Nutrigenetics and the Rhythms of Life

Hello!

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Lifecode GX ®

— Professional Genotype Analysis —

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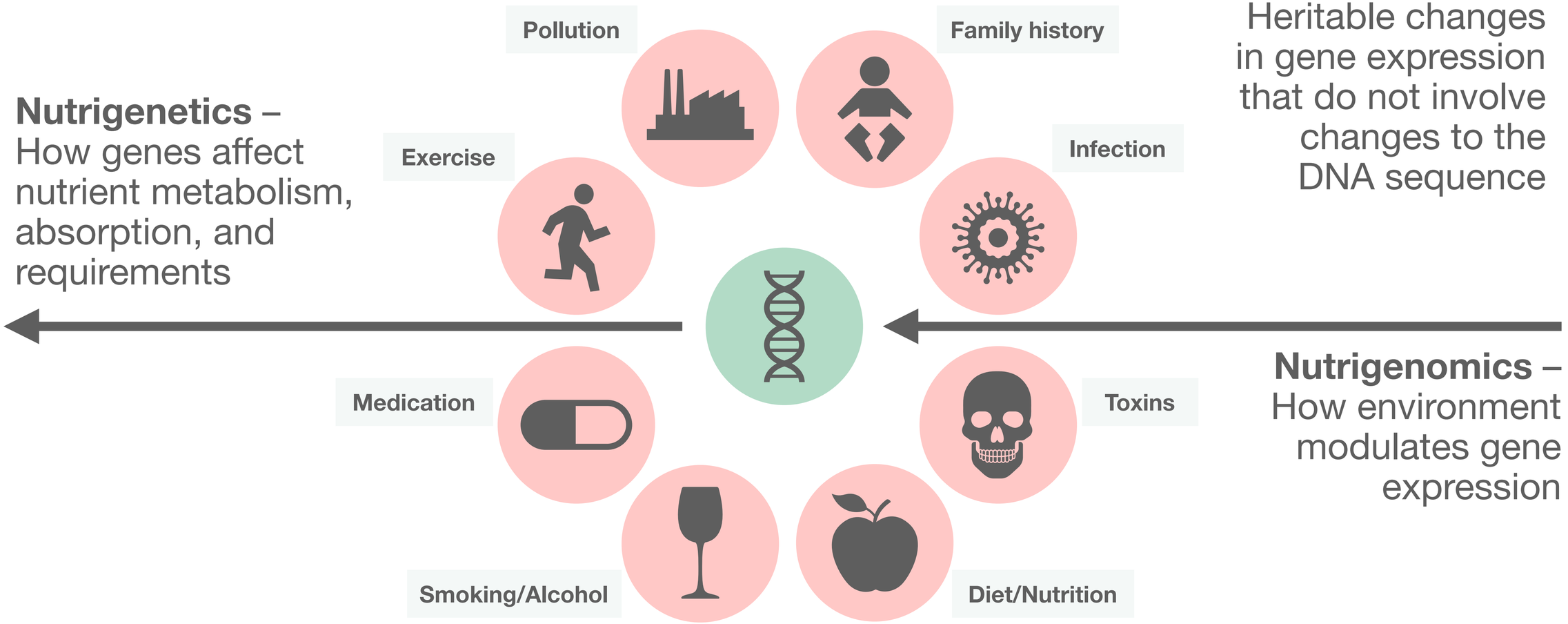
Education

Nutritional Genomics

Epigenetics – Heritable changes in gene expression that do not involve changes to the DNA sequence

Nutrigenetics – How genes affect nutrient metabolism, absorption, and requirements



Nutrigenomics – How environment modulates gene expression

SNPs

- Single Nucleotide Polymorphisms
- Small variations in nucleotide sequence
- Altered gene function

Sensory perception

Exteroception

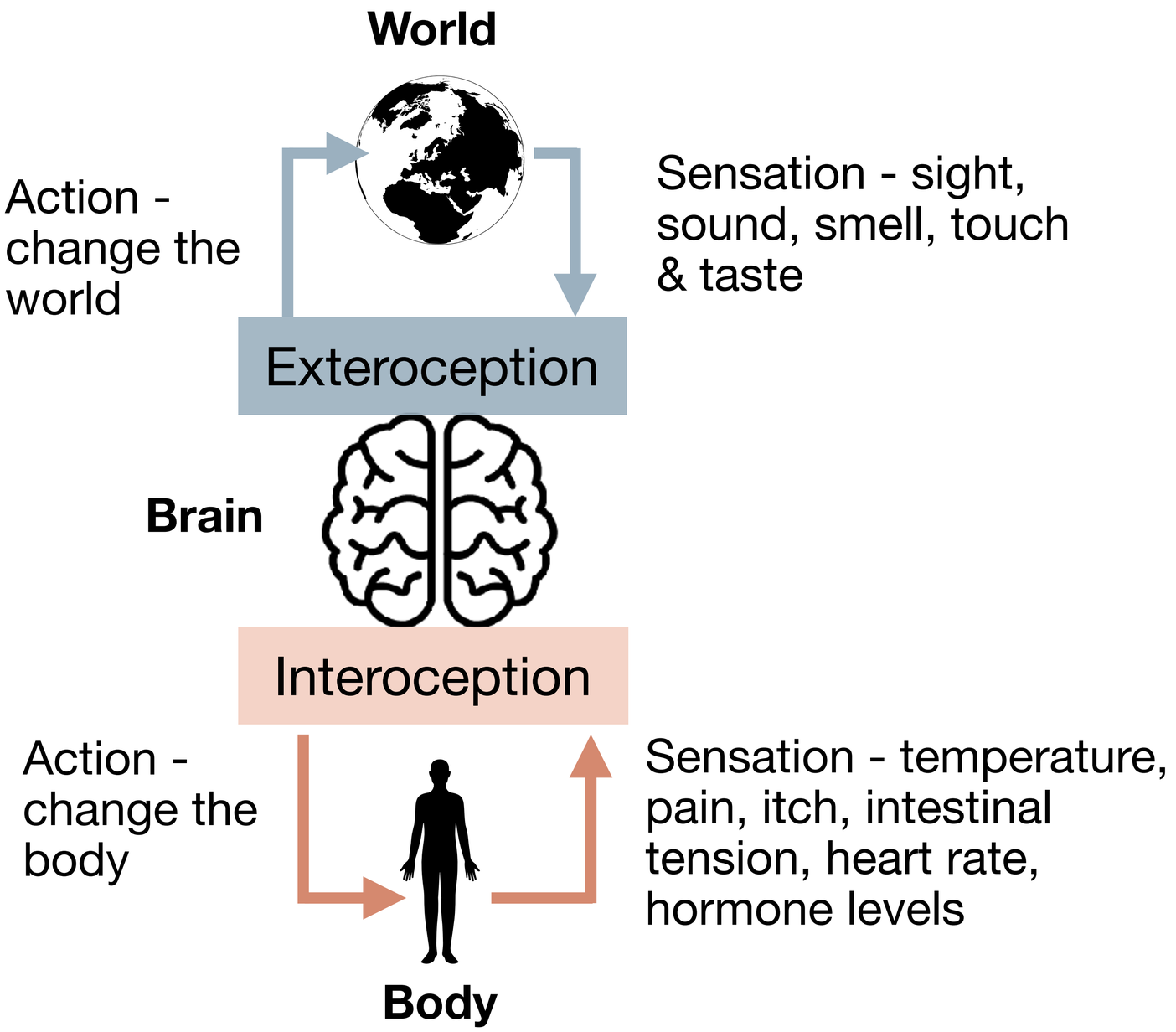
- **Light**, Sound, Smell, Taste & Touch

Interoception

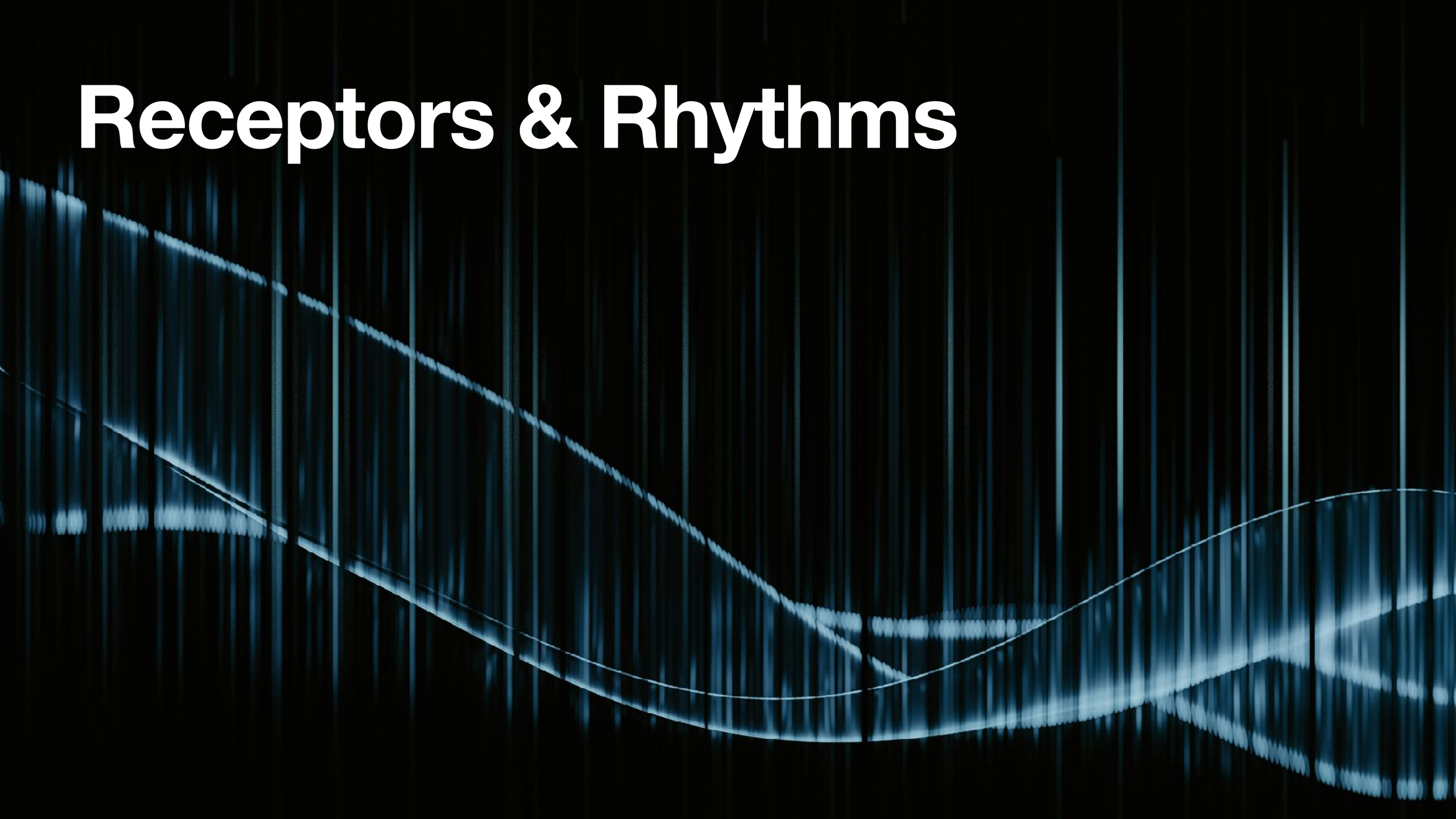
- Perception of **internal** sensations, such as **hunger**, thirst, pain, and fatigue

Homeostasis + Allostasis

The brain is always predicting - matching what it expects with what it feels

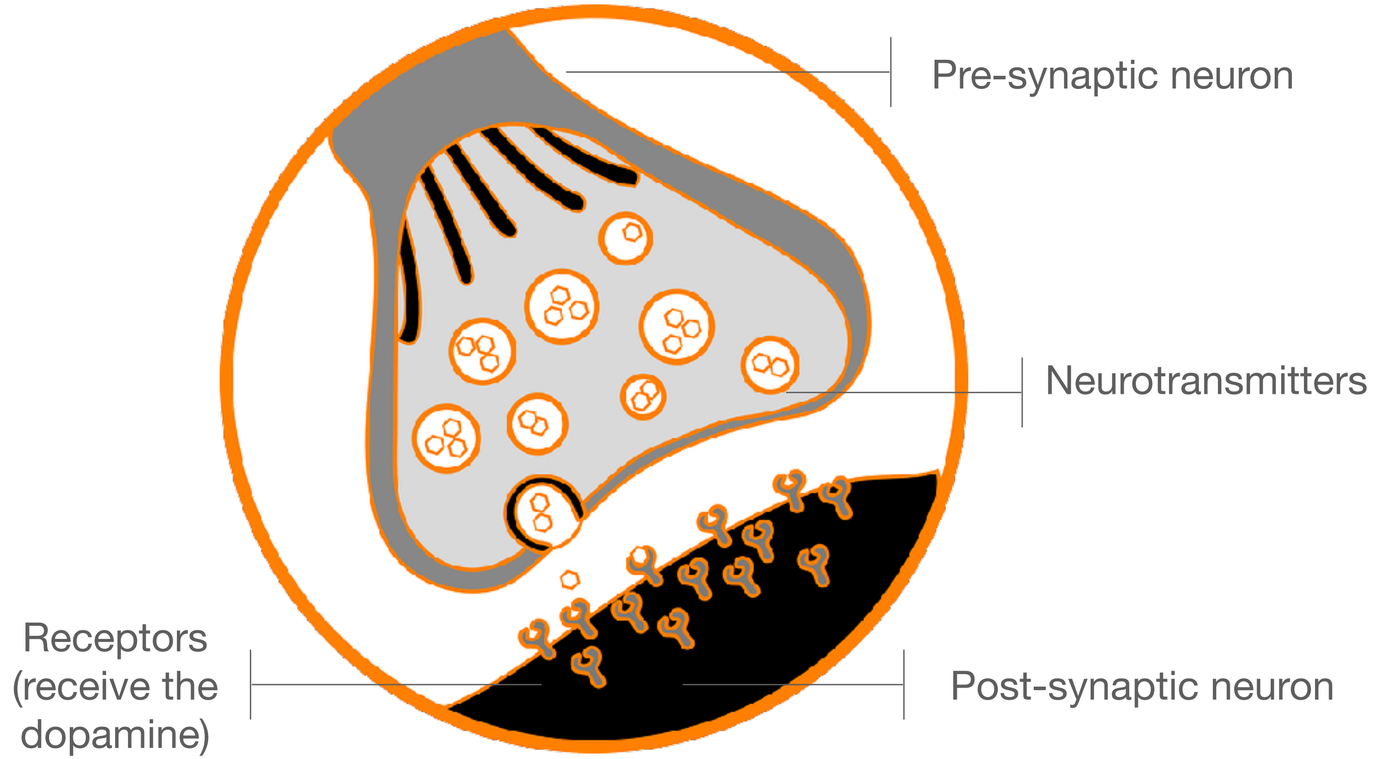


Receptors & Rhythms



Receptors + Responses

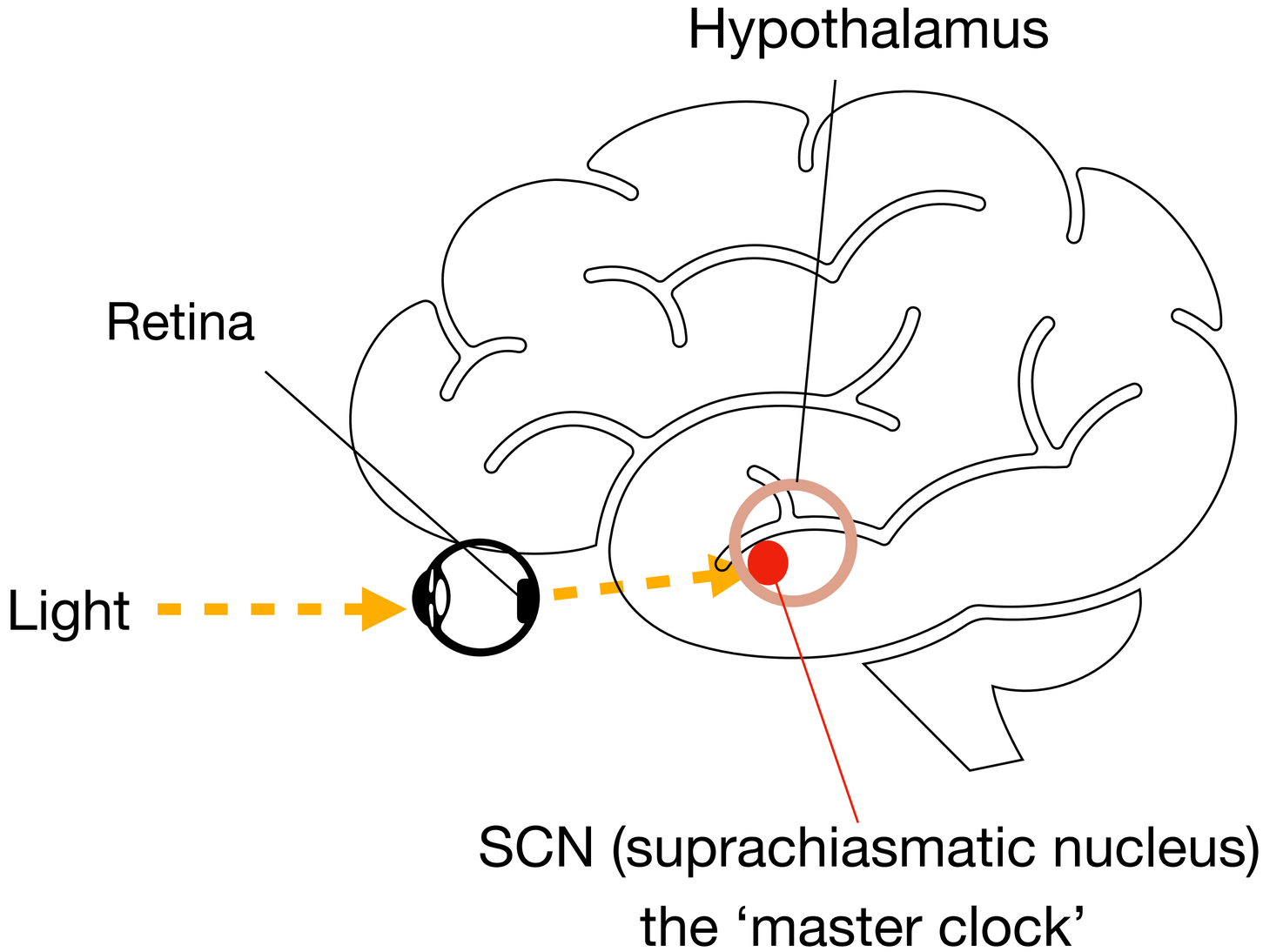
- Receive signals - from the world (external environment) and the body (internal environment)
- Transduce - trigger a cascade of events that lead to a cellular response
- Dopamine, Oestrogen, Insulin, Vitamin D and Calcium, as well as Light…



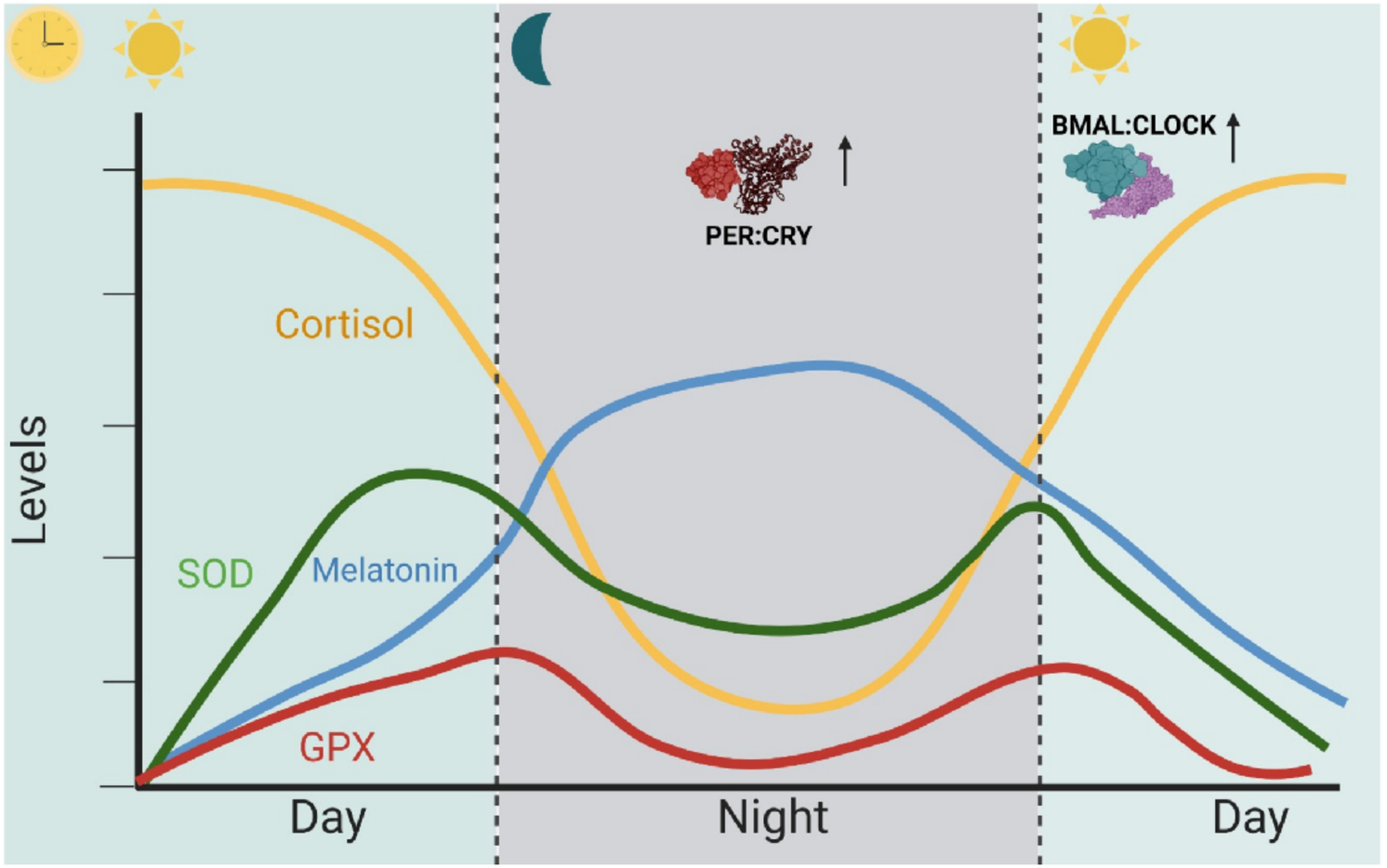
Photoreceptors

- **Rhodopsin** (rods) + **photopsin** (cones) - images, patterns, motion & colour
- **Melanopsin** detects light (non-visual) to sync the SCN and maintain **circadian rhythm**

All depend on retinal

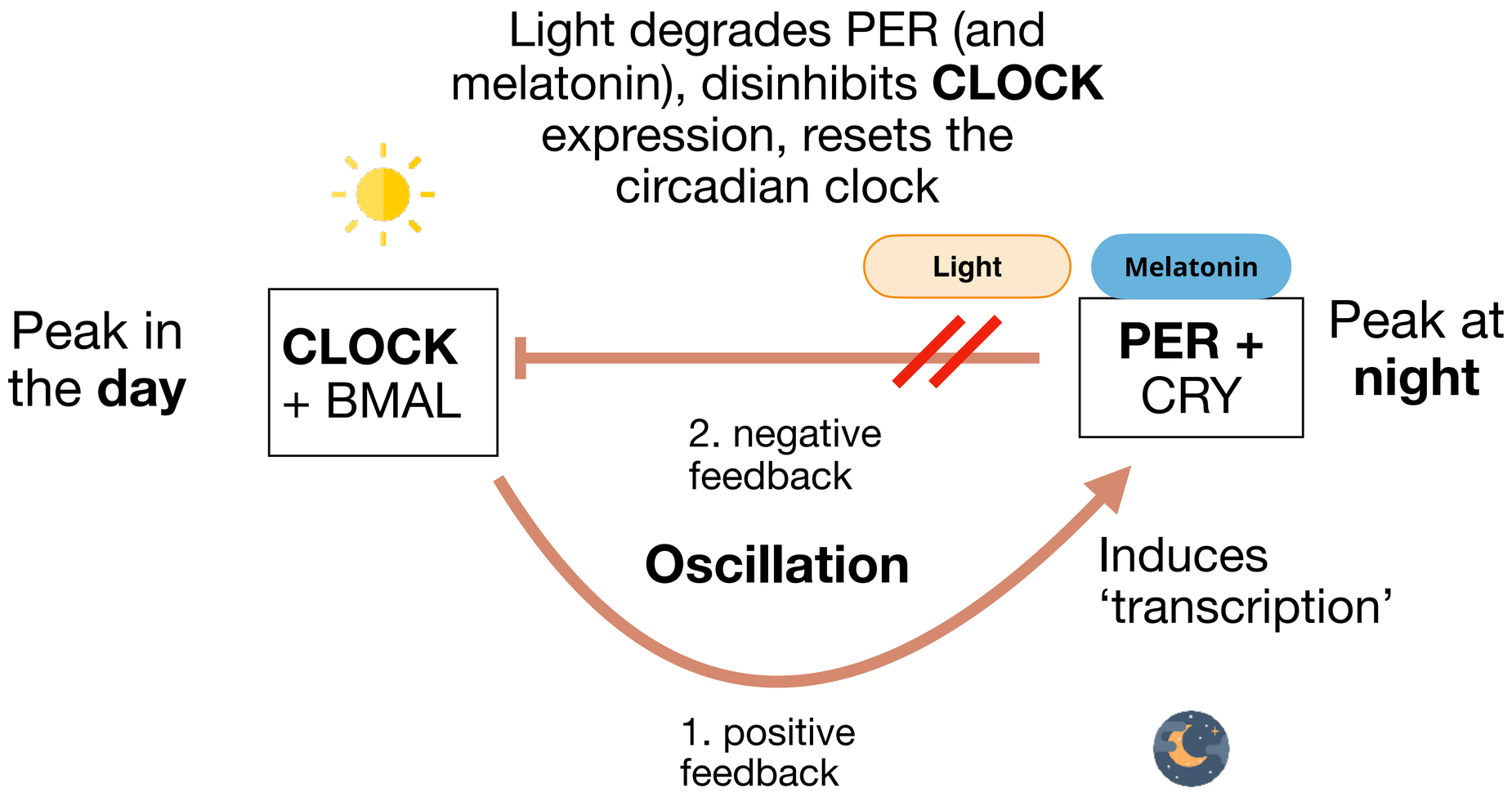


Circadian Rhythms



Trujillo-Rangel, W.Á et al

Clock Genes


Light degrades PER (and melatonin), disinhibits **CLOCK** expression, resets the circadian clock
Light
Melatonin
Peak in the **day**
CLOCK + BMAL
PER + CRY
Peak at **night**
2. negative feedback
Oscillation
Induces 'transcription'
1. positive feedback

CLOCK

Circadian Locomotor Output Cycles Kaput

- T311C SNP - delayed sleep onset (insomnia), normal wake time. Longer active period. **Shorter sleep duration - insufficiency**
- Dysregulated appetite (↑FTO, ↑ghrelin), MetS - overweight, type 2 diabetes
- Dysregulated **melatonin ↓evening, ↑morning (grogginess)**. Mood issues - MDD, bipolar

Consider the impact on peripheral clocks - metabolic etc. - as well as sleep

Aim to advance the clock – increase dawn light (priority), reduce dusk light

PER

Period Circadian Regulator

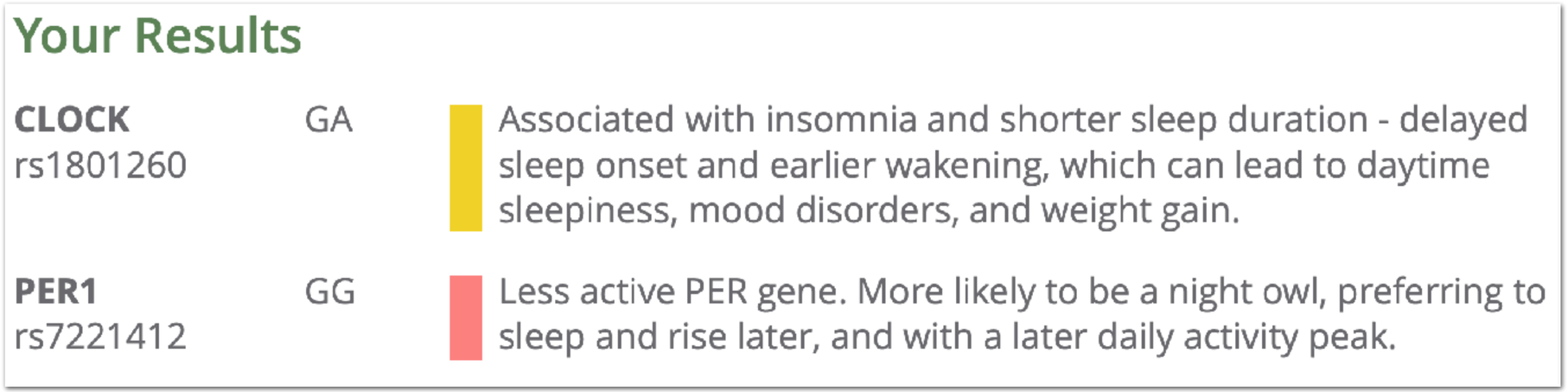
- Later sleep onset AND later waking
- Altered sleep **timing**. Displaces the peak phases. Later peak (67mins!)
- **Sleep insufficiency - <u>if</u> forced to wake early**
- Cognitive decline, depression, DNA damage

Go with it to some extent - know Your peak mental focus and physical performance time

Societal norms may challenge you

Nutrient Core: CLOCK genes

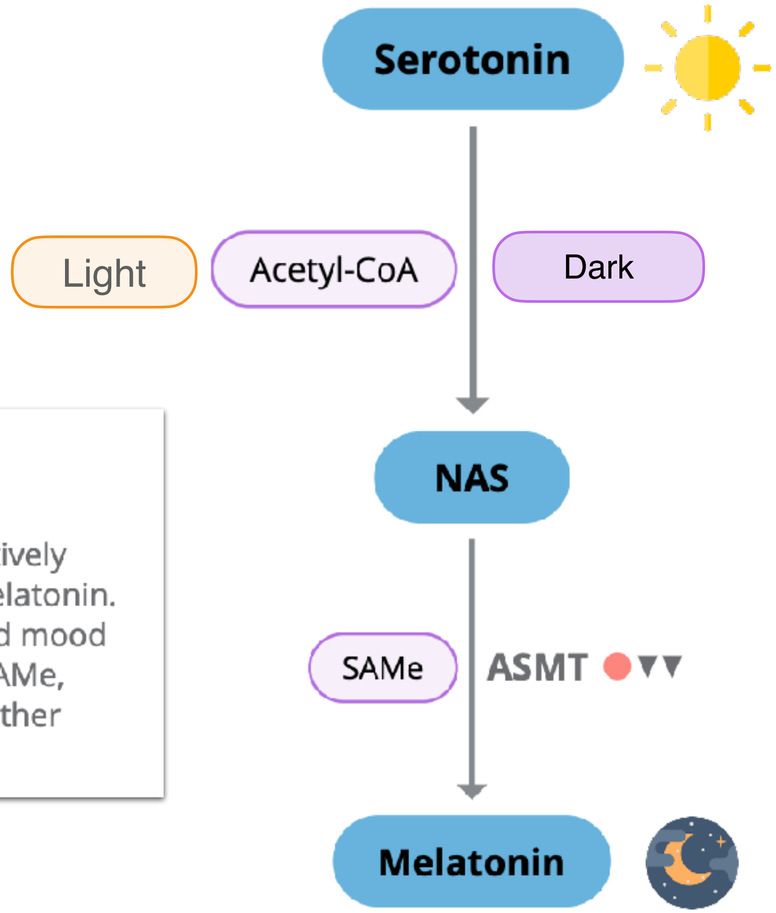
Genetic variants on the **CLOCK** gene are associated with **shorter sleep duration** whereas **PER1** variances are associated with **delayed sleep onset (night owl tendency)**



Go with it? Consider peripheral clocks too!

Melatonin Synthesis

Melatonin is produced in a Circadian rhythm



Detailed Results for Melatonin

ASMT GG▼▼
rs4446909

The G allele reduces the expression of ASMT which negatively impacts the conversion of N-acetyl-serotonin (NAS) to melatonin. Low levels of melatonin are linked to sleep disruption and mood disorders. Support ASMT activity by ensuring sufficient SAMe, the master methyl donor. Low methylation status will further impact melatonin synthesis.

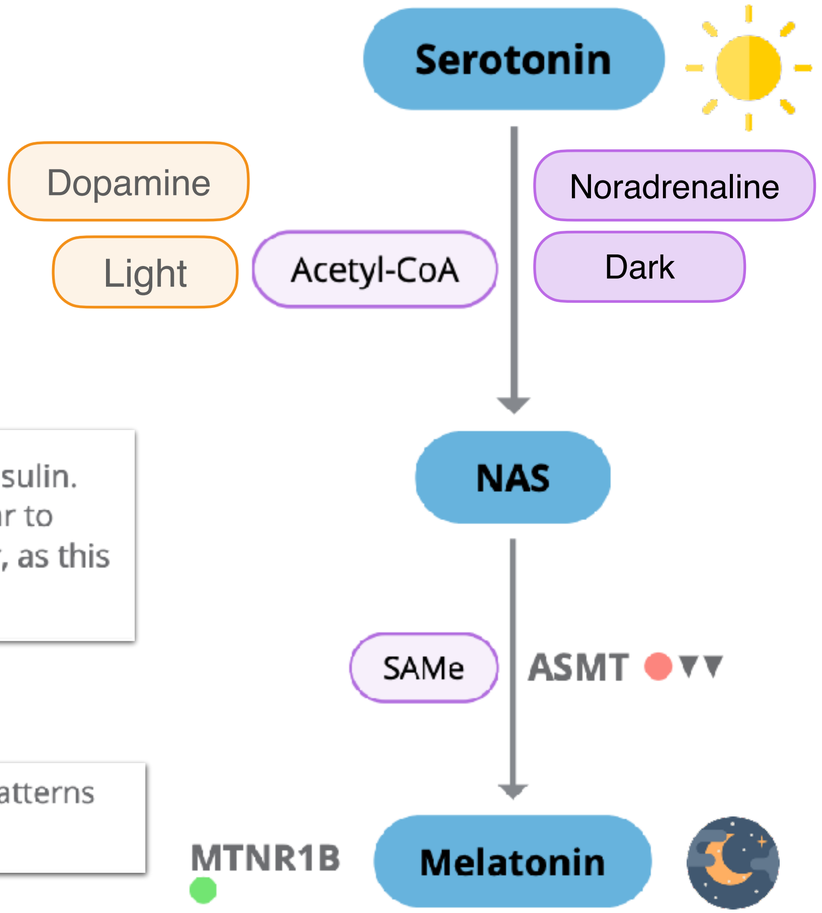
Methylation!

Melatonin Receptor

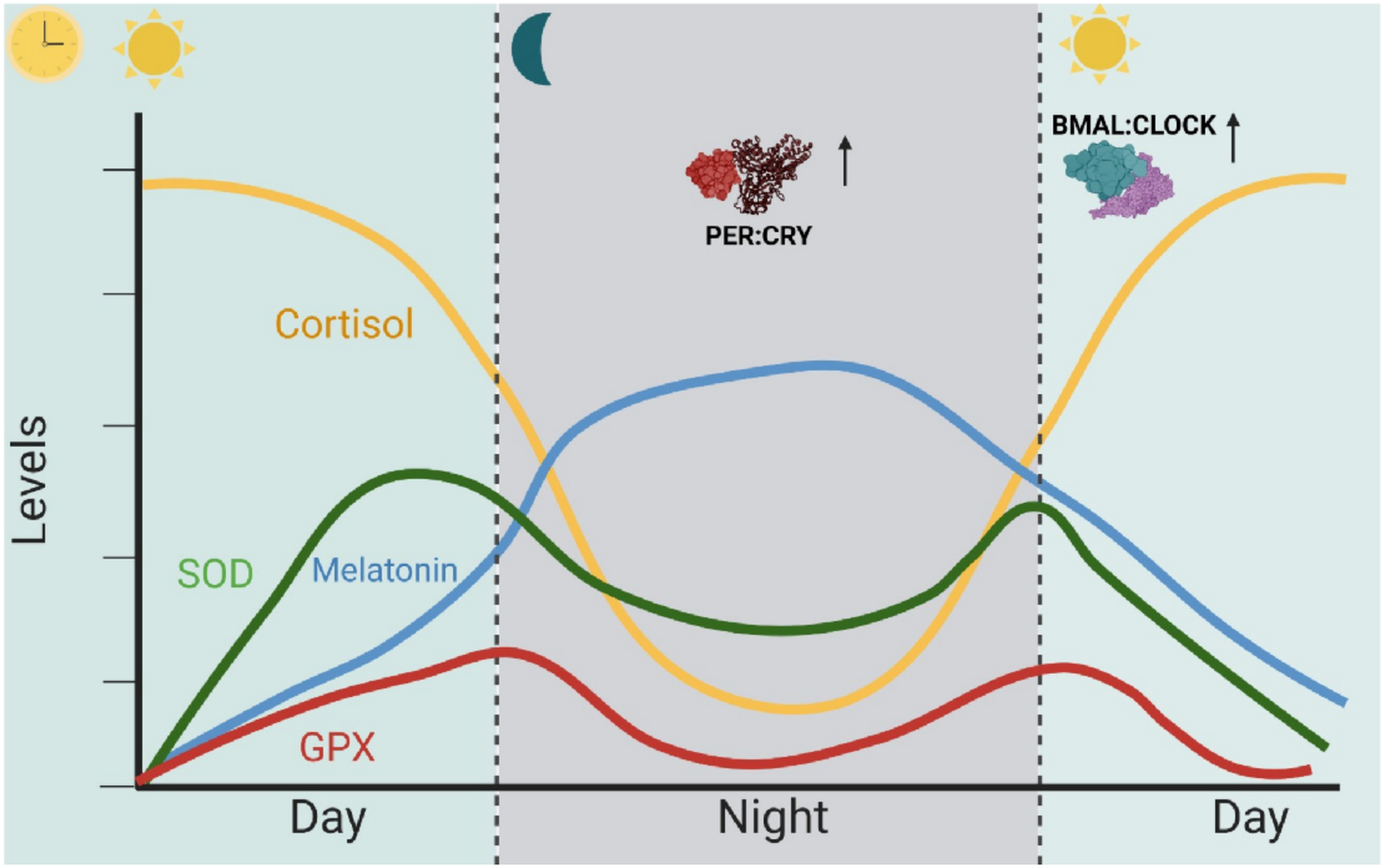
Insulin + Melatonin do not mix

Risk of Type 2 diabetes,
particularly in shift workers

MTNR1B rs10830963	GC▲	Increased sensitivity to melatonin and suppression of insulin. Avoid consumption of simple carbohydrates (sugar) near to sleep and wake times, when melatonin levels are higher, as this can increase the risk of type 2 diabetes.
MTNR1B rs10830963	CC	Normal melatonin receptor activity. No impact on sleep patterns or blood sugar metabolism.



Circadian Rhythms



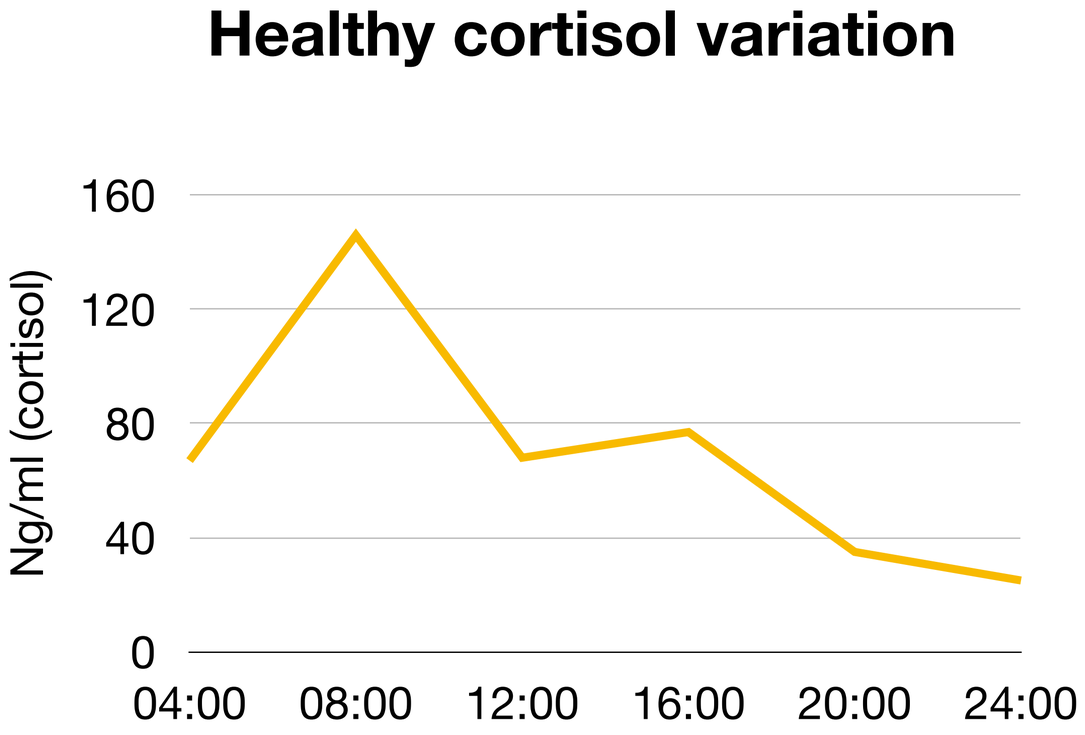
Trujillo-Rangel, W.Á et al

Cortisol

- Circadian rhythm signalling
- Stress response
- Blood glucose regulation
- Immune modulation
- Inflammation control
- Blood pressure regulation
- Energy mobilisation
- Cognitive alertness

Diurnal Variations in Cortisol

- The cortisol awakening response (CAR) provides a surge in energy
  - Raises blood glucose levels and metabolism
- Synchronisation of peripheral (organ) clocks – circadian alignment



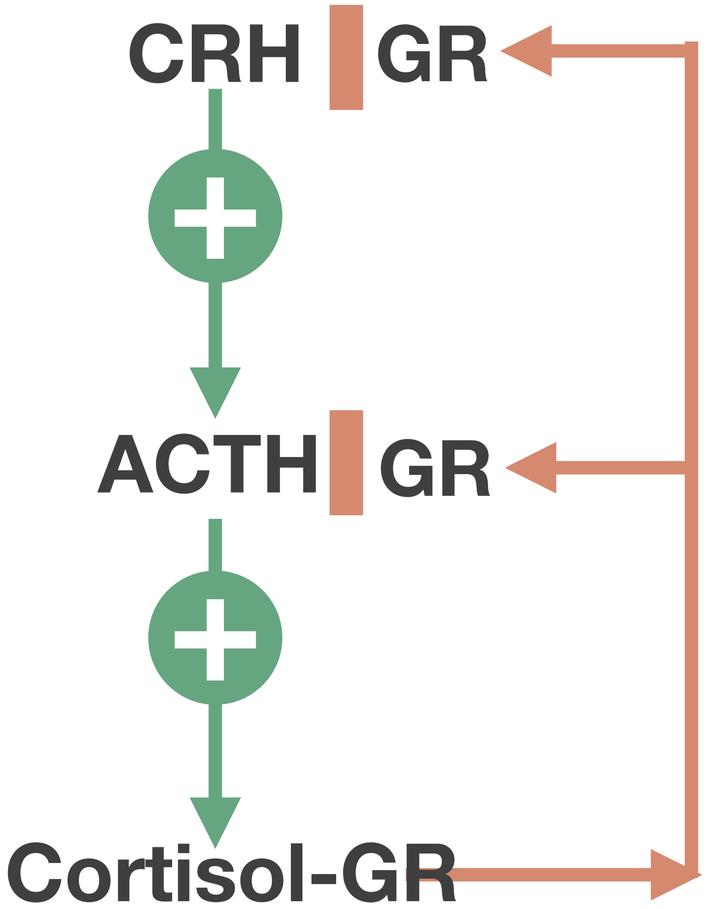
Cortisol levels peak roughly 30 minutes after waking, then drop steeply then more gradually

Cortisol Regulation

Hypothalamus
Corticotropin Releasing Hormone

Pituitary
Adrenocorticotropic Hormone

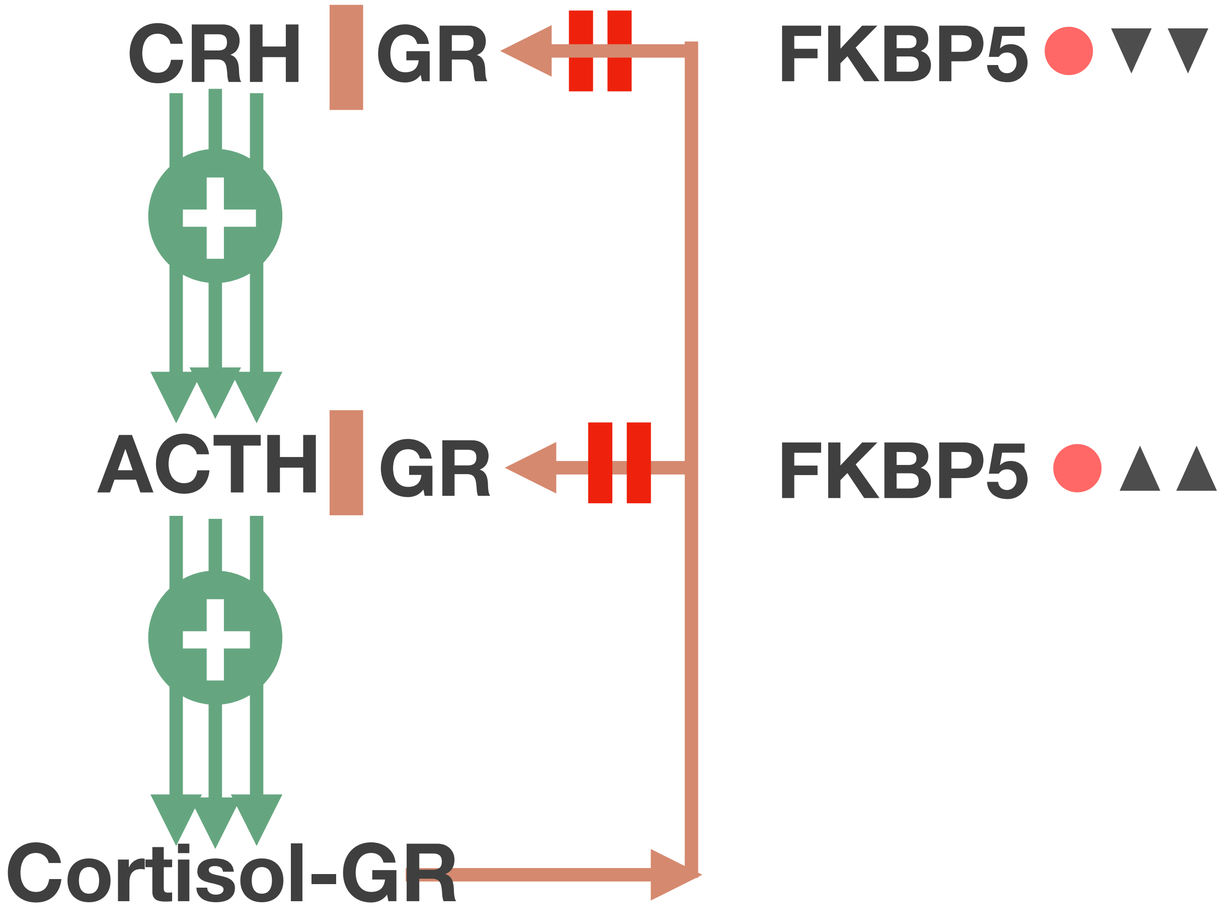
Adrenals
Cortisol – glucocorticoid made in zona fasciculata of the adrenal cortex



Glucocorticoid receptor (GR) is crucial for regulation of cortisol by negative feedback

FKBP5 Variation

- FKBP5 upregulation – due to SNPs + environment (trauma)
- Reduces GR affinity for cortisol
- Blocks the negative feedback
    - Increasing cortisol production



Acute vs Chronic Stress

- Cortisol → activates GR
- GR → induces FKBP5
- FKBP5 → reduces GR sensitivity

Short-term → protective short-loop brake / adaptive buffer

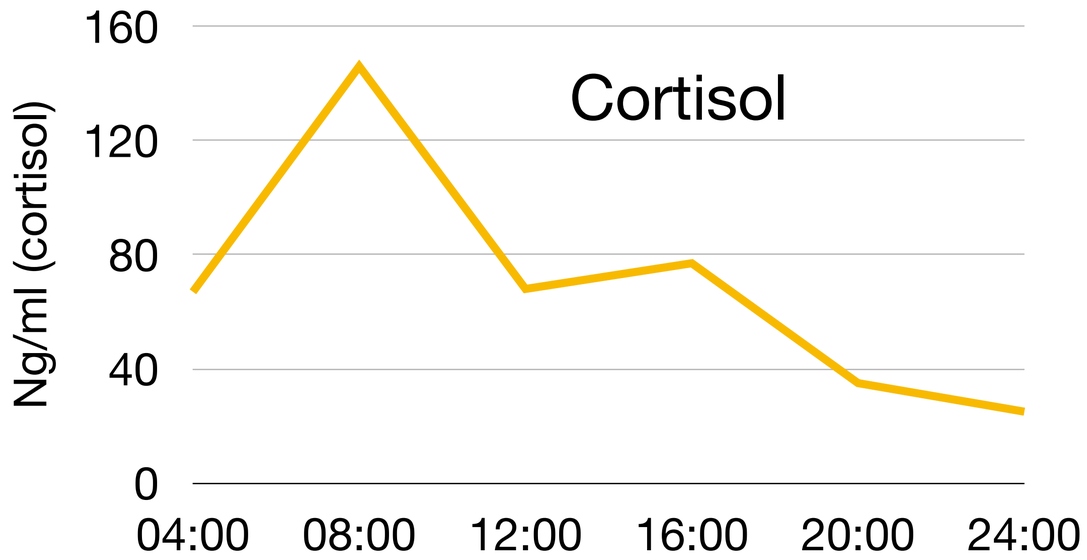
- Negative feedback becomes less effective → prolonged activation
- Higher cortisol required to achieve the same effect

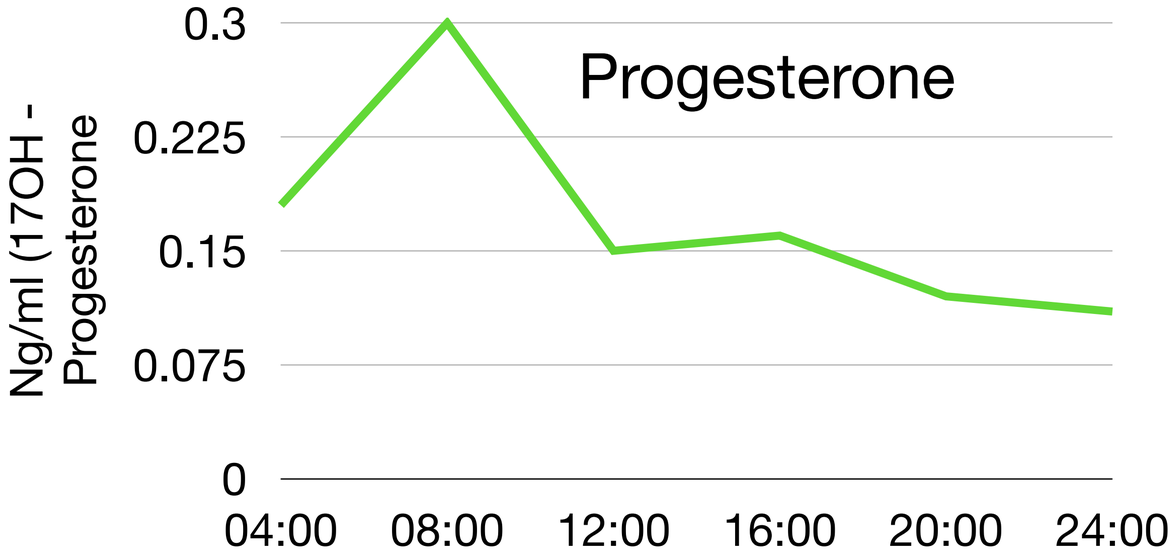
Long-term → maladaptive GR resistance

Effect = cortisol level × glucocorticoid receptor (GR) sensitivity

Diurnal Variations in Steroid Hormones

- In the follicular phase of the menstrual cycle – adrenal production
- Cortisol and progesterone follow the same rhythm
  - As do androgens and pregenens

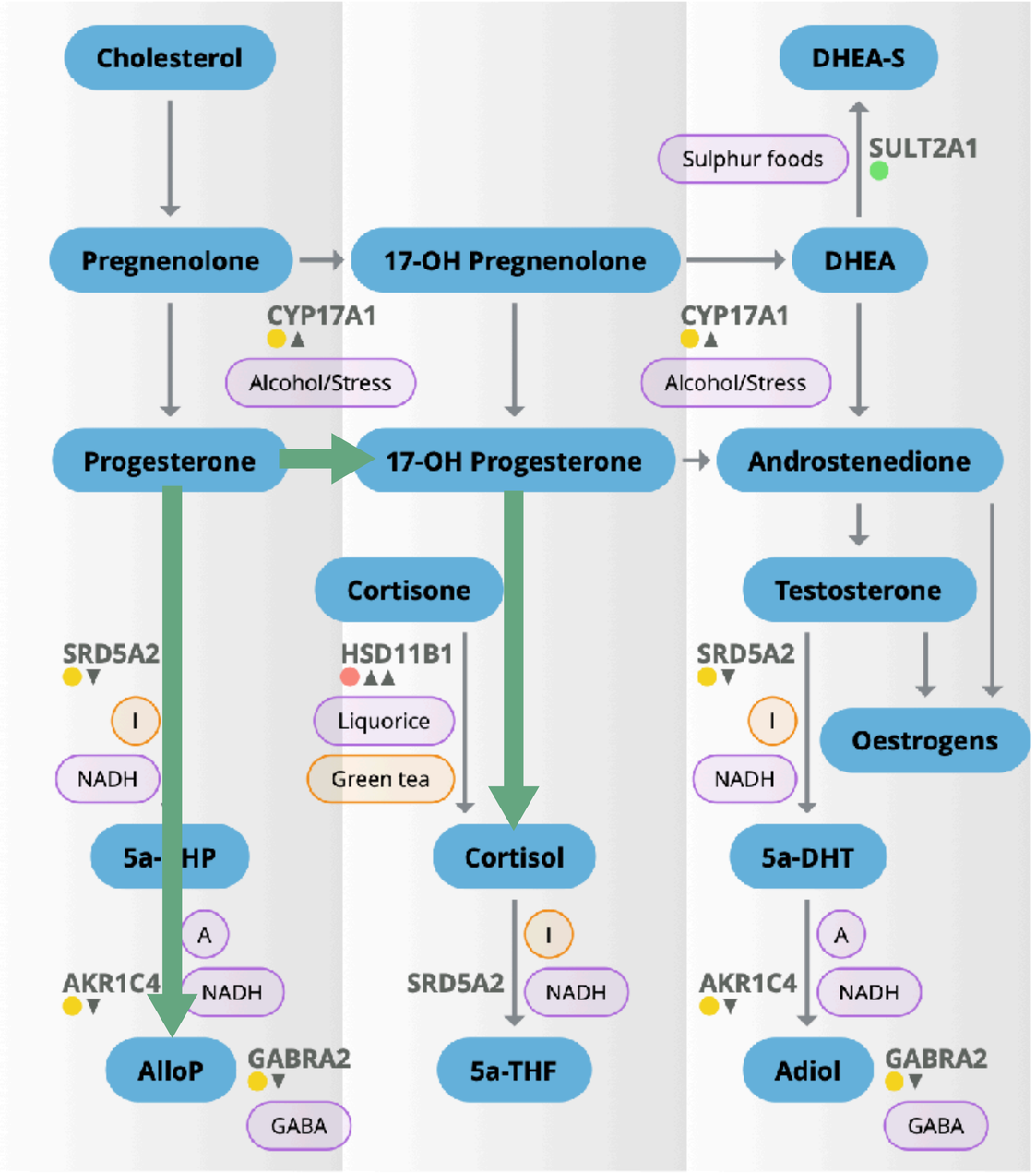




Cortisol – Progesterone

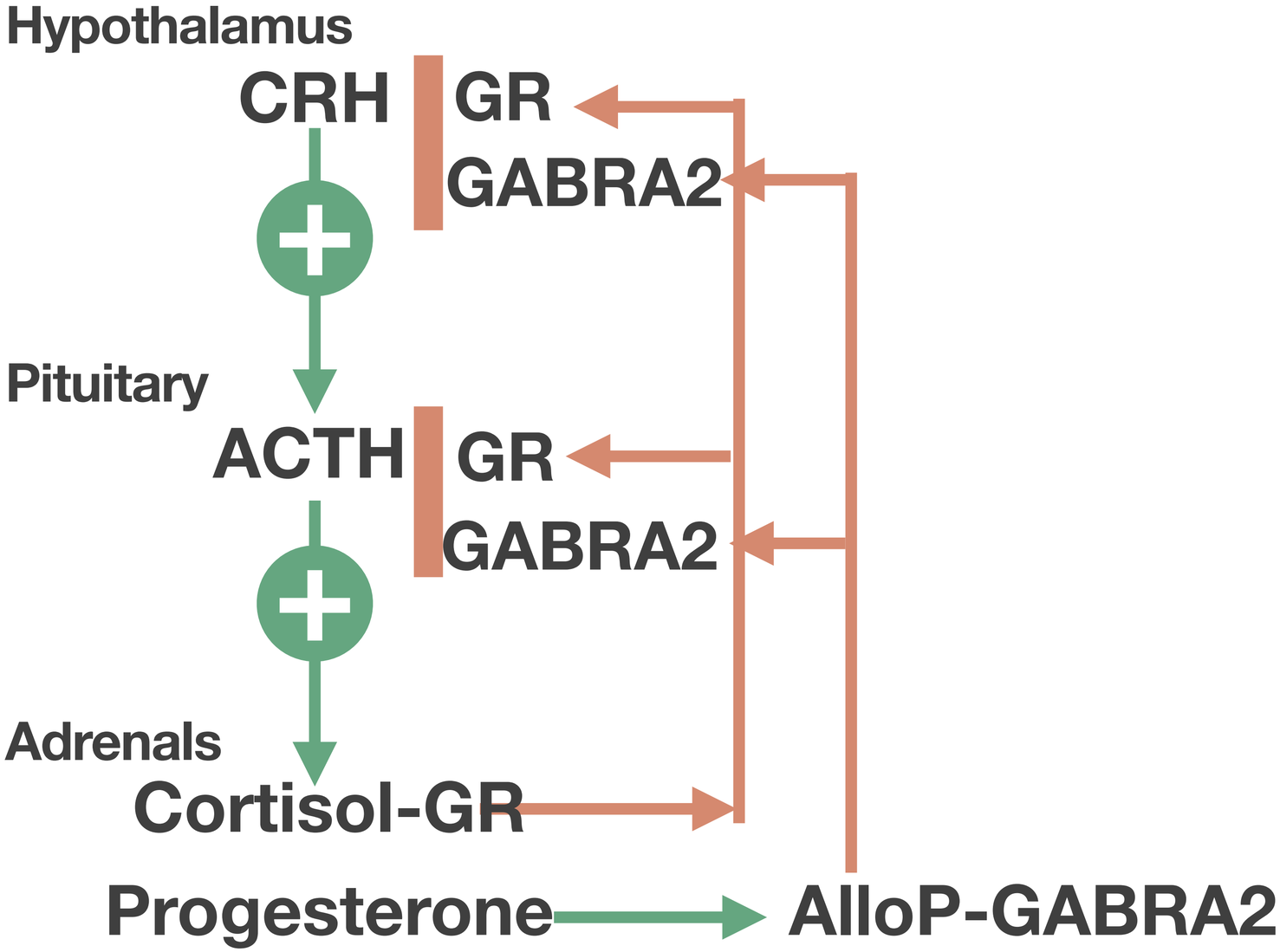
Progesterone precursor to:

- **Cortisol** – ‘fight or flight’, stress hormone
- **AlloP** – ‘calm’, anti-anxiety, inhibitory neurosteroid via its connection with the GABA receptor **GABRA2**



HPA Regulation

The progesterone metabolite and neurosteroid **AlloP** also provides negative feedback on the HPA axis via the GABA receptor GABRA2



GABRA2 Genetic Variance (SNPs)

GABRA2
rs279858

TT	No variance. Normal GABRA2 receptor activity and sensitivity to GABA
CT ▼	Decreased GABRA2 receptor activity and reduced sensitivity to GABA. Associated with increased risk of anxiety and poor impulse control
CC ▼▼	Decreased GABRA2 receptor activity and reduced sensitivity to GABA. Associated with increased risk of anxiety and poor impulse control

Genes X Environment

Fight or flight

Cortisol + Adrenaline

AlloP + GABA

FKBP5 ● ▲▲

Environmental Factors

- Chronic Stress
- Circadian Disruption
- Trauma

Environmental Factors

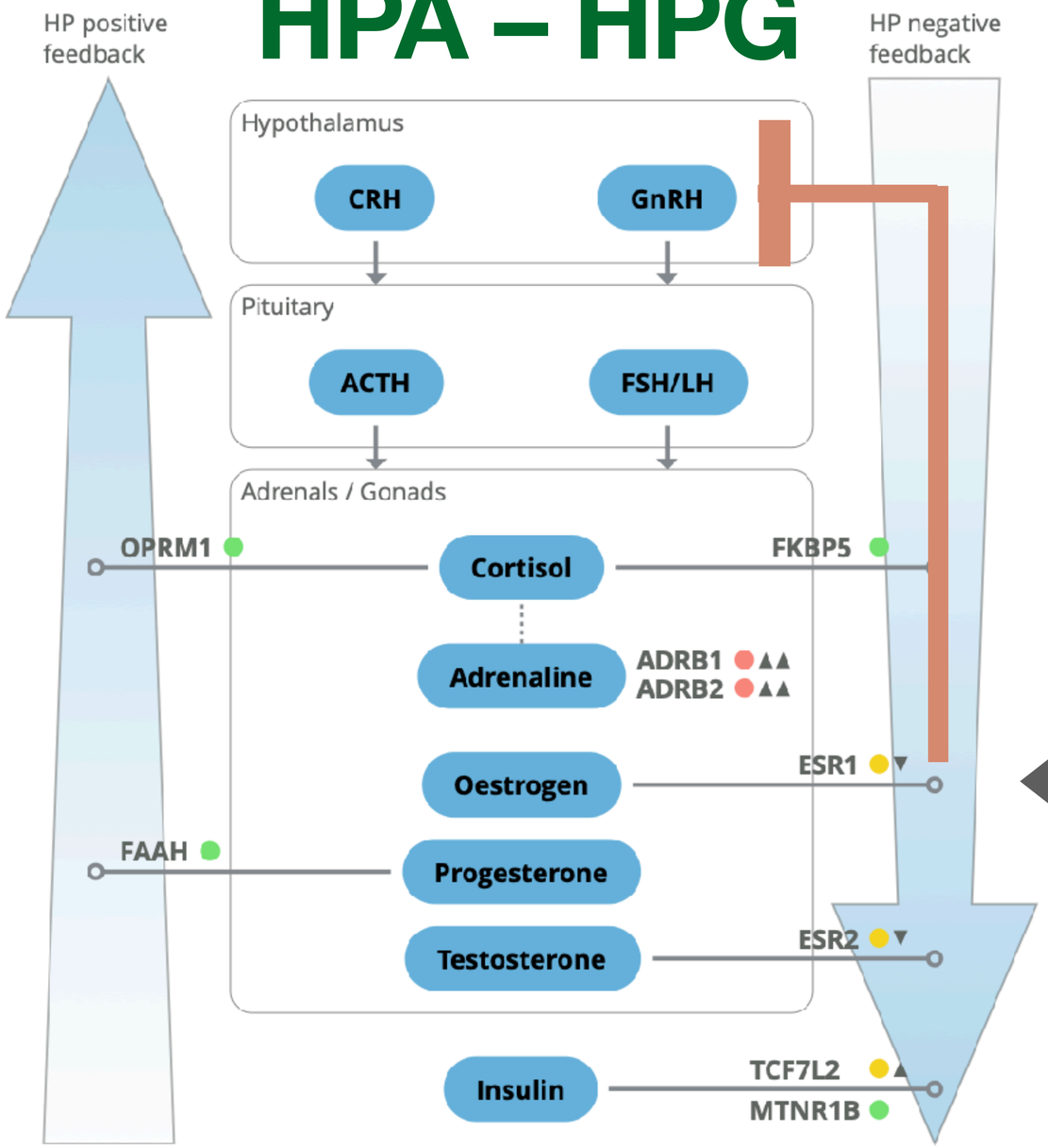
- Alcohol use disorder
- Adrenal insufficiency
- Nutrient insufficiency
  - Zinc, B6

GABRA2 ● ▼▼

Calm, anti-anxiety and mood stabilising

Oestrogen

Negative feedback principle – as for cortisol, alloP



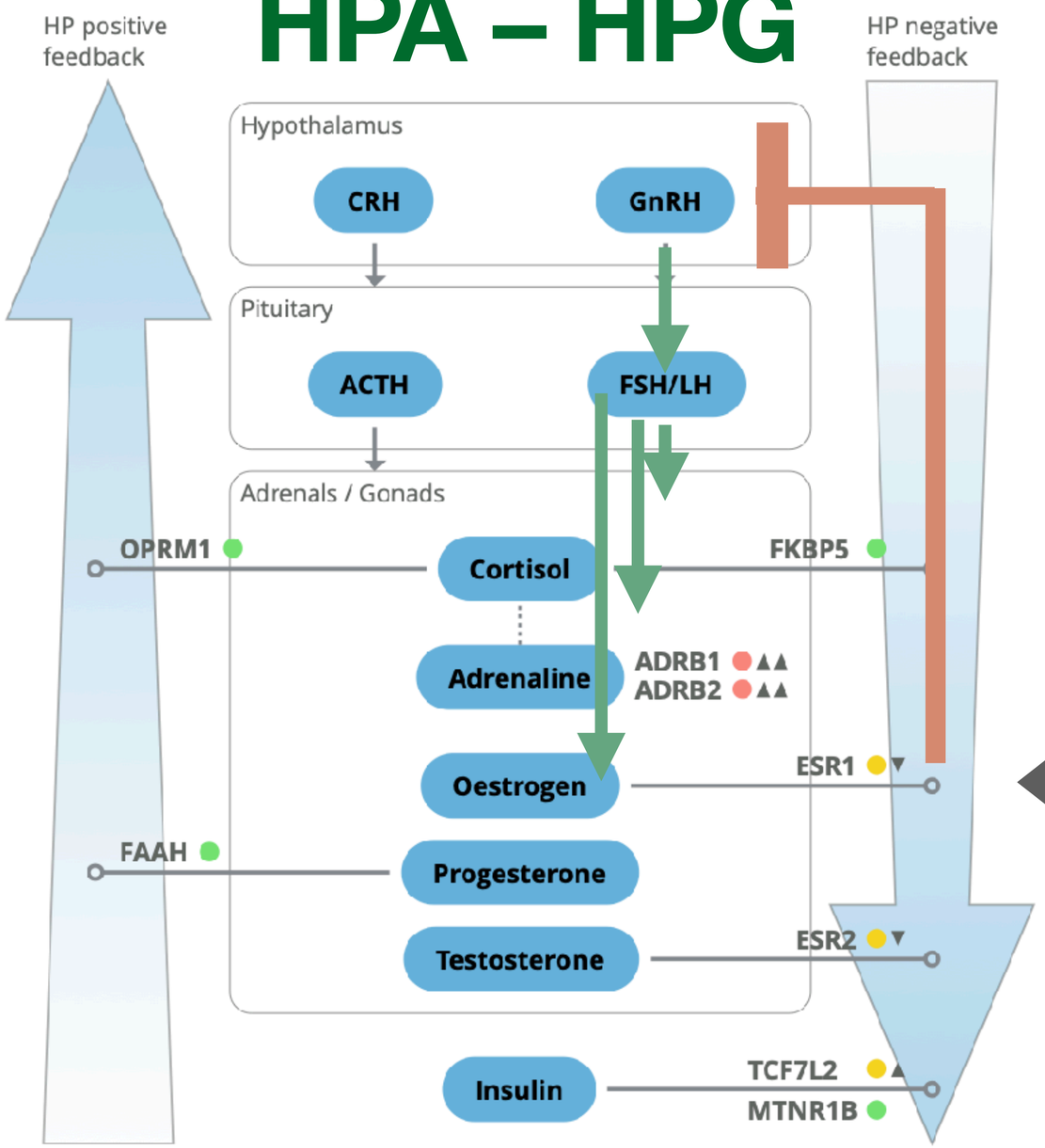
Oestrogen - negative feedback via ESR1

Down-regulates GnRH

Oestrogen

Tendency towards high O

- Problem when O is high – reproductive years, peri-menopause, OCP
- Less problematic when O is low



ESR1 SNP - reduced negative feedback (allowing feedforward)

Receptor Adaptability and Resilience

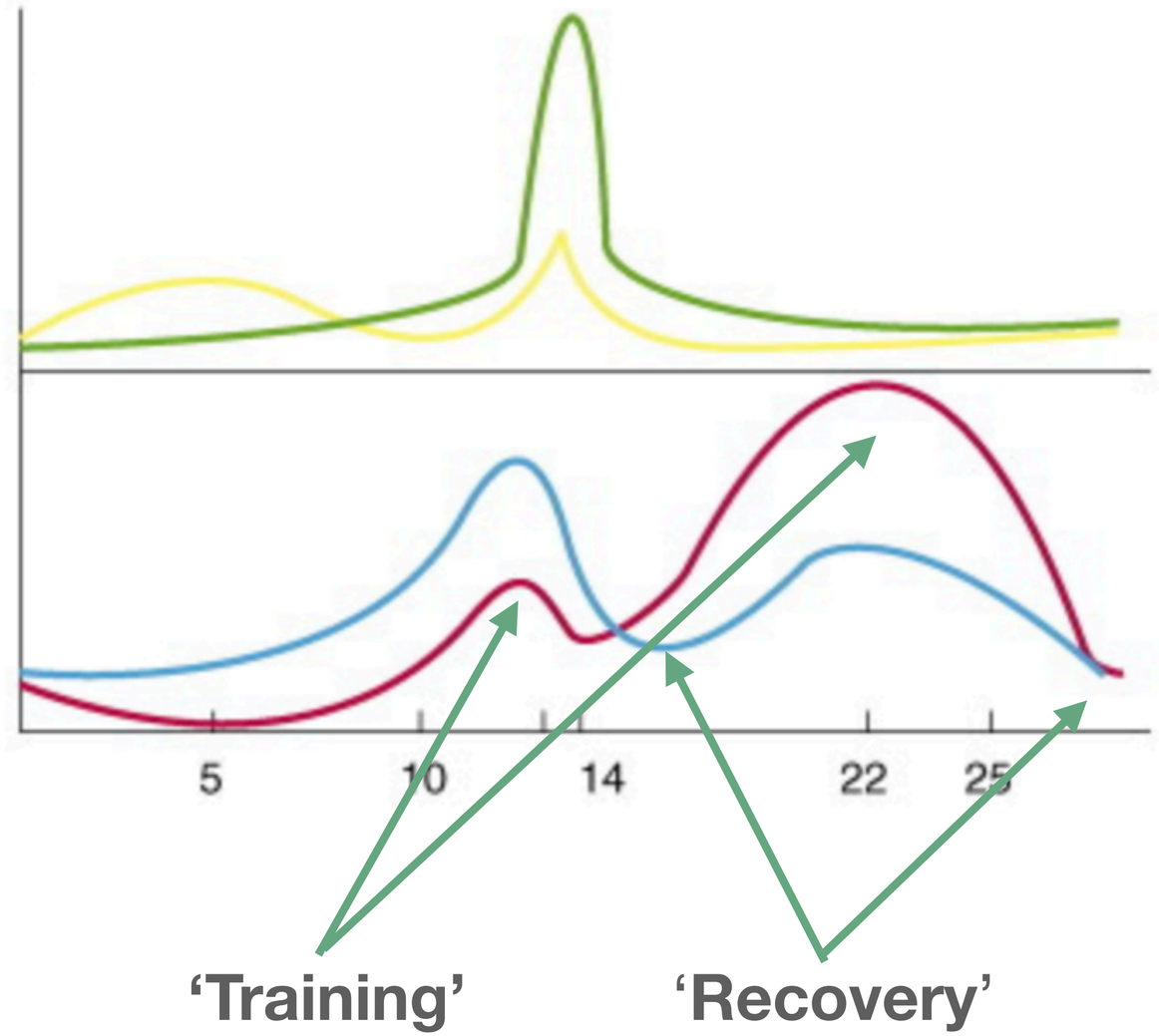
Impact of the Environment

ESR1

ESR2

Receptor expression/ sensitivity

Cyclical gene expression



Monthly whole-body metabolic workout!

Oestrogen-Mimicking Compounds

Impact of the Environment

BPA

Soy

Dioxins

Mycotoxins

Coffee

Parabens

Flaxseed

Phthalates

Red Clover

Xeno Oestrogens
‘Foreign’

Harmful

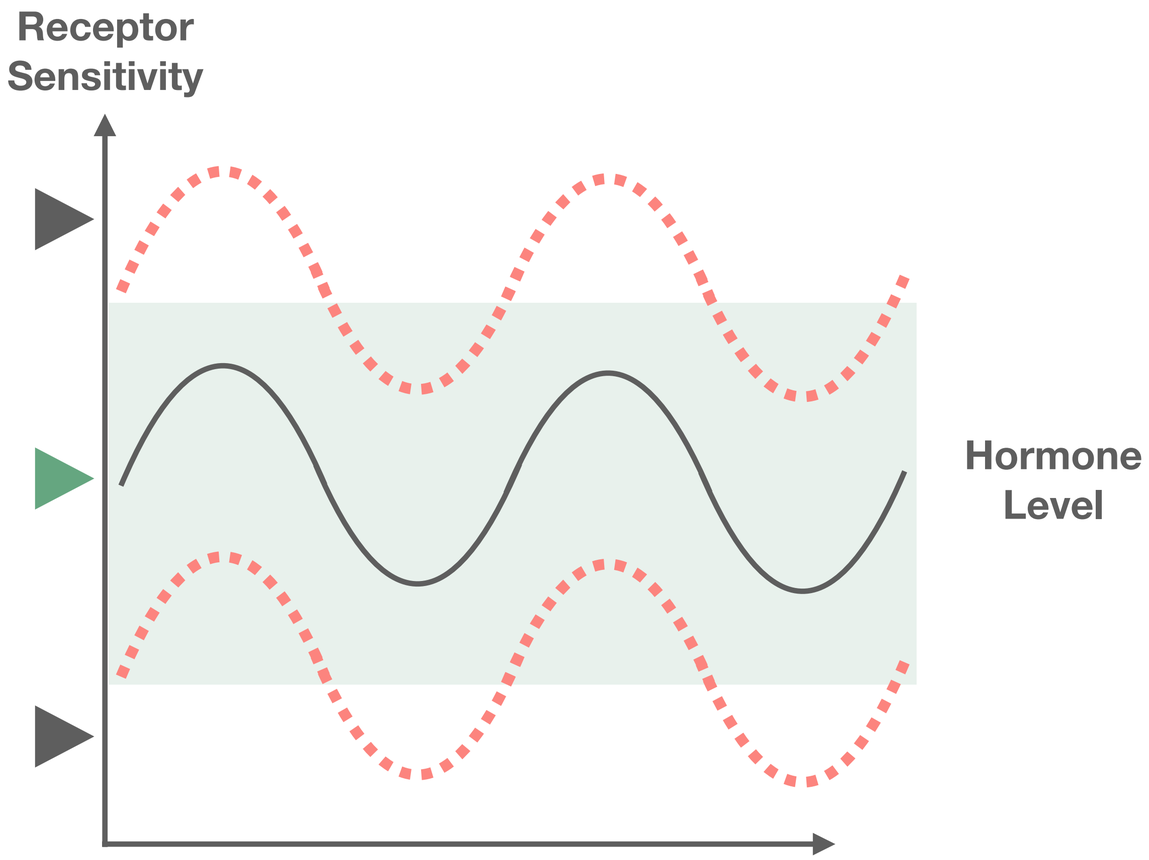
Phyto Oestrogens
‘Plant’

Can be beneficial

Detoxification

Receptor Sensitivity

- **Normal receptor** – easier to stay in the healthy bracket in periods of low and high oestrogen
- **High sensitivity** – more likely to achieve normal responses in periods of low oestrogen
- **Low sensitivity** – more likely to achieve normal responses in periods of high oestrogen

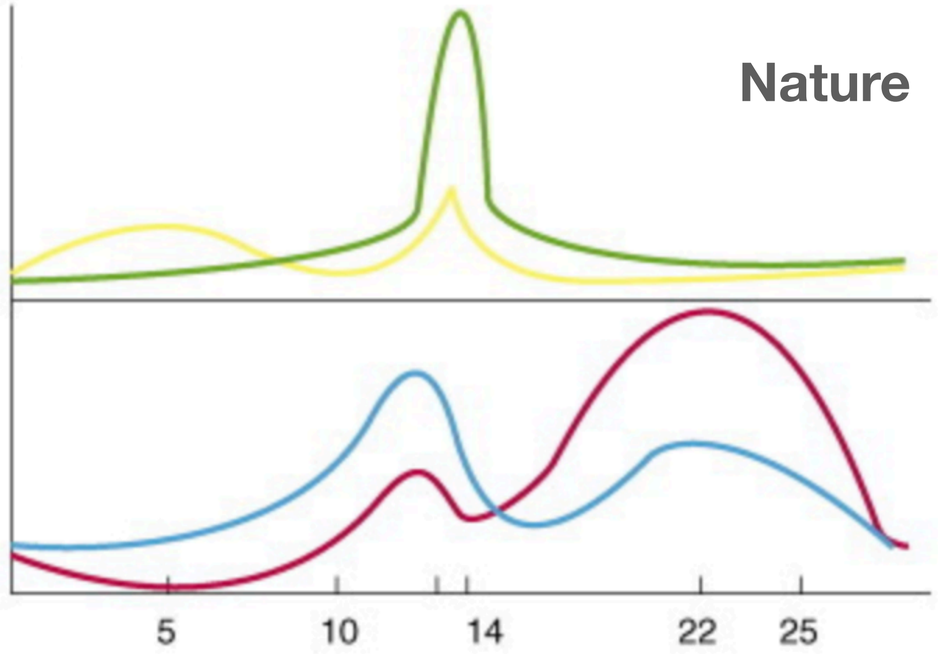


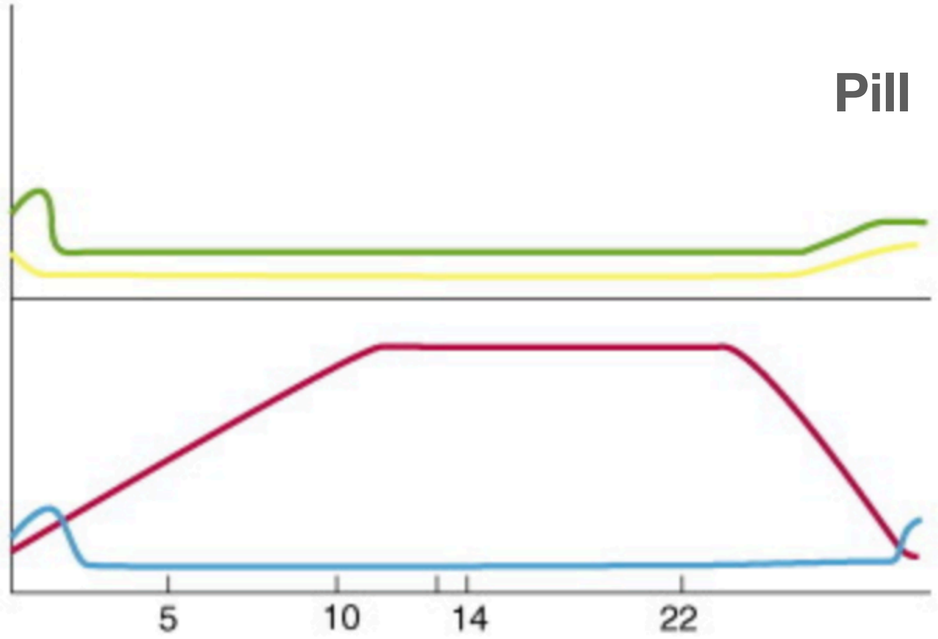
Nature vs Pill

Acting on False Data

Break down of communication

No work out/ practice



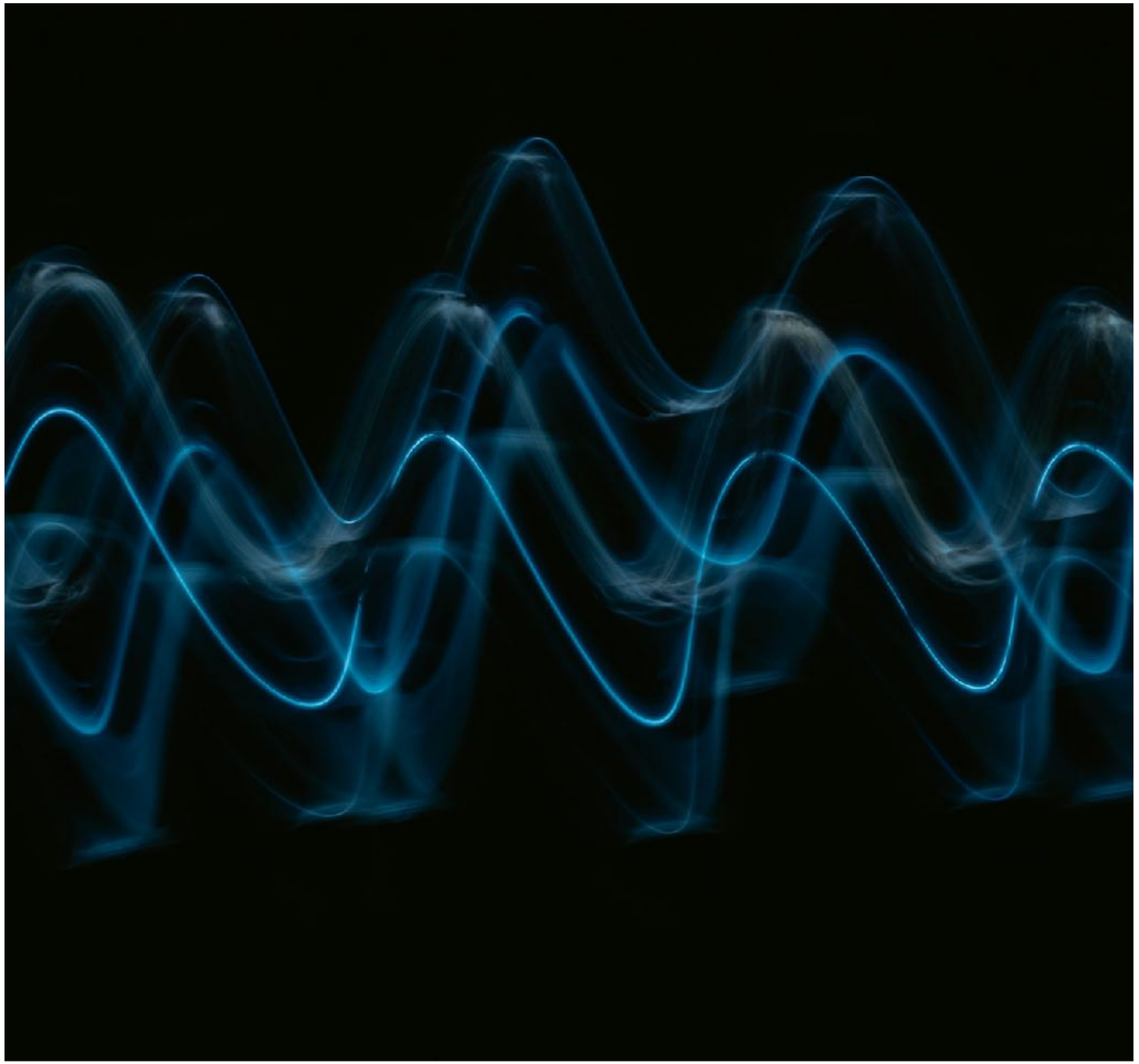


Progesterone – red
Oestrogen – blue
FSH – yellow
LH – green

‘Bad Signal’

- Abnormal receptor function makes it more difficult for the system to **calibrate the feedback mechanism**, which are crucial for maintaining balance/allostasis

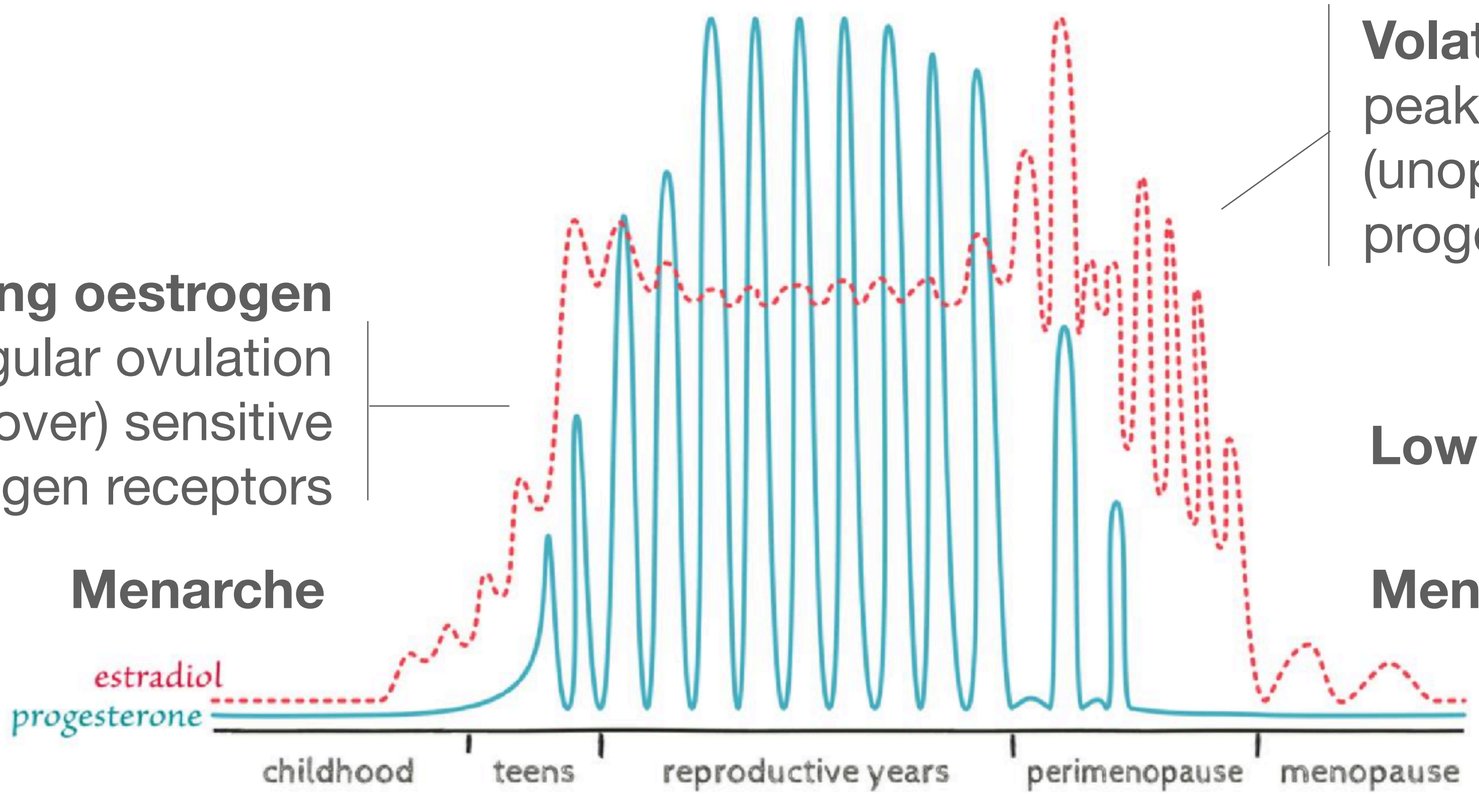
- In other words, if receptors don’t work well, feedback mechanisms act on **‘false’ data!**



Oestrogen Through the Lifespan

Rising oestrogen
Irregular ovulation
Super (over) sensitive oestrogen receptors

Menarche



Volatile oestrogen - peaks & troughs (unopposed by progesterone)

Low oestrogen

Menopause

How Well Trained Are The Receptors

Nutrigenetics is the only type of testing that gives you insights into receptor function

It’s All About Context

G × E

FKBP5	**X**	**Stress, ACEs**
ESR1	**X**	**Xenoestrogens, OCP, Stress**
MTNR1B	**X**	**Shift work, blood sugar**
VDR	**X**	**Sunlight, diet**
GABRA2	**X**	**Low Progesterone, Stress, Alcohol**

“All the trees are losing their leaves, and not one of them is worried.”

Donald Miller

Lifecode GX® Reports

- **FKBP5, MTNR1B, GABRA2 – Hormones and Nervous System**
- **ESR1 – Hormones**
- **CLOCK, VDR – Nutrient Core**

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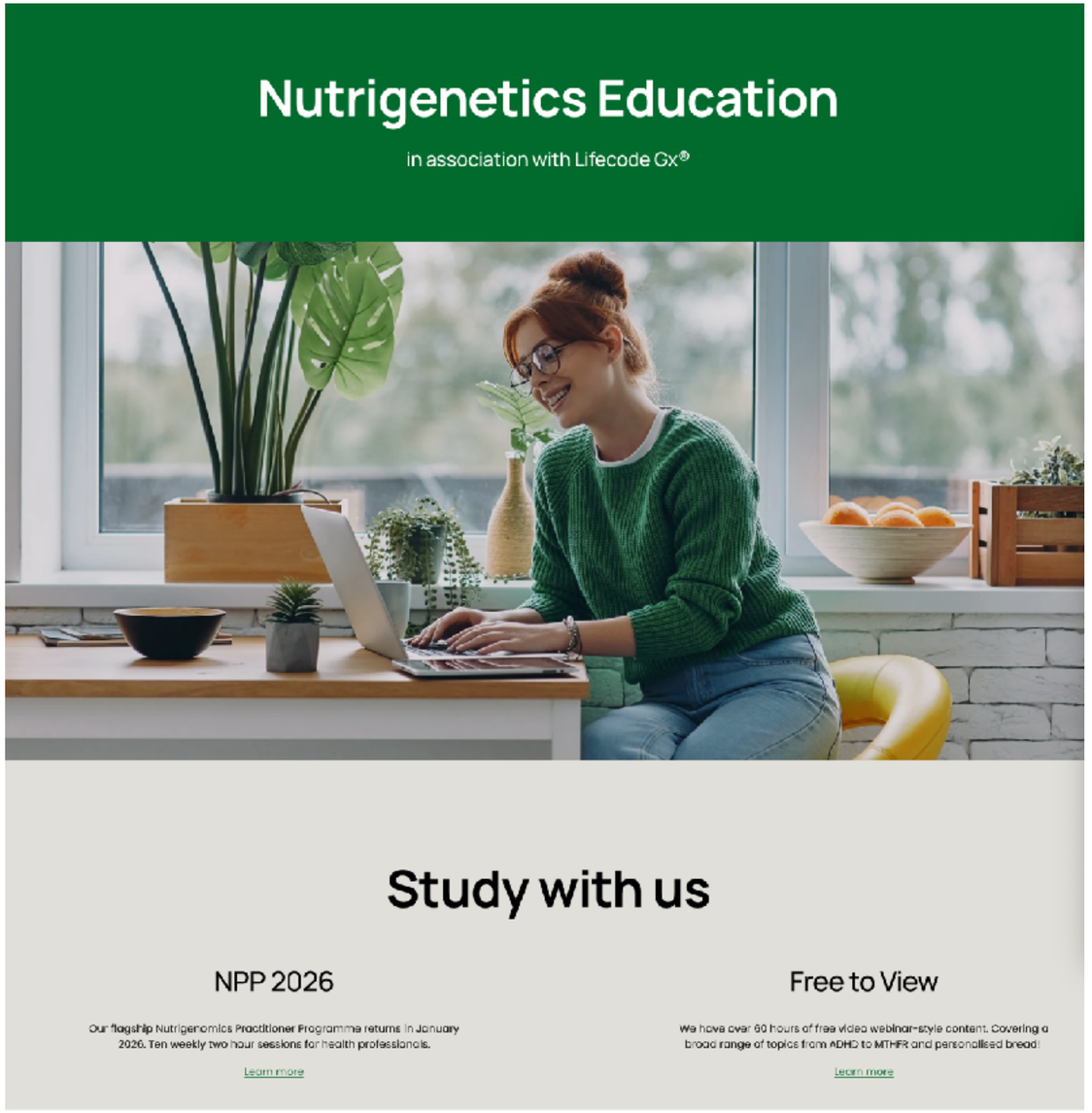

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