Inflamation

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- Inflammatory processes are necessary for survival, including organism homeostasis and the defense against pathogens.
- Best recognized as a localized response to injury from a variety of insults (e.g., microbial pathogens, trauma, neoplasia, toxins).
- inflammation is also important in tissue remodeling during development and in the clearance of cell debris during tissue turnover.

- inflammation has been recognized by the four cardinal signs:
- Celsus: calor (**heat**), rubor (**redness**)**,** dolor (**pain**), and tumor **(swelling**).
- A fifth sign, functio laesa (**loss of function**), was proposed by the 19th century German pathologist Virchow to underscore inflammation's potential for tissue damage.

- Inflammation involves the interplay of the innate and adaptive immune responses.
- The immunologic and nervous systems, and the coagulative and fibrinolytic cascades.
- Inflammatory responses are driven, in a complex and integrated manner, by the simultaneous effects of a wide range of molecular mediators.

- In health, inflammation is a self-limited response to a specific injury;
- after the injury is repaired, the inflammatory focus clears, and homeostasis is restored.
- On occasion, however, the inflammatory response is triggered inappropriately, is excessive for the problem at hand, or fails to resolve after the trigger is removed.

- Excessive inflammation may result in response to a persistent host antigen being mistaken as foreign (as **in rheumatic fever** or poststreptococcal glomerulonephritis) or from a decreased ability to clear immune system stimulants such as apoptotic cells or immune complexes(as in **systemic lupus erythematosus** [SLE]);
- in these cases, an autoimmune response drives undesirable and potentially destructive inflammation.

- In autoinflammatory syndromes (e.g., **familial Mediterranean fever** and tumor necrosis factor receptor [TNF]–associated periodic fever syndrome [**TRAPS**]), the inflammatory cells may have intrinsic defects that lead to persistent or recurrent undesirable inflammation.

acute or chronic

- Whereas the acute, or early, phase of inflammation is characterized by microvascular changes and neutrophilic infiltration, cells from the monocytic lineage predominate in the chronic inflammatory response. Inflammatory responses can be either acute or chronic.

- acute and chronic inflammatory response have many exceptions.
- For example, monocytic lineage cells may dominate from the beginning of an inflammatory response (as in tuberculosis), but neutrophils may persist in some forms of chronic inflammation (as in polyarteritis nodosa).

Resident tissue **macrophages** from the monocytic line may also provide the early sentinel signals that initiate acute inflammation, as is the case in gout and pseudogout.

- In other forms of vascular inflammation, the activation of tissue-derived **mast cells** results in vasodilation and vascular leak.

These inflammatory mediators are highly diverse but can be loosely grouped into the following categories:

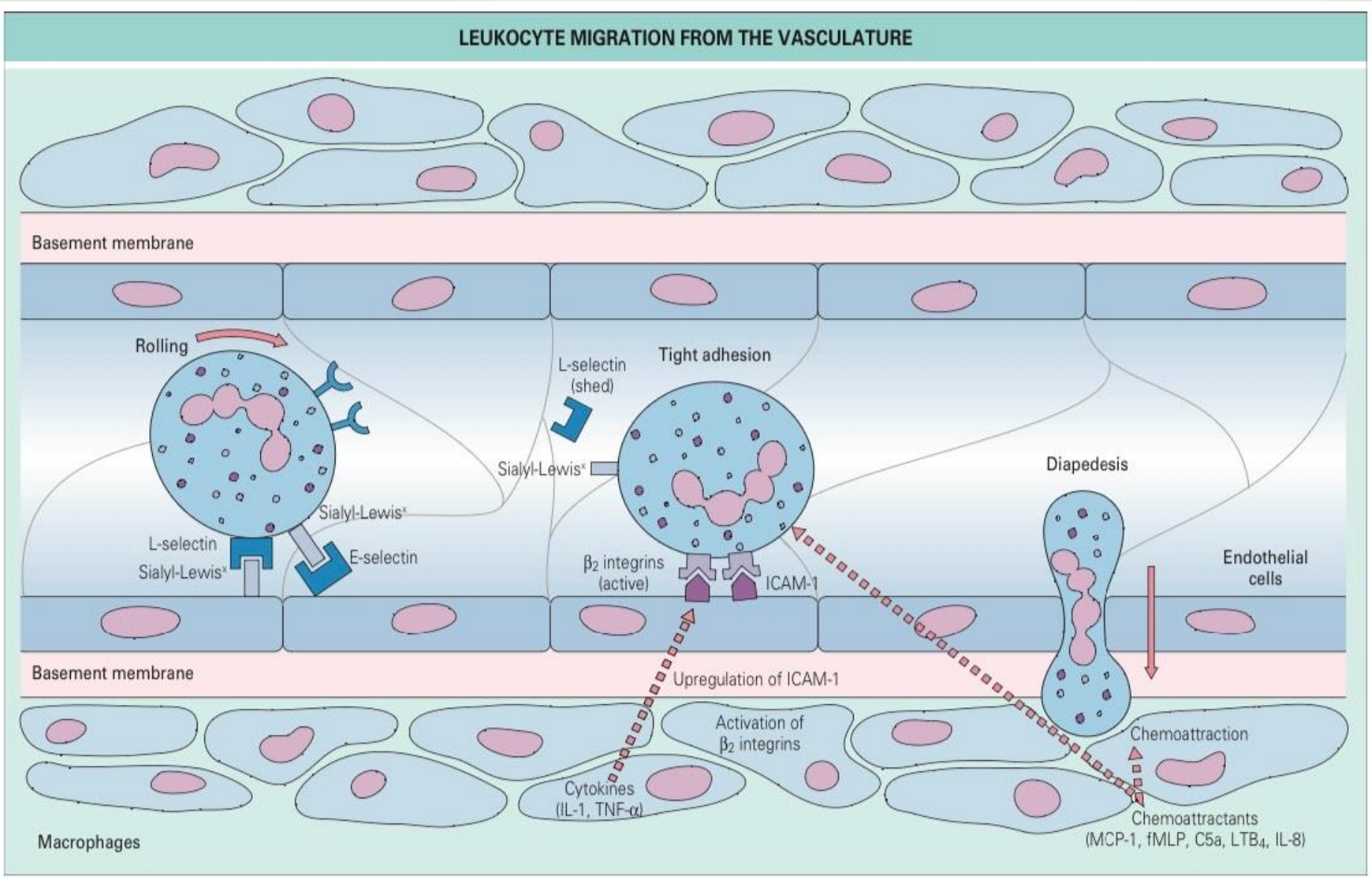
- (1) growth factors and cytokines,
- (2) arachidonic acid derivatives and lipid mediators,
- (3) the complement system,
- (4) proteases,
- (5) neuropeptides,
- (6) free radicals and reactive oxygen species.

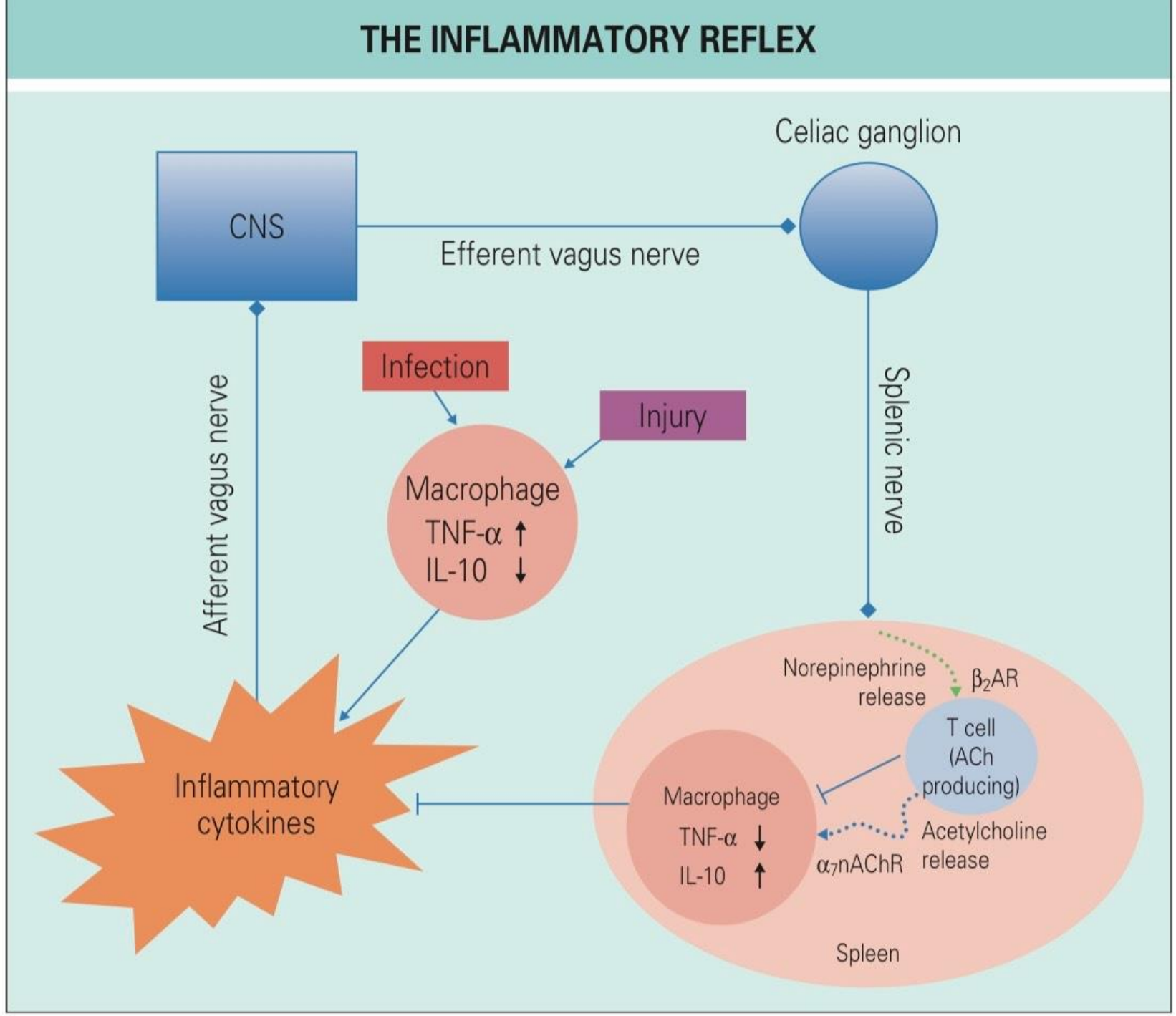
- Within minutes of tissue injury, activation of the innate immune system induces cytokine production that results in a multisystem acute phase response involving the **liver, vascular system, bone marrow, and CNS**.
- Many elements of the reaction can be regarded as part of the innate response and are defensive or adaptive in nature.

- Although the acute phase response can trigger numerous **neuroendocrine**, **hematopoietic**, and **metabolic effects**, the changes in plasma proteins synthesized by hepatocytes are monitored as signs of underlying inflammation .

ENDOTHELIAL CELL ACTIVATION AND LEUKOCYTE ADHESION

- Many of the leukocytes that participate in inflammation circulate within the bloodstream.
- To localize to the extravascular tissue, leukocytes must exit the vasculature (**diapedesis**) and migrate to the extravascular space (**chemotaxis**).
- Arterioles vasodilate and endothelial cells contract, exposing the basement membrane; blood flow slows and **plasma extravasates**.
- leukocytes slow and increase their contact with the endothelium.
- In response to bacteria or other affronts, resident tissue immune cell (**macrophages, dendritic cells, and fibroblasts**) generate interferons, as well as proinflammatory mediators such as **IL-1β and TNF-α.**


LEUKOCYTE MIGRATION FROM THE VASCULATURE
Basement membrane
Rolling
L-selectin
Sialyl-Lewis^x
Sialyl-Lewis^x
E-selectin
L-selectin
(shed)
Tight adhesion
Sialyl-Lewis^x
β_2 integrins
(active)
ICAM-1
Diapedesis
Endothelial
cells
Basement membrane
Upregulation of ICAM-1
Activation of
β_2 integrins
Cytokines
(IL-1, TNF-α)
Chemoattraction
Chemoattractants
(MCP-1, fMLP, C5a, LTB$_4$, IL-8)
Macrophages


THE INFLAMMATORY REFLEX
Celiac ganglion
CNS
Efferent vagus nerve
Afferent vagus nerve
Infection
Injury
Macrophage
TNF-α ↑
IL-10 ↓
Splenic nerve
Norepinephrine release
β2AR
T cell (ACh producing)
Inflammatory cytokines
Macrophage
TNF-α ↓
IL-10 ↑
α7nAChR
Acetylcholine release
Spleen

THE NERVOUS SYSTEM IN INFLAMMATION

- The nervous system registers inflammation in the periphery via sensory nerves and directs the immune system through a variety of messengers,
- autonomic neurotransmitters (e.g., **acetylcholine [Ach]**)
- neuropeptides such as **substance P,**
- that can be either proinflammatory or anti inflammatory.

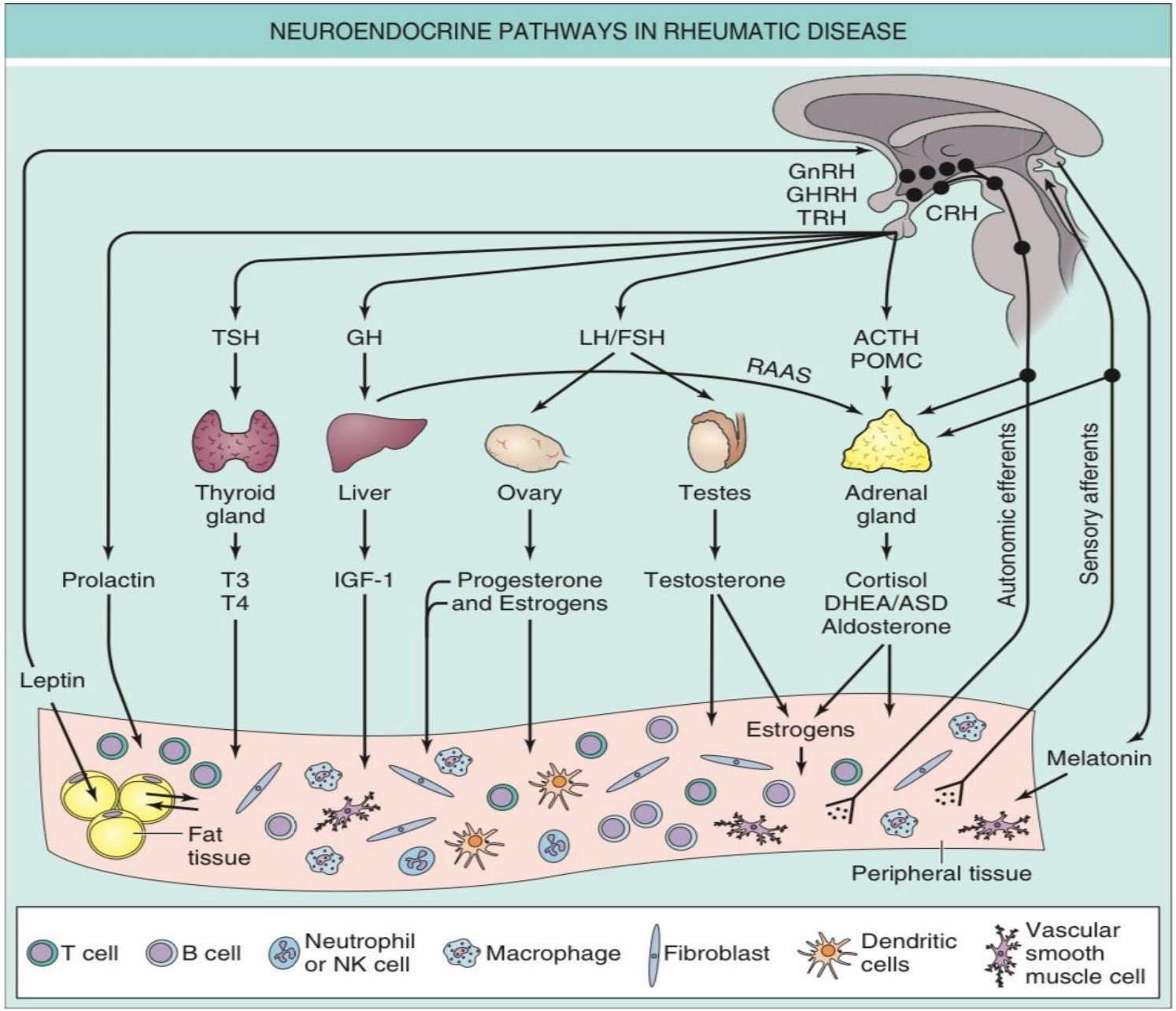
- **The CNS also controls inflammatory responses :**
- release of neuroendocrine hormones such as melanocyte-stimulating hormone **(MSH)** and corticotropin-releasing factor (**CRF**), which dampen inflammation.
- **The immune system regulates the CNS;**
- release of cytokines, growth factors, and other mediators;
- cytokine release in the periphery, for instance, can induce the hypothalamic–pituitary–adrenal axis to **release glucocorticoids.**

AUTONOMIC INFLUENCES ON INFLAMMATION

- The autonomic nervous system (ANS) is hardwired into the immune system;
- **parasympathetic** branches from the **vagal nerve** and **sympathetic nerve** fibers synapse upon the major organs of immunity, including the spleen, lymph nodes, thymus, bone marrow, and the gut's mucosa-associated lymphoid tissue.

Neuroendocrine mechanisms

- The **hypothalamus** continuously receives data about the body's environment and, in response to **stress signals** such as
- **IL-1β**, releases corticotropin releasing factor (**CRF).**
- CRF activates the pituitary to secrete adrenocorticotropic hormone (ACTH), in turn stimulating the adrenal glands to produce and secrete **glucocorticoids**, potent endogenous anti inflammatory immunomodulators.
- **MSH,** which derives from the same precursor (POMC) as ACTH, is also secreted by the **pituitary gland** and can suppress inflammation.


NEUROENDOCRINE PATHWAYS IN RHEUMATIC DISEASE
GnRH
GHRH
TRH
CRH
TSH
GH
LH/FSH
ACTH
POMC
RAAS
Thyroid gland
Liver
Ovary
Testes
Adrenal gland
Autonomic efferents
Sensory afferents
Prolactin
T3
T4
IGF-1
Progesterone and Estrogens
Testosterone
Cortisol
DHEA/ASD
Aldosterone
Leptin
Estrogens
Melatonin
Fat tissue
Peripheral tissue
T cell
B cell
Neutrophil or NK cell
Macrophage
Fibroblast
Dendritic cells
Vascular smooth muscle cell

- acute phase response accompanies both **acute and chronic** inflammatory states and is associated with a wide variety of disorders, including infection, trauma, infarction, inflammatory arthritides and other systemic autoimmune and inflammatory diseases, and various neoplasms.
- **Acute phase proteins** are defined as those proteins whose serum concentrations increase or decrease by at least **25 percent** during inflammatory states .
- Such proteins are termed either positive or negative acute phase reactants (APR), respectively.

- Hepatic stimulation of acute phase proteins is induced by cytokines released by activated monocytes, macrophages, neutrophils, natural killer (NK) cells, and endothelial cells acting at the front lines of the inflammatory response.
- The main cytokine influencing the liver is **IL-6**, once called the hepatocyte-stimulating factor.
- Acute phase reactants (APR) are inflammation markers that exhibit significant changes in serum concentration during inflammation.
- These are also important mediators produced in the liver during acute and chronic inflammatory states.

- **Interleukin-6 (IL-6**) is the primary cytokine responsible for inducing the production in the liver.
- **IL-1**, tumor necrosis factor-alpha (**TNF-alpha**), and interferon-gamma (**IFN-gamma)** can also induce the production of acute-phase reactants.
- Acute phase reactants cause several adverse effects.
- **These include fever, anemia of chronic disease, anorexia, somnolence, lethargy, amyloidosis, and cachexia (fat and muscle loss, anorexia, weakness).**

- Acute phase reactants can be classified as **positive or negative**, depending on their serum concentrations during inflammation.
- **Positive acute phase reactants** are upregulated, and their concentrations increase during inflammation.
- **Negative acute phase reactants** are downregulated, and their concentrations decrease during inflammation..

- **Positive acute phase reactants** include **procalcitonin, C-reactive protein, ferritin, fibrinogen, hepcidin, and serum amyloid A.**

- **Negative acute phase reactants** include **albumin, prealbumin, transferrin, retinol-binding protein, and antithrombin**

Thank you