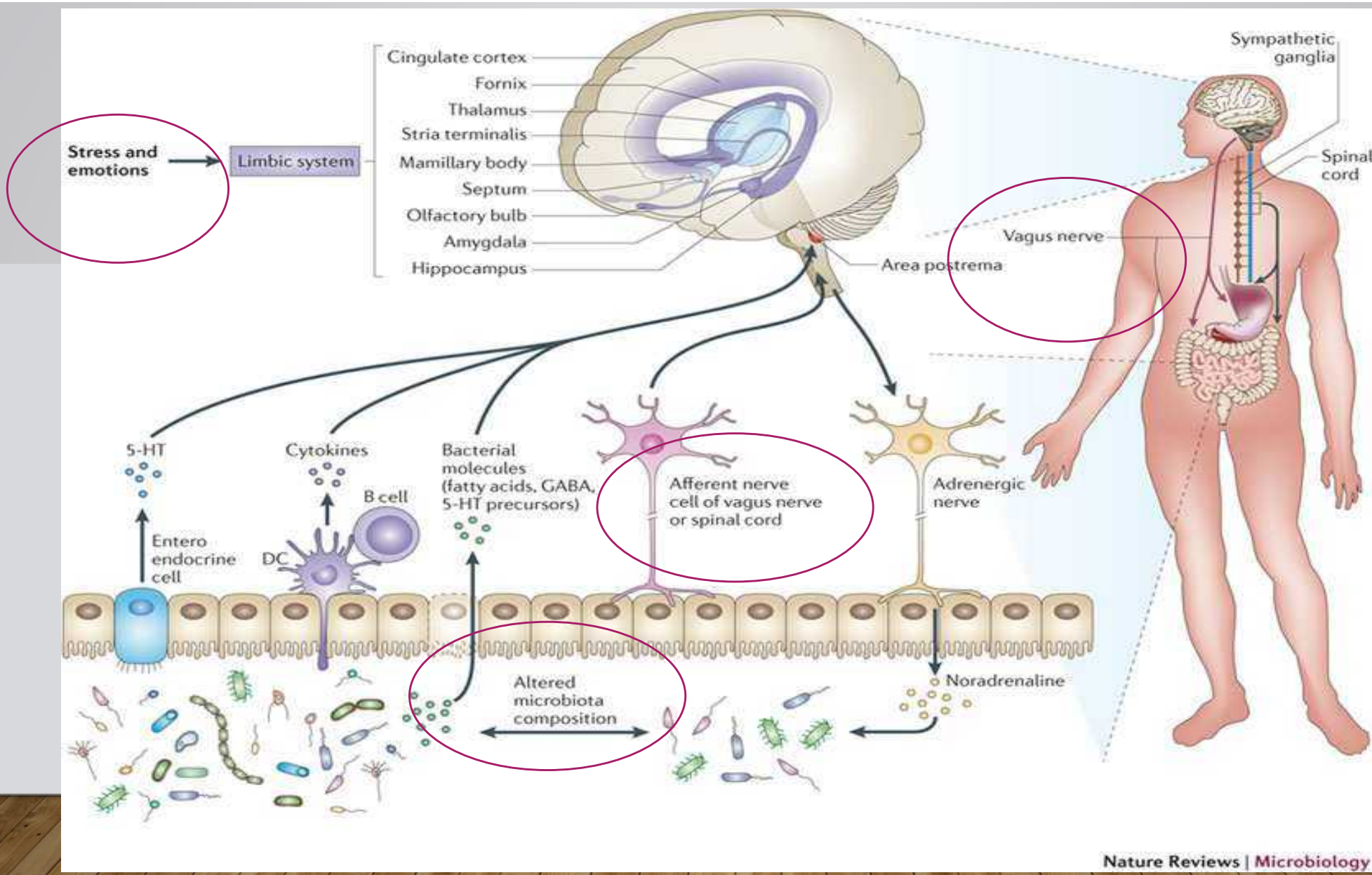
## Mental parameters

MCS = mental health;  
 MH = emotional well-being;  
 SF = social functioning;  
 VT = vitality.

## Physical parameters

GH = general perception;  
 PF = physical functions ;  
 RP = role limitations;  
 BP = burden pain;  
 PCS= physical compliance score





LET'S SUMMARIZE  
WHAT IS GOING ON...

---





# THE « THREE WINDS » THEORY...

STRESS



RESCUE  
BY FOOD



REWARD  
SUGAR



# THE VICIOUS CIRCLE OF REWARD...



« *Stop eating when you are still a little hungry* »  
ancient beduin proverb

### 3. THE GUT-BRAIN AXIS INFLUENCES SKIN QUALITY

---

WHY IS THE BRAIN-GUT CONNECTION RELEVANT TO SKIN BEAUTY AND AGING ?





# BECAUSE MOOD IS DEPENDING ON THE GUT-BRAIN AXIS

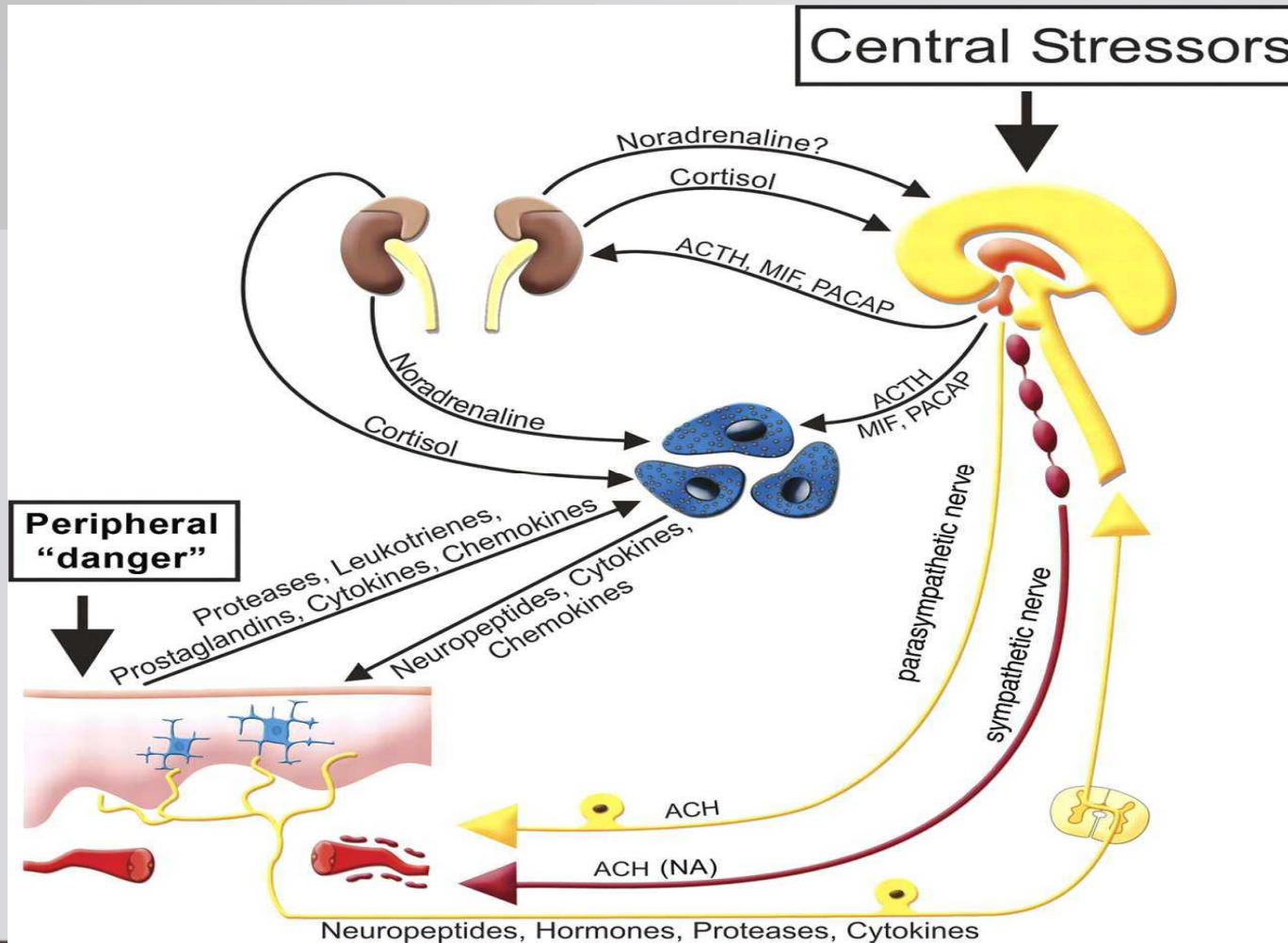
---

« *Stress is an alert system, very similar to a general defence system, such as **inflammation.*** »

**Hans Selye**



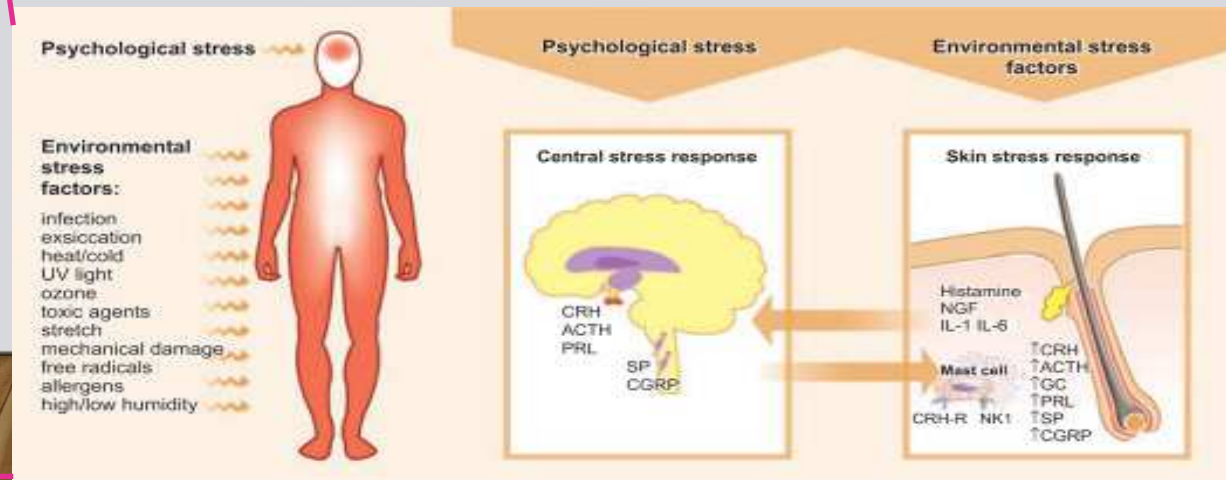
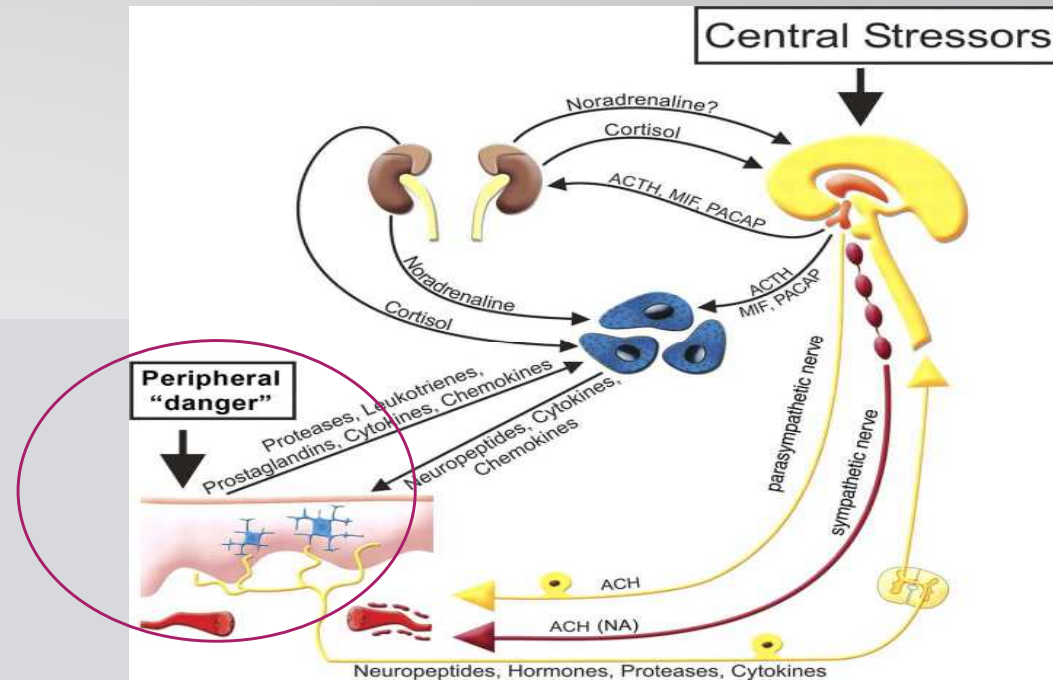
# THE BRAIN-SKIN CONNECTION



# SKIN IS SENSING STRESS

The skin displays a fully functional peripheral HPA system

Infection  
 Exsiccation  
 Heat/cold  
 UV light  
 Ozone  
 Toxic agents  
 Stretch  
 Mechanical damage  
 Free radicals  
 Allergens  
 High/low humidity



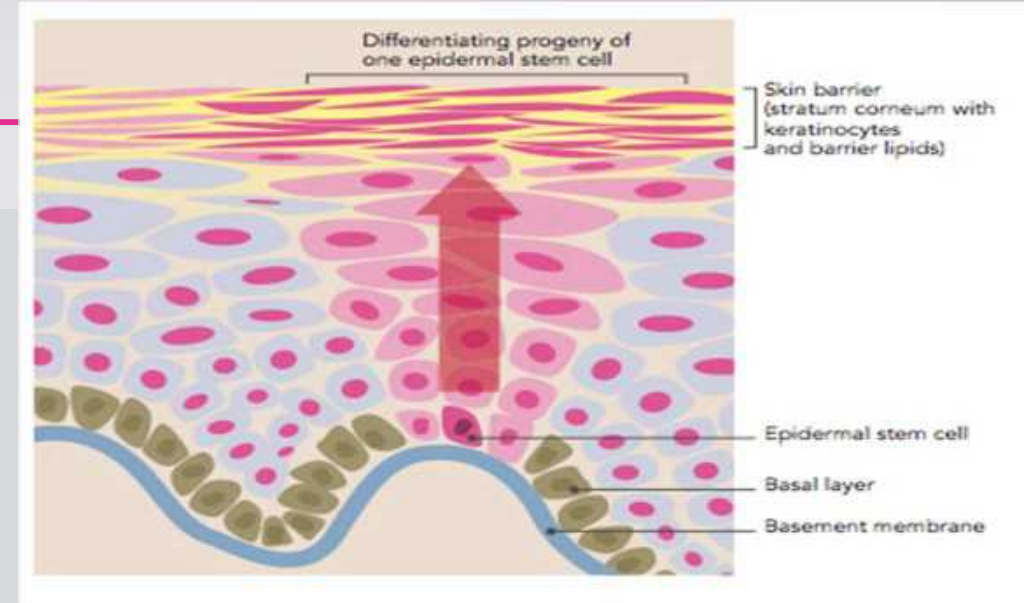
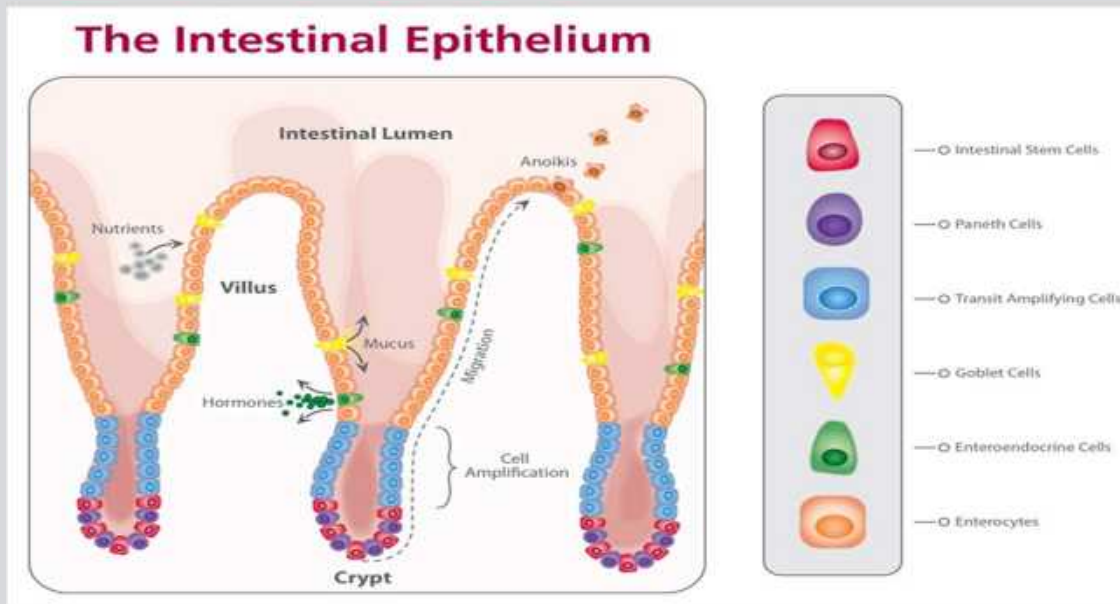




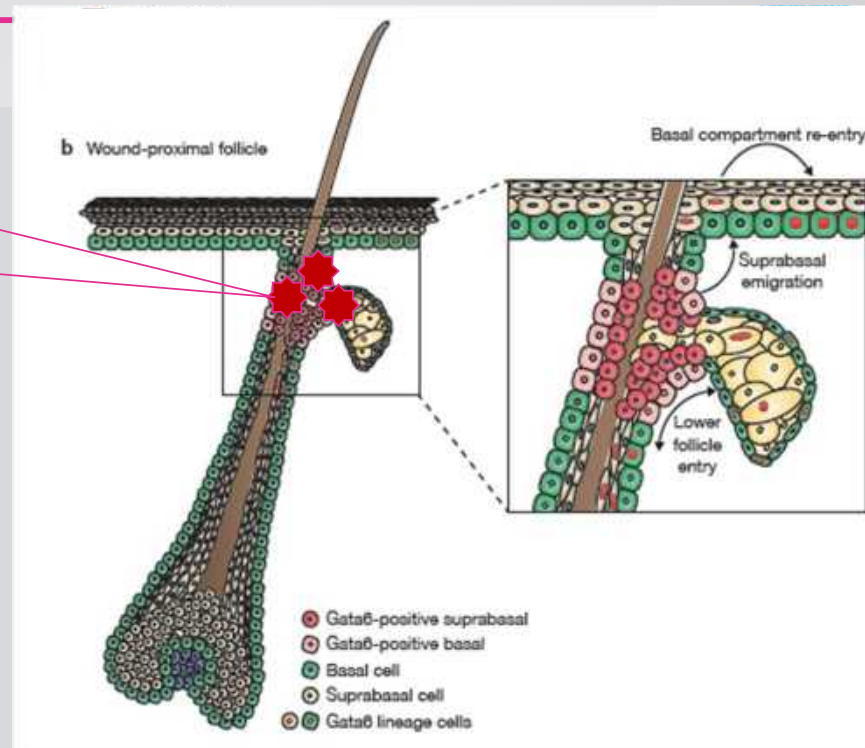
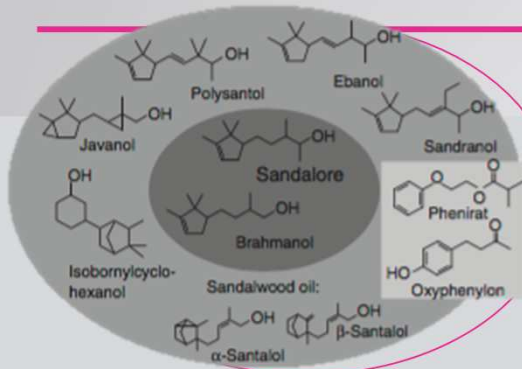
MODULATE INFLAMMATION TO IMPROVE THE SKIN ?

**FEEDING OR FASTING ?**

# INTENSE GUT AND SKIN RENEWAL AFTER PERIODIC FASTING



# SMELL AND SKIN REPAIR



## A Synthetic Sandalwood Odorant Induces Wound-Healing Processes in Human Keratinocytes via the Olfactory Receptor OR2AT4

Daniela Busse<sup>1</sup>, Philipp Kudella<sup>1</sup>, Nana-Maria Grüning<sup>1,7</sup>, Günter Gisselmann<sup>1</sup>, Sonja Ständer<sup>2</sup>, Thomas Luger<sup>3</sup>, Frank Jacobsen<sup>4</sup>, Lars Steinsträßer<sup>4,8</sup>, Ralf Paus<sup>5</sup>, Paraskevi Gkogkolou<sup>6</sup>, Markus Böhm<sup>6</sup>, Hanns Hatt<sup>1</sup> and Heike Benecke<sup>1,9</sup>



# WHAT TO EAT TO STAY YOUNG AND...SEXY ?



Today we know that to improve health and skin quality,  
we can compensate salty / sweet craving with supplements

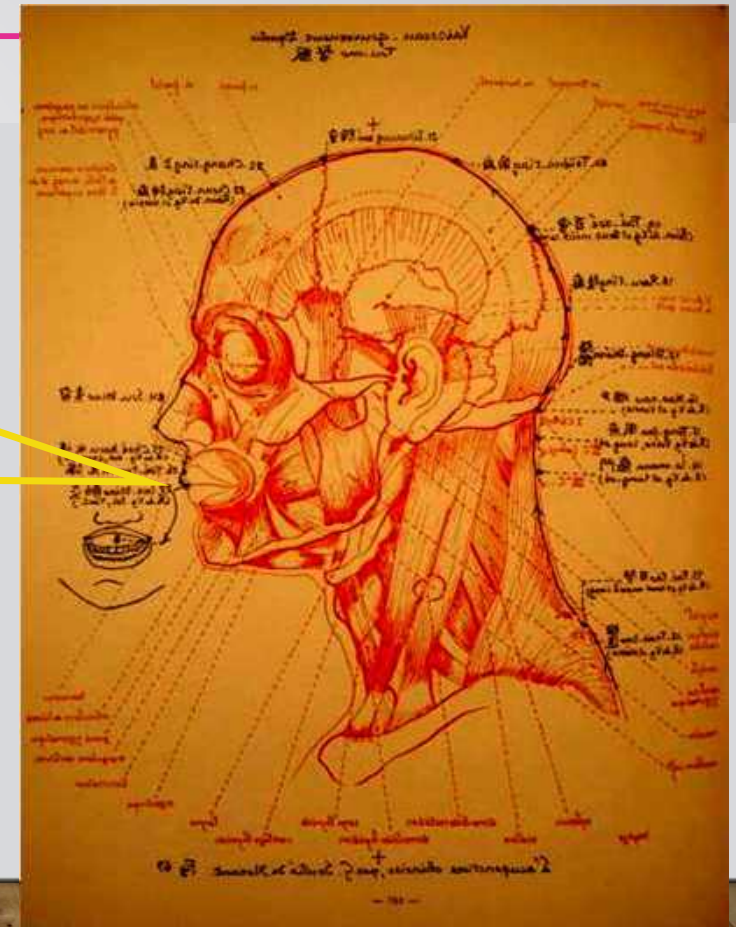
---





# STIMULATING THE VAGUS NERVE OUR GREATEST ANTI-INFLAMMATORY TOOL

- A taste you like...  
potently induces vagal activation



George Soulié de Morant in : *Précis de la vraie acupuncture chinoise* Mercure de France, 1932 Paris



# ATTENTIONNATE SKIN TOUCH FROM A FRIEND

---



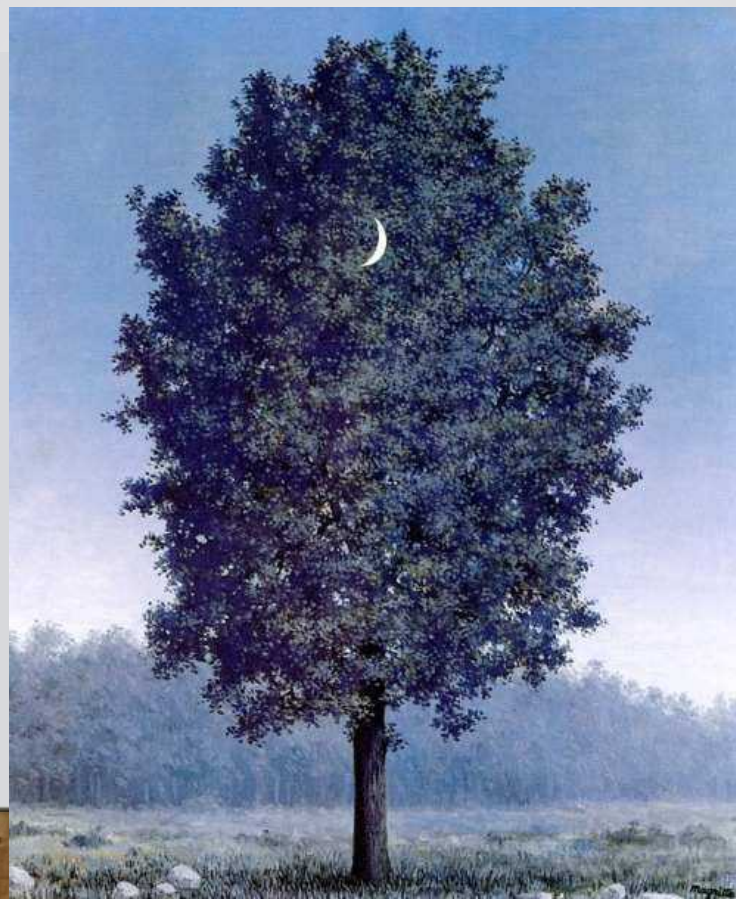
Social grooming



Emma Thompson & Greg Wise

# SIGHT : WATCHING A HEALING IMAGE

---



# But also ...

Breathing – cardiac coherence

Enchanting sounds

Smell of a perfume





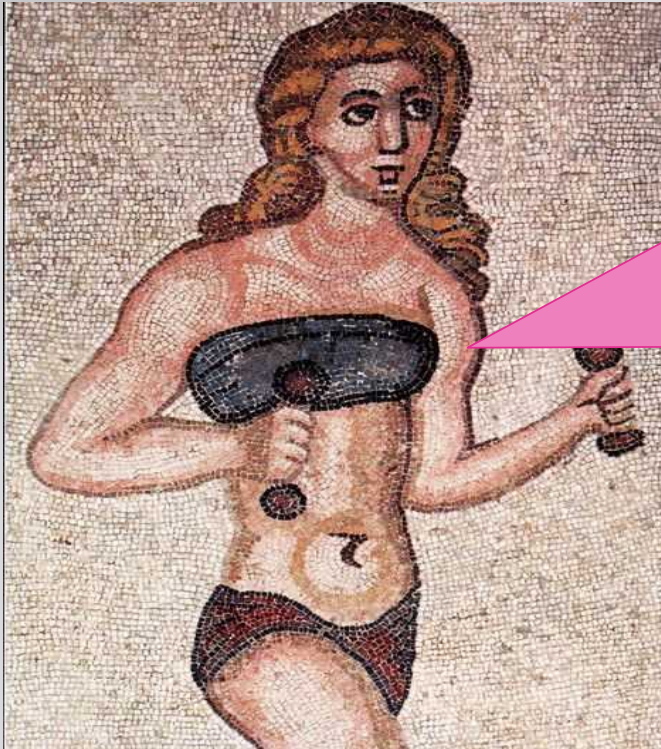
## « Pleasures... »

They deeply activate the vagal system, induce a relaxation and repair reaction of the body, accompanied by a **decrease of all biochemical markers of inflammation.**



# PLEASURE MAY INCLUDE PHYSICAL ACTIVITY

---



Myokines display several capacities :

- SPARC myokine prevents colon cancer
- Myokines > BDNF protect against neurodegenerative diseases
- Meteorin-like 1 METRNL promotes beige fat thermogenesis / **anti-inflammatory**
- Myonectin regulates the absorption of fatty acids by the liver
- Musclin increases physical endurance by biogenesis of mitochondria.

# IN SUMMARY, THE GUT-BRAIN CONNECTION INFLUENCES SKIN QUALITY...

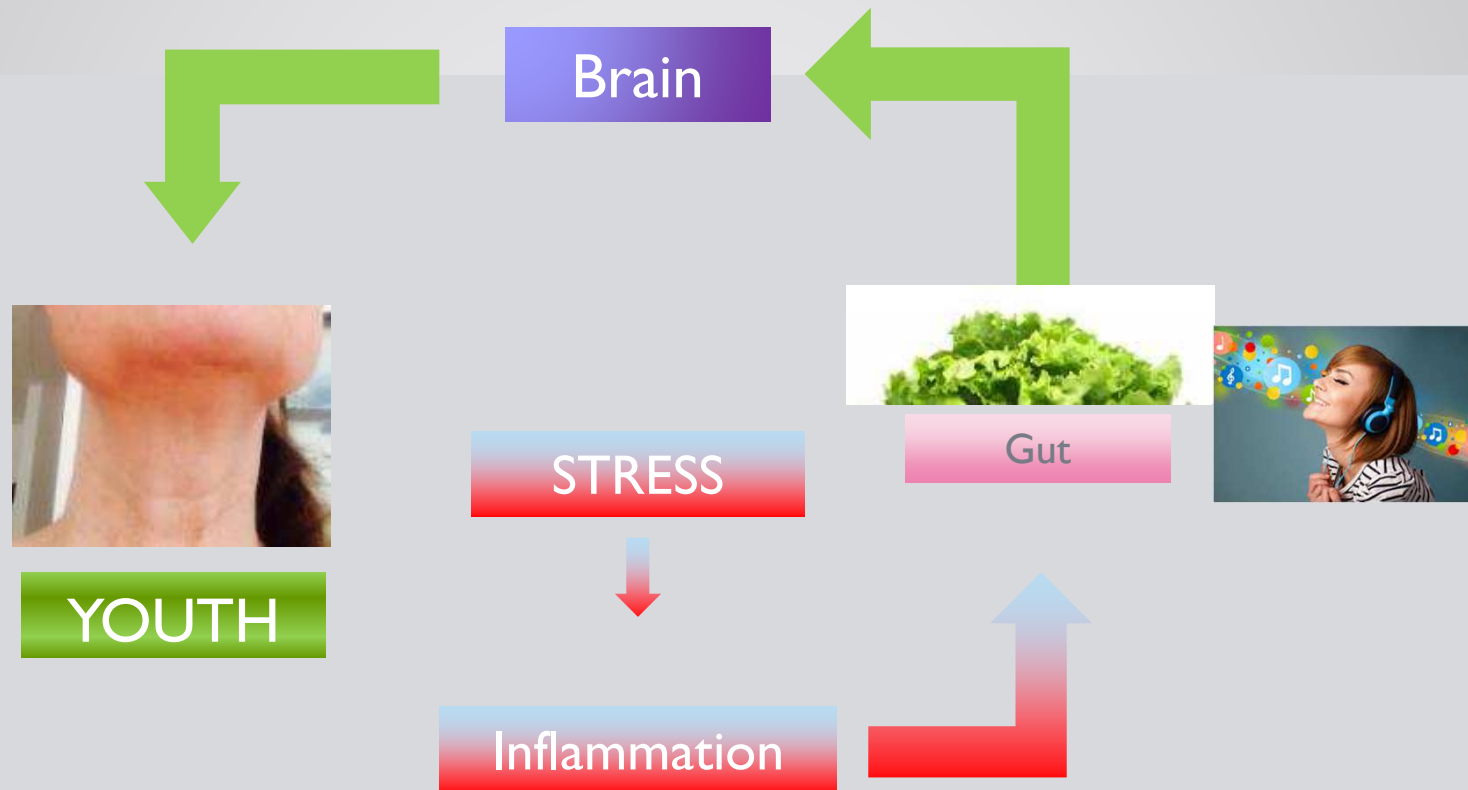
---

- ◆ Stress can destabilize the **gut barrier function**, thus generalizing the inflammatory reaction.
- ◆ Chronic inflammation fuels aging.
- ☞ Nutrition may become a potent inductor of epigenetic modifications.



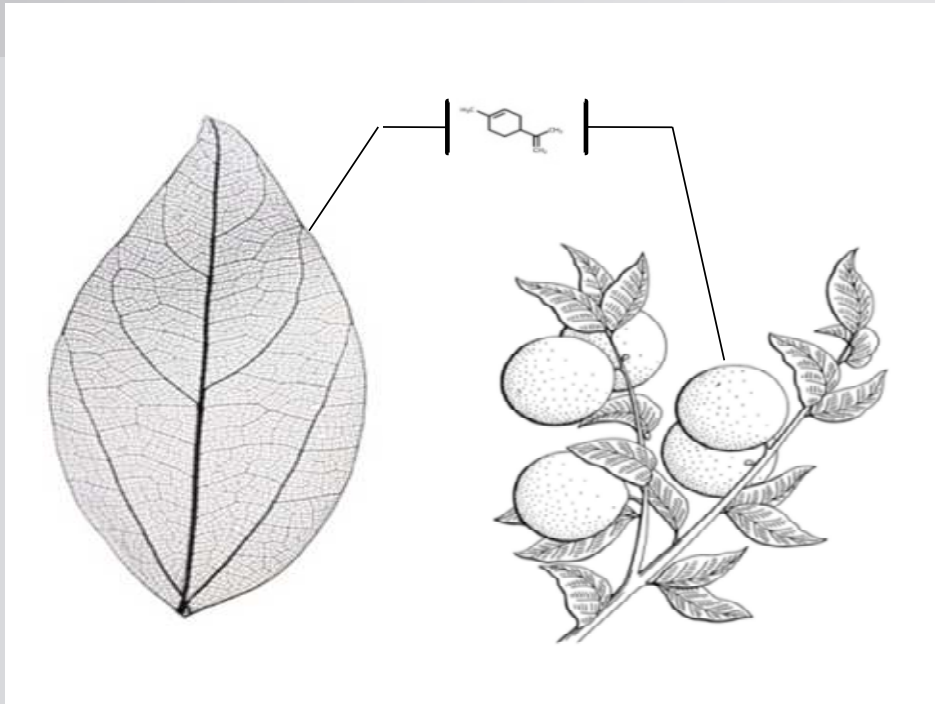
# ...BUT, THE GUT-BRAIN CONNECTION CAN ALSO AMELIORATE SKIN QUALITY

---



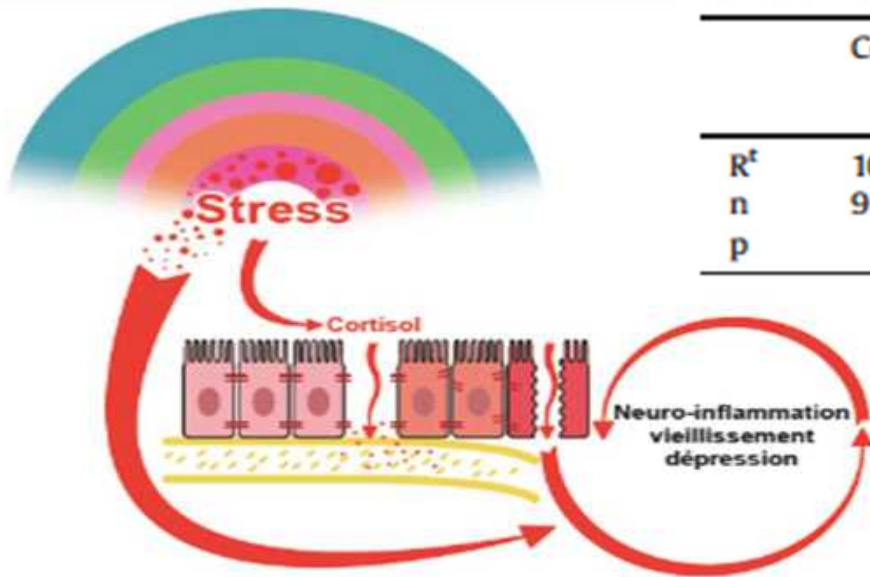
# SOLUTIONS FROM NATURAL SUBSTANCES

---



- ◆ Initially discovered in *Halfordia kendack*, in Vietnam, the molecular complex AISA was then identified in orange peel.
- ◆ After cold pressure extraction and calibration by AISA technology, the AISA bioactive compound is generated.

# BARRIER RESTORATION



**Table 1**  
OPE containing 95% of *d*-Limonene: effect on epithelial barrier function.

	Control	OPE			
		75 $\mu$ M	150 $\mu$ M	750 $\mu$ M	1500 $\mu$ M
$R^t$	107 $\pm$ 3%	106 $\pm$ 4%	112 $\pm$ 3%	132 $\pm$ 3%	153 $\pm$ 4%
n	9	6	6	6	6
p		n.s.	n.s.	<0.001	<0.001

Measure of the electric ( $\text{in } \Omega \cdot \text{cm}^2$ ) resistance as % of the initial resistance  $R_t$ .

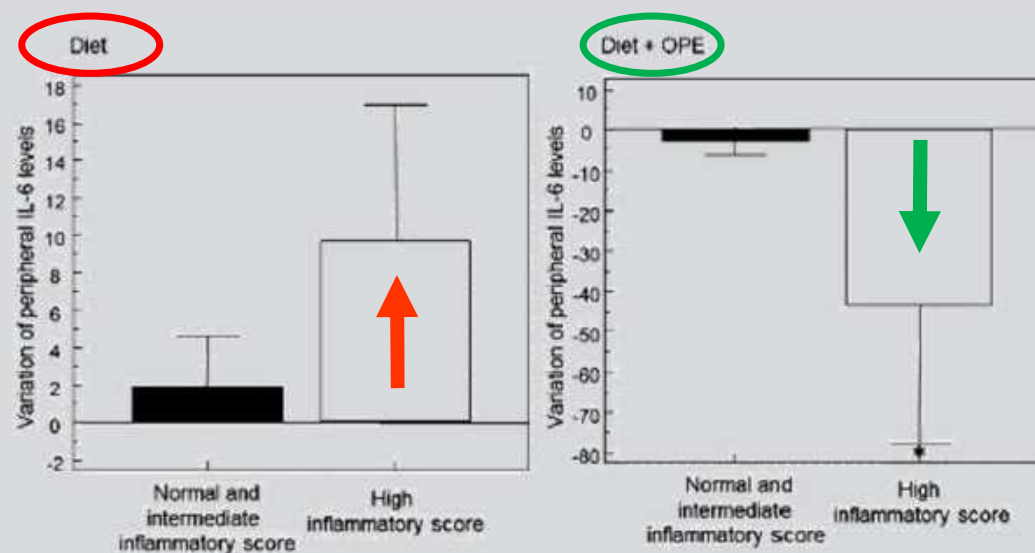


# ANTI-INFLAMMATORY EFFECT IN HUMAN HEALTHY VOLUNTEERS



Assay of IL-6 as function of the basic inflammatory profile

A controlled diet plus a supplementation by AISA **decrease** the levels of circulating IL-6

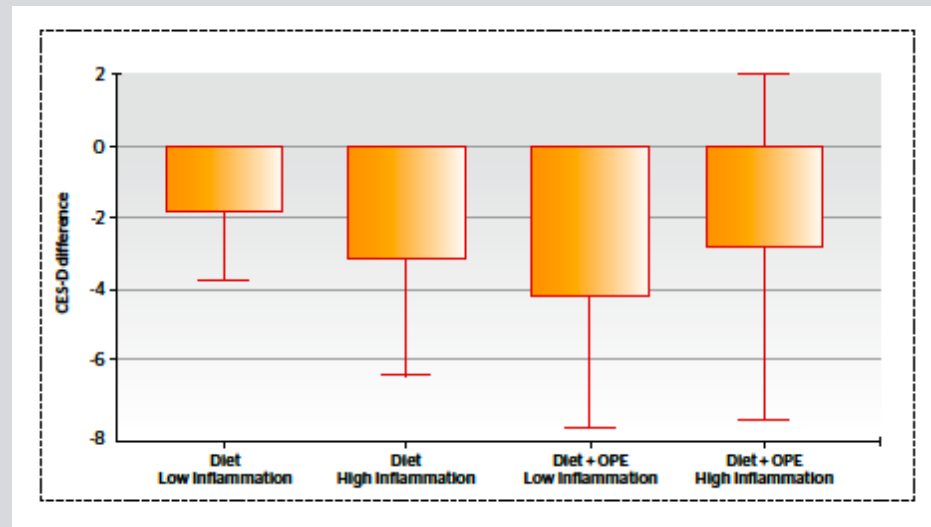


# THE CES-D\* SCORE VARIES ACCORDING TO THE INFLAMMATORY PROFILE

\* Center for Epidemiological Studies Depression Score



Questionnaires show a **significant** decrease by AISA = mood modulation



# PSORIASIS DEPENDS ON DYSBIOSIS AND CHRONIC INFLAMMATION

## EFFICACY – INTERMEDIATE PSORIASIS

PSORIASIS study : 10 patients open label - 45 days



D0



D45

SKIN

NAILS

SCALP



# REDNESS A MAJOR SIGN OF INFLAMMATION

## INFLAMMATION AND SKIN REDNESS AFTER LASER TREATMENT



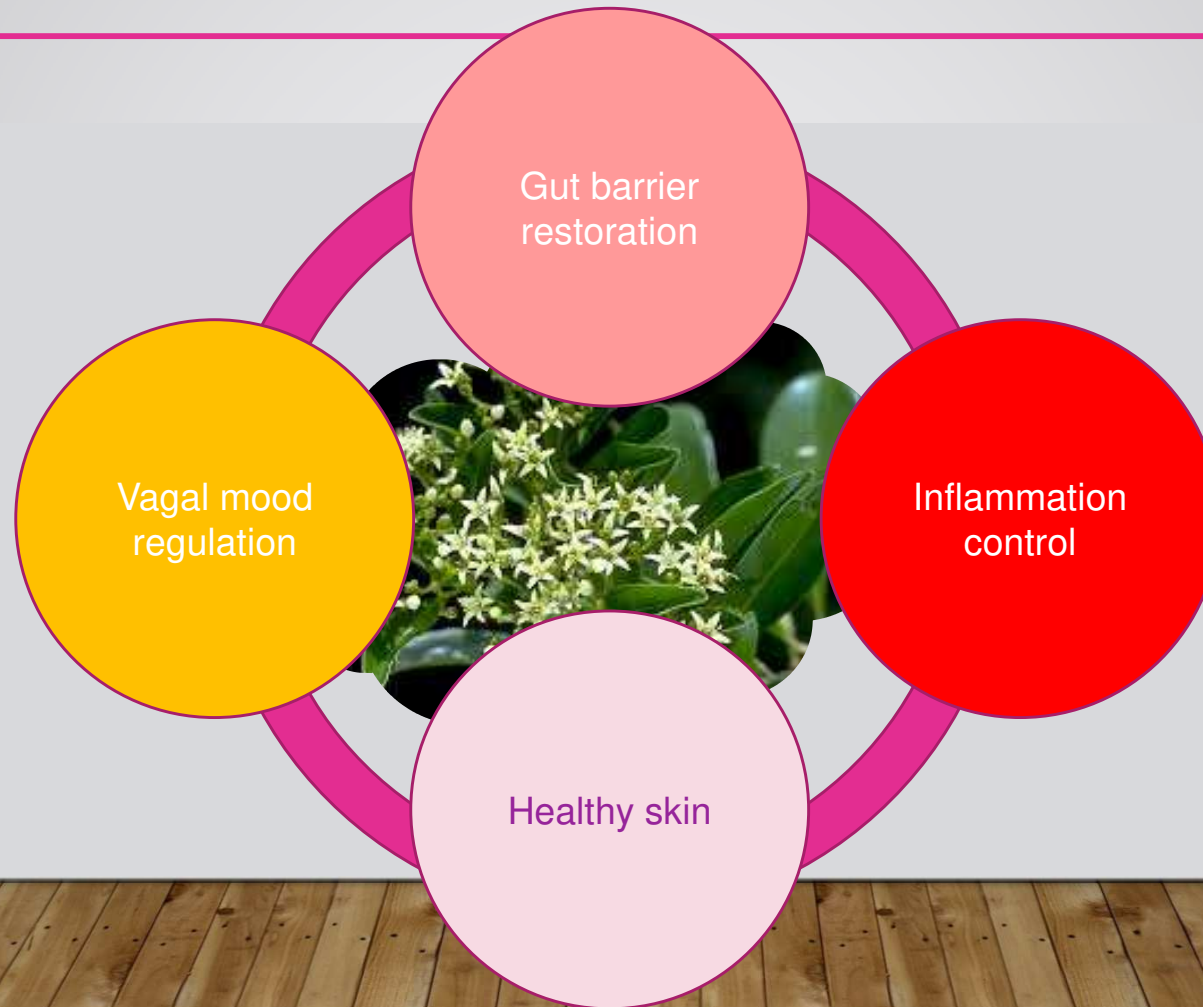
WITHOUT AISA



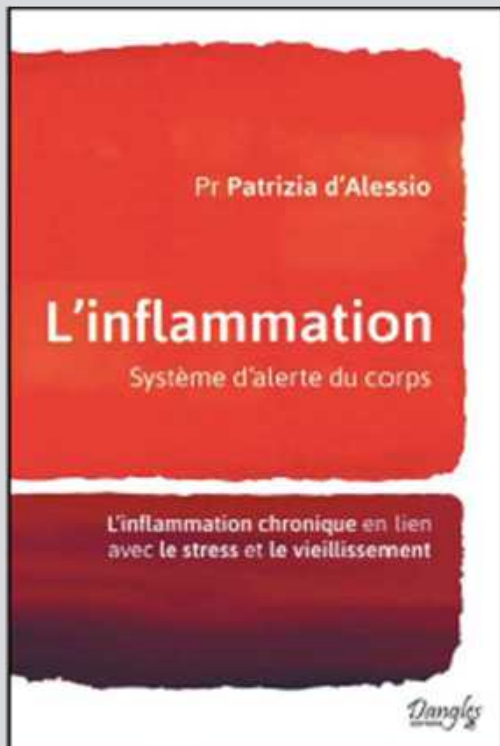
WITH AISA

# A FOUR POINT CONUNDRUM SOLVED BY ONE BIOACTIVE COMPOUND

---



THANK YOU FOR YOUR ATTENTION



[patriz.dalessio@gmail.com](mailto:patriz.dalessio@gmail.com)

[www.aisa-tx.com](http://www.aisa-tx.com)

[www.aisa-care.com](http://www.aisa-care.com)





Jean-François Bisson, Chantal Menut, Claudio Franceschi, Valeria M Ursini,  
Joerg D Schulzke, Marie C Béné, Olivier Herault