Homeostasis 3

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Outline of homeostasis

1. Internal environment of living organisms and the principles of homeostatic regulations
2. Homeostatic regulations – the endocrine system
3. Examples of physiological parameters regulated by the endocrine system
   - Potassium ion level in blood plasma
   - Calcium ion level in blood plasma
4. Examples of regulations involving the endocrine as well as the nervous system
   - Water balance
   - Body temperature regulation
5. Homeostatic regulations by the immune system
6. The role of the nervous and endocrine systems in immune regulations
7. Principles of the behavioural control of homeostasis
   - Feeding behaviour

Immune system

Function:

- **Defense against tissue damage:**
  - **Bacterial or viral infection, other pathogens**
  - **Ischemic, traumatic damage**
  - **Bleeding**
  - **Tumor cells**

Components:

- **Barriers: skin, mucose, lung, blood-brain barrier**
- **Innate (or natural) immune system**
- **Adaptive immune system**

Comparison of innate and adaptive immune systems

Innate immune system: inflammatory processes

Not antigen-specific

Does not have a threshold

Works immediately

Has no memory

Linearly amplified

Adaptive immune system:

Antigen-specific

Does have a threshold

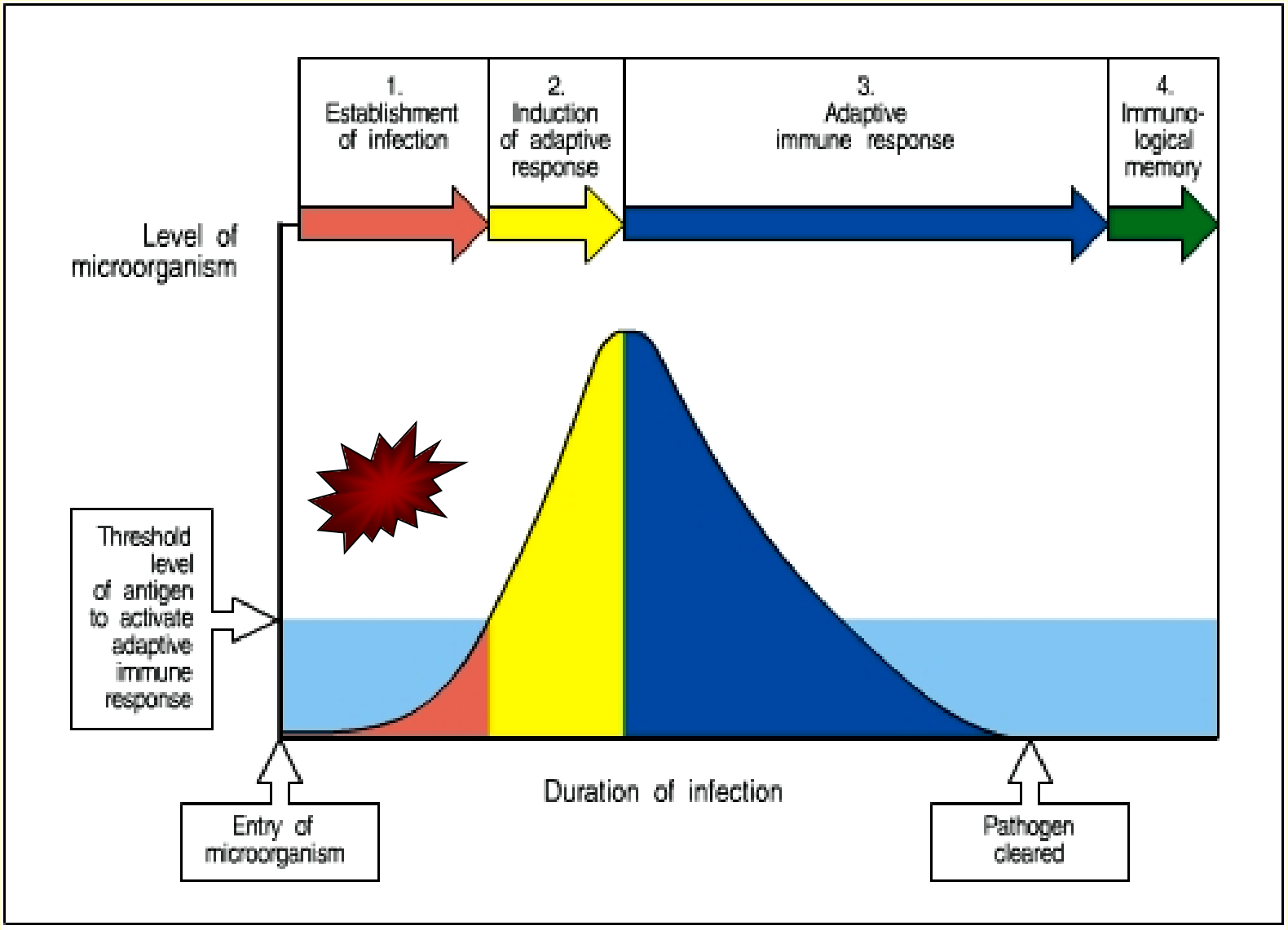
Works with a latency

Does have a memory

Exponentially amplified

Which one includes more significant interaction with the endicrine and nervous system?

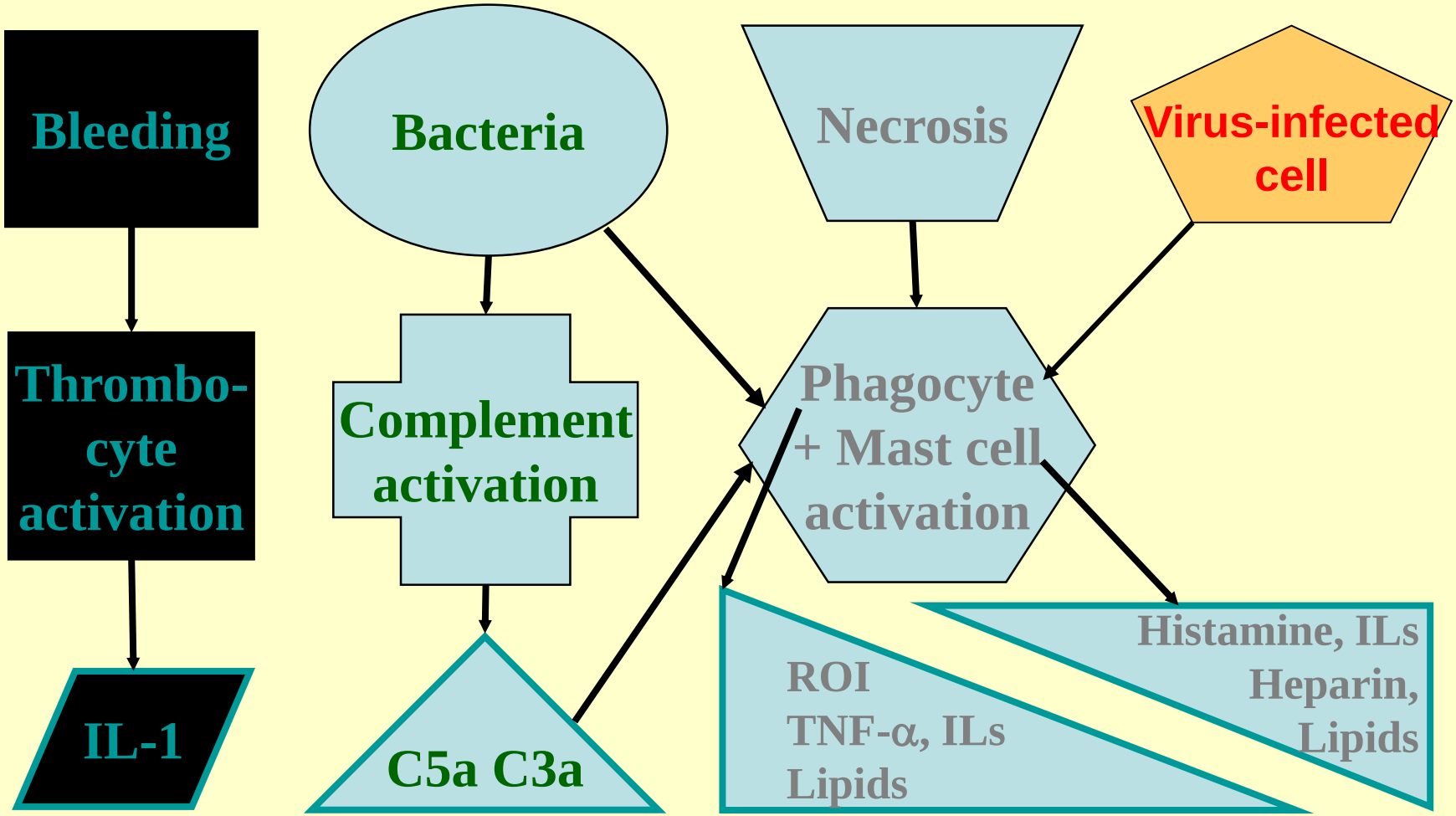
Time course and major events of adaptive responses



Innate immune responses can be divided into 2 steps

Step 1: inflammation	Step 2: acute phase reaction (APR)
Immediate	Starts with a latency
Local	Systemic
Without threshold	Above threshold
Goal: separation and elimination of damaged tissue, regeneration	Goal: maintain inflammation but also prevent its spreading

Initiation of inflammation (0-6 hours)



IL: interleukin; ROI: reactive oxygen intermedier, TNF: tumor necrosis factor

Mechanisms of the activation of phagocytes by bacteria

Resident **macrophages** and arriving **granulocytes** are both **phagocytes**.

Receptors on the surface of phagocytes:

1. Pattern recognition receptors

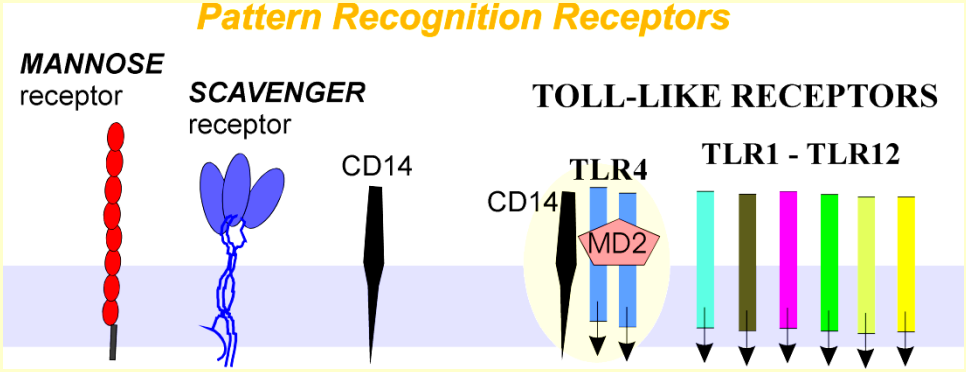
E.g. Lipopolysaccharid (LPS; a bacterial endotoxin) receptor: CD14(+TLR4)

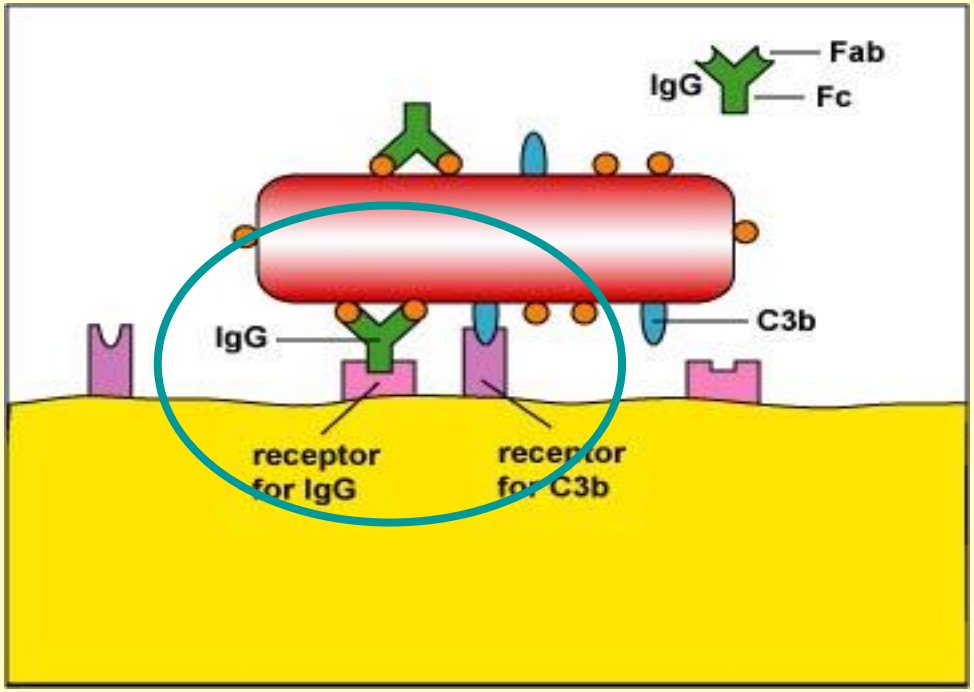
2. Receptors of the complement system

3. IgG receptors

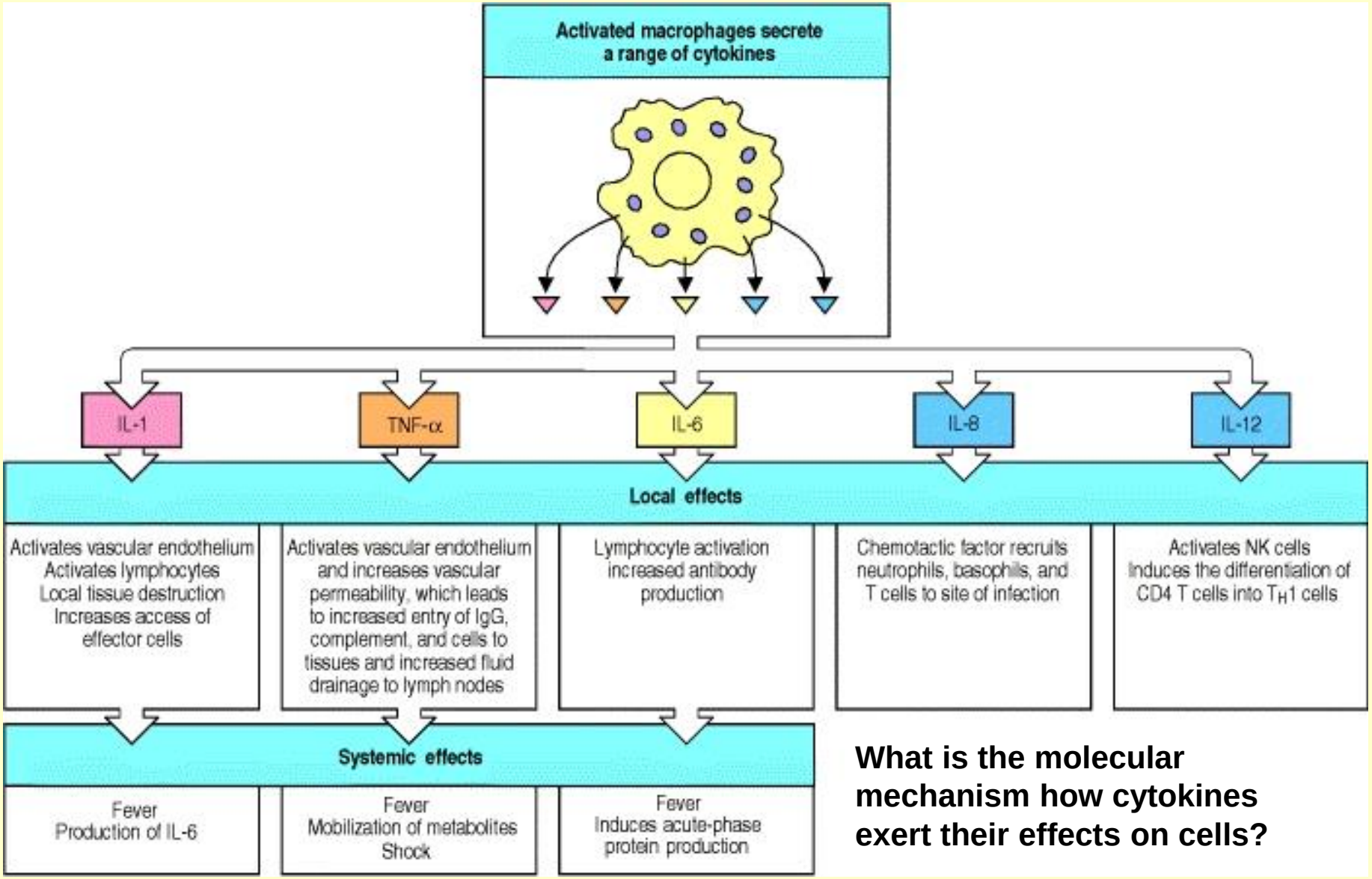
(Necrosis causes activation by Damage-associated molecular patterns - DAMPs)

The response of phagocytes to activation:
1. Phagocyte bacteria or necrotic cell
2. Production of cytokines



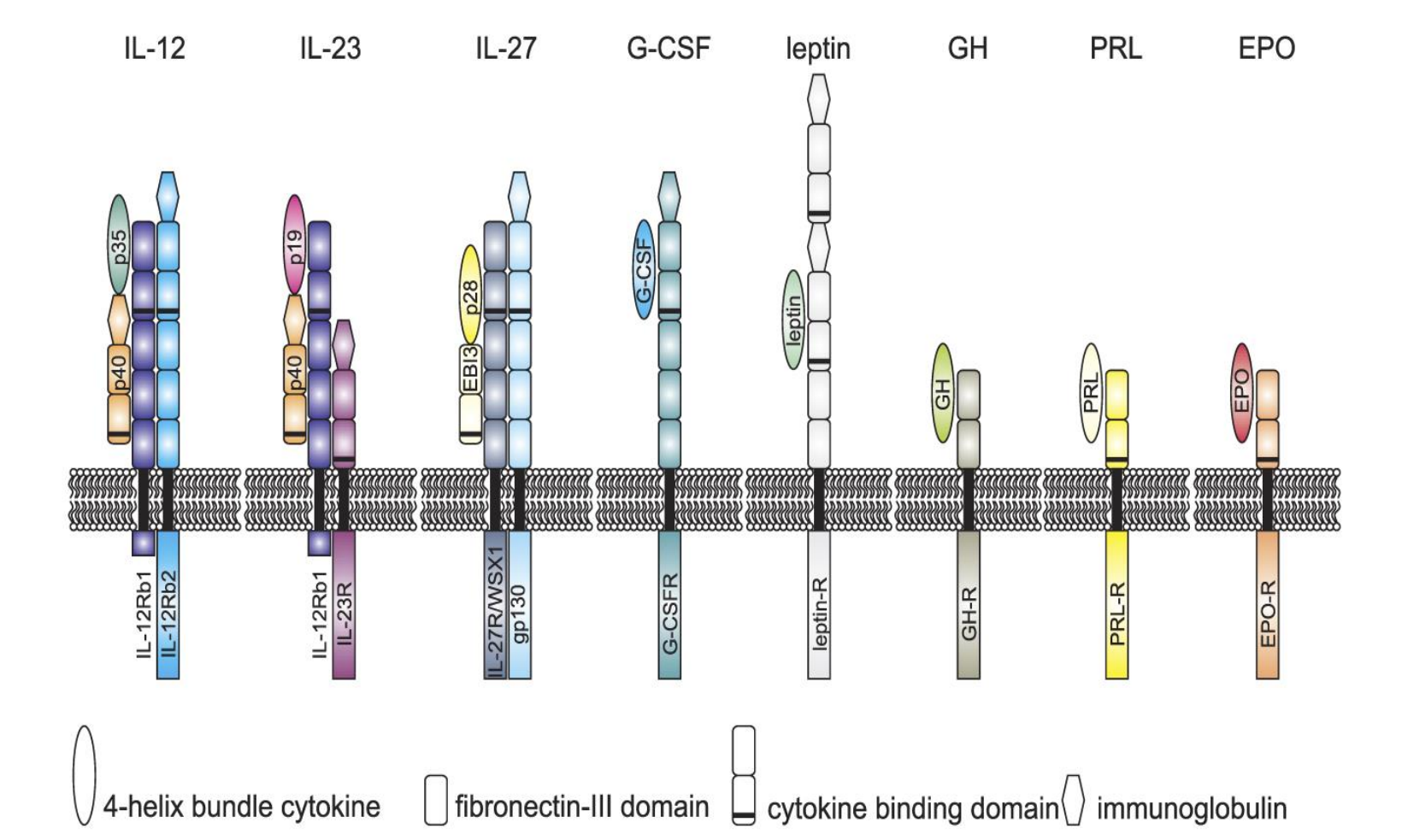


Cytokines produced by macrophages, and their functions

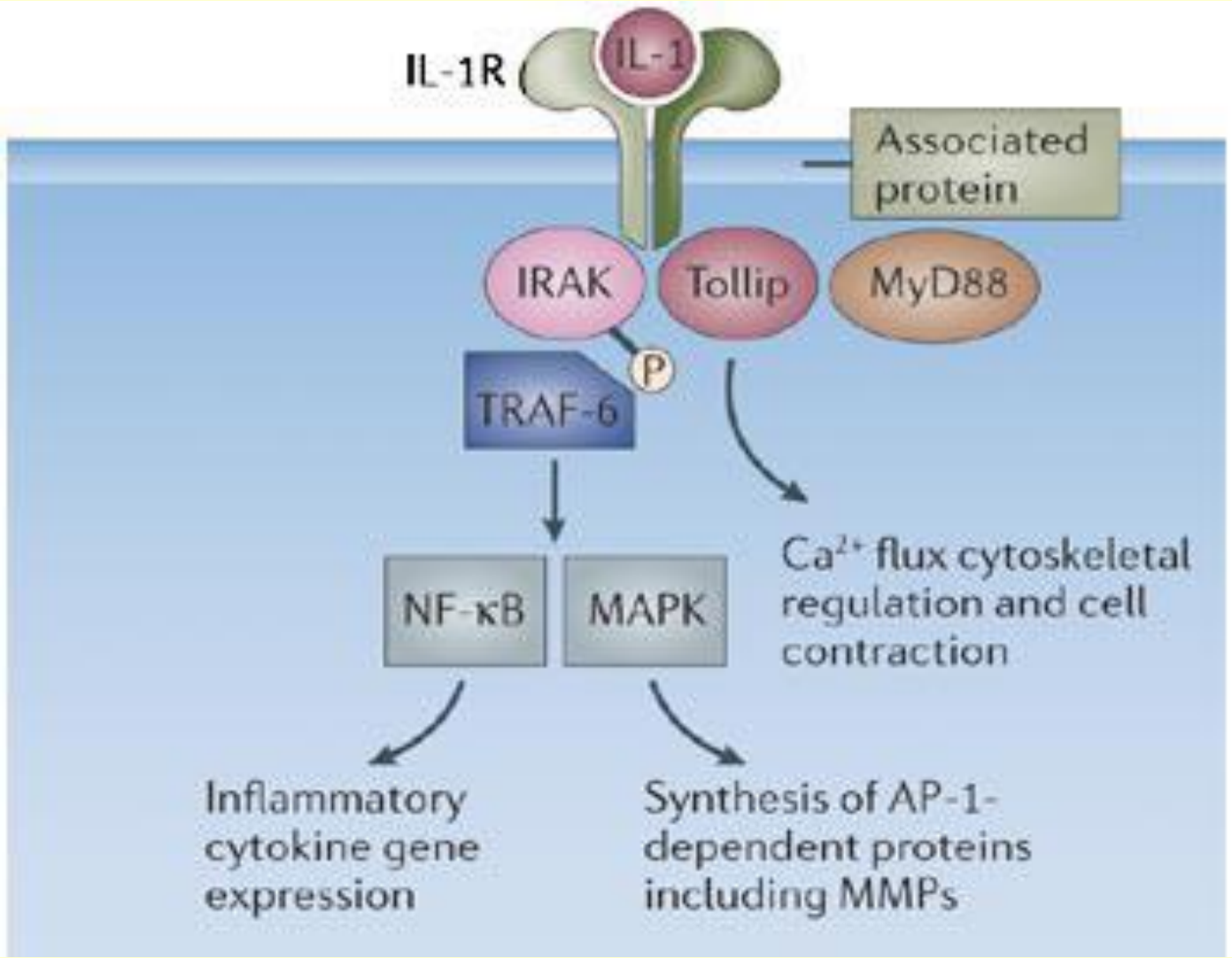


What is the molecular mechanism how cytokines exert their effects on cells?

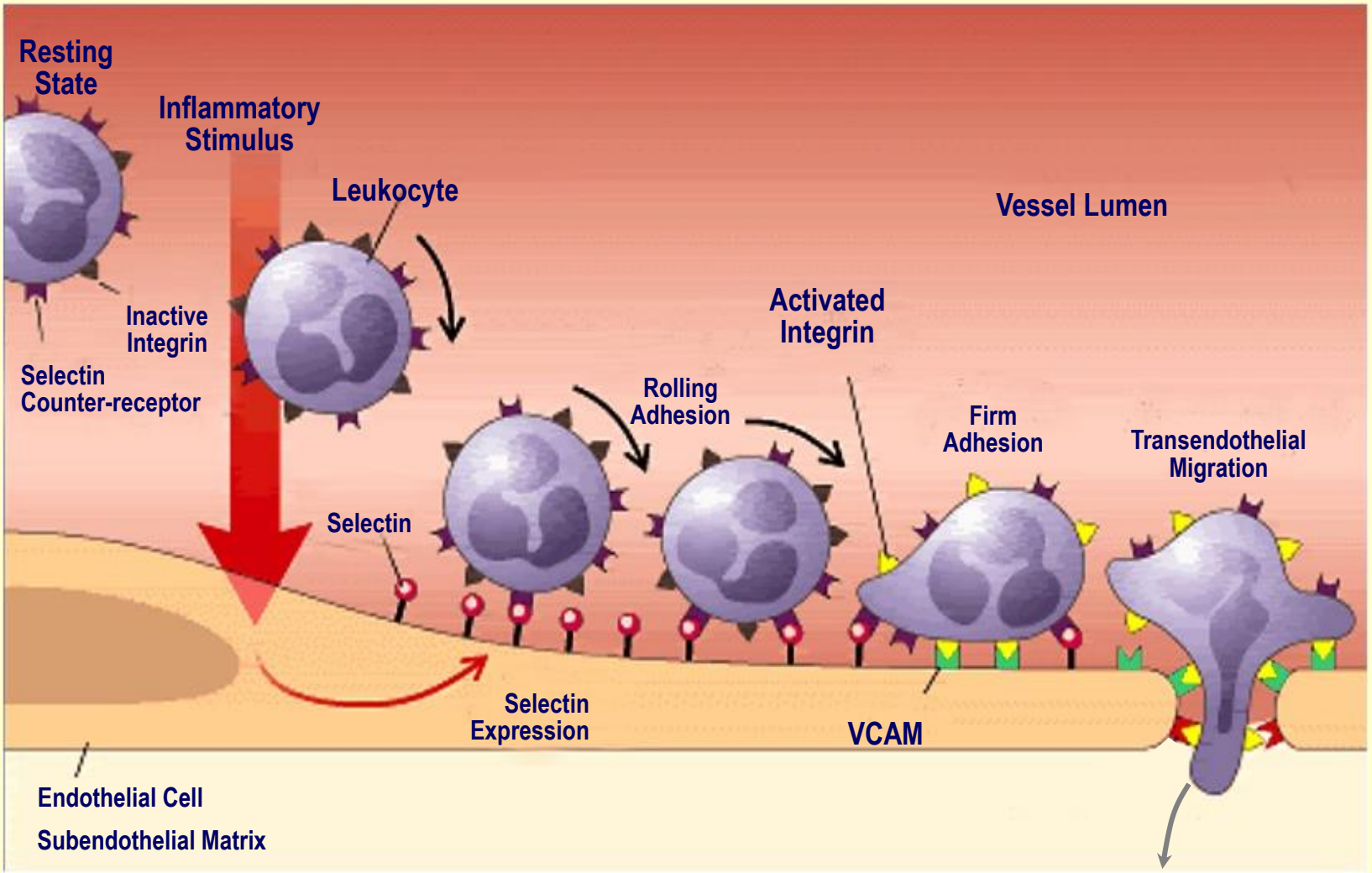
Cytokine receptors



Signal transduction of IL-1



Leukocyte infiltration to the site of inflammation

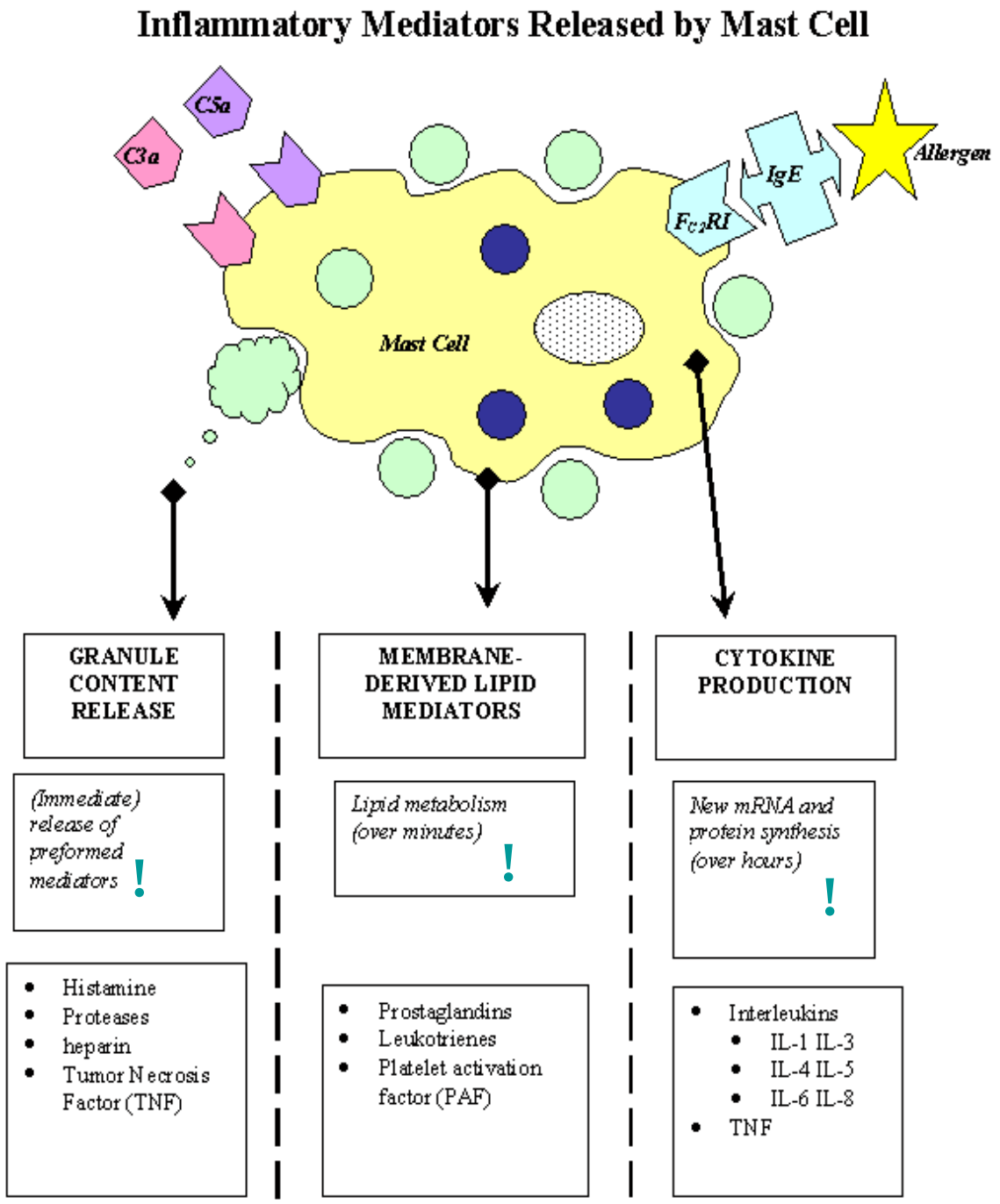


Mast cell activation results in:

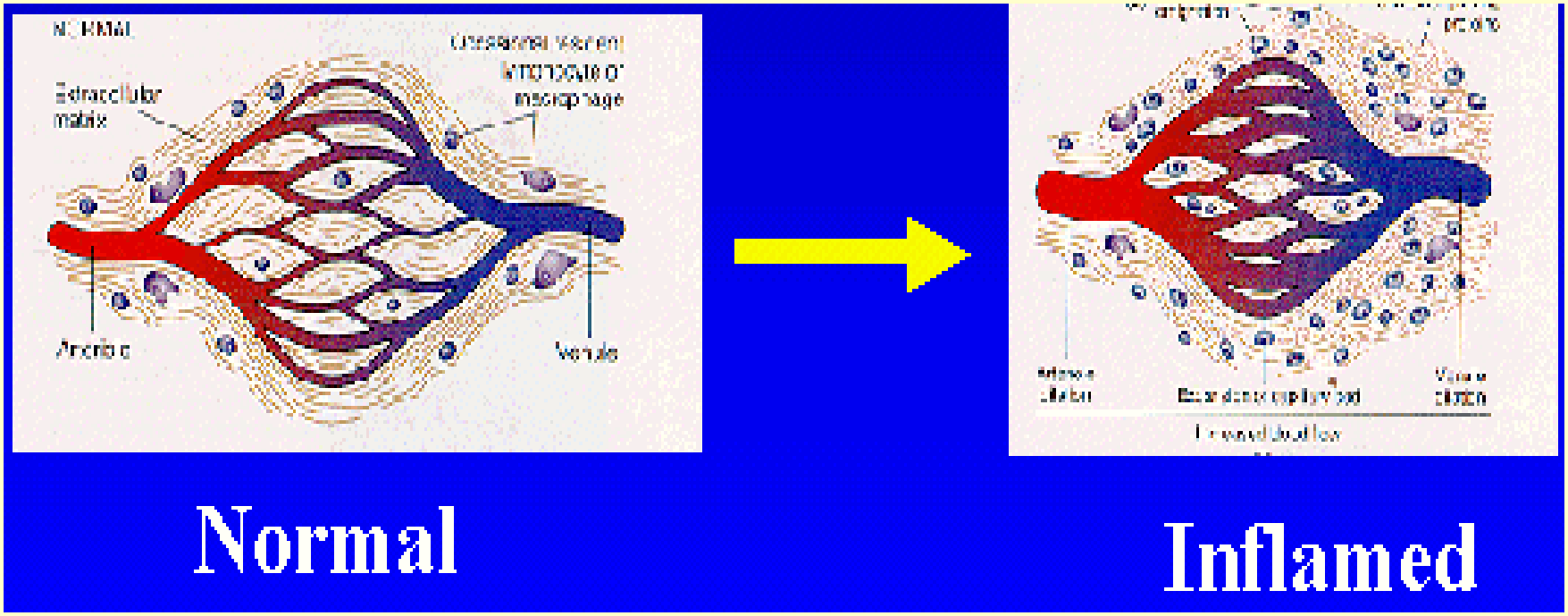
1. degranulation
2. lipid mediator synthesis
3. cytokine production

Consequences:

- Vasodilatation
- Increase of tissue permeability
- Activation of additional cells
- Activation of nociceptive sensory nerve terminals

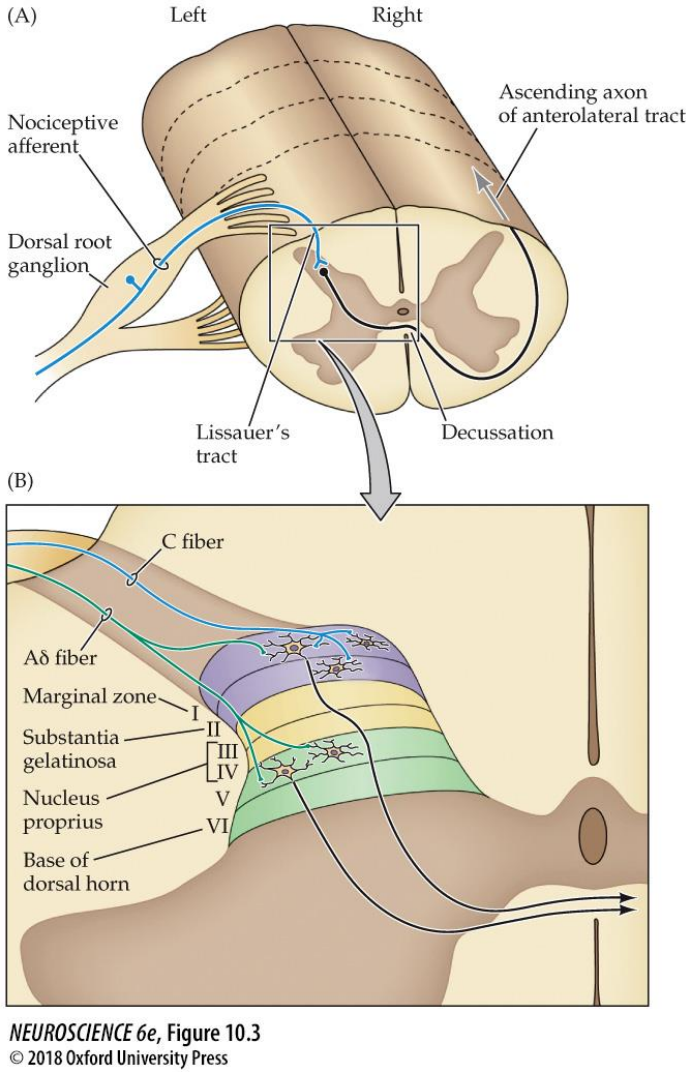


Vasodilation by mast cells

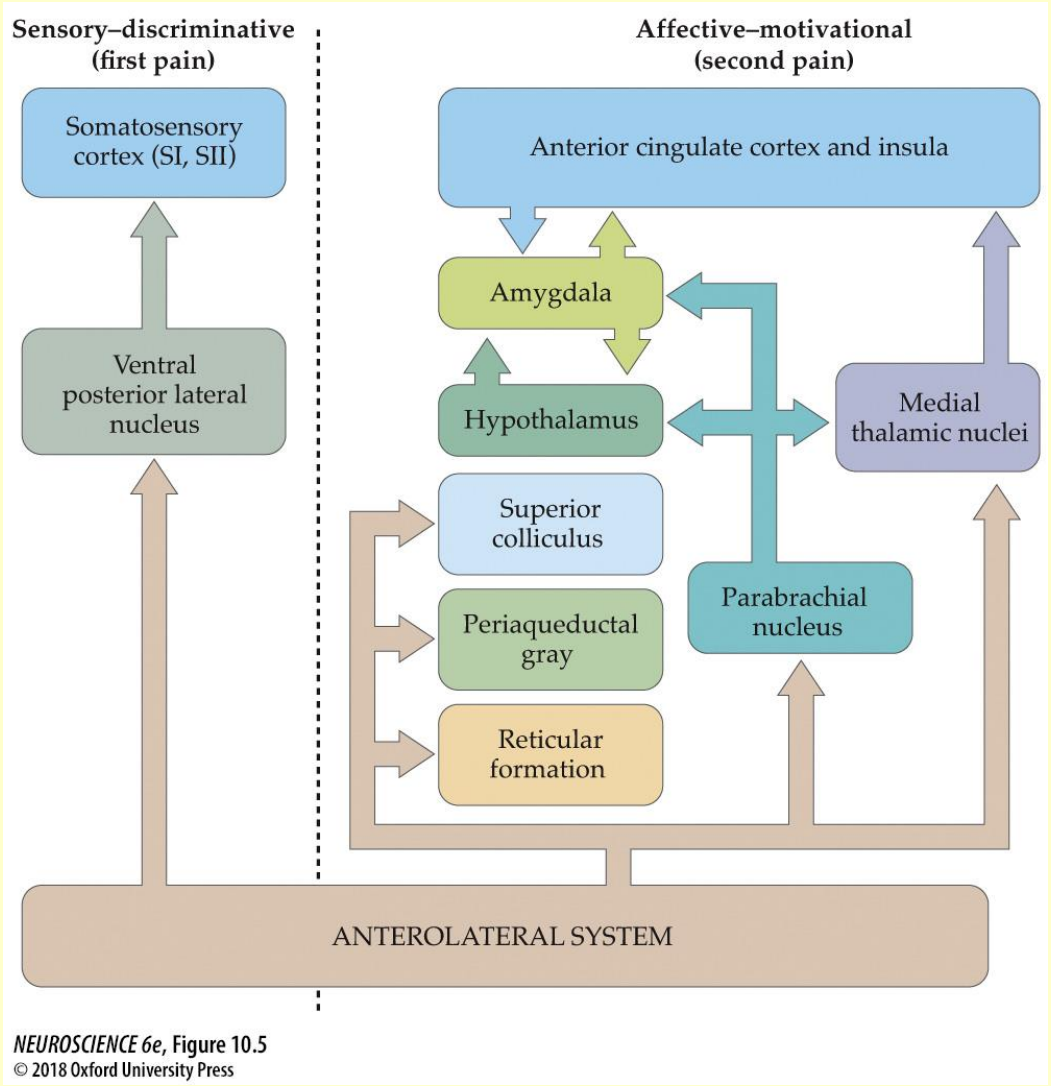


- Mostly by histamine via G-protein-coupled receptors

Nociceptive ascending neuronal pathways



NEUROSCIENCE 6e, Figure 10.3

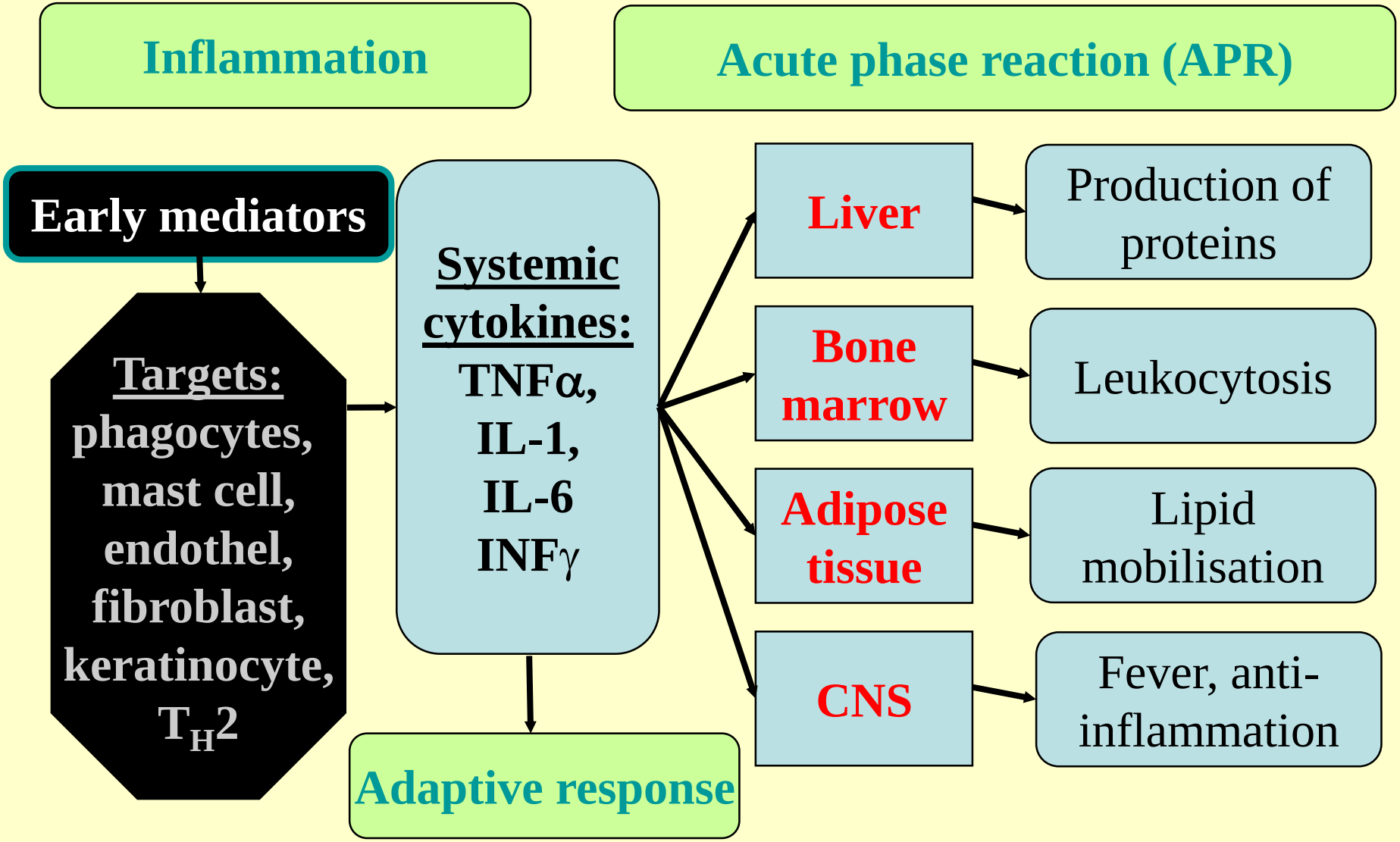


NEUROSCIENCE 6e, Figure 10.5

The role of nociceptive sensory system in inflammation

- Materials (e.g. histamine, prostaglandins) released by mast cells stimulate nociceptive sensory terminals, which contributes to
  - Local pain sensation (via thalamus)
  - Behavioural response aimed at avoiding the use of the inflammed area (via limbic cortex)
  - Activation of stress pathways (via hypothalamus)
  - Release of substance P from the sensory terminals upon inflammation: G-protein coupled receptor of substance P is present in macrophages, through which substance P increases local inflammation (local action)

Progression of the innate immune response (6-12 hours)



The mechanisms of inducing fever

- Pyrogene: any substance that leads to fever
- Endogenous pyrogenes:

  - Some cytokines produced by macrophages:

  Interleukin 1 (α and β), interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNFα)

- Exogenous pyrogenes:

  - Any inflammatory reaction that activates macrophages. Bacterial lipopolysaccharide (LPS) is particularly effective in inducing fever.

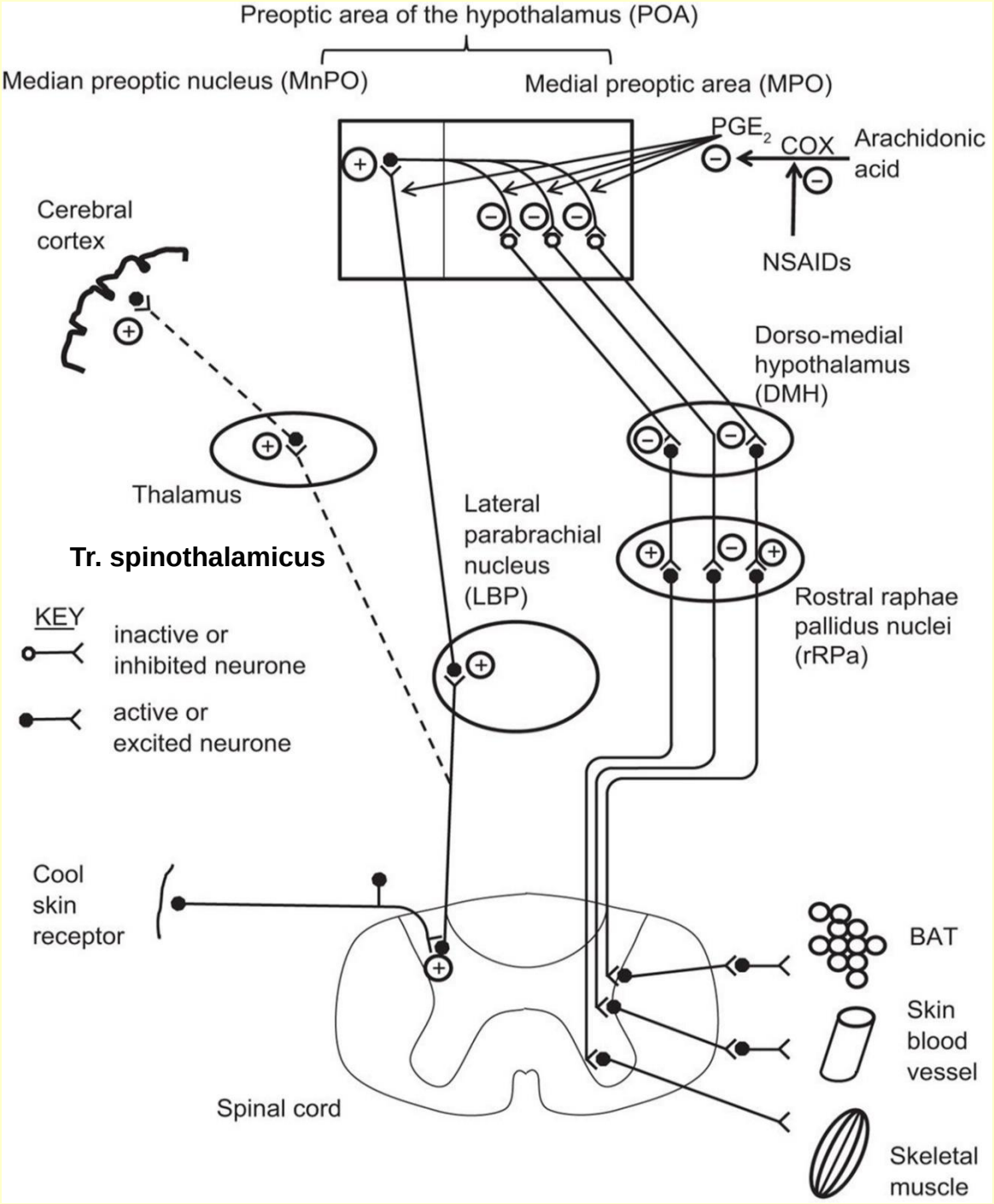
Mechanism of action: Pyrogenes influence the set point of the thermoregulatory pathway.

Where is their site of action?

Action of PGE2 on preoptic neurons of the thermoregulatory pathway

PGE2 is synthesized in preoptic endothels in response to cytokine hormones.

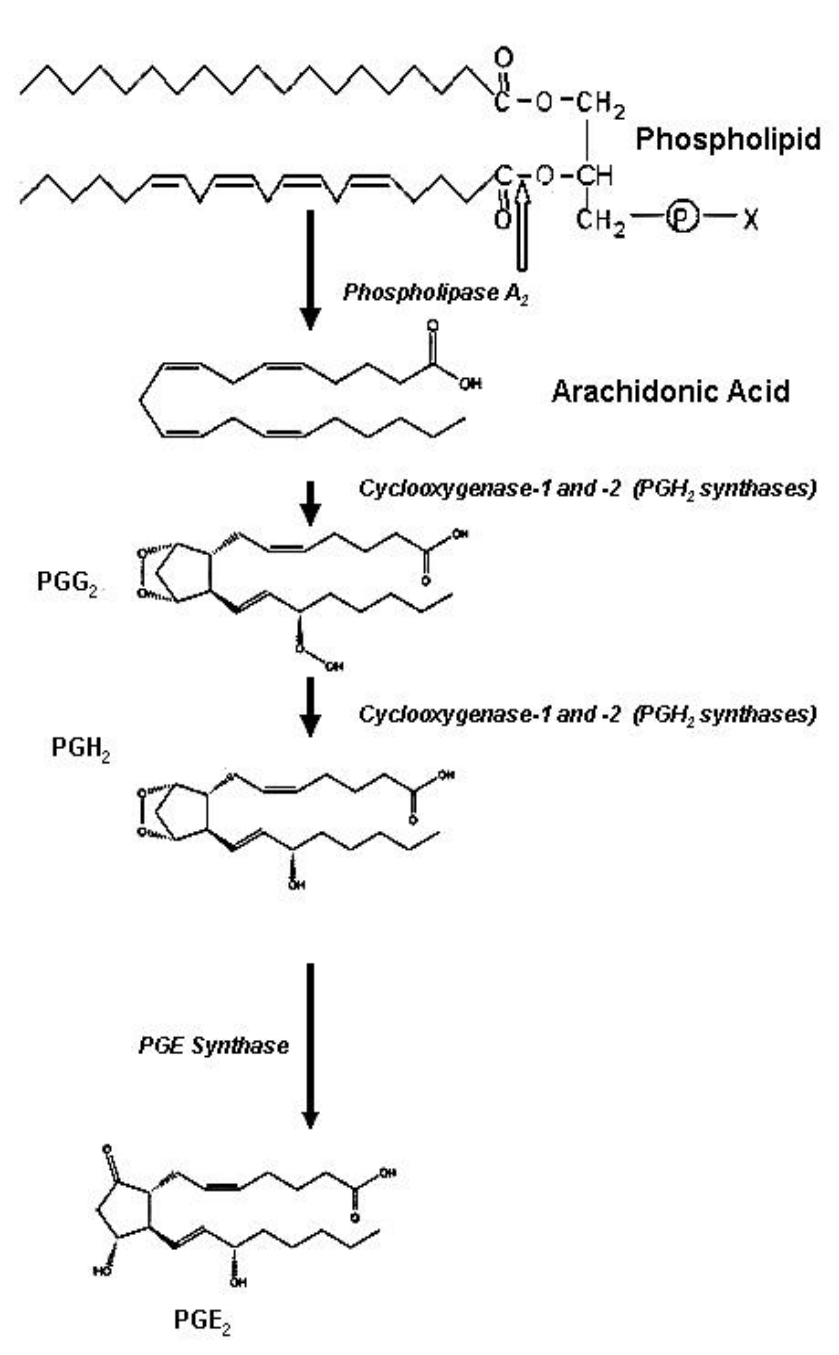
Then, PGE2 penetrates through the blood-brain barrier as a membrane-soluble molecule to reach nearby preoptic target neurons.



Synthesis of Prosta-glandin E2 (PGE2)

- From arachidonic acid
- Using the following enzymes:
  - cyclooxygenase-2 (COX-2),
  - prostaglandin E2 synthase
- Pyrogenes stimulate the enzymes thereby inducing PGE2 synthesis

Anti-fever drugs inhibit these enzymes



The effects of fever

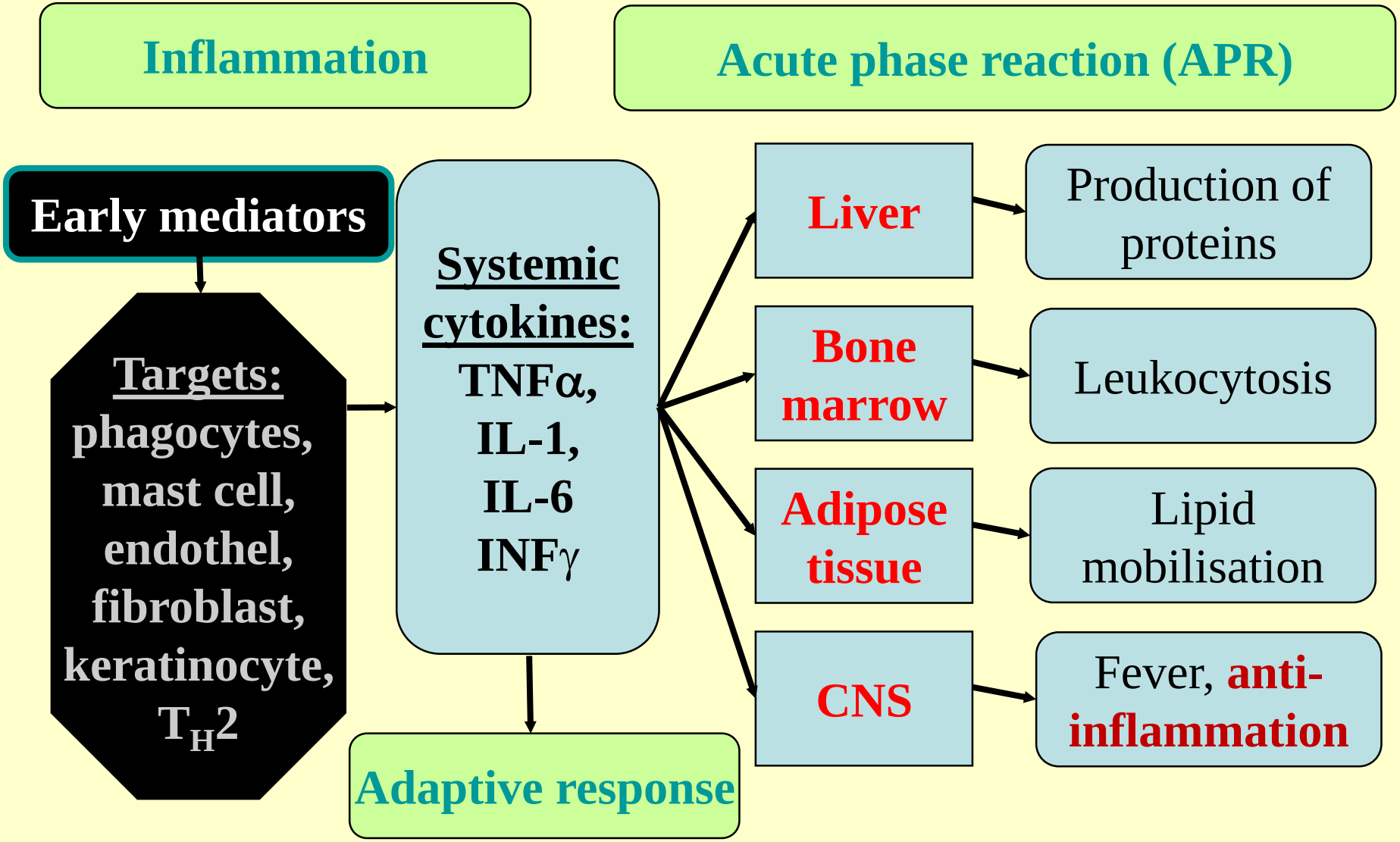
– Proliferation of bacteria and viruses decreases

– T–cell proliferation increases

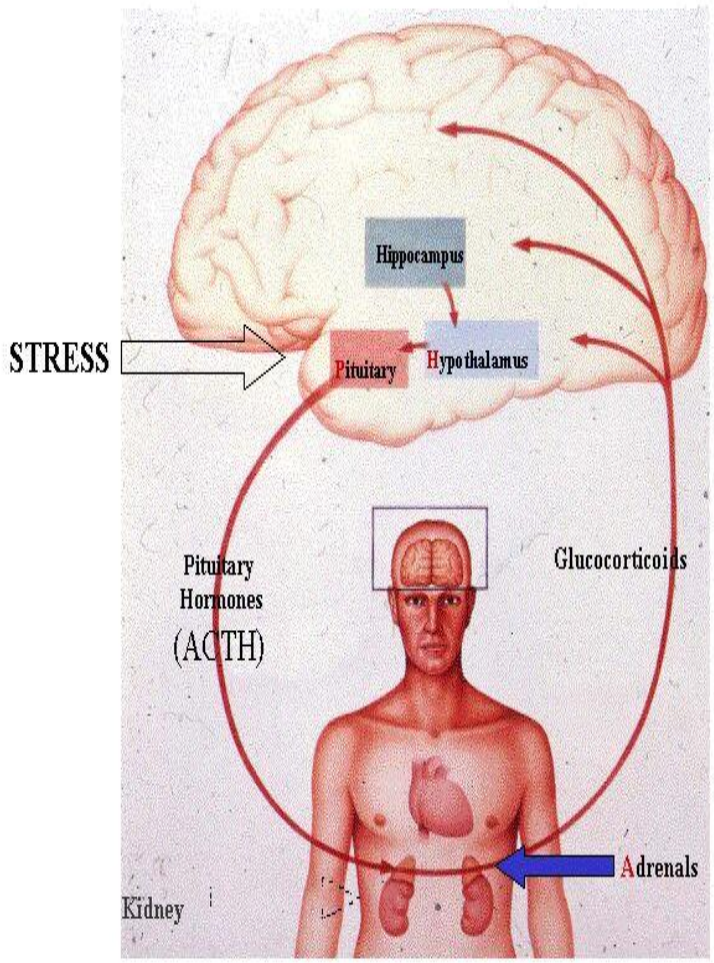
– Lymphocyte transformation is enhanced

– Gamma-interferon production is elevated

Progression of the innate immune response (6-12 hours)



Relationship of the immune system with the HPA (Hypothalamic-Pituitary-Adrenal) axis



Cytokine

↓ IL1, IL6, TNFα, INFγ

Hypothalamus

↓ CRH (Corticotropin Releasing Hormone)

Pituitary gland

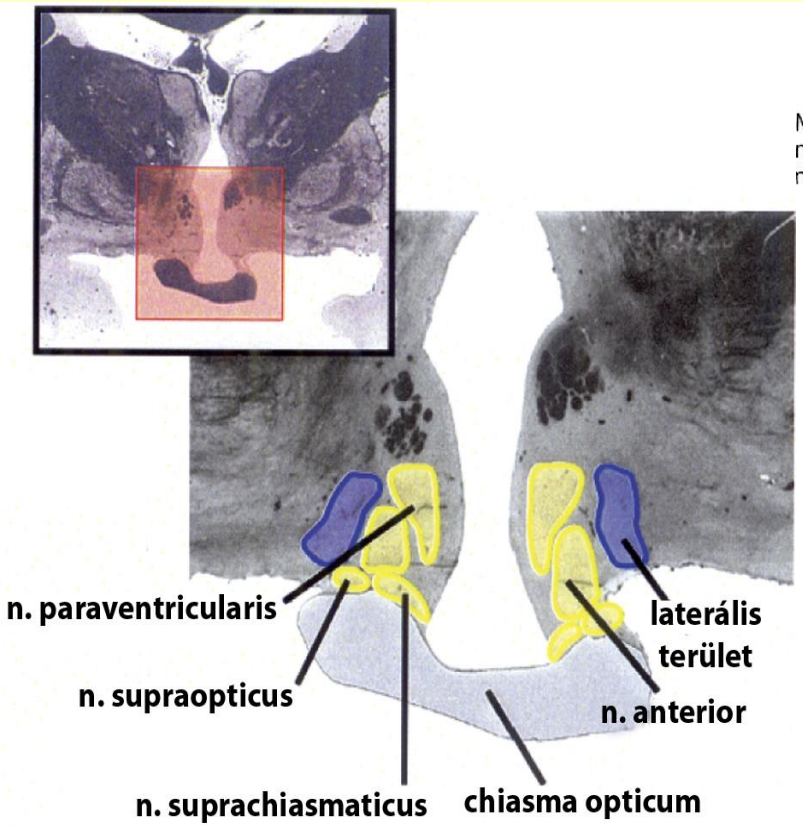
↓ ACTH (Adrenocorticotropic Hormone)

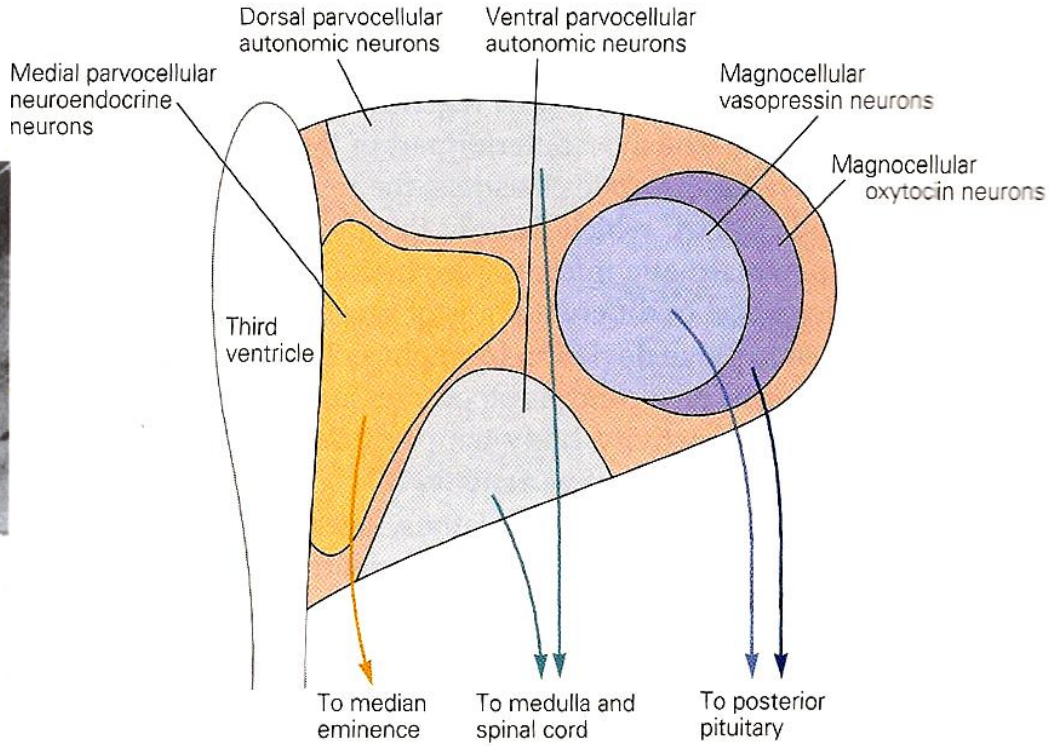
Adrenal gland

↓ Glucocorticoid

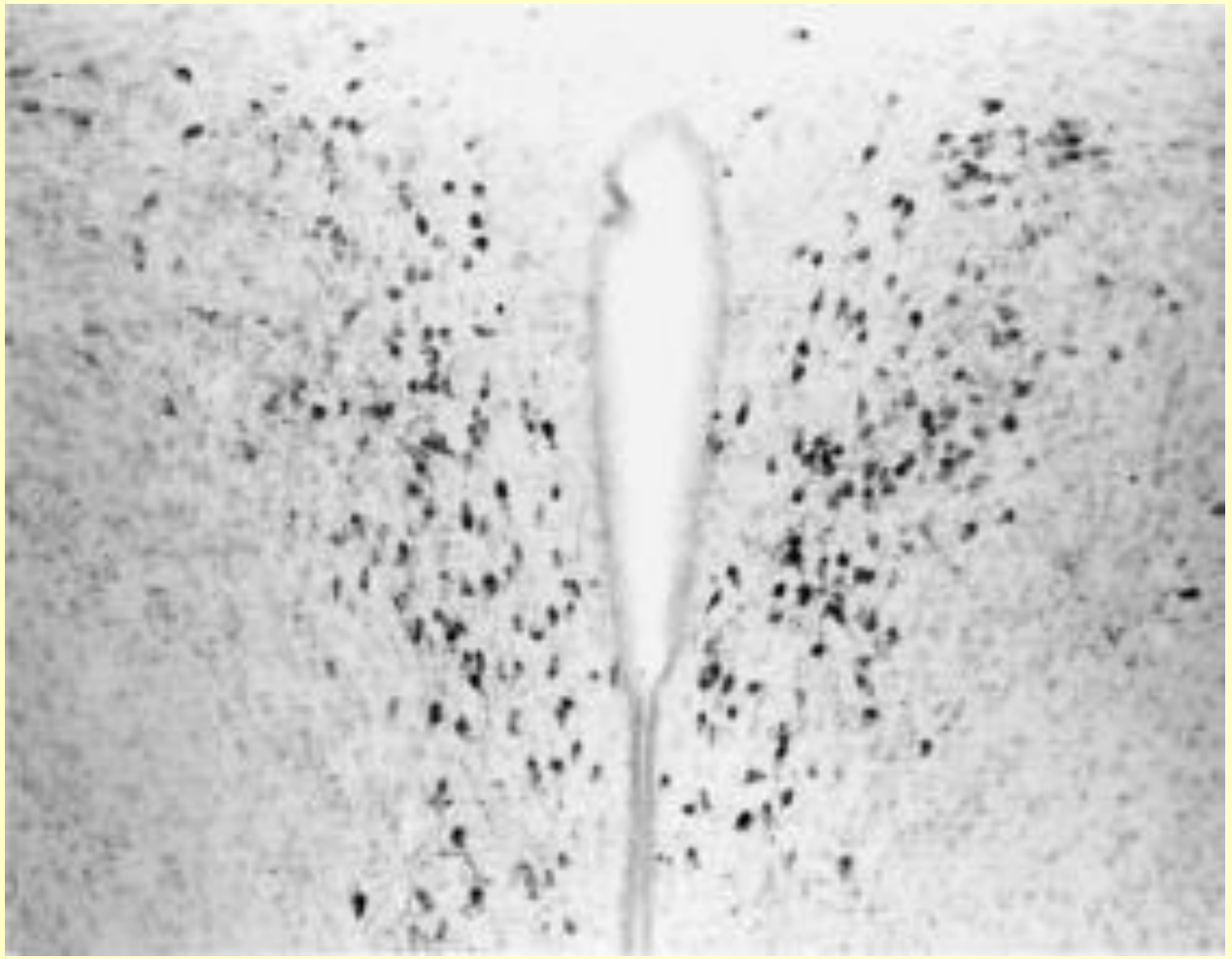
Immune system

Paraventricular hypothalamic nucleus



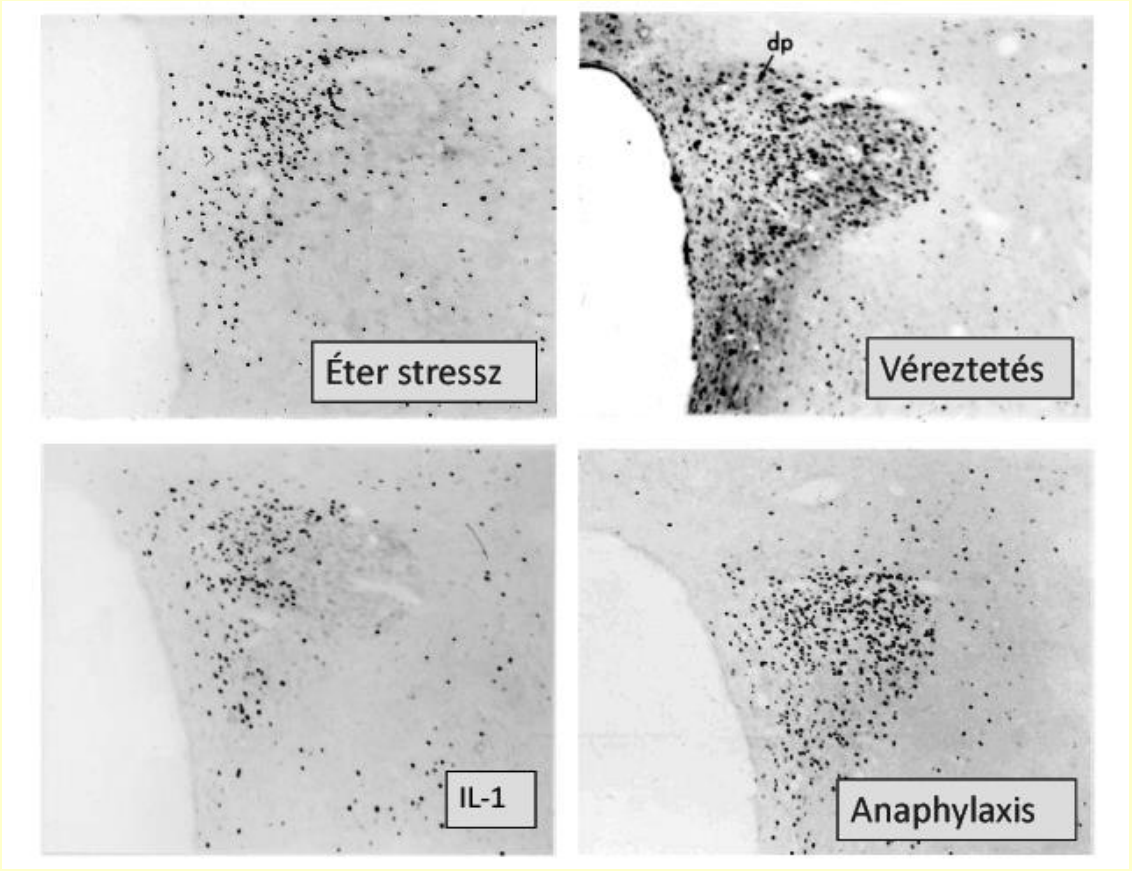


Corticotropin-releasing hormon (CRH)-expressing neurons in the PVN



Inflammatory cytokine hormones activate PVN similar to other stressors

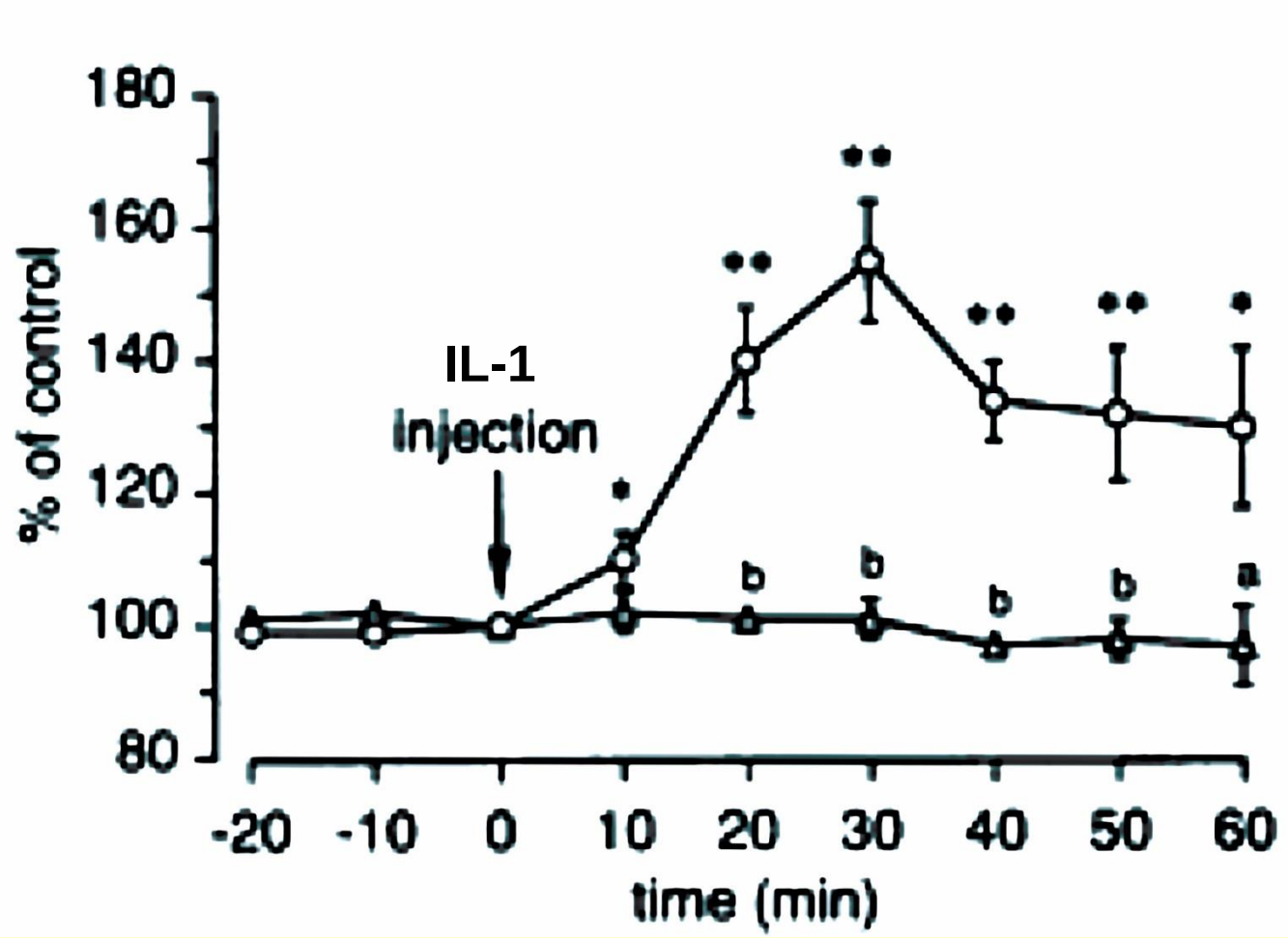
Paraventricular nucleus (PVN) – c-Fos immunolabeling



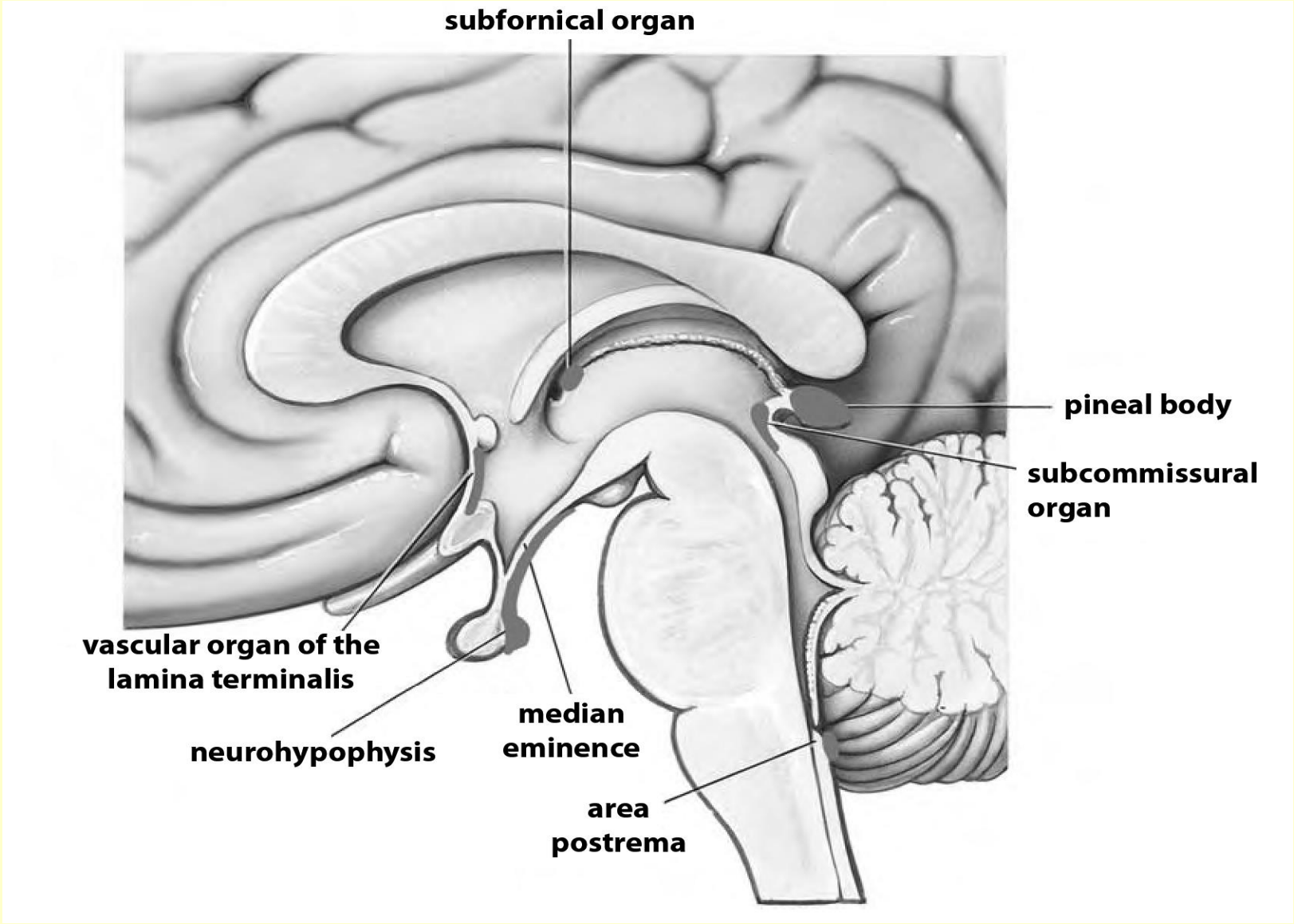
How does the action of cytokine hormones reach PVN?

They cannot penetrate blood-brain barrier and do not act via endothels like for fever.

Activity of the vagal nerve in response to IL-1 injection

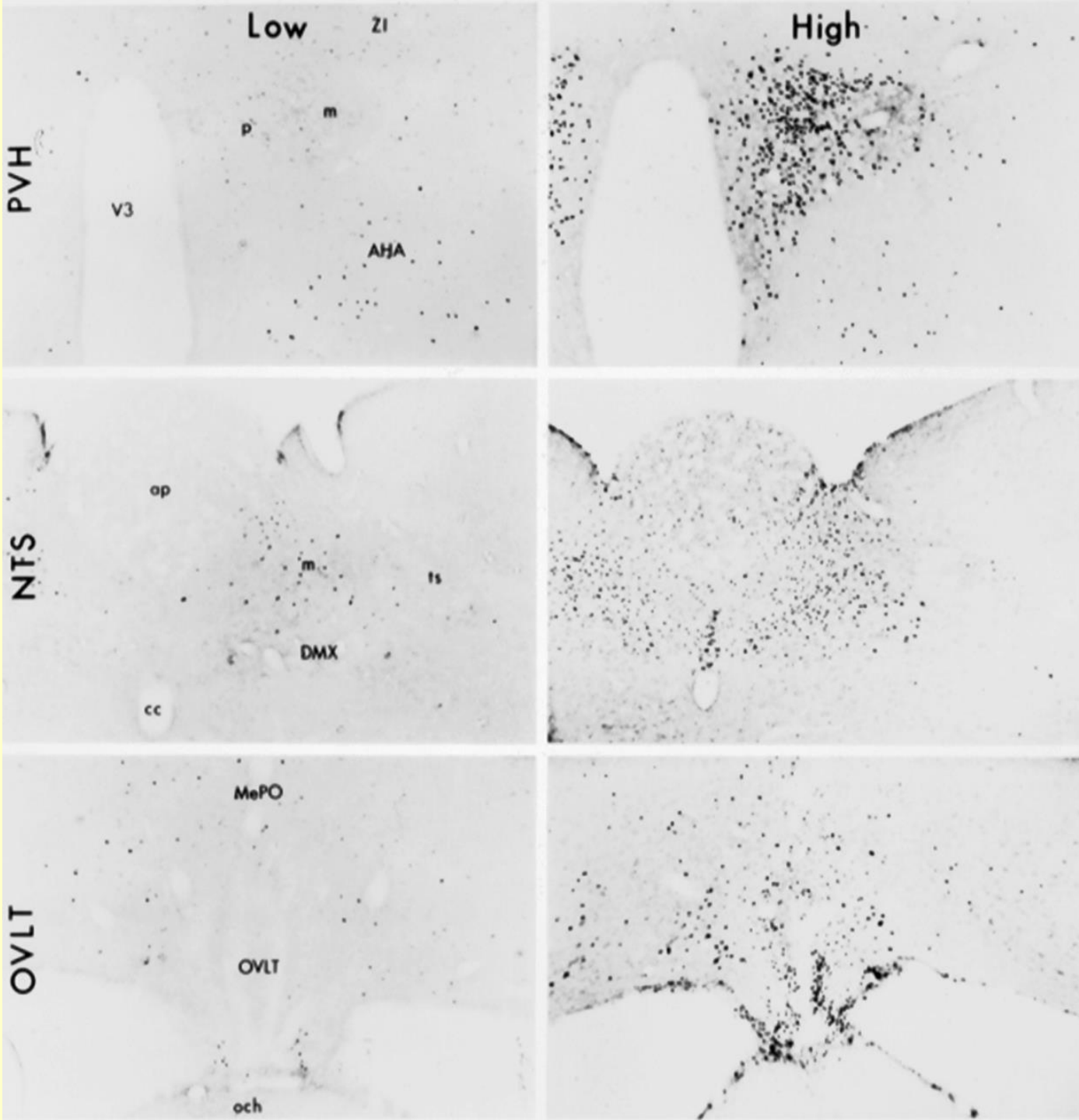


Circumventricular organs – humoral inputs



The effect of IL-1 on neuronal activation (c-fos expression) in different brain areas

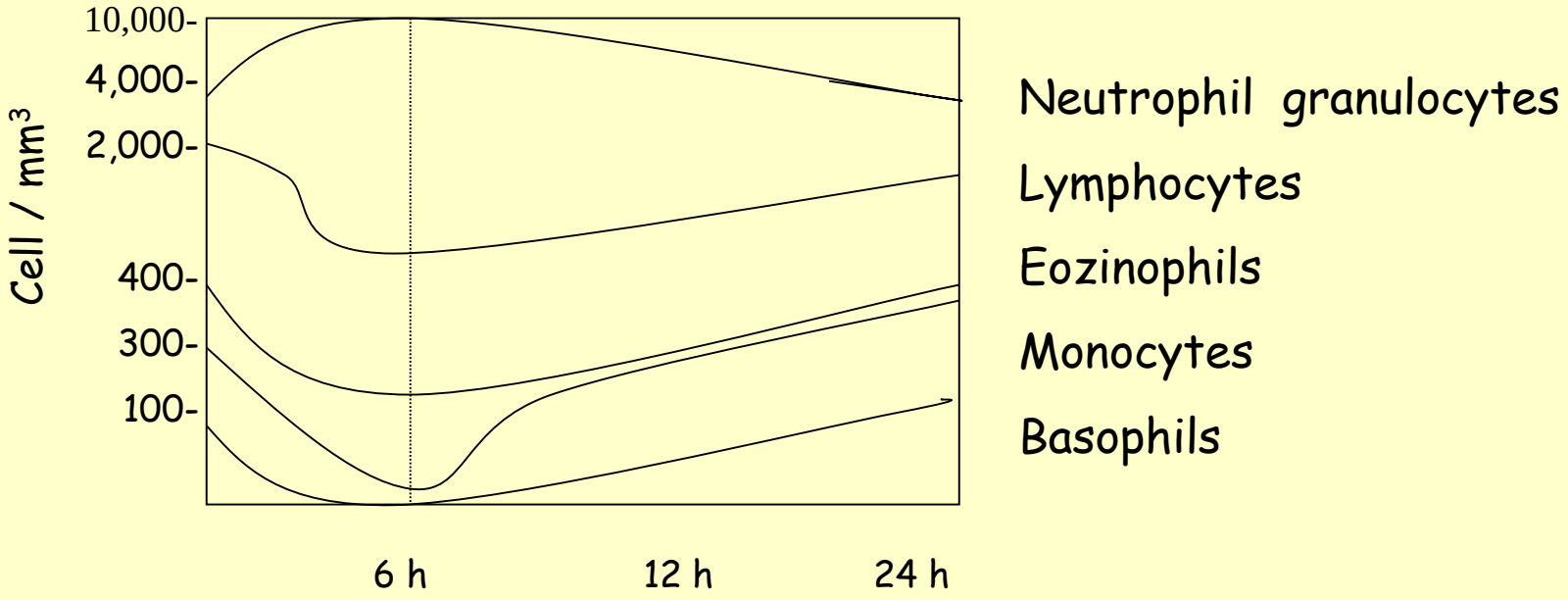
CONCLUSION: Cytokine hormones reach PVN via viscerosensory afferents and also through circumventricular organs



Anti-inflammatory actions of corticosteroids

Activity	Effect
↓ IL-1, TNF, GM-CSF, IL-3, IL-4. IL-5, IL-8	↓ Inflammation (mediated by cytokines)
↓ NOS (nitric oxide synthase)	↓ NO, causing reduced vasodilation
↓ Foszfolipase A2 Ciklooxygenase2	↓ Prostaglandins, Leukotriens, reduced fever, reduced pain
↑ Adhesion molecules	↓ Reduced migration
Induction of Endonucleases	Apoptosis of limfocytes, leukocytes

The effect of glucocorticoids on the number of leukocytes



Immunosuppression therapy

To eliminate unwanted immune response:

- Allergy
- Autoimmune diseases
- Organ transplant

a, Antigen-specific immune suppression – selective tolerance

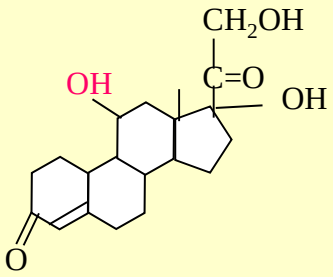
b, Not-antigen- specific

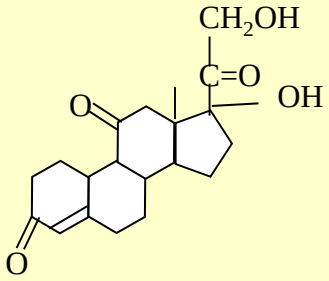
- Corticosteroids (in supraphysiological, pharmacological doses)
- CY-A, FK 506, Rapamycin (T cell proliferation inhibitor)
- Radiation therapy
- Cytostatics

Natural and artificial glucocorticoids

Synthetic products:

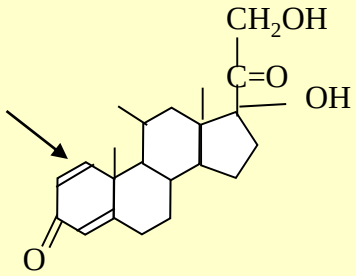
Cortisol

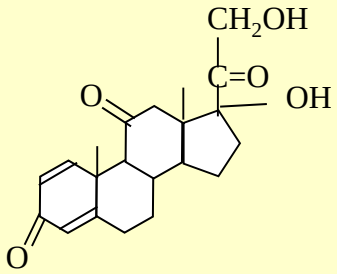




Cortizon

Prednizolon

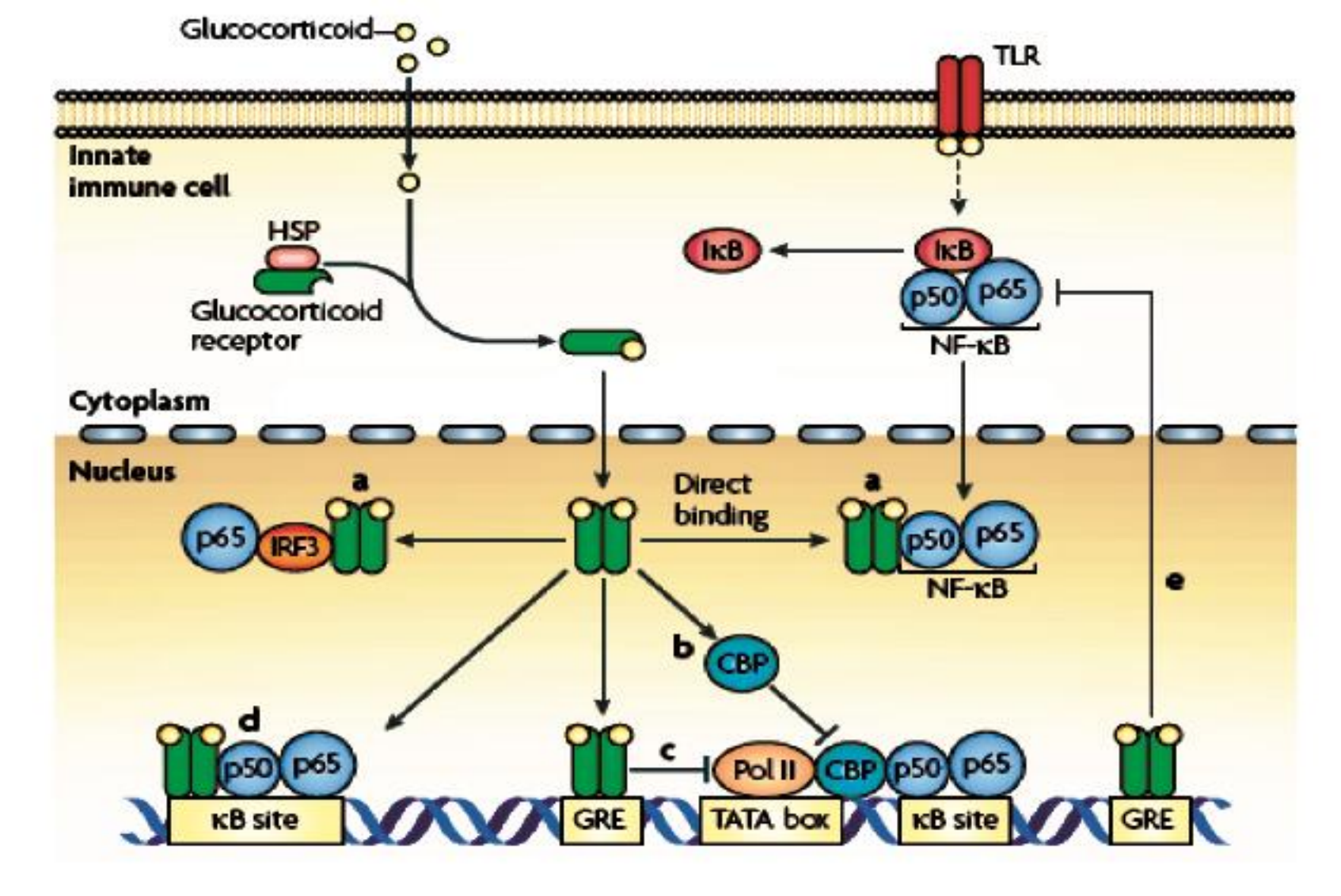




Prednizon

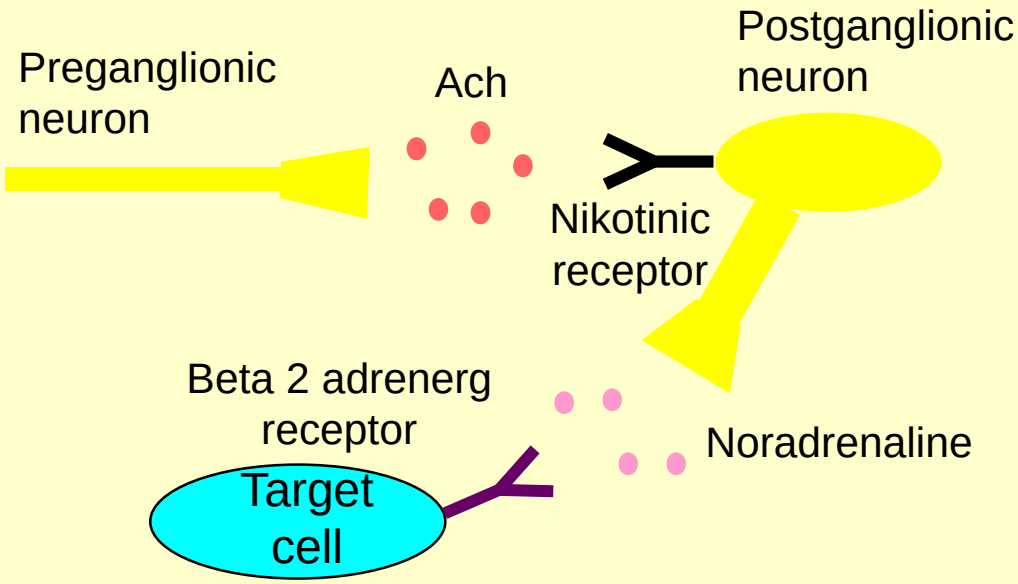
(4x more effective than Cortizon)

Anti-inflammatory mechanism of glucocorticoids



HSP: heat shock protein; GRE: glucocorticoid receptor element; TLR: toll-like receptor

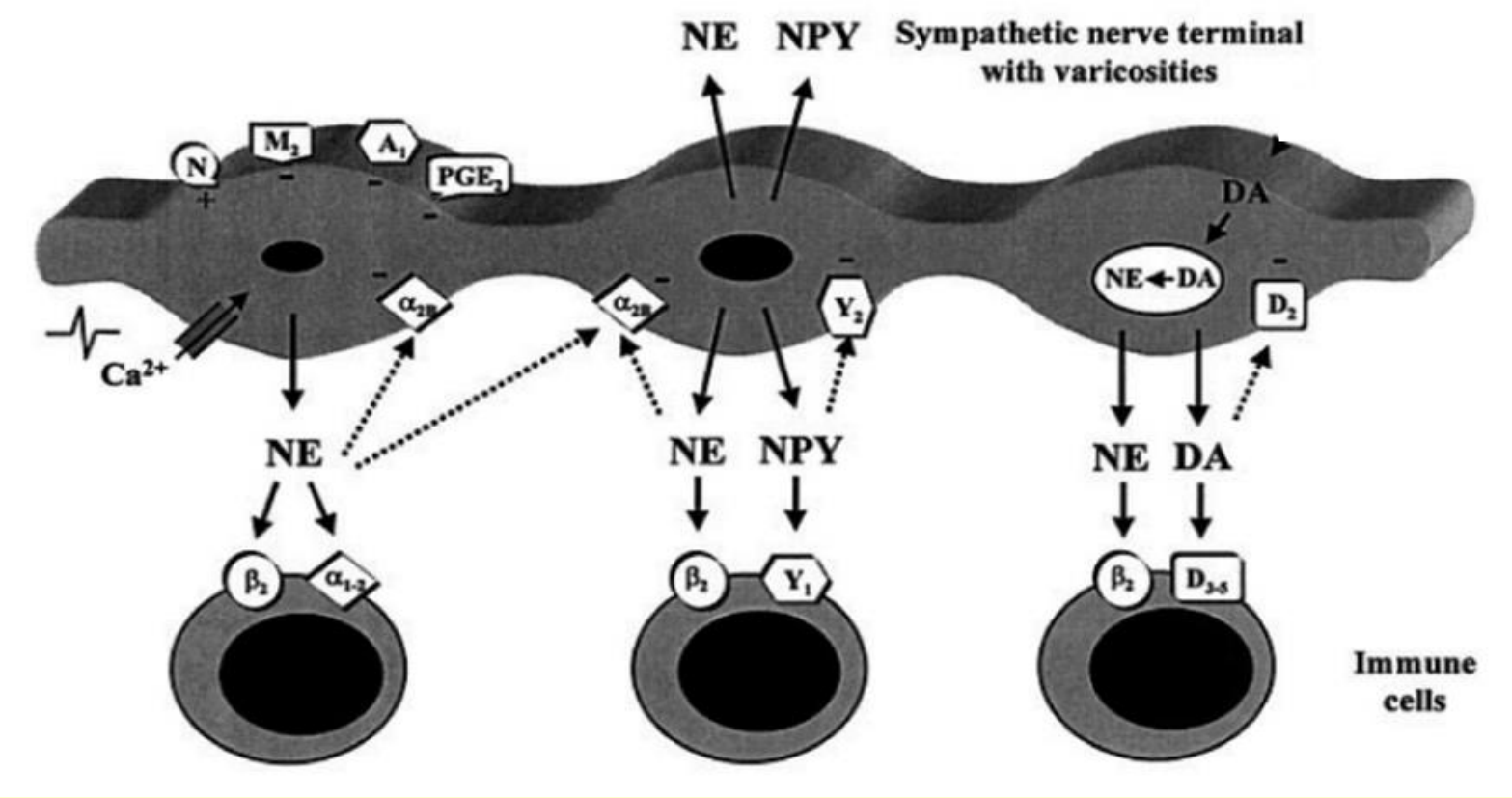
The effect of the sympathetic nervous system on the immune system



Macrophages and lymphocytes possess beta 2 adrenerg receptors, which inhibit their actions

Additional effects of the sympathetic nervous system on inflammation

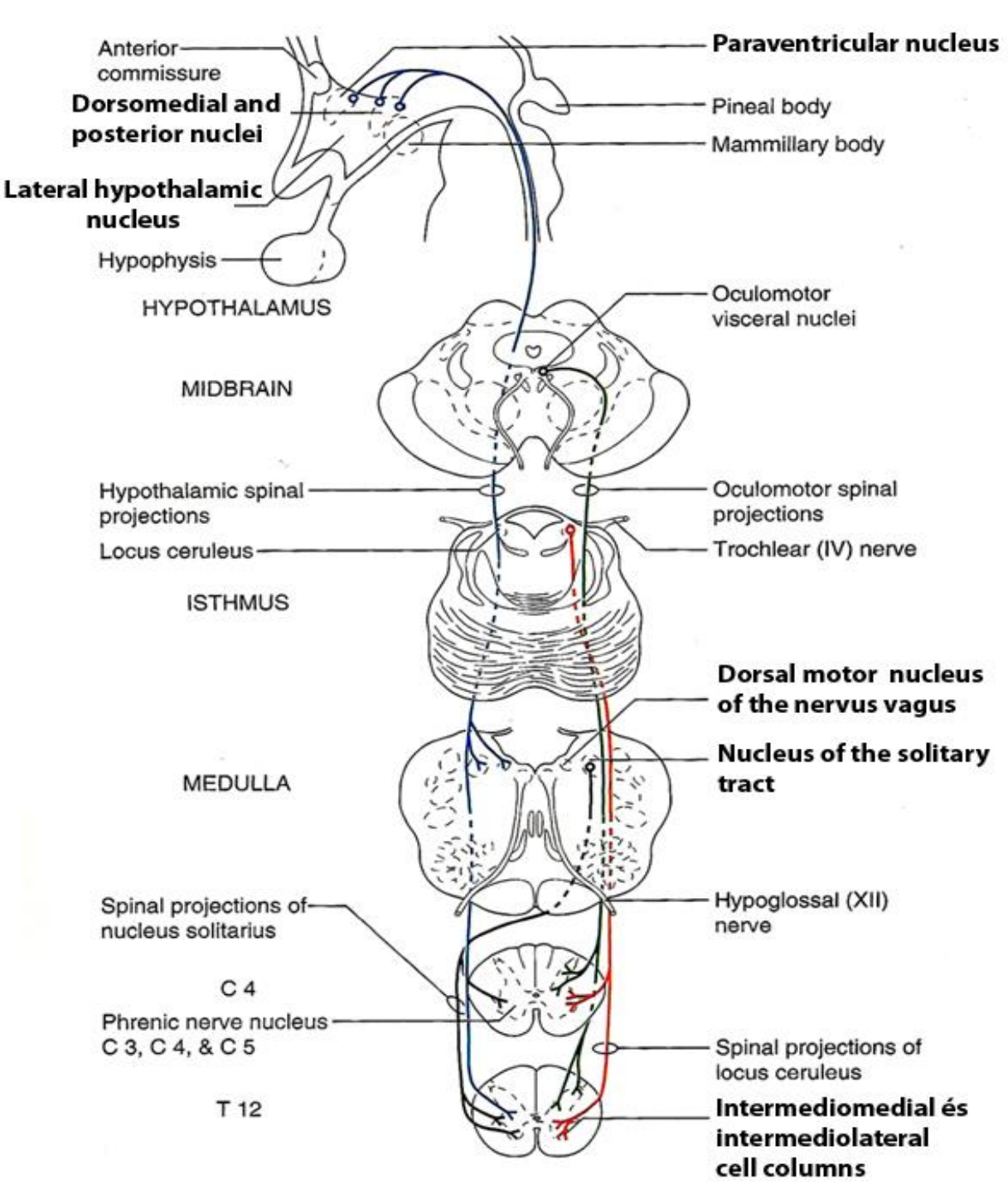
- In additon to noradrenaline, dopamine and neuropeptide Y are also released from sympathetic terminals
- Immune cells have receptors for these modulators as well, through which they inhibit their migration, activation and proliferation, which all contribute to the localization of inflammation



How is the autonomic nervous system activated by the immune system?

1. Local reflexes
- spinal cord for sympathetic responses
- nucleus of the solitary tract (NTS) for parasympathetic responses

2. Via higher brain centers.
-E.g., the hypothalamo-spinal tract and other descending pathways can also affect autonomic functions

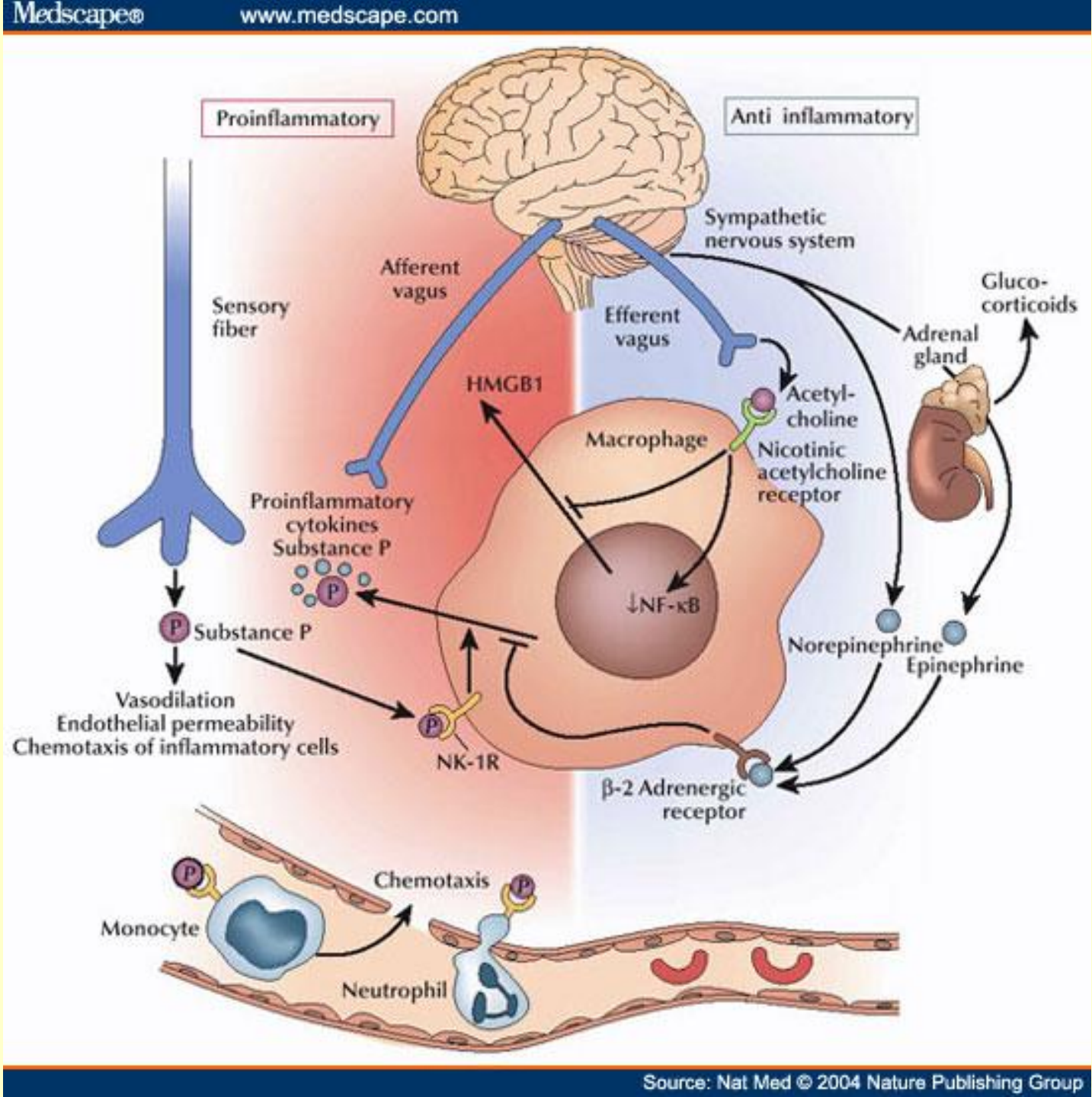


Neuro-modulation of inflammation

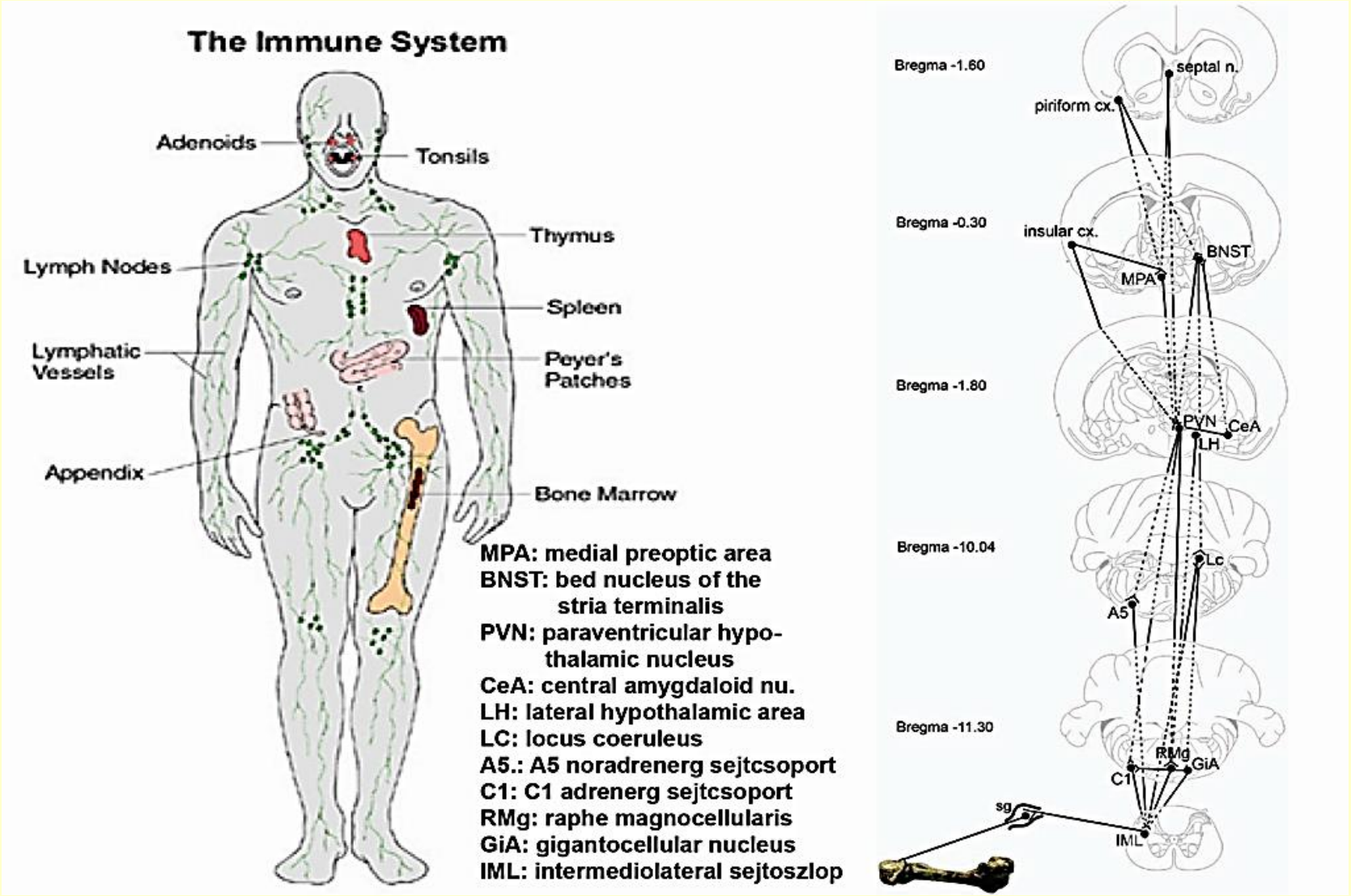
1. sensory terminal (stimulatory)

2. sympath. (inhibitory)

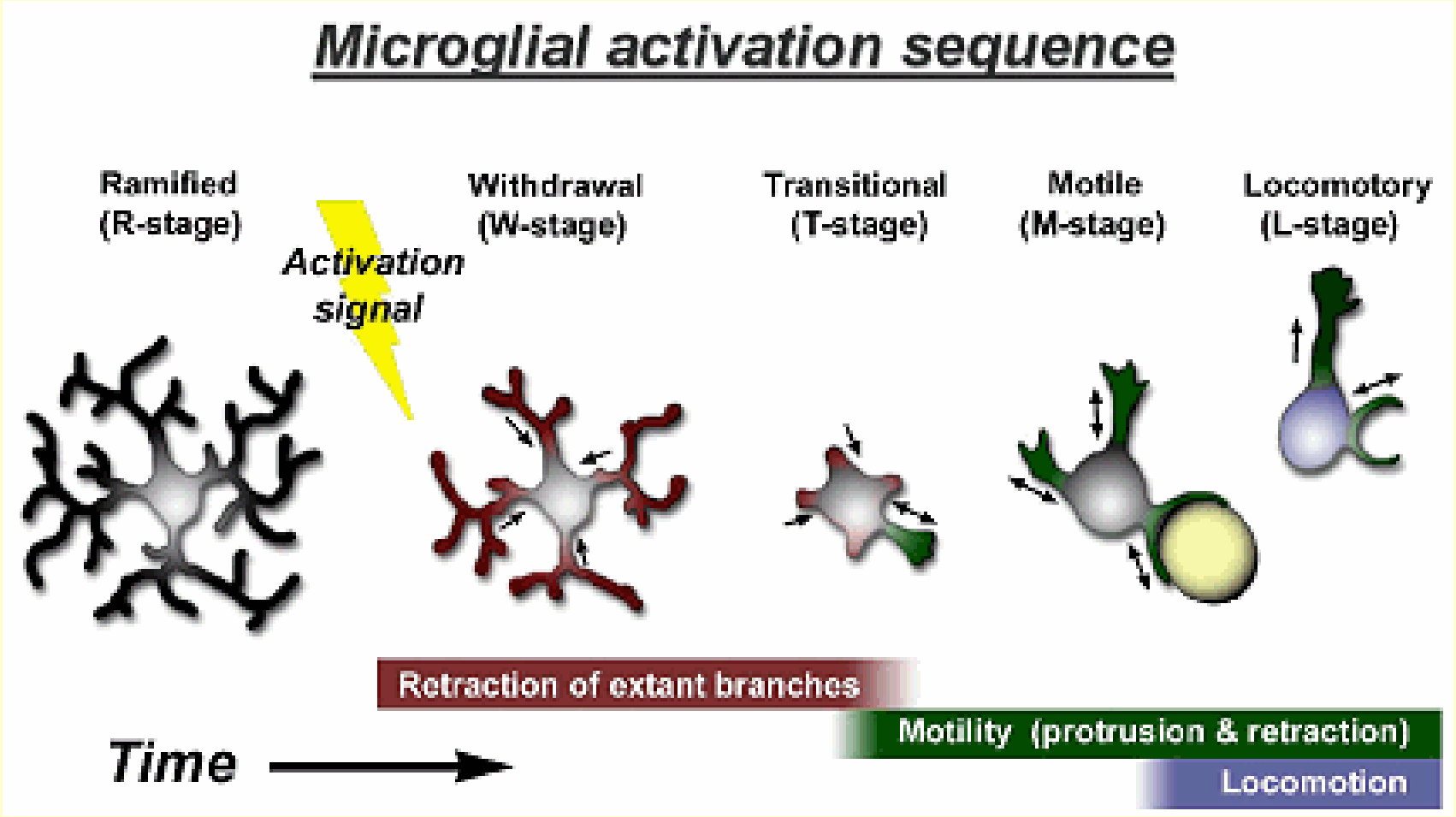
3. parasymp. (inhibitory) via nicotinic Ach receptors located on macrophages



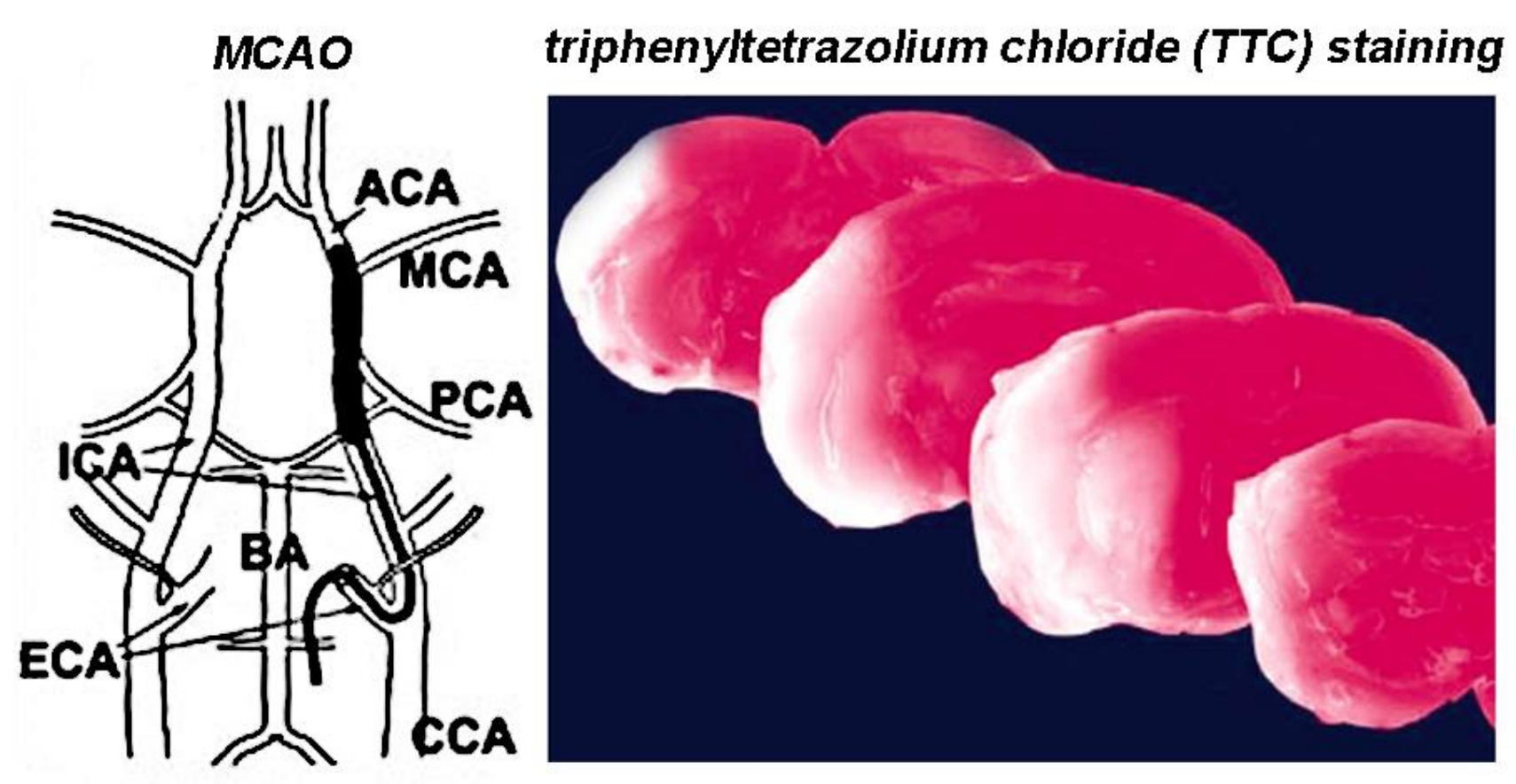
An additional way how the nervous system can influence the immune system: direct (autonomic) innervation of organs specifically involved in immune response



Stages of microglial activation

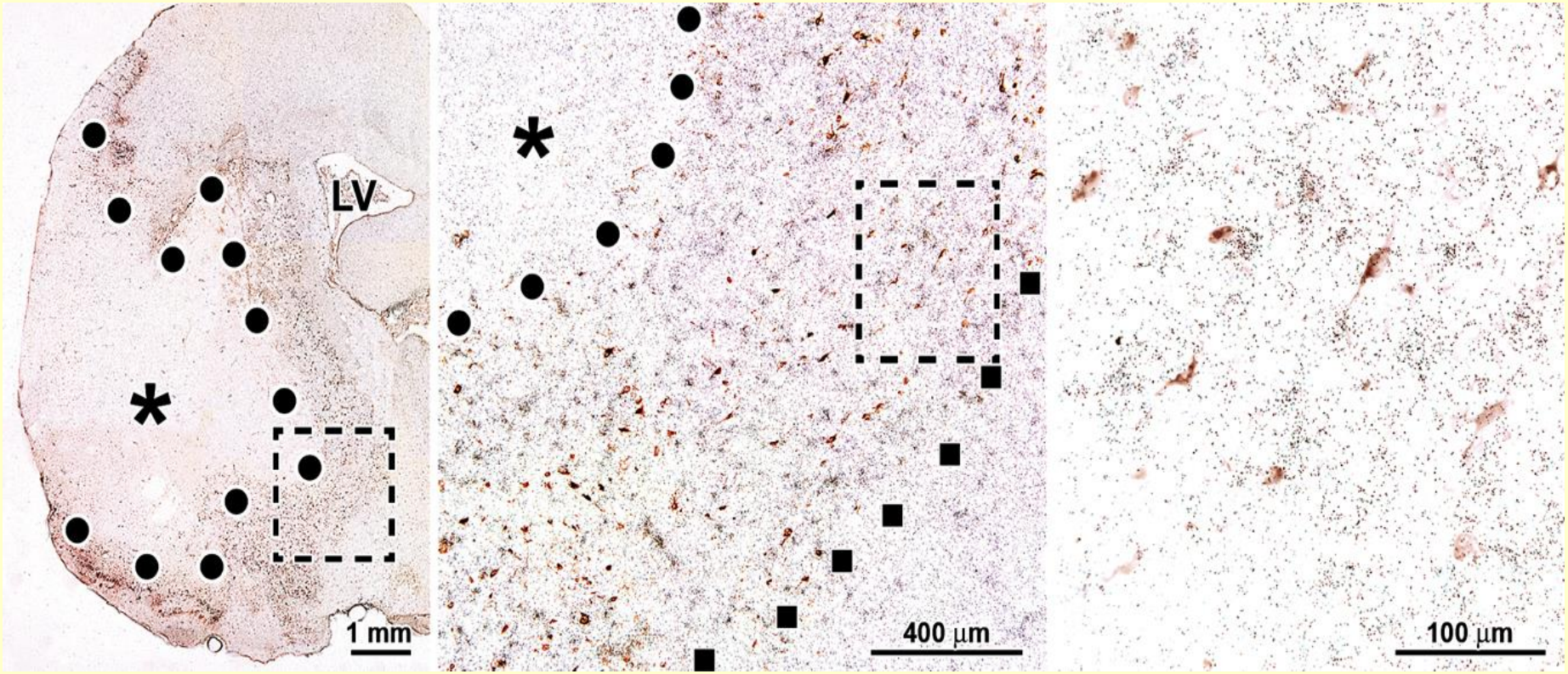


Model of focal ischemia in brain: middle cerebral artery occlusion (MCAO)



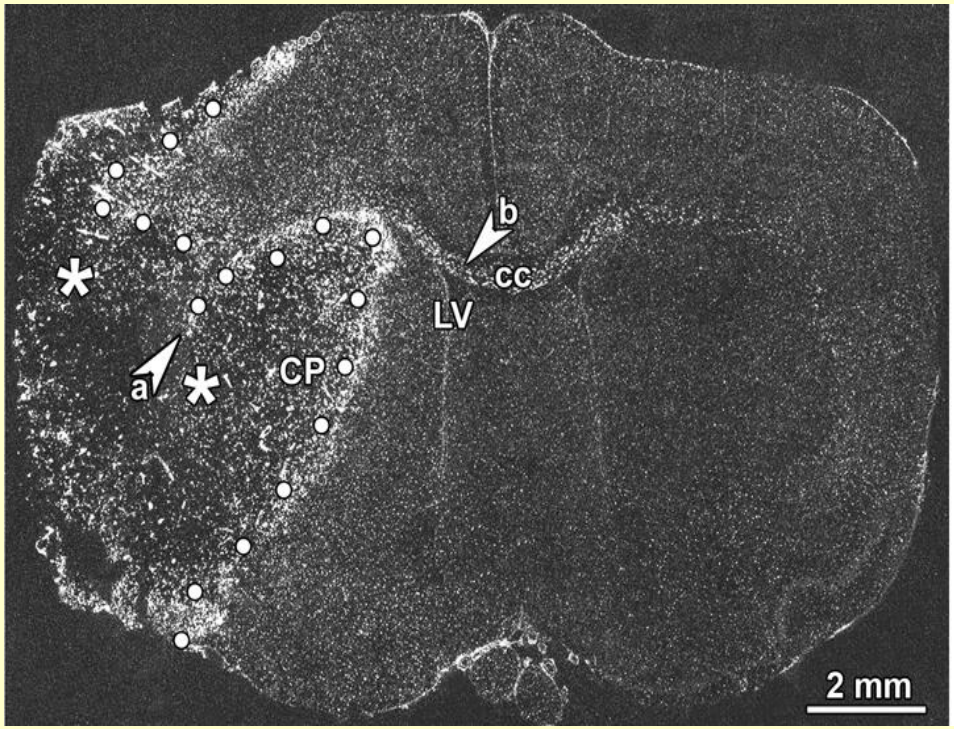
TGF-β1-positive microglia in the penumbra 1 day after MCAO

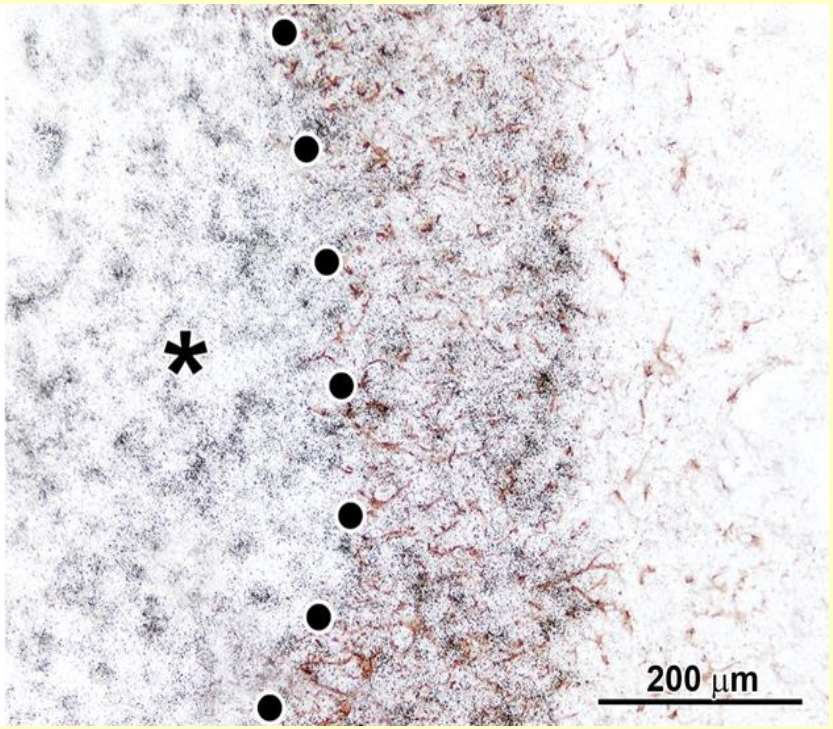
TGF-β1 in situ hybridisation histochemistry + Hsp70 immunolabeling (penumbra marker)



Microglial cell in the infarct area 3 days after lesion

TGF-β1 in situ hybridisation histochemistry + GFAP immunolabeling (astrocyte marker)

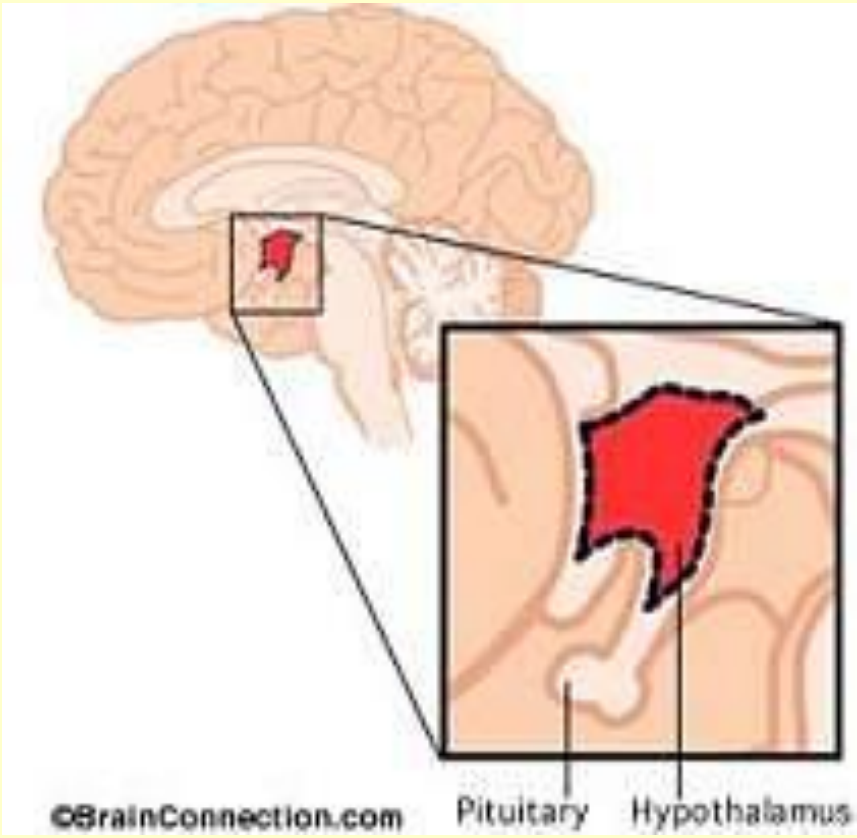




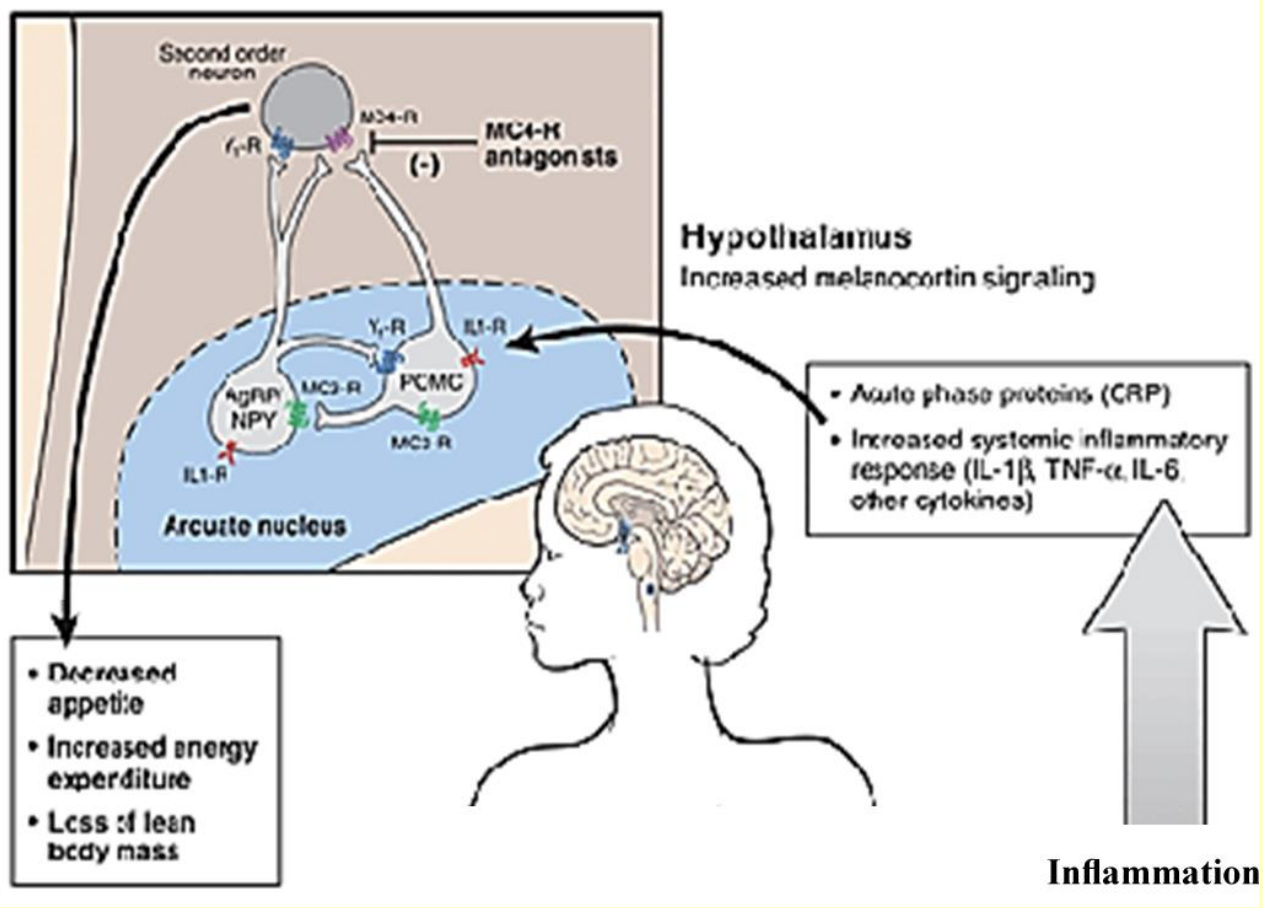
Acute phase reaction of the central nervous system

Systemic cytokines activate the hypothalamus

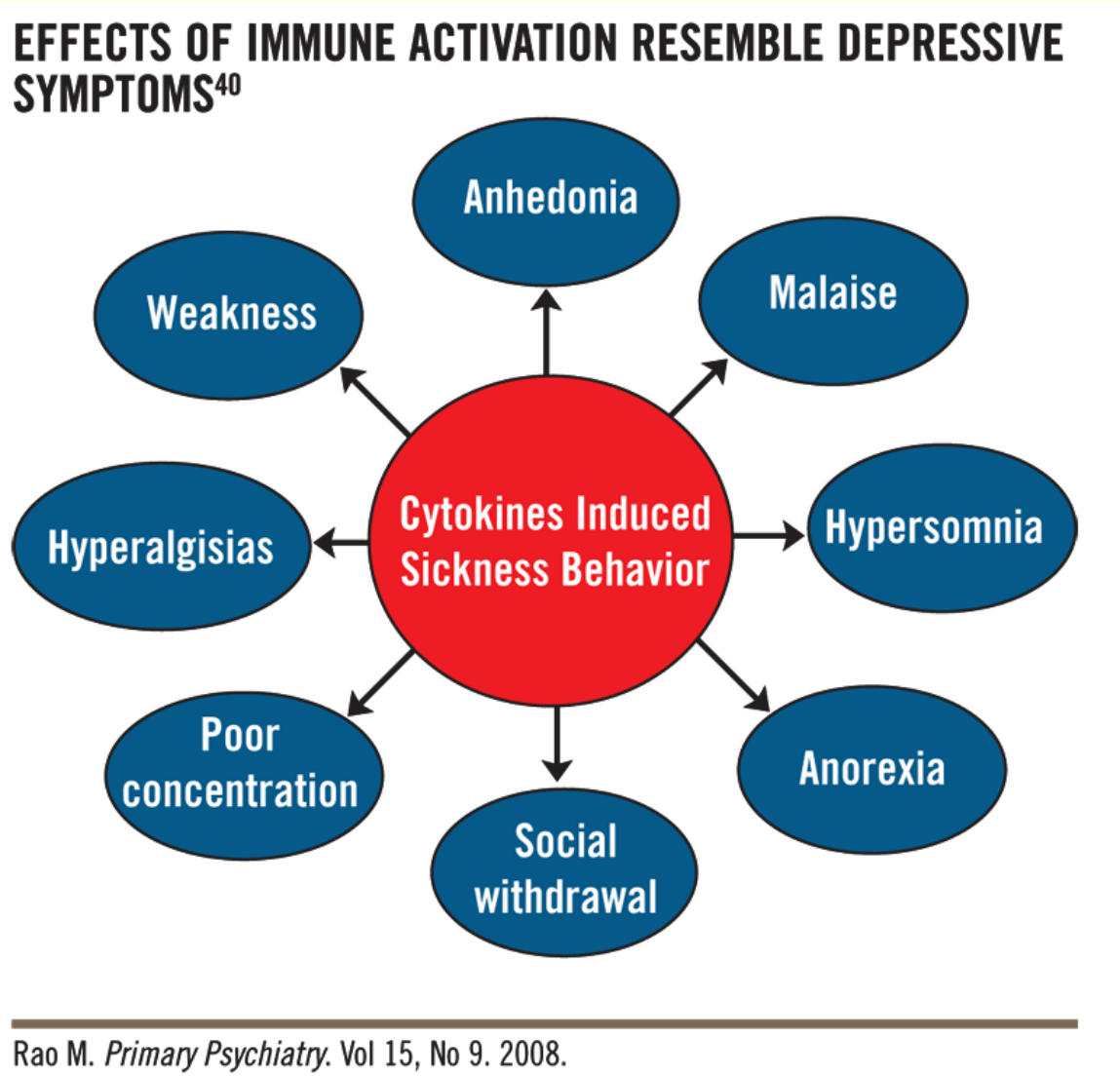
- **Systemic inhibition of the immune system**
  - **HPA axis**
  - **Vegetative nervous system**
- **Fever**
- **Behavioral effects:**
  - **No appetite**
  - **Drowsiness**
  - **Lack of exploratory and sexual behaviors**



Systemic inflammatory mediators reduce appetite by acting on hypothalamic food intake regulatory neurons



Immune activation produces sickness behaviours, symptomes that resemble to depression



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   - Water balance
   - Body temperature regulation
5. Homeostatic regulations by the immune system
6. The role of the nervous and the endocrine systems in immune regulations
7. Principles of the behavioural control of homeostasis
   - Feeding behaviour

Factors, which determine behaviour

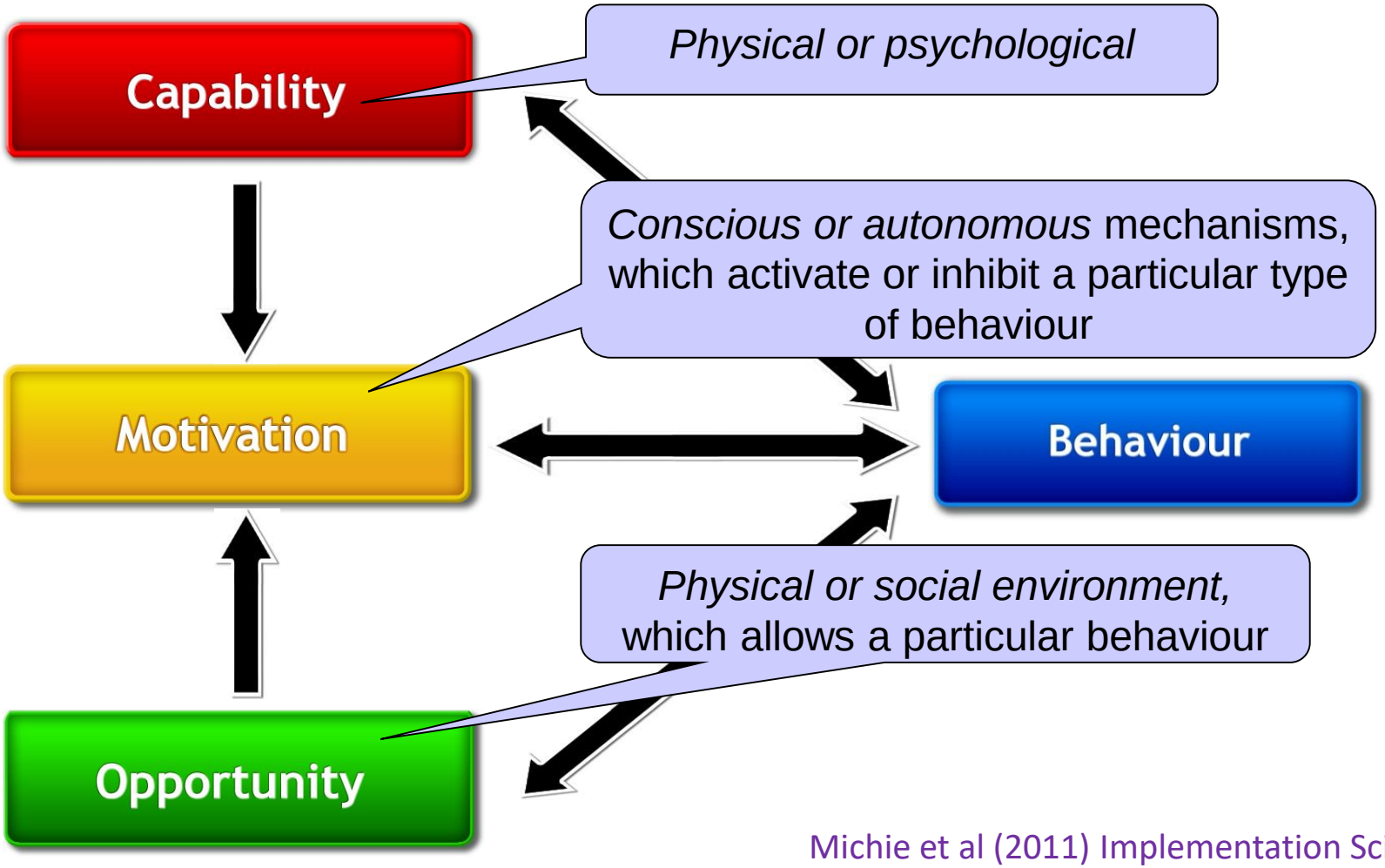
Motivation (or drive):

The state of the brain, as to what degree an individual wants (or will) perform a particular behavioural element.

Capability:

The state of the organism whether, and to what degree an individual is able to perform a particular behavioural element.

The COM-B model: the behaviour is formed as a result of the interaction of 3 necessary conditions



Michie et al (2011) Implementation Science

Types of motivations

Basic motivations:

- Physiological demands (where the goal of the behaviour is to maintain homeostasis): e.g. hunger, thirst, feeling warm, pain, sleepiness

- Social motivations: e.g. sexual, maternal behaviours, belonging to a group, being understood by a conspecific

Higher order motivations:

- Emotions: e.g. fear, happiness, sadness, disgust, surprise, curiosity, angriness

- Social emotions: e.g. proudness, jealousy, enviness, love

- Cognitive motivations: e.g. desire for knowledge, understanding

- Social cognitive motivations: e.g. teaching

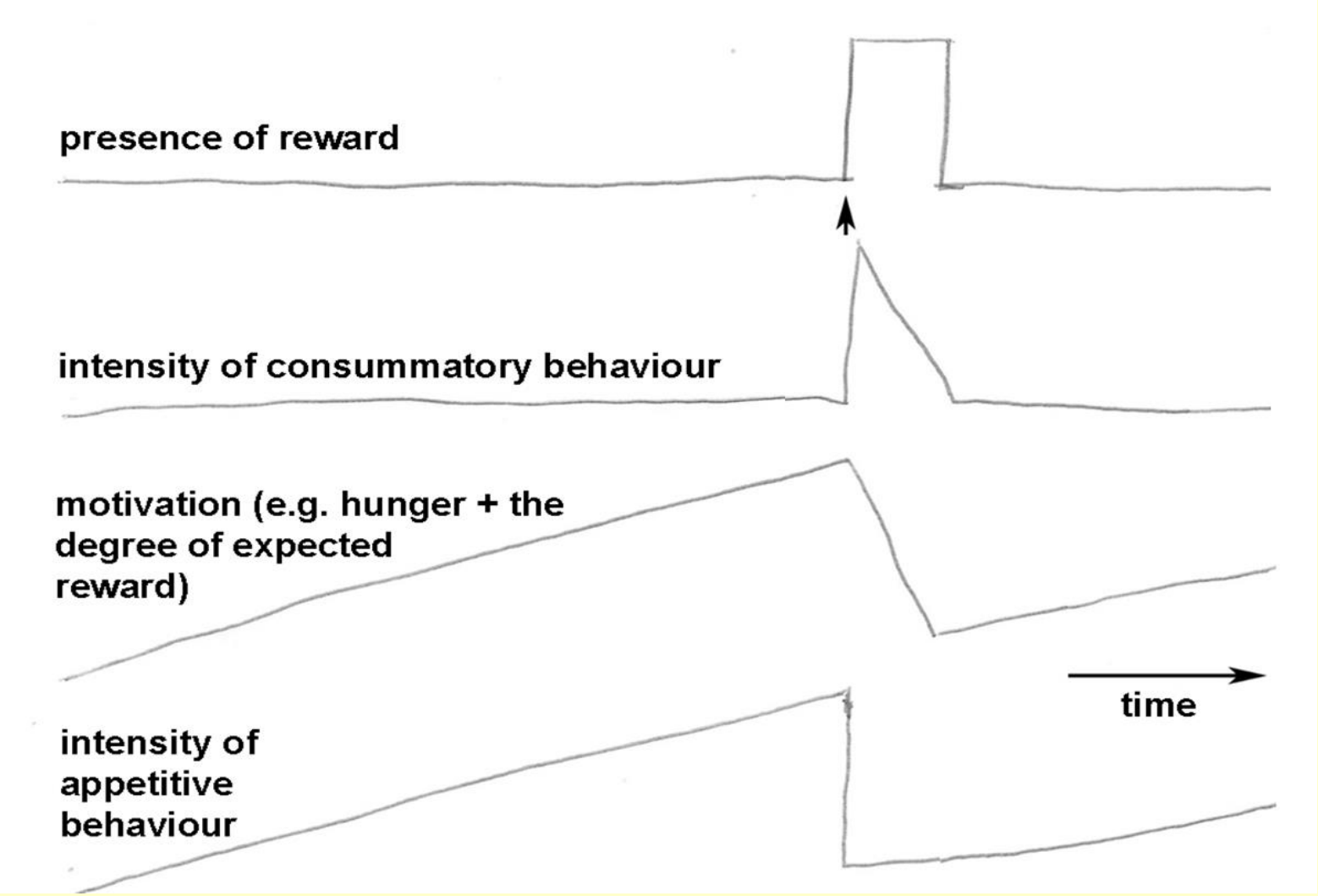
Drive theory based on the temporal alteration of basic motivations - Hull, 1952

Basic motivations, such as physiological demands (hunger, thirsts, sexual desire) increase gradually until consummation, during which they suddenly drop

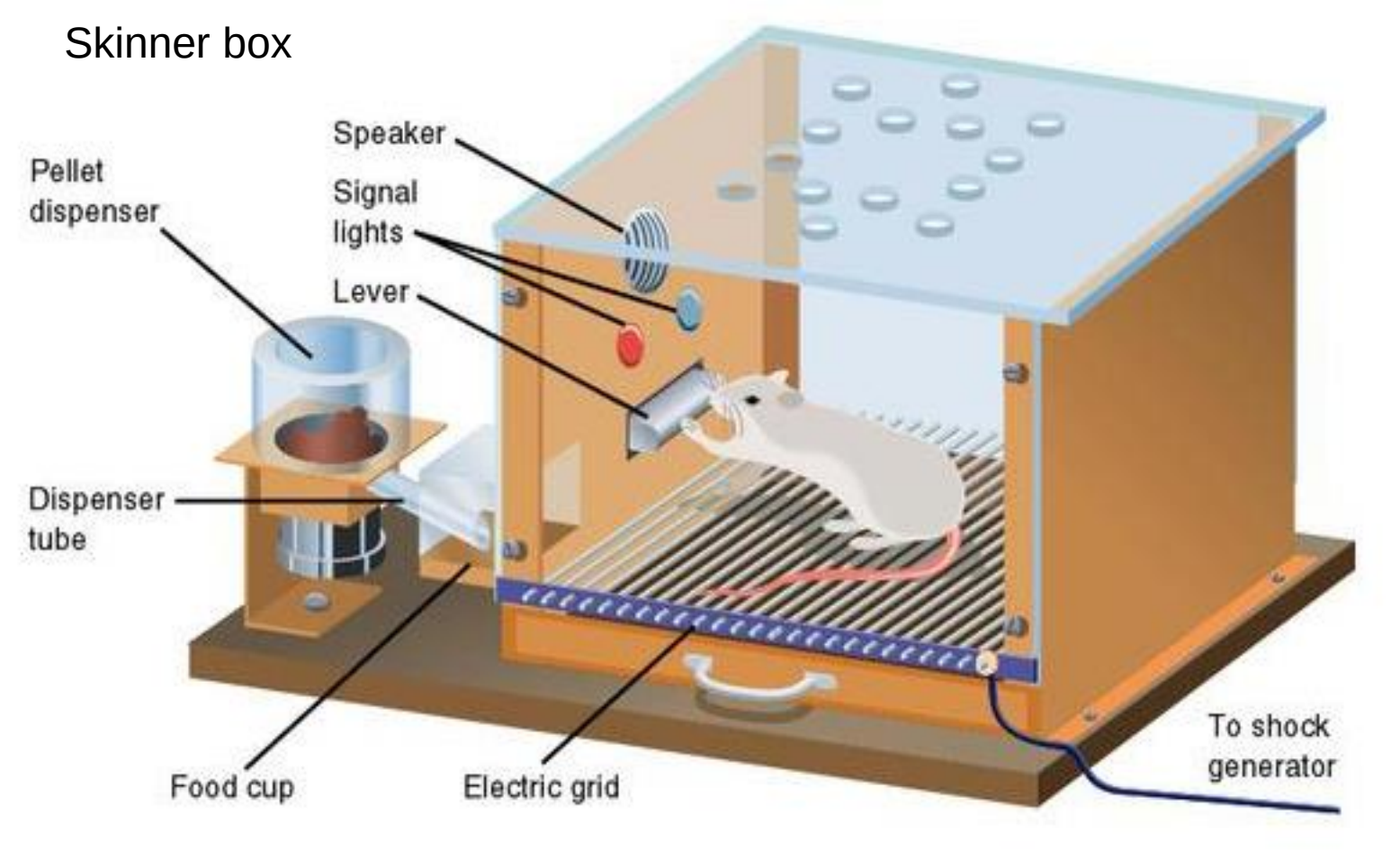
- Deprivation of physiological demands enhances motivation, which energetizes the organism and leads to so-called appetitive (goal directed) behaviours.

- Reaching the goal allows consummatory behaviours, which fulfill the physiological demand and decrease the particular motivation.

Time course of motivation, appetitive and consummatory behaviours determined by the reward according to the drive theory

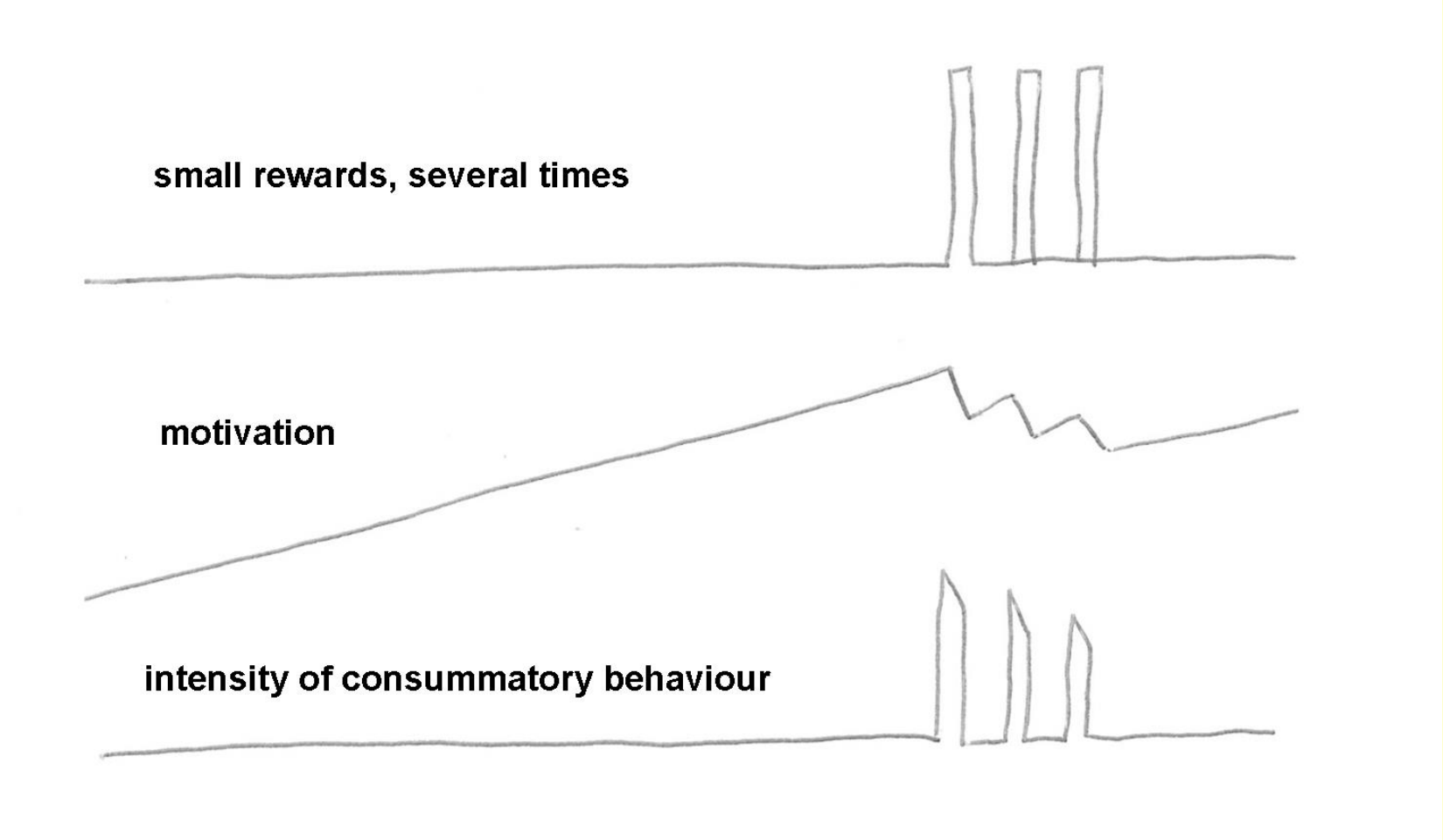


Assessing motivation in animal experiments 1. Measuring the intensity of appetitive behaviours



Measuring the intensity of - lever pressing
- nose poke

The effect of small rewards applied experimentally in the Skinner box on the motivation and consummatory behaviours



Assessing motivation in animal experiments 2. Measuring conditioned place preference

The ratio of stay in the reward-associated compartment

Neurobiological approach to the drive theory

Critiques of the theory:

- Not all motivation derives from physiological demand, and more complex motivations may not decrease during consummation (e.g. curiosity).

Testing the theory in neurobiology

- Does the theory has any neurobiological correlation in the brain?

Outline of homeostasis

1. Internal environment of living organisms and the principles of homeostatic regulations
2. Homeostatic regulations – the endocrine system
3. Examples of physiological parameters regulated by the endocrine system
   - Potassium ion level of blood plasma
   - Calcium ion level of blood plasma
4. Examples of regulations involving the endocrine as well as the nervous system
   - Water balance
   - Body temperature regulation
5. Homeostatic regulations by the immune system
6. The role of the nervous and the endocrine systems in immune regulations
7. Principles of the behavioural control of homeostasis
   - Feeding behaviour

Ghrelin is an orexigenic (food intake increasing) hormone

- Ghrelin is a peptide hormone comprising of 28 amino acids
- Its receptor is the growth-hormone-secretagogue receptor (GHS-R)
- Injection causes hunger in humans, the only such hormone known
- Increased food intake in both human and animal models following both peripheral and central administration
- It is released from the stomach as soon as food is removed from the stomach while the presence of food inhibits its secretion

Ghrelin serum level in human in relation to the meals

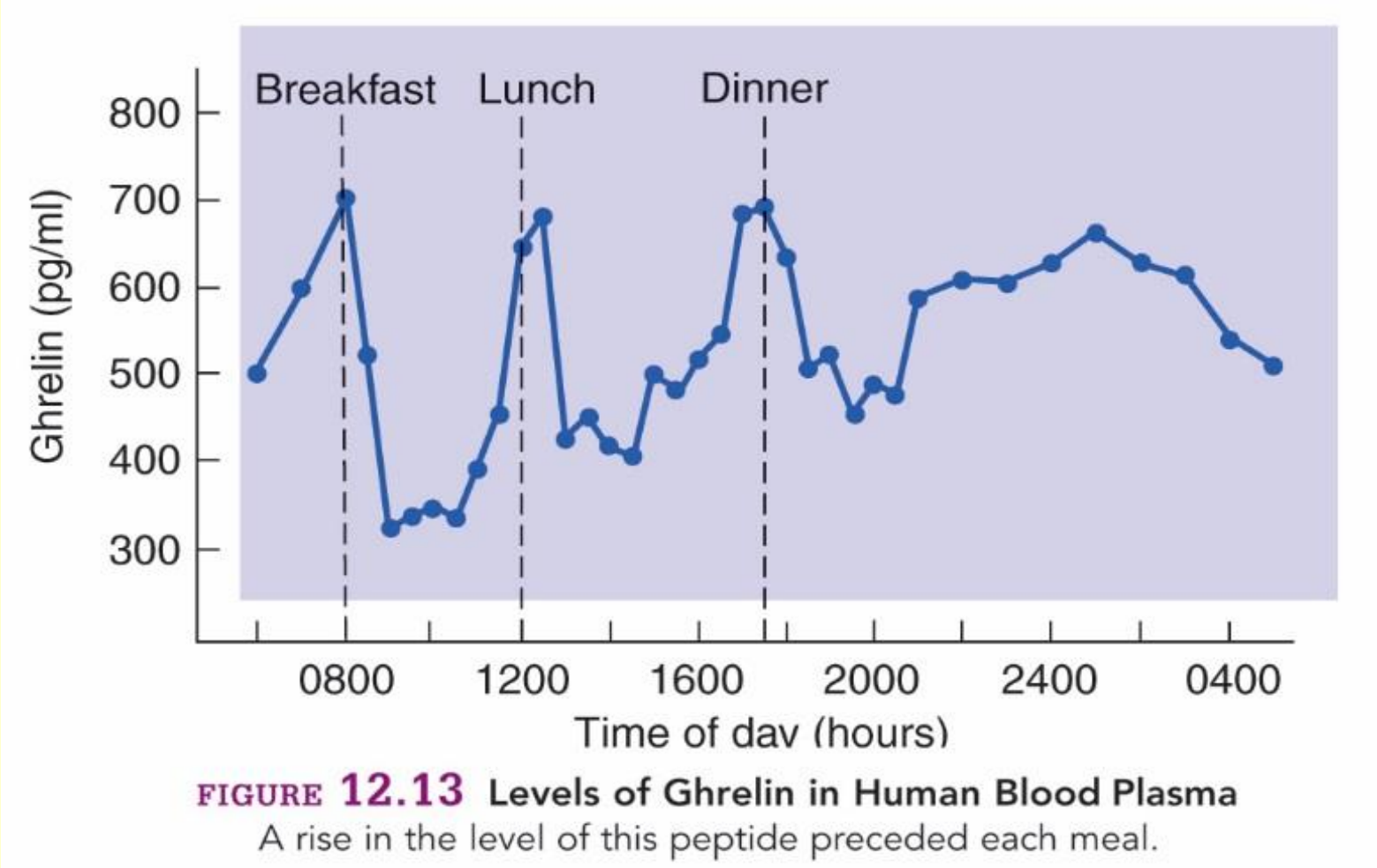


FIGURE 12.13 **Levels of Ghrelin in Human Blood Plasma**
A rise in the level of this peptide preceded each meal.

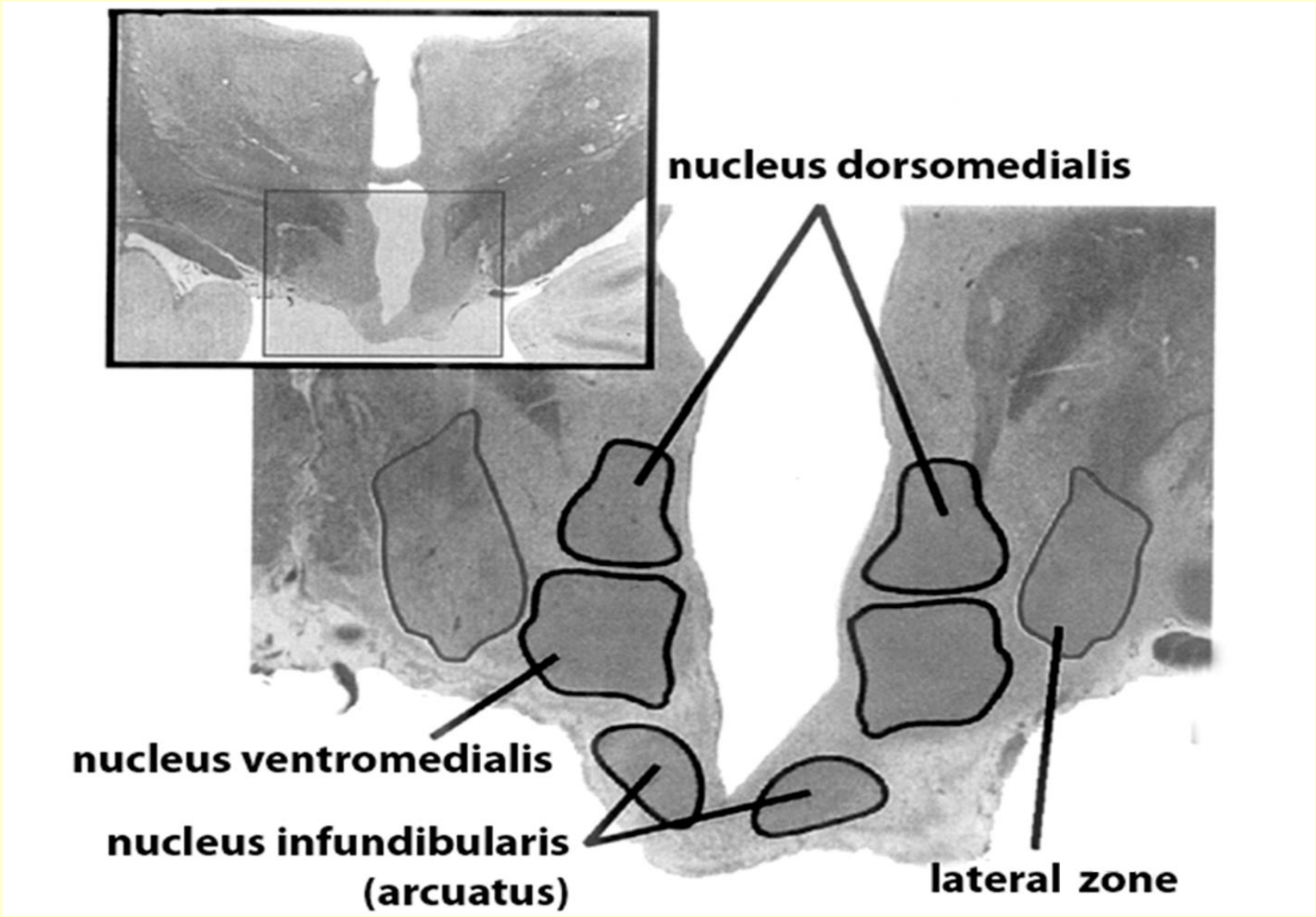
Neil R Carlson, 2013, Physiology of Behavior

Ghrelin, the hormone responsible for feeling hungry

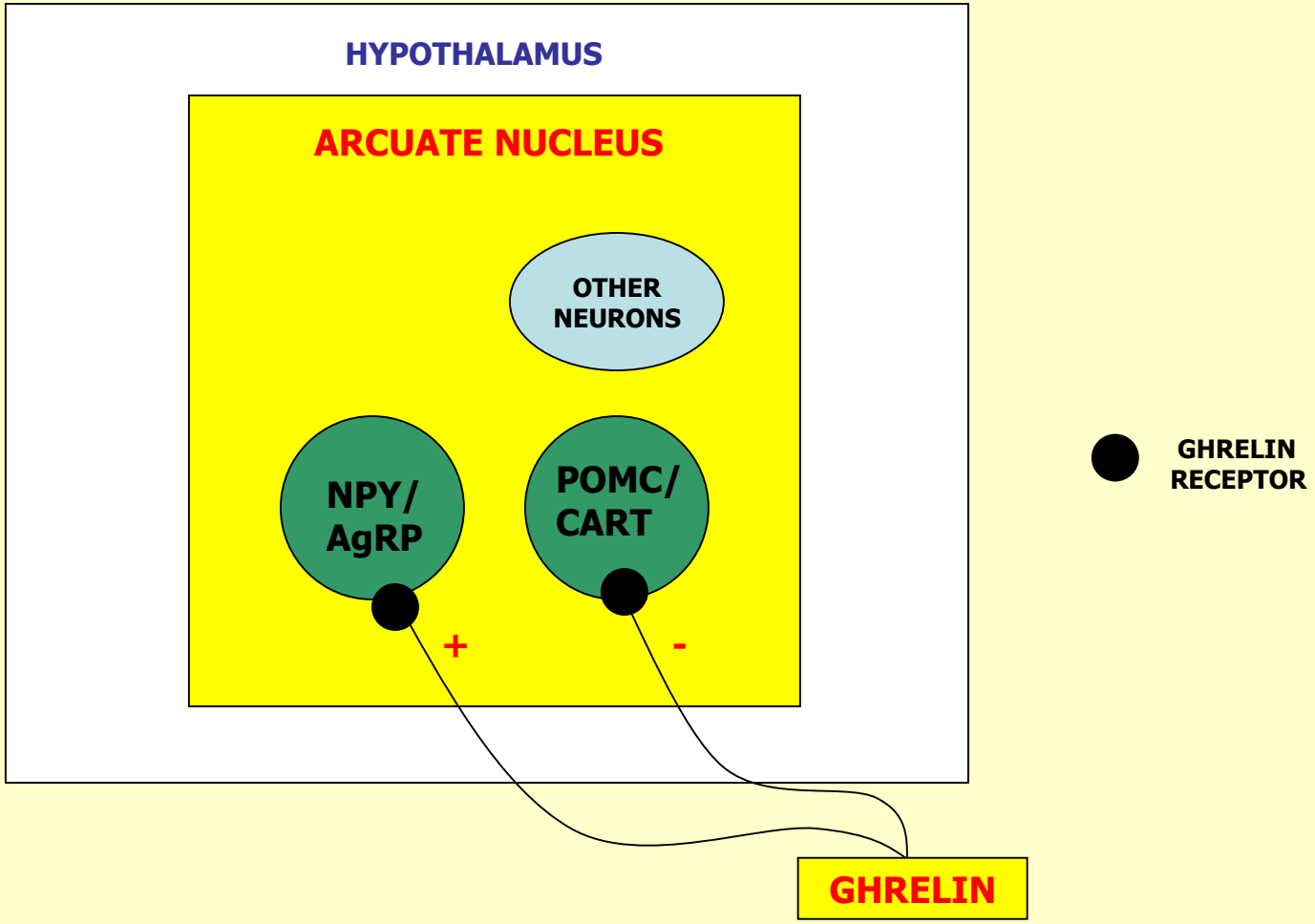
- Blood levels of ghrelin rise in starvation and decrease postprandially (that is after having eaten)
- Ghrelin injection in human induces hunger and increases food intake in animals and human, too.
- Mice lacking either ghrelin or its receptor are protected from diet-induced obesity (although the feeding behaviour does not differ from control mice under normal feeding conditions arguing for the existence of other important mechanisms of feeding)

Since **ghrelin** is the only hormone with hunger-inducing properties, it may qualify as the orexigenic hormone **responsible for motivation of feeding.**

Tuberal hypothalamic region



Target neurons of ghrelin in the arcuate nucleus of the hypothalamus



Thank you for your attention!