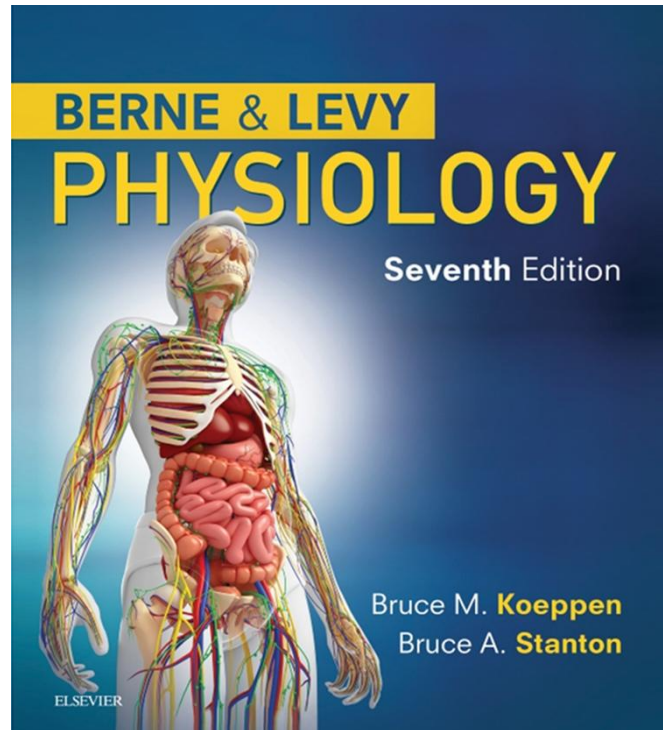
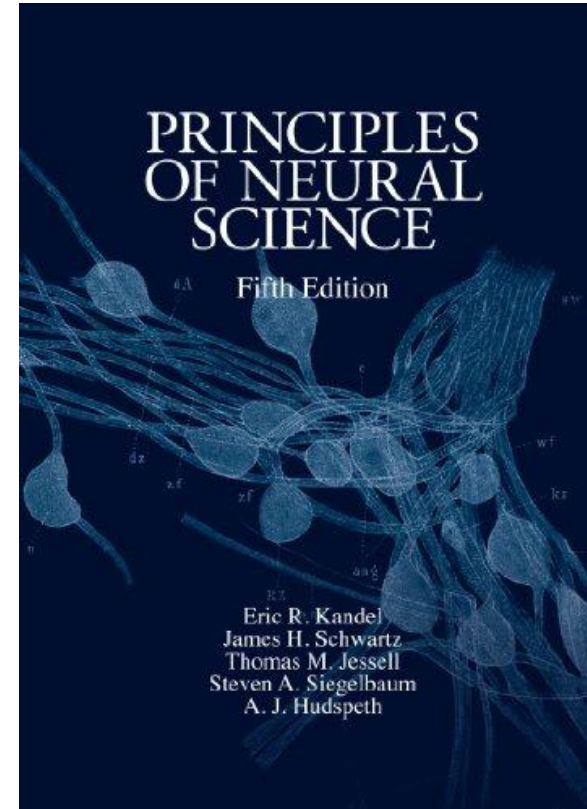


# The Autonomic Nervous System

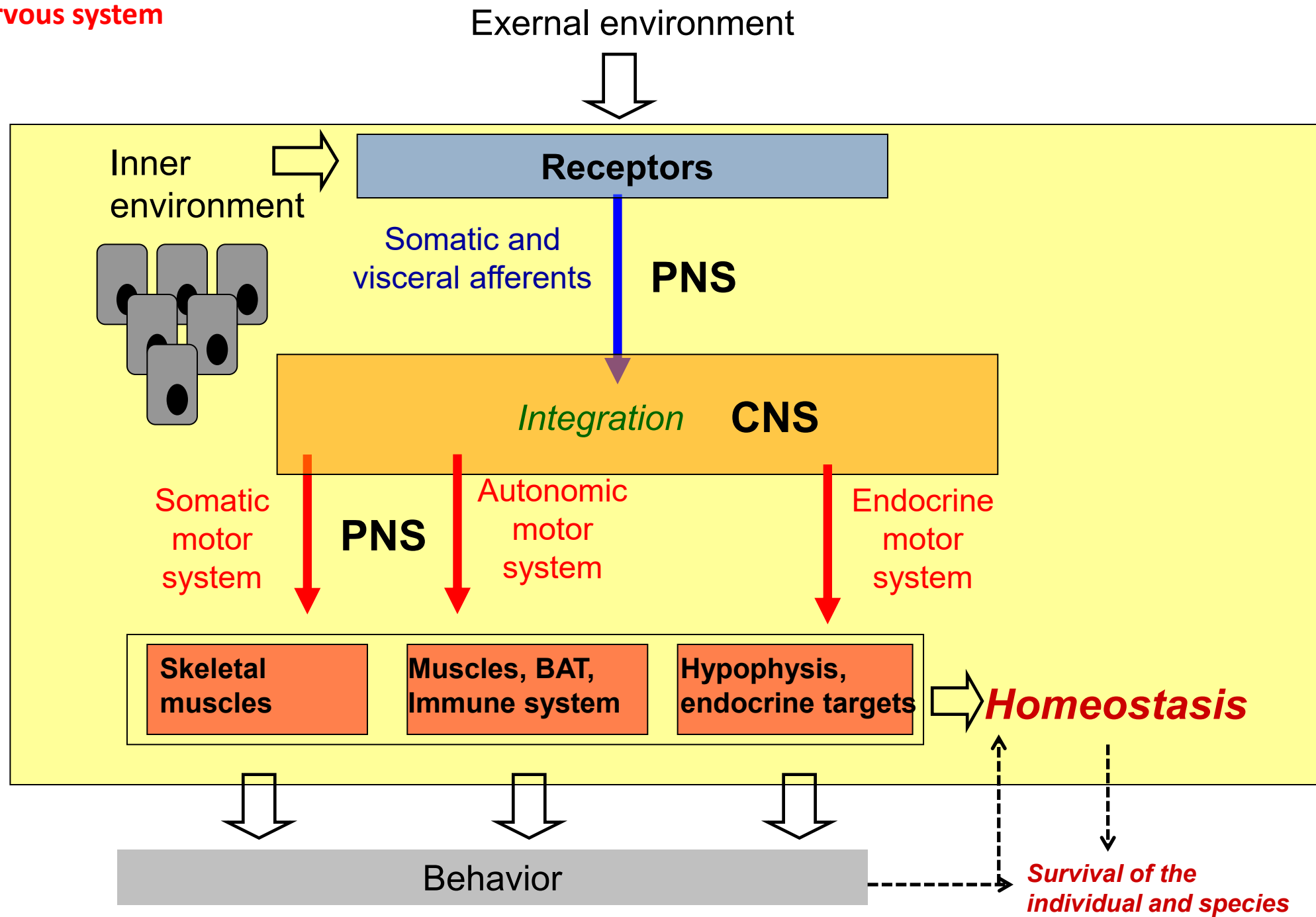


Chapter 11



Chapter 47

# Autonomic nervous system



# AUTONOMIC NERVOUS SYSTEM

Motor part of the nervous system that regulates our internal organs. Targets are:

SMOOTH MUSCLE  
SKELETAL MUSCLE  
GLANDS  
ADIPOCYTES  
IMMUNE SYSTEM

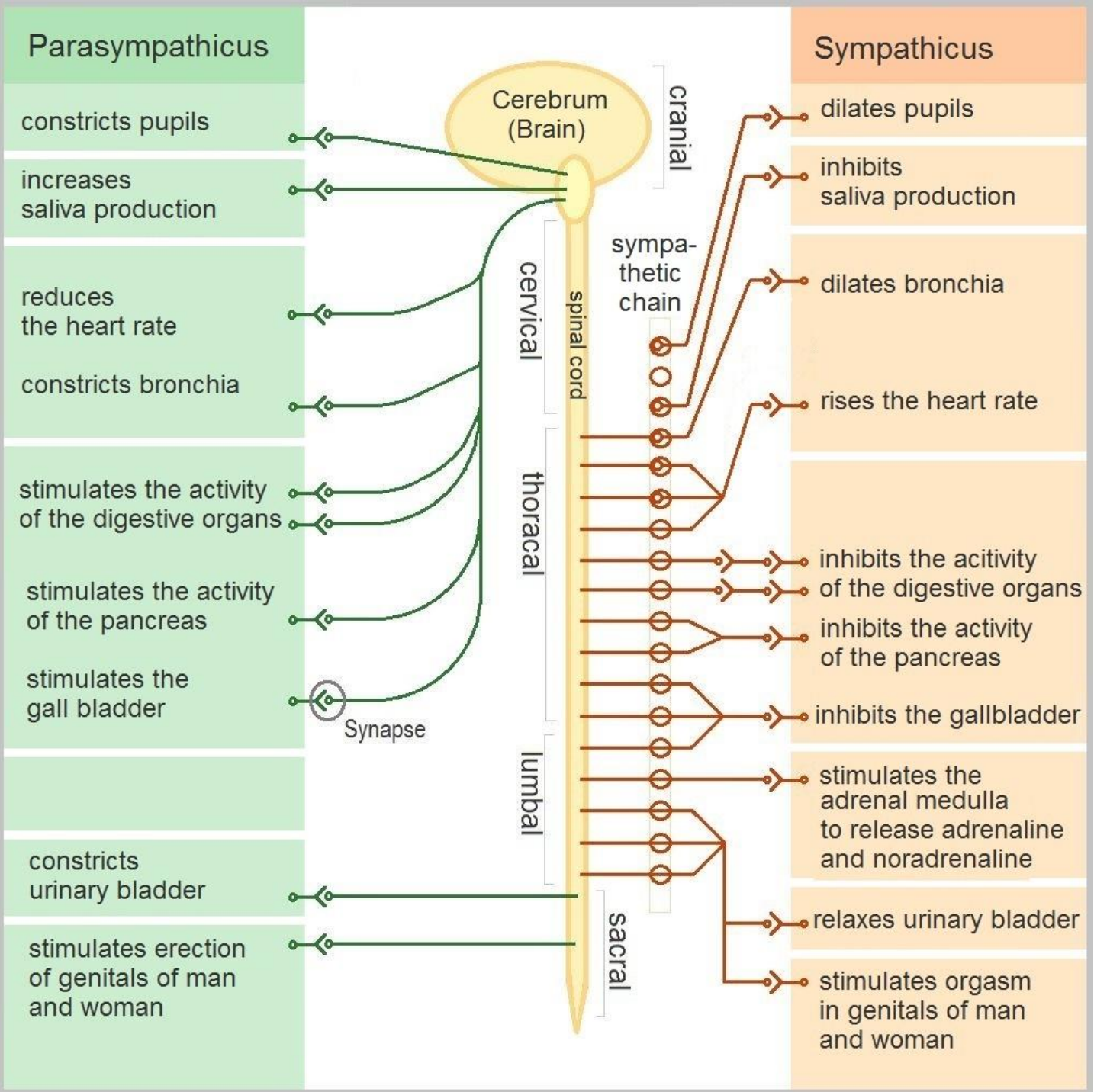
We can't control it (autonomic)

**THE AUTONOMIC NERVOUS SYSTEM IS DIVIDED IN:**

**A. SYMPATHETIC NERVOUS SYSTEM**

**B. PARASYMPATHETIC NERVOUS SYSTEM**

**C. ENTERIC NERVOUS SYSTEM**



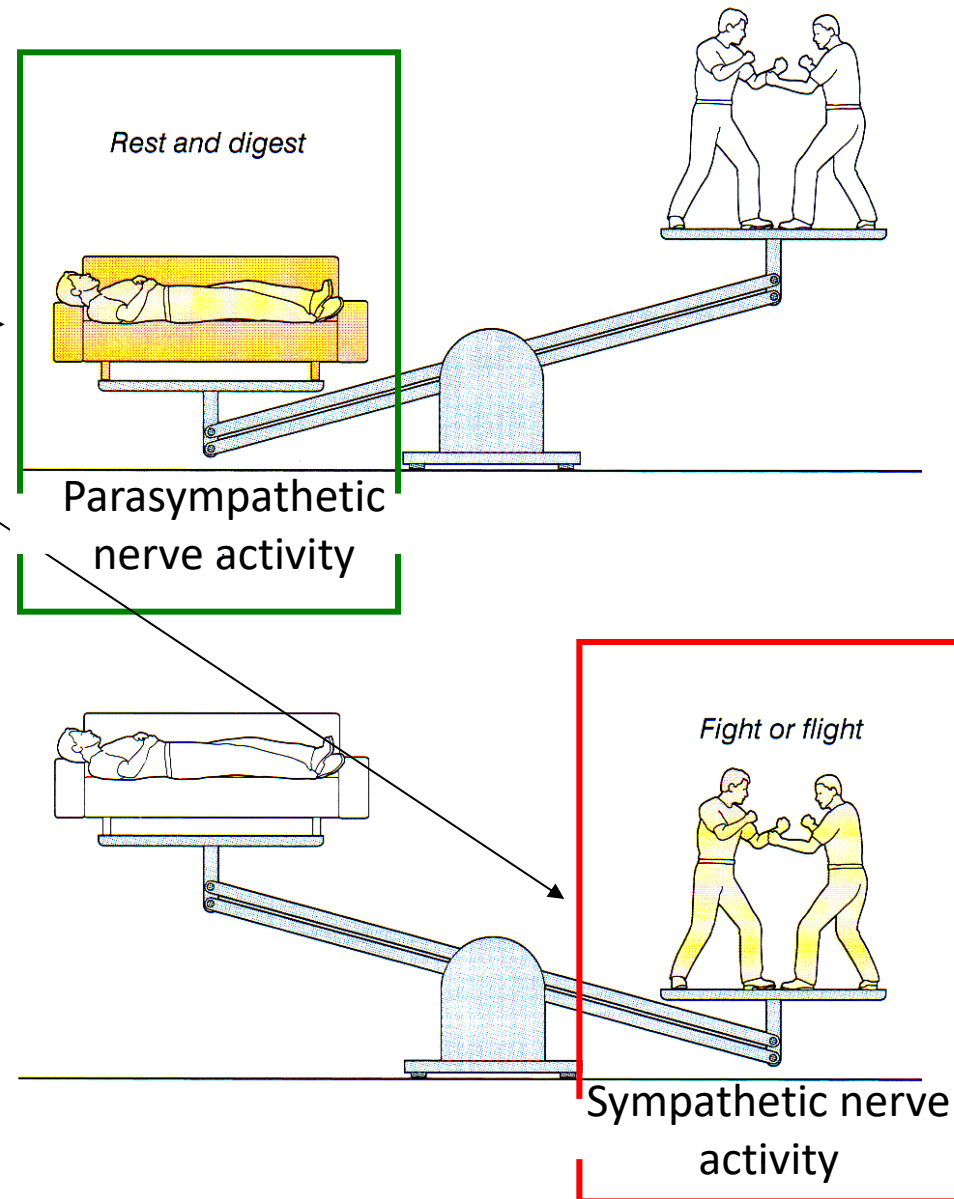
Wikipedia  
 By Geo-Science-International - Own work, CC0,  
<https://commons.wikimedia.org/w/index.php?curid=47377075>

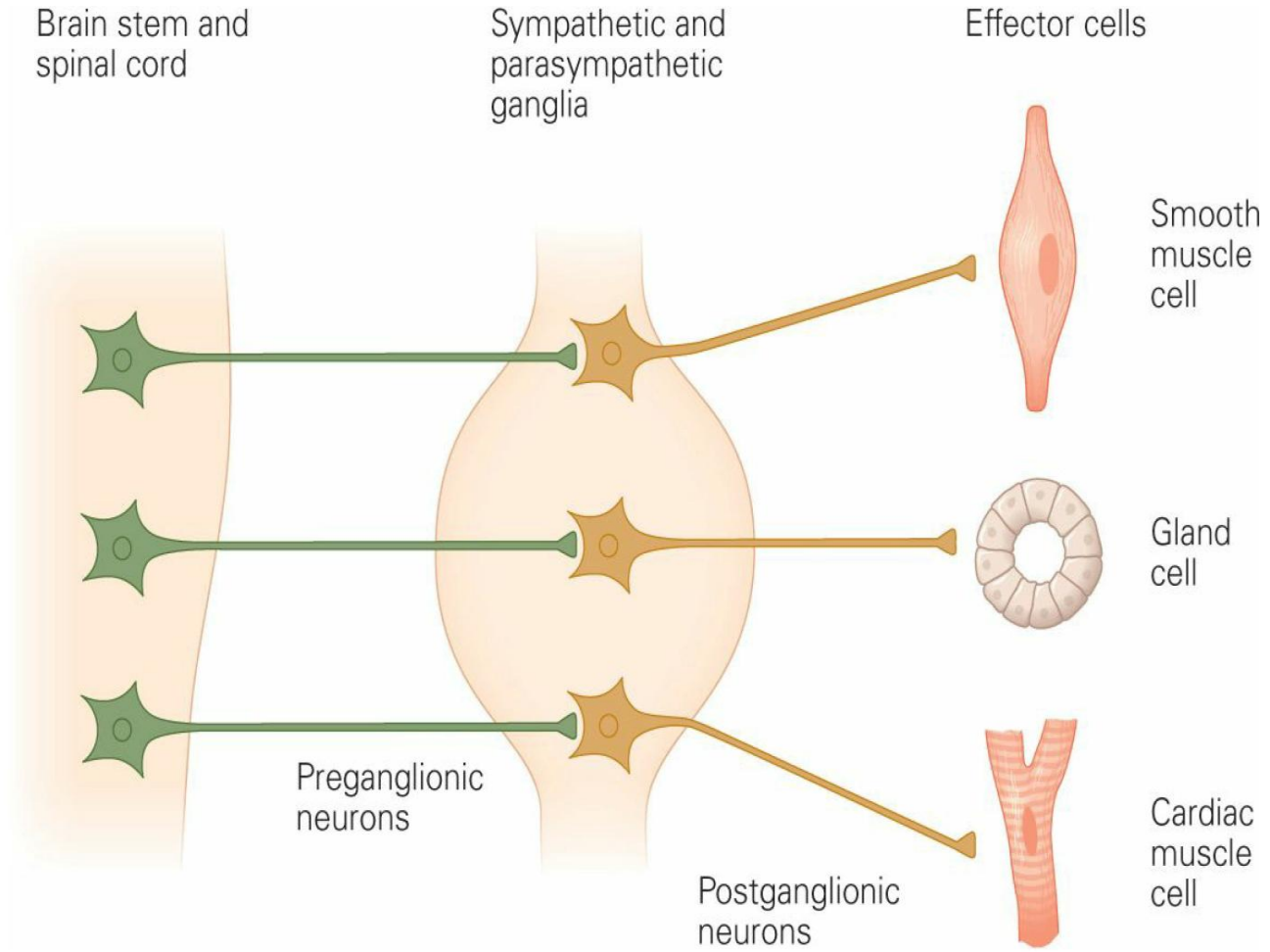
# AUTONOMIC TONE

In basal conditions there is a tonic activity of the sympathetic and parasympathetic nervous systems

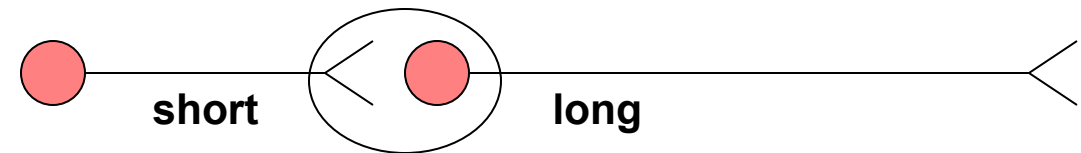
This activity is unbalanced in favor of one or the other in opposite environmental or behavioral conditions

While the notion of a generalized and massive intervention on all the organs of the two branches in extreme behavioral conditions remains valid for educational purposes, more and more data are accumulating that show how the action of the SNA can be realized in a selective and discreet way on some organs in response to specific stimuli

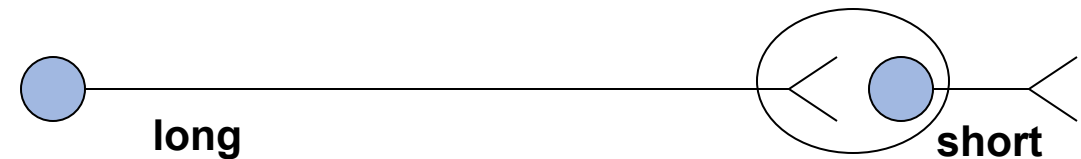




**SYMPATHETIC NERVOUS SYSTEM**



**PARASYMPATHETIC NERVOUS SYSTEM**



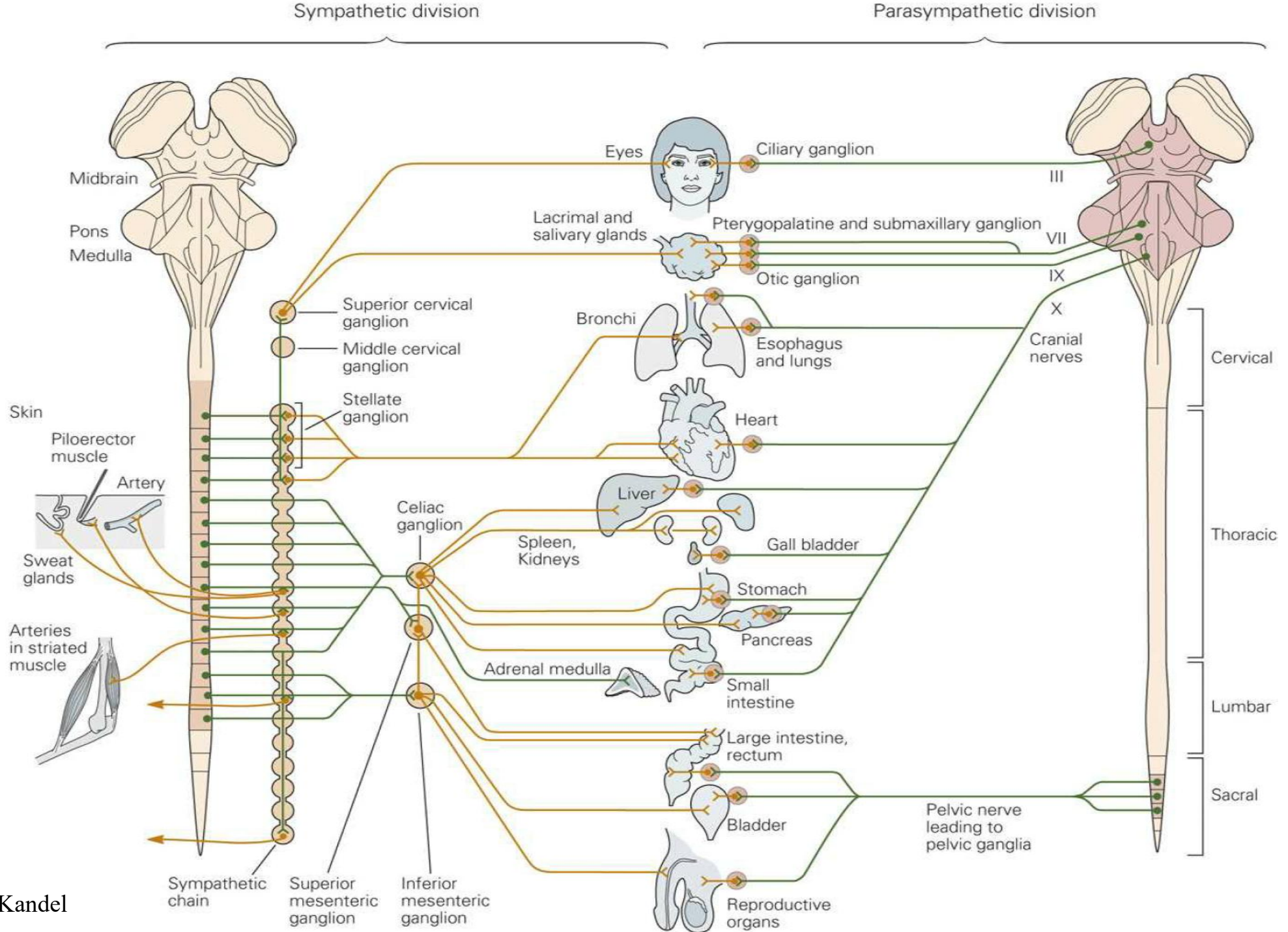


Fig. 47.2 Kandel

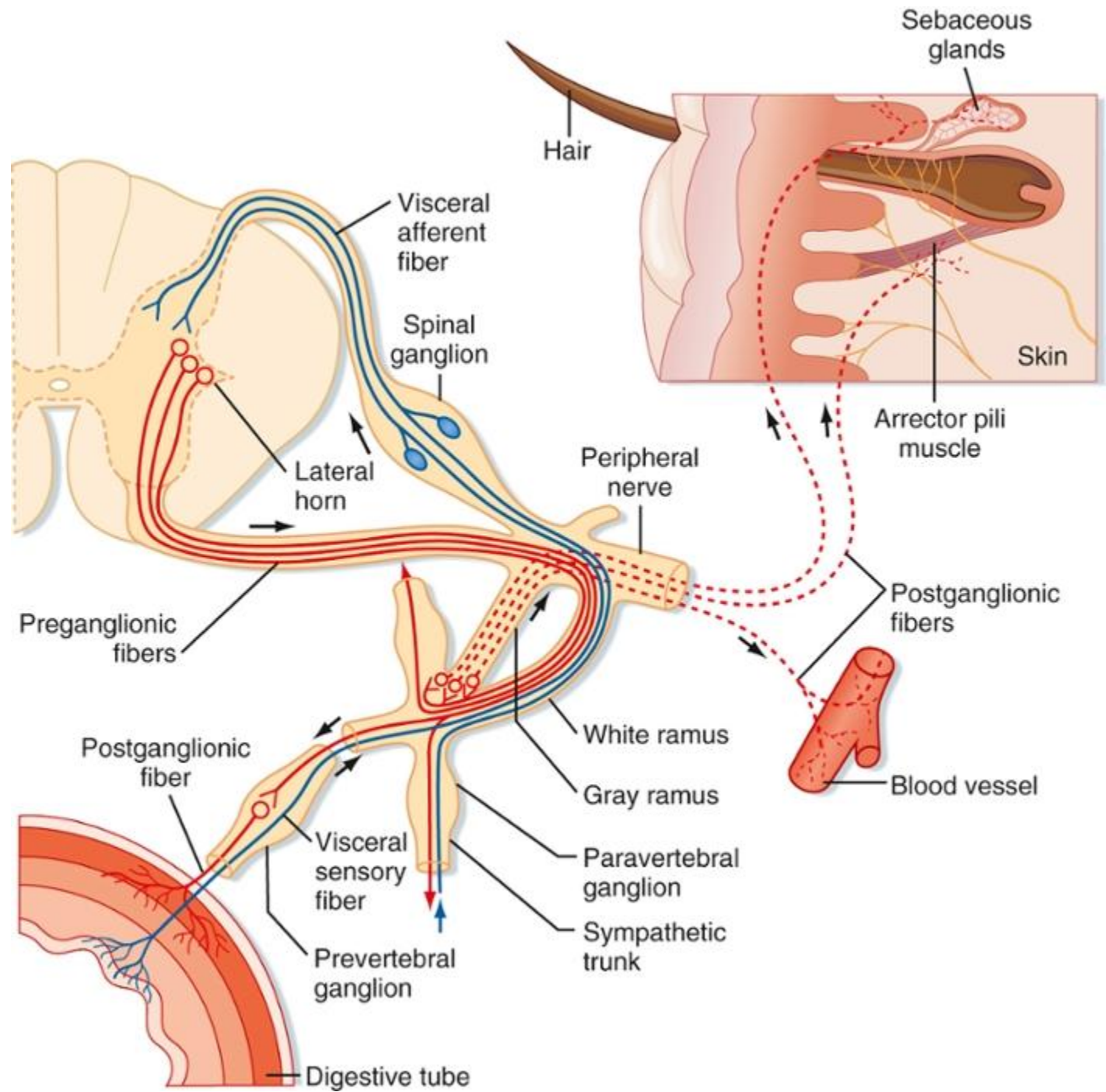


Fig. 11.2 Berne Levy

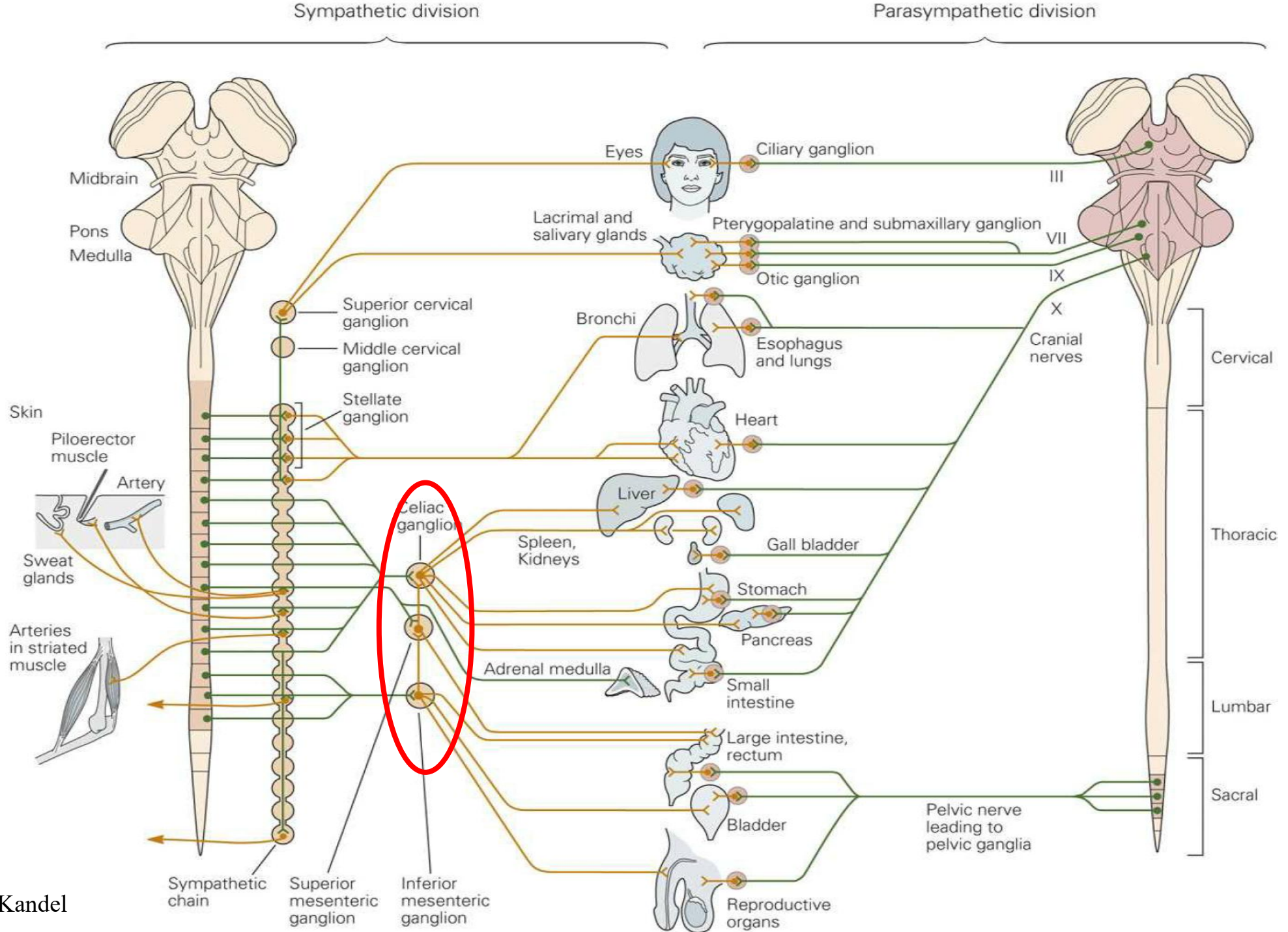
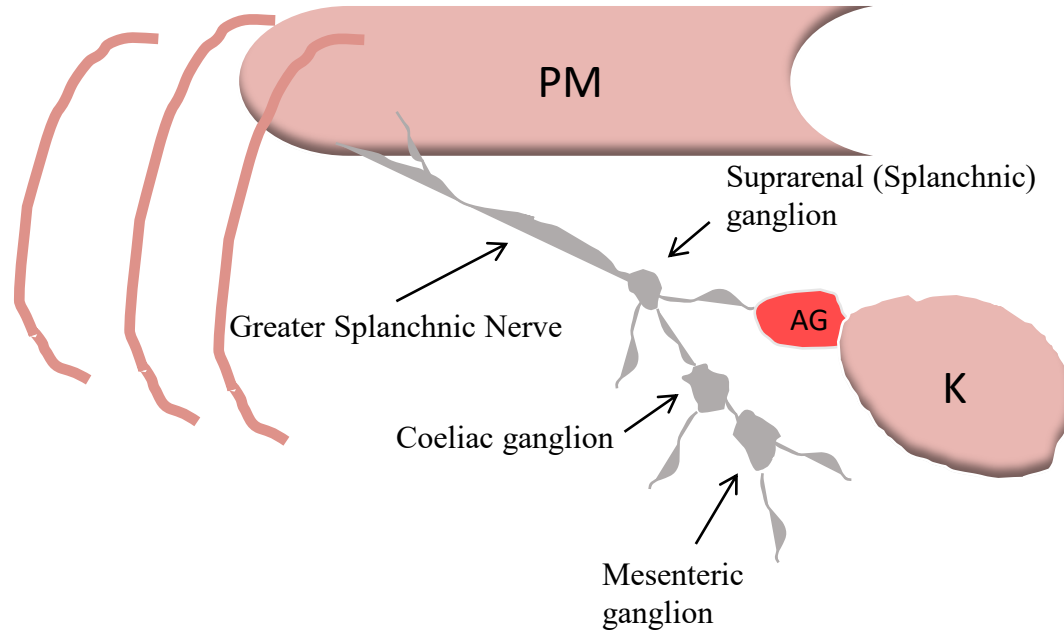


Fig. 47.2 Kandel

# Schema of the anatomy



PM: Psoas Muscle  
AG: Adrenal gland  
K: Kidney

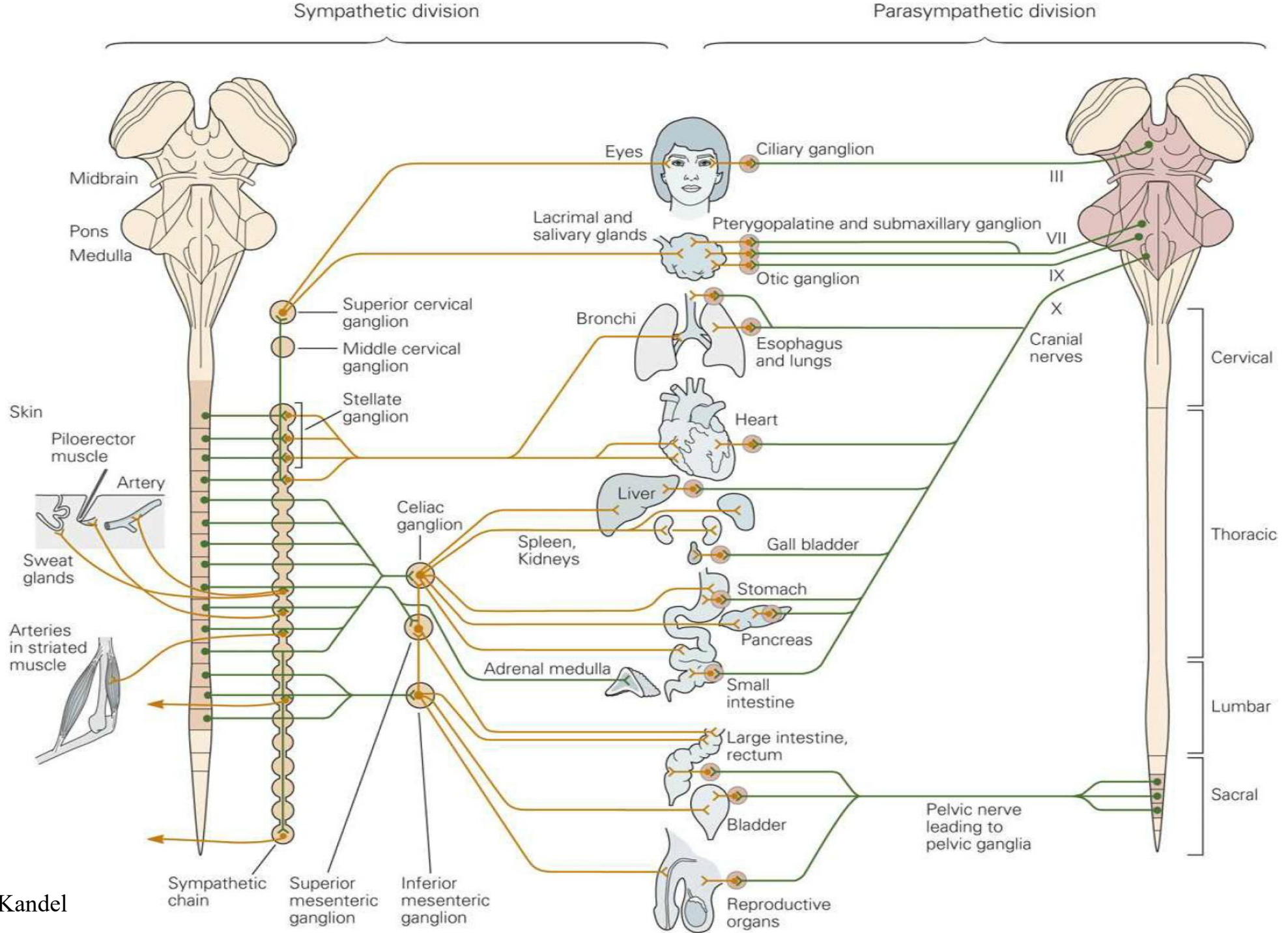


Fig. 47.2 Kandel

# The Enteric Nervous System

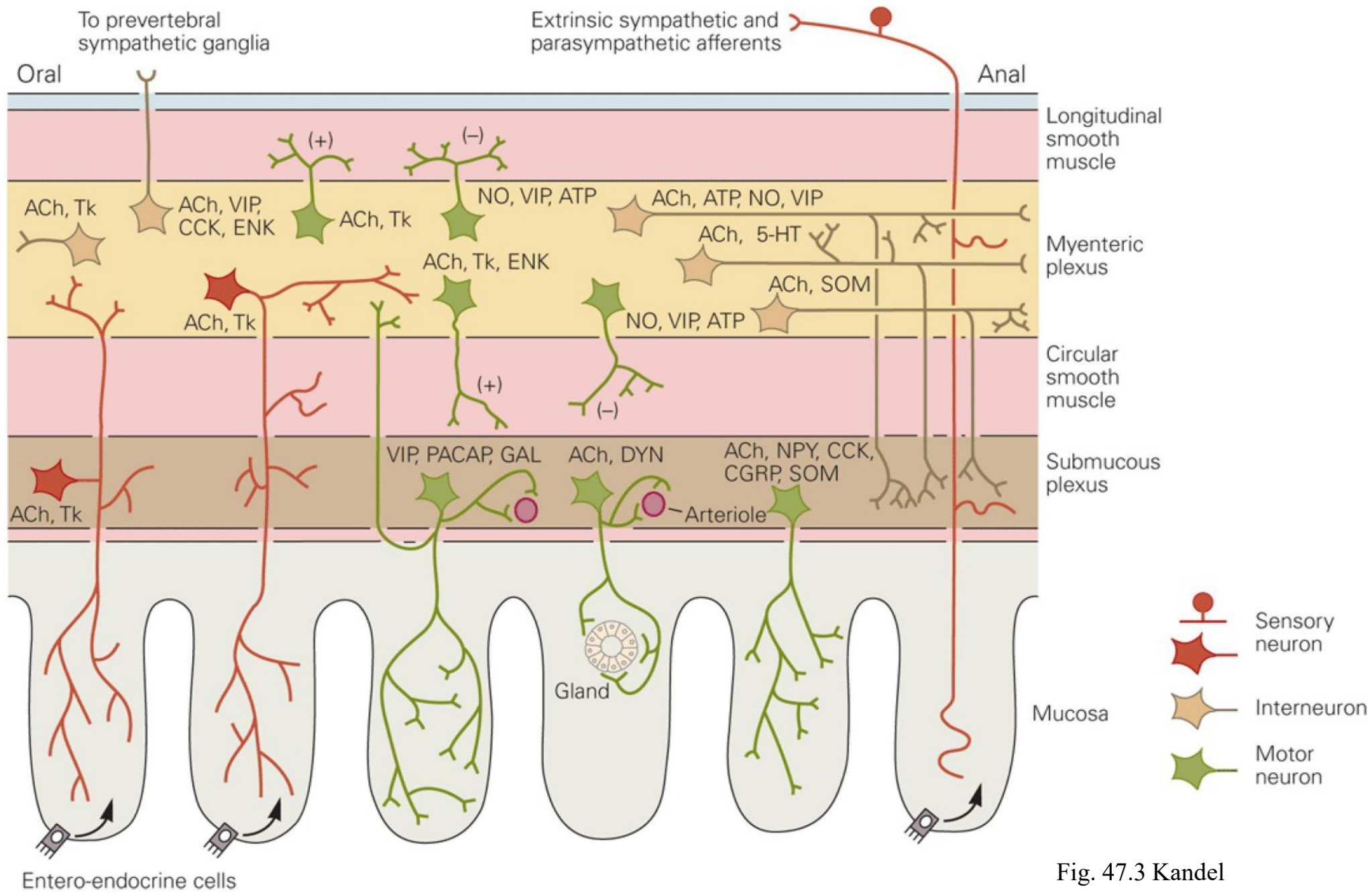


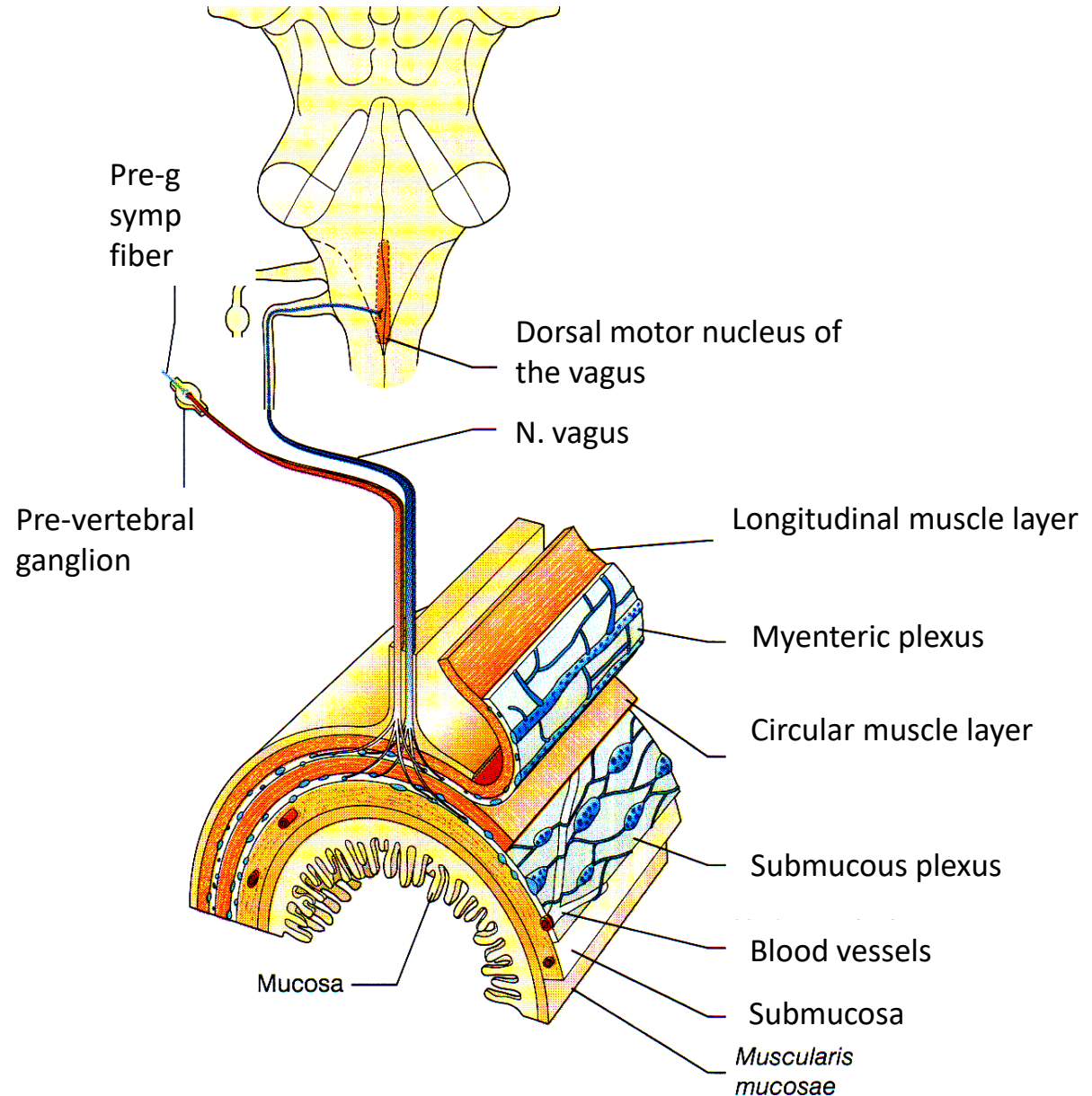
Fig. 47.3 Kandel

# Sympathetic and parasympathetic control of the enteric nervous system

The plexuses of the enteric nervous system receive:

Post-ganglionic sympathetic fibers

Pre-ganglionic parasympathetic fibers



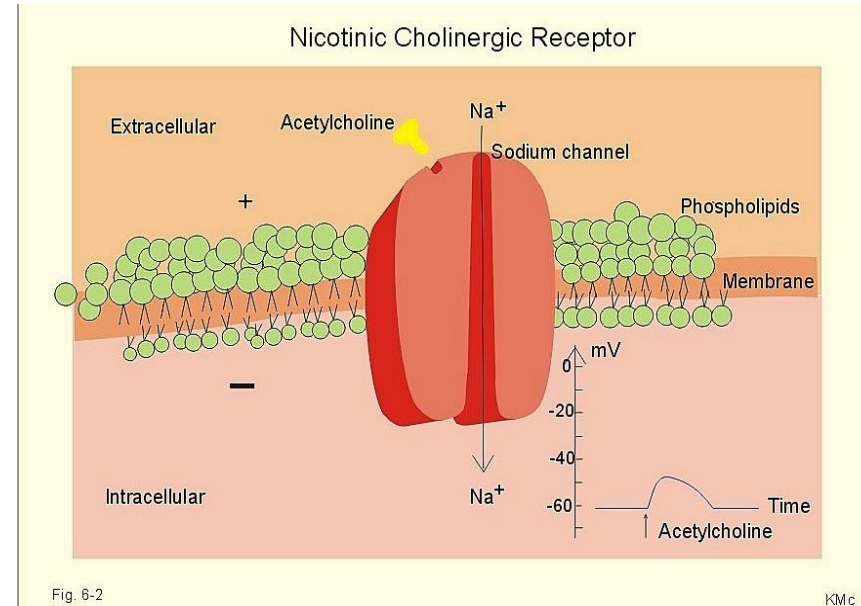
## SYNAPTIC ORGANIZATION OF ANS GANGLIA

The sympathetic and parasympathetic preganglionic neurons release **Acetylcholine**, which binds to **nicotinic** and **muscarinic** receptors located on the postganglionic neuron membrane

# SYNAPTIC ORGANIZATION OF ANS GANGLIA

## ACh Nicotinic receptors are:

- i) **ionotropic** (cationic);
- ii) **subtype N<sub>2</sub>** - different from that found in skeletal muscle cells (**N<sub>1</sub>**);
- iii) **Blocked by Hexamethonium** (**N<sub>1</sub>** receptors are blocked by tubocurarine)



[http://www.mfi.ku.dk/ppaulev/chapter6/chap6\\_bog2.htm](http://www.mfi.ku.dk/ppaulev/chapter6/chap6_bog2.htm)

The link between acetylcholine and the nicotinic receptor determines the onset of a rapid local (depolarizing) potential

## SYNAPTIC ORGANIZATION OF ANS GANGLIA

The muscarinic receptors are metabotropic and are activated **only** after prolonged stimulations (trains of impulses, maintained for a few seconds).

In postganglionic neurons a hyperpolarizing current, the **M current**, is present at basal conditions due to the opening of numerous passive channels for  $K^+$ . The activation of muscarinic receptors determines the closure of the  $K^+$  channels with blockade of the M current, causing a slow depolarization.

**Thus, ACh release induces a biphasic electrical signal in postganglionic neurons:**

**Fast EPSP (nicotinic) followed by a  
Slow EPSP (muscarinic)**

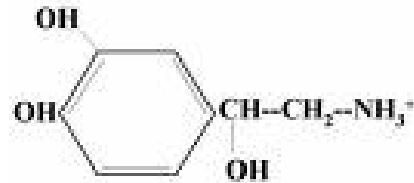
# SYNAPTIC ORGANIZATION OF ANS GANGLIA

Many autonomic ganglia also contain **interneurons**

- **catecholaminergic** (Dopamine),
- called "**small, intensely fluorescent (SIF) cells**" (identifiable with fluorescent dyes)
- which mainly have **inhibitory** effects on the postganglionic neuron

# POST-GANGLIONIC SYMPATHETIC NEURONS

Neurotransmitter: **NORADRENALINE**



*Exception: eccrine sweat glands (acetylcholine)*

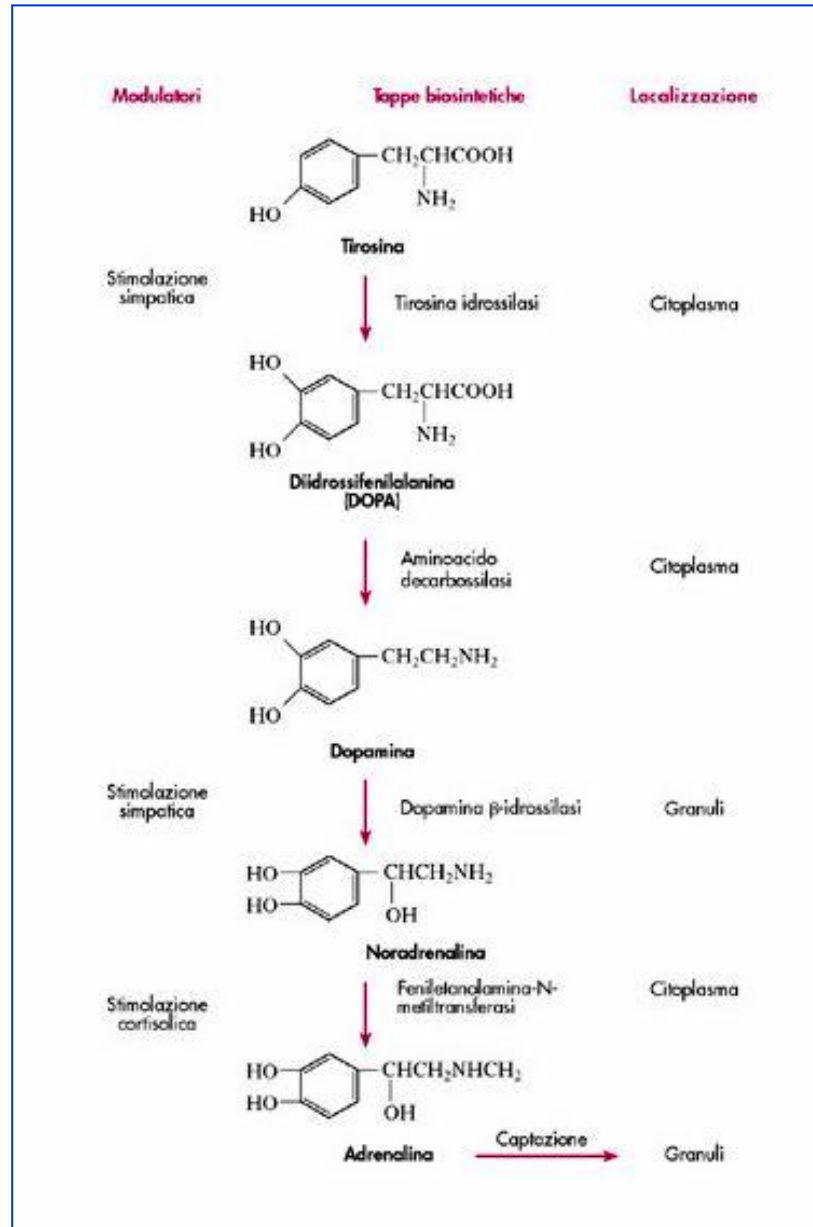
Postganglionic sympathetic neurons can co-release, together with NA, other substances such as **somatostatin**, **neuropeptide Y** and **ATP**, with slow postsynaptic effects

## ADRENAL MEDULLA

The adrenal medulla is an endocrine gland, considered homologous to a sympathetic ganglia:

- it is innervated by pre-ganglionic sympathetic fibers
- it originates from the neuroectoderm
- it synthesizes and secretes in the bloodstream noradrenaline and adrenaline (*chromaffin cells*)

# THE ADRENAL MEDULLA IS THE ONLY "SYMPATHETIC POSTGANGLIONIC CELL"



- Chromaffin cells of the adrenal medulla, differently from postganglionic sympathetic neurons, express the enzyme **Phenylethanolamine-N-methyl-transferase, PNMT** (NA → A)

Cortisol released from the adrenal cortex induces the PNMT expression in the medulla stimulating Adrenaline synthesis

## **ADRENAL MEDULLA**

The activity of the Adrenal medulla increases generally in conditions of generalized sympathetic activation:

- **physical exercise**
- **Stress**
- **Immune challenge**

## **(NOR)ADRENERGIC RECEPTORS**

The effects of NA and A on target organs are mediated by **alpha or beta adrenergic receptors**

The adrenergic receptors are metabotropic

# (NOR)ADRENERGIC RECEPTORS

	<b>alpha-receptors</b>		<b>beta-receptors</b>		
	<b>Alpha1</b>	<b>Alpha2</b>	<b>Beta1</b>	<b>Beta2</b>	<b>Beta3</b>
<b>Agonists:</b>	Phenylephrine <b>NA =/&gt; Adr</b>	Clonidine <b>NA &gt; Adr</b>	Isoproterenol Dobutamine <b>Adr = NA</b>	Isoproterenol Salbutamol <b>Adr &gt; NA</b>	Mirabegron <b>NA &gt; Adr</b>
<b>Antagonists:</b>	Prazosin	Yohimbine	Propranolol Athenolol	Propranolol Butoxamine	Carvedilol

# (NOR)ADRENERGIC RECEPTORS

**Second messengers involved in intracellular signal transduction:**

## RECEPTOR

## SECOND MESSENGER

ALPHA 1

Increase  
**DAG e Inositol-triphosphate (IP3),**  
(increase citosol [Ca<sup>++</sup>])

ALPHA 2  
(prevalently autoreceptors)

Reduction **cAMP**

BETA 1

Increase **cAMP**

BETA 2

Increase **cAMP**

BETA 3

Increase **cAMP**

# SYMPATHETIC INFLUENCES

## CARDIOVASCULAR FUNCTION

### Heart (**Beta 1 receptors**)

SA, AV nodes

enhanced automaticity (tachycardia)

increased pulse conduction speed

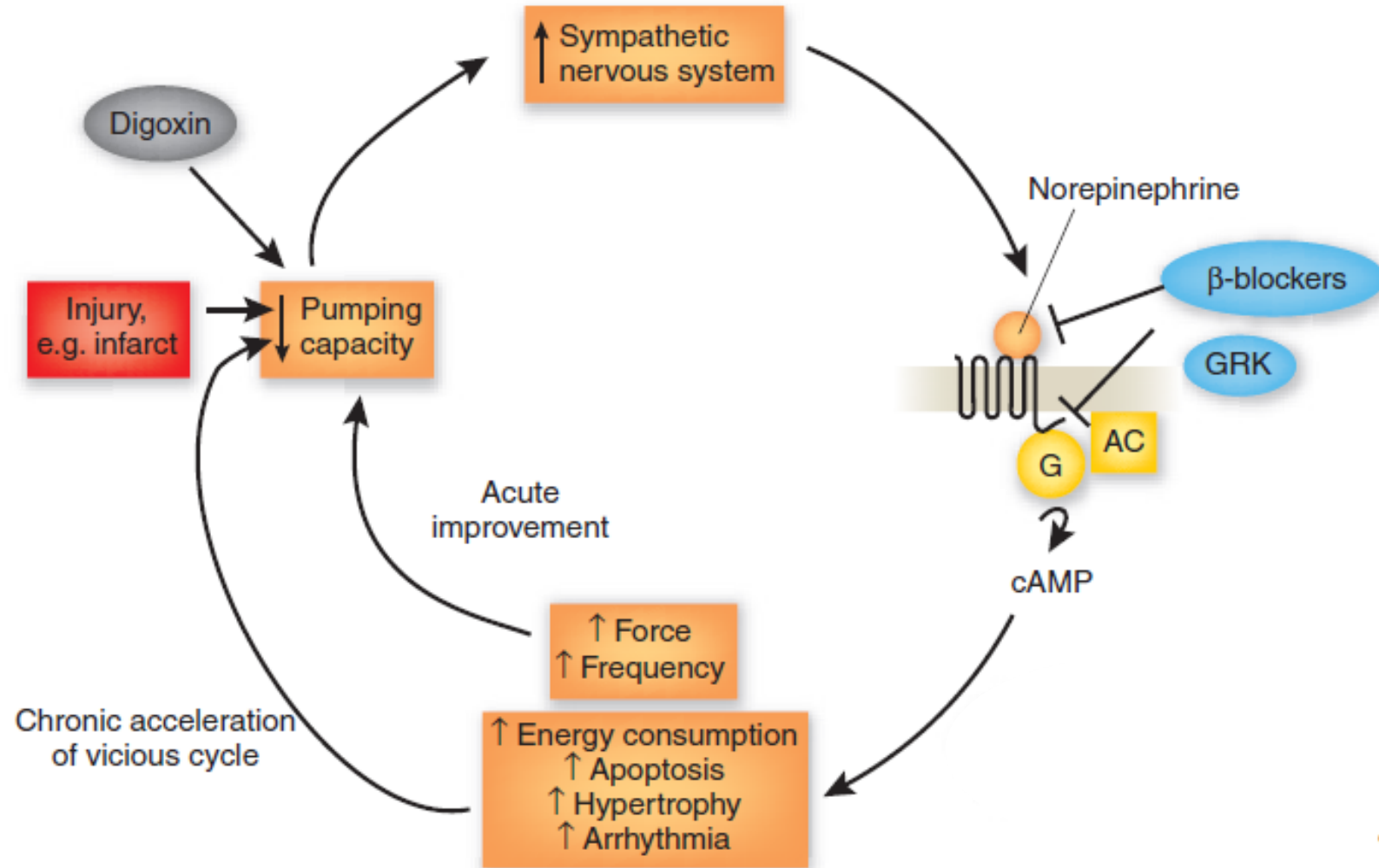
Atrial and ventricular myocardium

enhanced excitability

increase in contraction force

# $\beta$ -adrenergic signaling in heart failure—adapt or die

Thomas Eschenhagen



Kim Caesar

# SYMPATHETIC INFLUENCES

## CARDIOVASCULAR FUNCTION

### Arteries

Cutaneous and splanchnic district  
vasoconstriction (**Alpha 1**)

The innervation is exclusively sympathetic. The basal tone activity of sympathetic nerves maintains a vasoconstrictor tone. Basal tone reduction produces vasodilation.

Muscle and cardiac district  
vasodilation (**Beta 2**)

*The control over the muscular district is mainly dependent on the metabolites produced during muscle activity*

### Veins

Venoconstriction (**Alpha 1**)

# SYMPATHETIC INFLUENCES

## RESPIRATORY FUNCTION

### Airways

bronchodilation (**Beta 2**)

### Ventilation

no direct effect

*SNA does not control the frequency and depth of breaths, which depend on the activity of skeletal muscles controlled by somatic nerves. This activity can be modified by higher nerve centers involved in central regulation of SNA*

# SYMPATHETIC INFLUENCES

## GI FUNCTION

*SNS modulates ENS*

### Stomach and Intestines

**Wall** (*motility*)

relaxation (**Beta 2, Alpha 2**)

**Sphincters**

contraction (**Alpha 1**)

**Secretions** (also exocrine pancreas)

inhibition or no effect (**Alpha 2**)

# SYMPATHETIC INFLUENCES

## RENAL FUNCTION

### luxtaglomerular apparatus

Induces renin secretion **Beta 2**

# SYMPATHETIC INFLUENCES

## URINARY FUNCTION

### Bladder

#### Wall

relaxation (**Beta 3**)

#### Internal sphincter

contraction (**Alpha1**)

# SYMPATHETIC INFLUENCES

## GENITO-REPRODUCTIVE FUNCTION

### Males

contrast erection (vasoconstriction)  
induces ejaculation (**Alpha 1**)

### Females

pregnant uterus  
contraction (**Alpha 1**)

non-pregnant uterus  
relaxation (**Beta 2**)

# SYMPATHETIC INFLUENCES

EYE (VISION)

## Ciliary muscle

relaxation (**Beta 2**)

*(crystalline convex reduction: better vision from afar)*

## Iris radial muscle (dilator)

contraction, with consequent pupillary dilation(**Alpha 1**)

(mydriasis)

# SYMPATHETIC INFLUENCES

## SALIVARY GLANDS

dense and viscous secretion (rich in amylase)

(**Beta 1** and **Alpha 1**)

# SYMPATHETIC INFLUENCES

## METABOLIC FUNCTION

### Liver

glycogenolysis and gluconeogenesis (**Beta 2**)

### Adipose tissue

lipolysis (**Beta 3**)

### Endocrine Pancreas

prevalent effect: reduction of insulin release  
(**Alpha 2**)

## SYMPATHETIC INFLUENCES

### IMMUNE FUNCTION

Inhibits the immune system (**Beta 2**).

## POST-GANGLIONIC PARASYMPATHETIC NEURONS

- parasympathetic postganglionic neurons release **ACETHYLCOLINE**
- The effects of ACh are mediated by **muscarinic receptors** (metabotropic)
- the typical agonist is **MUSCARINE**, contained in the poisonous mushroom Amanita Muscaria
- the muscarinic effect of ACh is selectively blocked by **ATROPINE**, a substance extracted from belladonna berries.
- Parasympathetic postganglionic neurons can co-release other substances (eg **VIP**) that have slower postsynaptic effects

# CHOLINERGIC RECEPTORS (TARGETS)

Second messengers involved in intracellular signal transduction:

## RECEPTOR

## SECOND MESSENGER

M1

Enhanced production of **DAG and Inositol-triphosphate (IP3)**,  
(increase citosol [Ca<sup>++</sup>])

M2

Reduction **AMPc**

M3

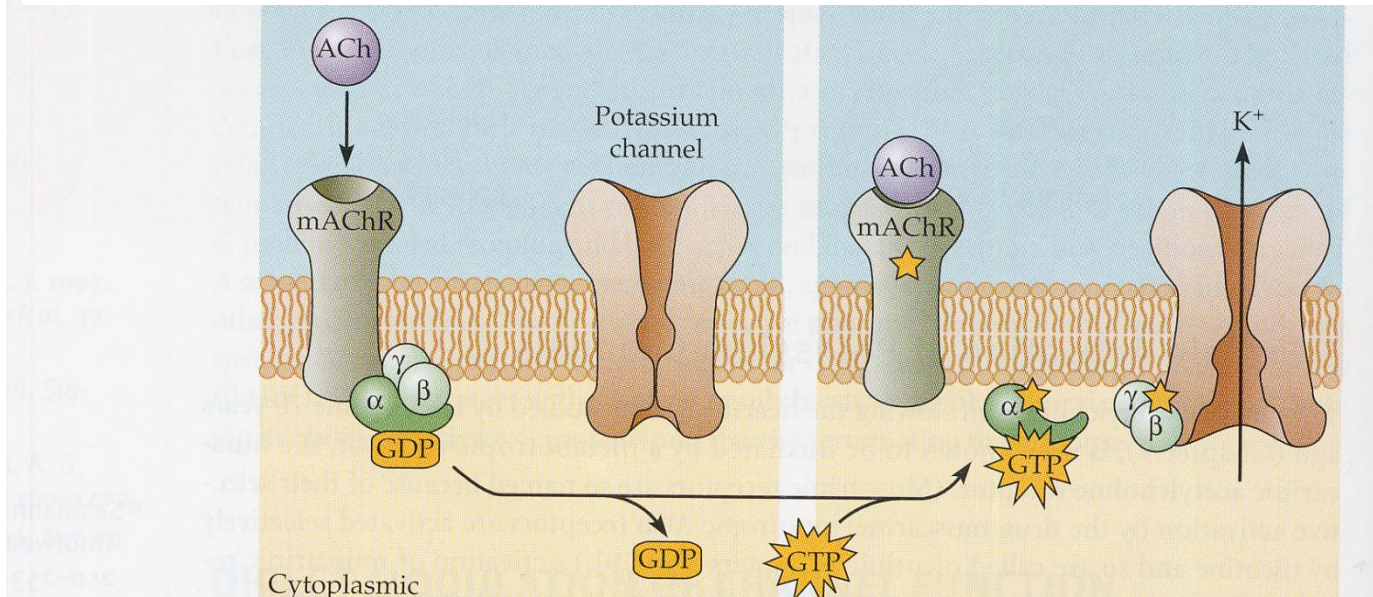
Enhanced production of **DAG and Inositol-triphosphate (IP3)**,  
(increase citosol [Ca<sup>++</sup>])

M4, M5,..

# CHOLINERGIC RECEPTORS (TARGETS)

## M2 Receptors:

direct action of the G protein (beta-gamma subunit) on K<sup>+</sup> channels in the sinoatrial node → hyperpolarization

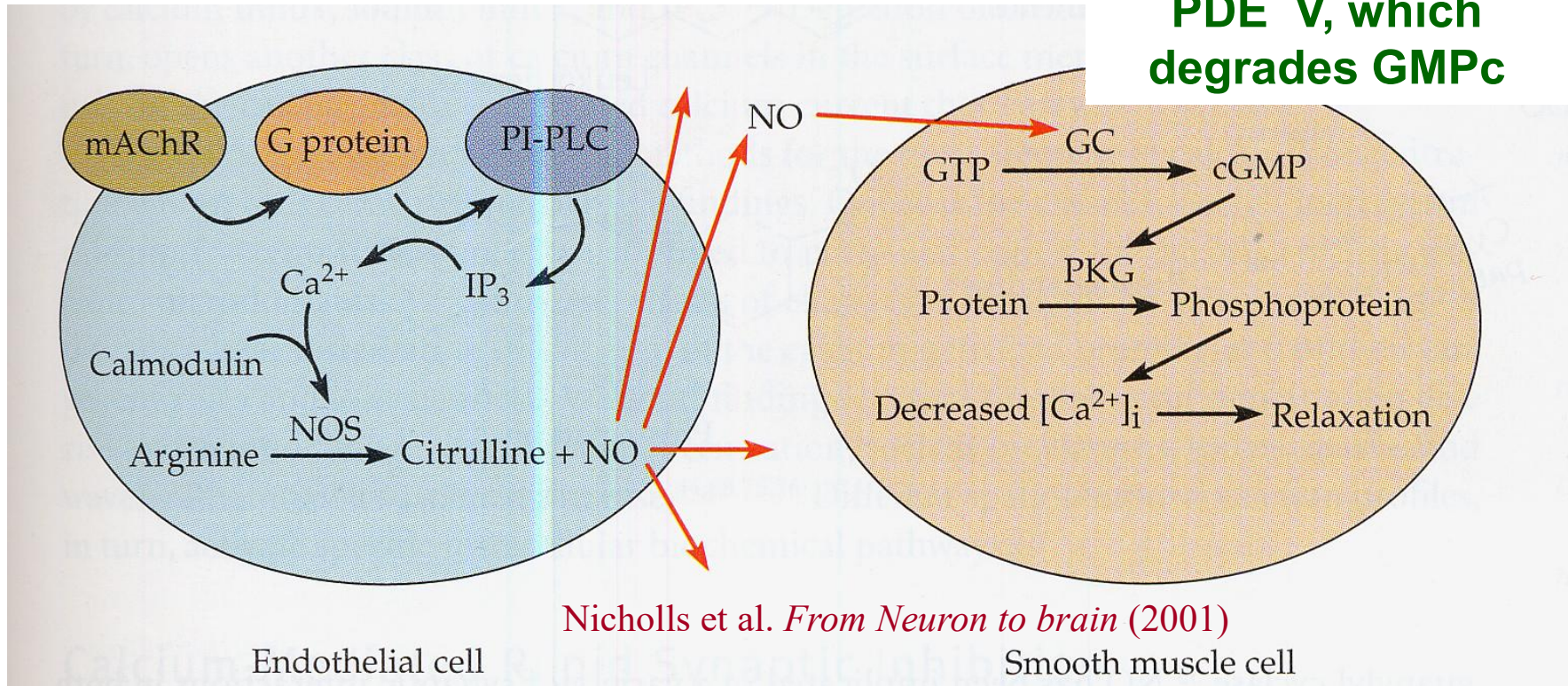


# CHOLINERGIC RECEPTORS (TARGETS)

## M3 Receptors:

induction of **nitric oxide (NO)** synthesis in the endothelium, whose release determines inhibition of smooth muscle fiber with consequent vasodilation:

- i) In the **cerebral district**
- ii) In the **genital district** (erection)



# PARASYMPATHETIC INFLUENCES

## CARDIOVASCULAR FUNCTION

### Heart (M2 receptors)

SA, AV nodes

reduced automaticity (bradycardia)

reduced pulse conduction speed

Atrial and ventricular myocardium

reduced excitability

decrease in contraction force

# PARASYMPATHETIC INFLUENCES

## CARDIOVASCULAR FUNCTION

### Arteries

Cerebral and genital district

vasodilation (M3), mediated by endothelial release of NO.

*In both cases there are nitrenergic nervous fibers*

In other districts parasympathetic innervation is absent

# PARASYMPATHETIC INFLUENCES

## RESPIRATORY FUNCTION

### Airways

bronchoconstriction (M3)

# PARASYMPATHETIC INFLUENCES

GI function

*PNS modulates ENS*

## Stomach and intestines

**Wall** (*motility*)

contraction (**M1 and M3**)

**Sphincters**

relaxation (**M3**)

**Secretions** (*also exocrine pancreas*)

stimulation

*gastric acid secretion* (**M1**)

# PARASYMPATHETIC INFLUENCES

## URINARY FUNCTION

### Bladder

#### Wall

contraction *M3*

#### Internal Sphincter

relaxation *NO/VIP* ( $\downarrow$   $\alpha1$ )

# PARASYMPATHETIC INFLUENCES

## GENITO-REPRODUCTIVE FUNCTION

### Males

erection (**M3 - NO**)  
gland secretions **M3**

### Females

clitoral tumescence (**M3 - NO**)  
gland secretions **M3**

# PARASYMPATHETIC INFLUENCES

## EYE-VISION

### Ciliary muscle

contraction **M3**

*(increased crystalline convexity with better proximal vision)*

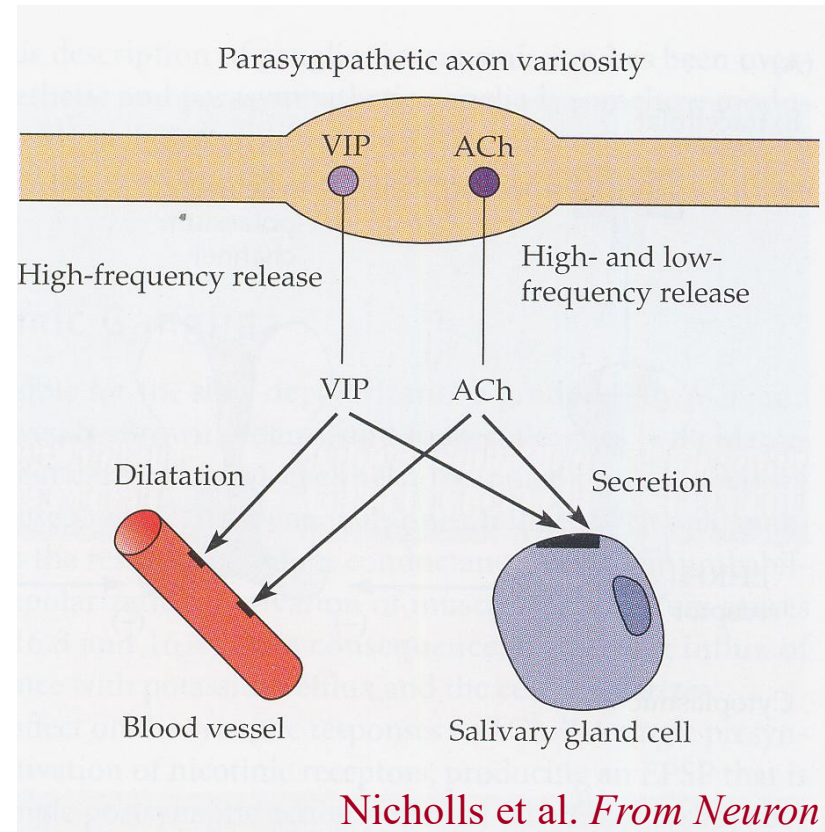
### Iris sphincter muscle (constrictor)

contraction, with consequent reduction of the pupillary diameter (MIOSIS) **M3**

# PARASYMPATHETIC INFLUENCES

## SALIVARY GLANDS

Serous secretion **M3** (*the co-released VIP acts as the main vasodilator*)



Nicholls et al. *From Neuron to brain* (2001)

FIGURE 1  
Neurons t  
peptide (V  
gland secr  
Stimulatio  
while at hi  
vasodilata

# PARASYMPATHETIC INFLUENCES

## METABOLIC FUNCTION

### Liver M3

(glycogen synthesis-*maybe*)

### Adipose tissue

*none*

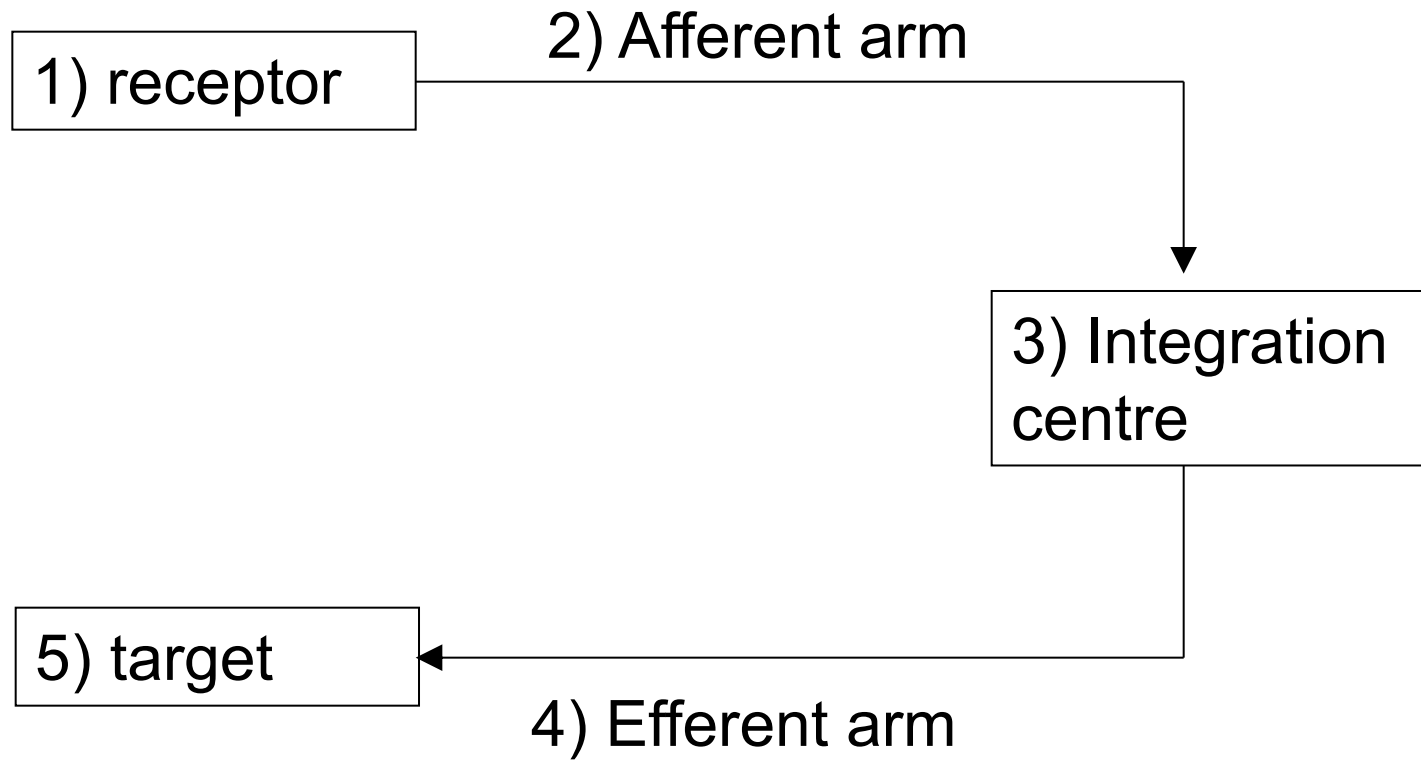
### Endocrine Pancreas M3

(*enhanced production of insuline and glucagone  
- maybe*)



# Autonomic reflex

## Reflex arc



# MICTURITION REFLEX

During bladder filling, the mechanoreceptors signal an increase in intravesical pressure

initially the pressure slowly increases because sympathetic nerves, reflexively, facilitate the releasing of the detrusor smooth muscle

when a filling level is reached that approaches the maximum bladder capacity (about 300 ml), the pressure increases and the afferent signal activates the sacral parasympathetic nerve and the Barrington pontine nucleus, whose activity, in turn, inhibits the sympathetic nerve, activates the parasympathetic nerves and inhibits the somatic motor neurons originating in the Onuf nucleus

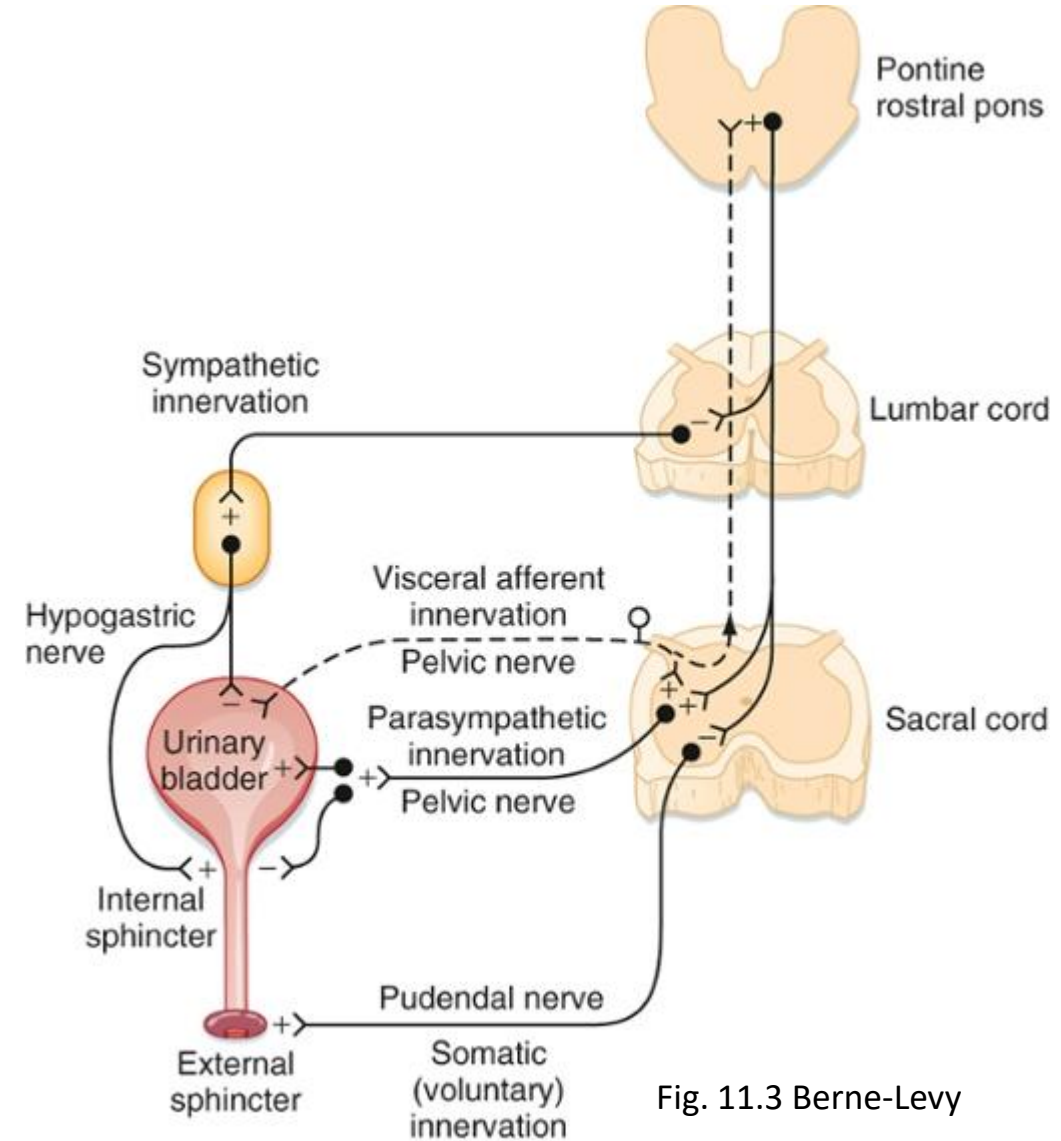
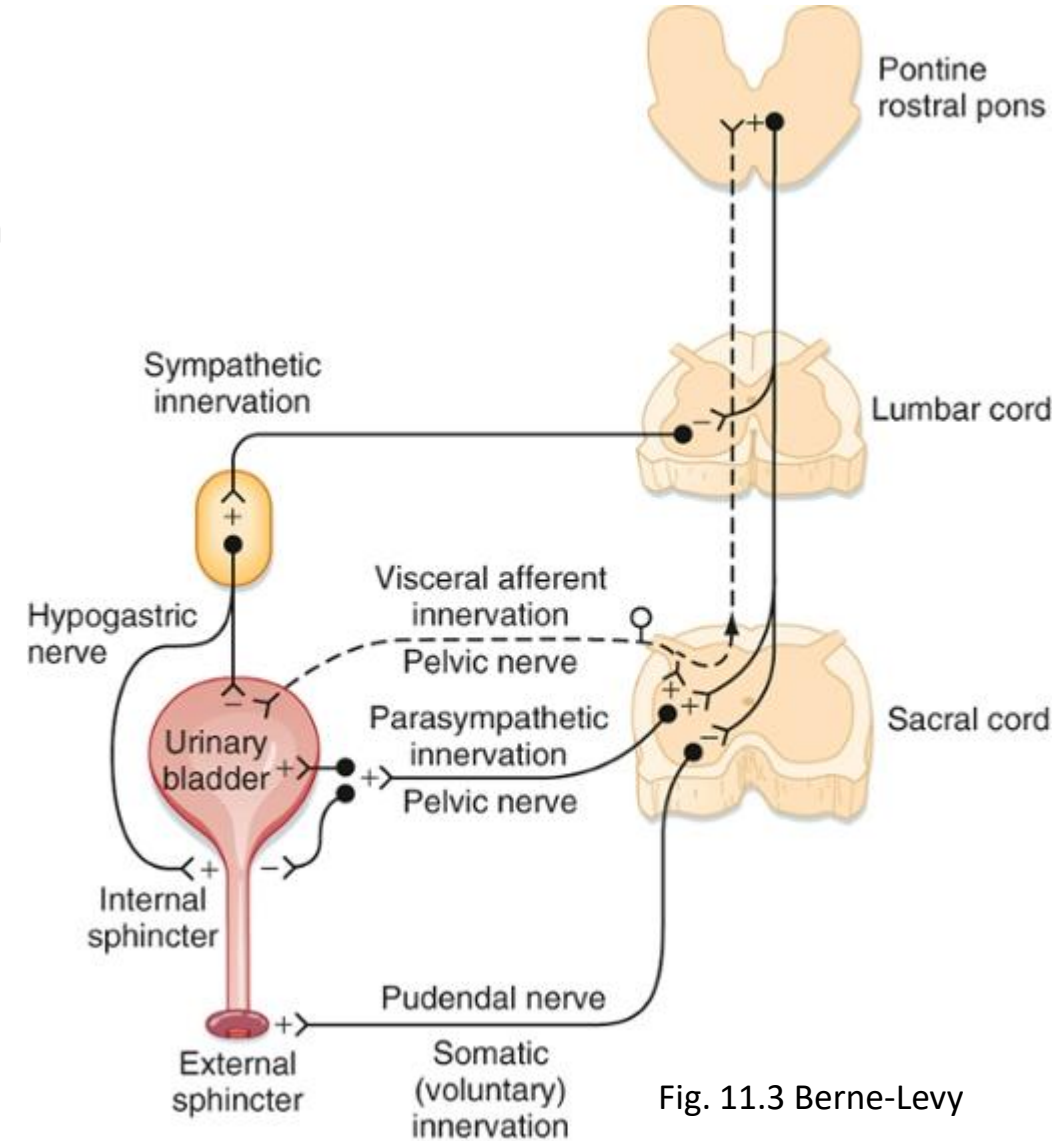


Fig. 11.3 Berne-Levy

# MICTURITION REFLEX

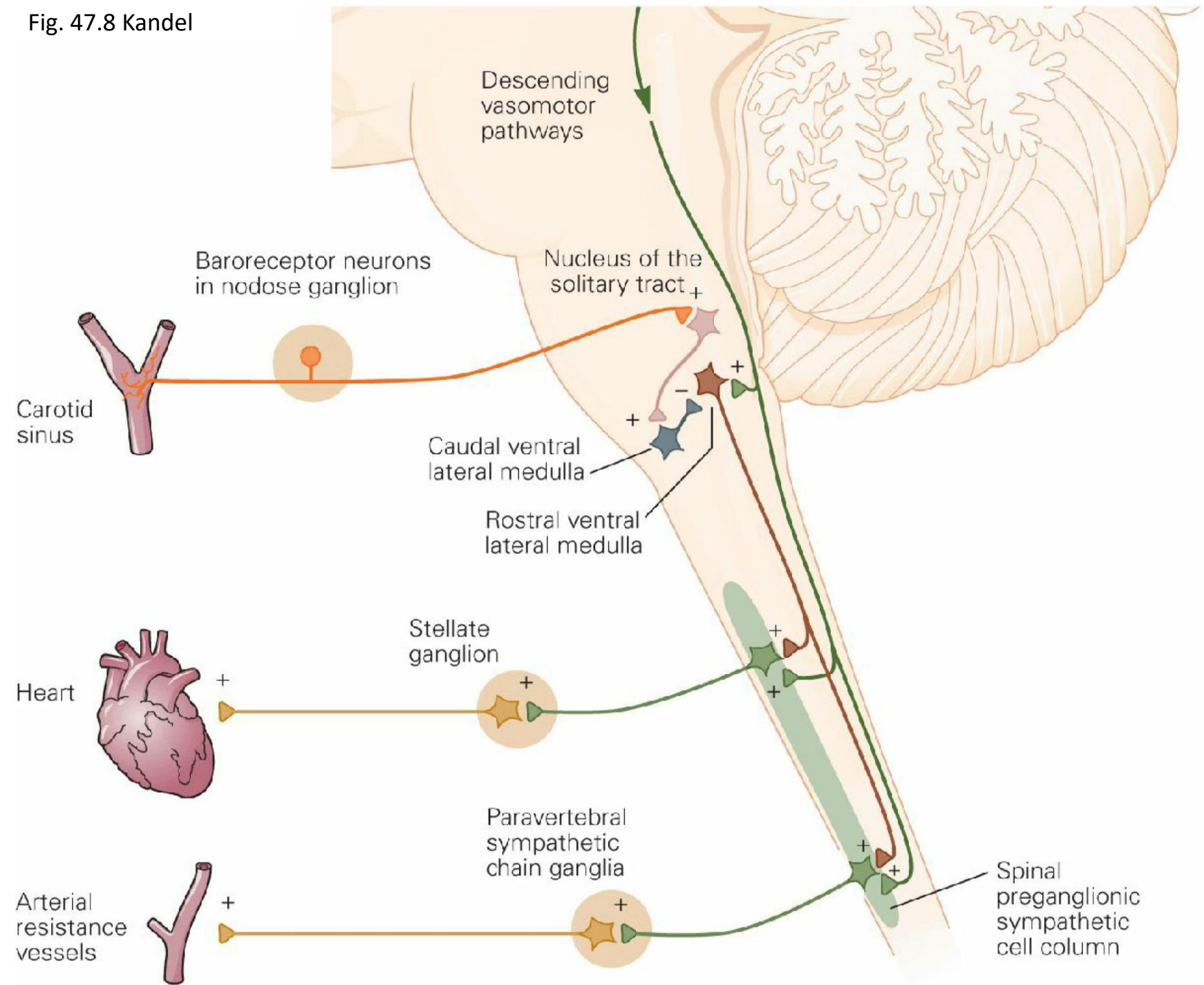
for urination to begin, however, it is necessary to remove, through a voluntary act, the tonic inhibition by the higher centers on the Barrington nucleus, favoring the reflex action linked to the distension of the bladder and promoting the relaxation of the striated external sphincter

once started, urination is maintained in a reflex way by the mechanoreceptive afferents, which detect the increase in tension in the detrusor contracted and continue to maintain the parasympathetic activation



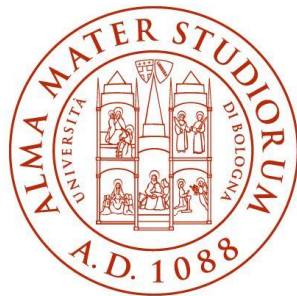
# The Baroreceptor Reflex for the control of blood pressure

Fig. 47.8 Kandel





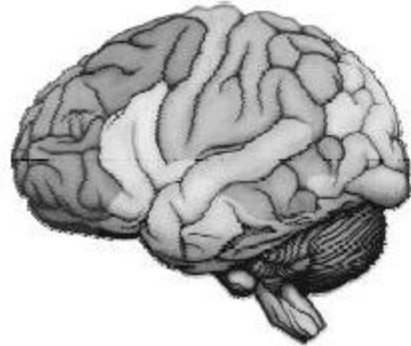
# The inflammatory reflex (the *real* inflammatory reflex)



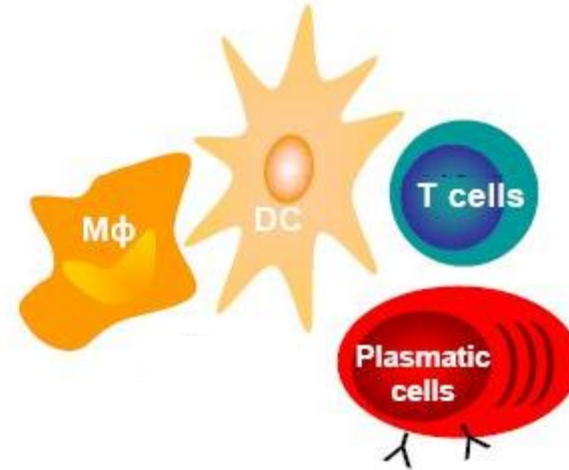
# The Body's Two Supersystems

# The Body's Two Supersystems

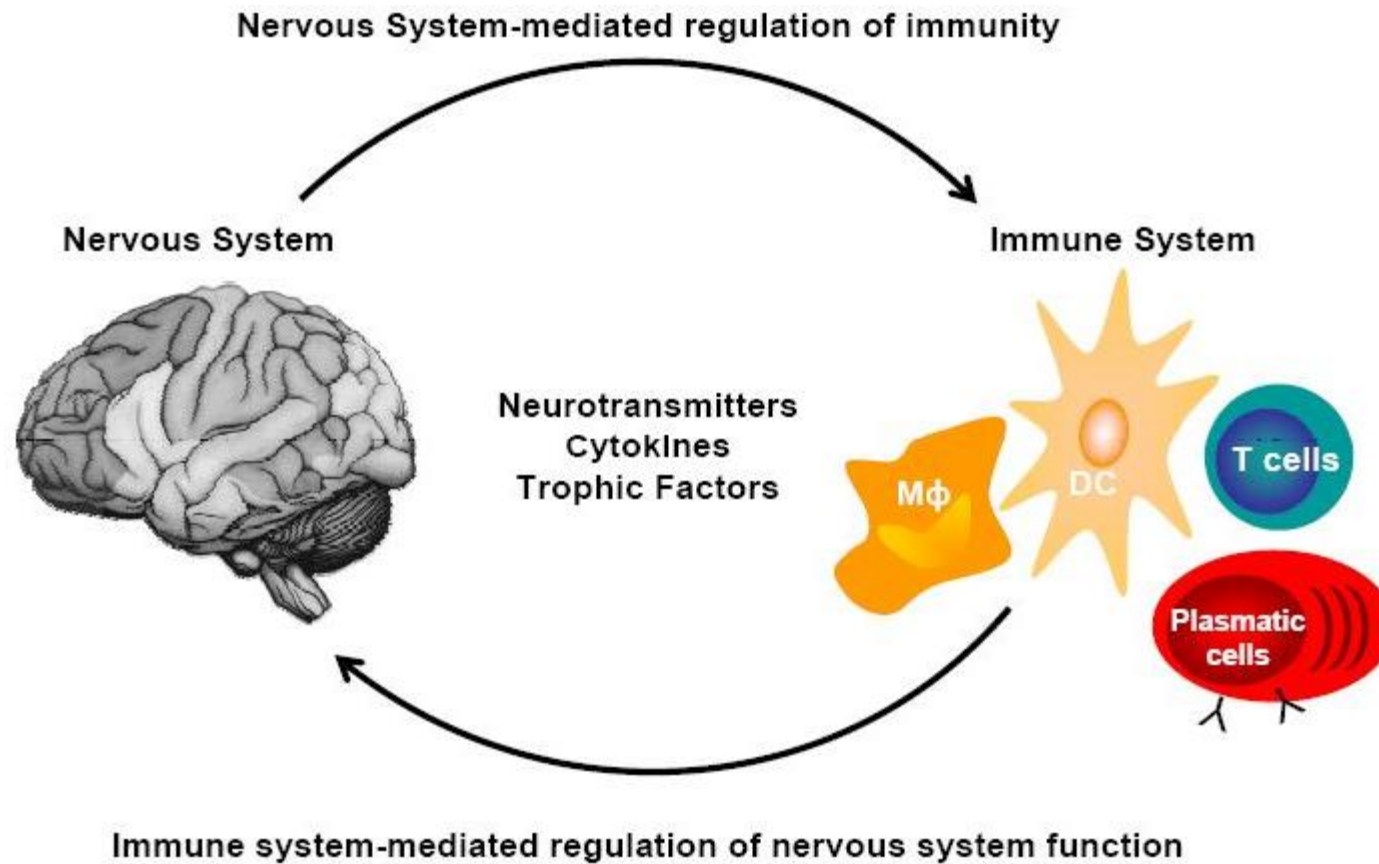
Nervous System



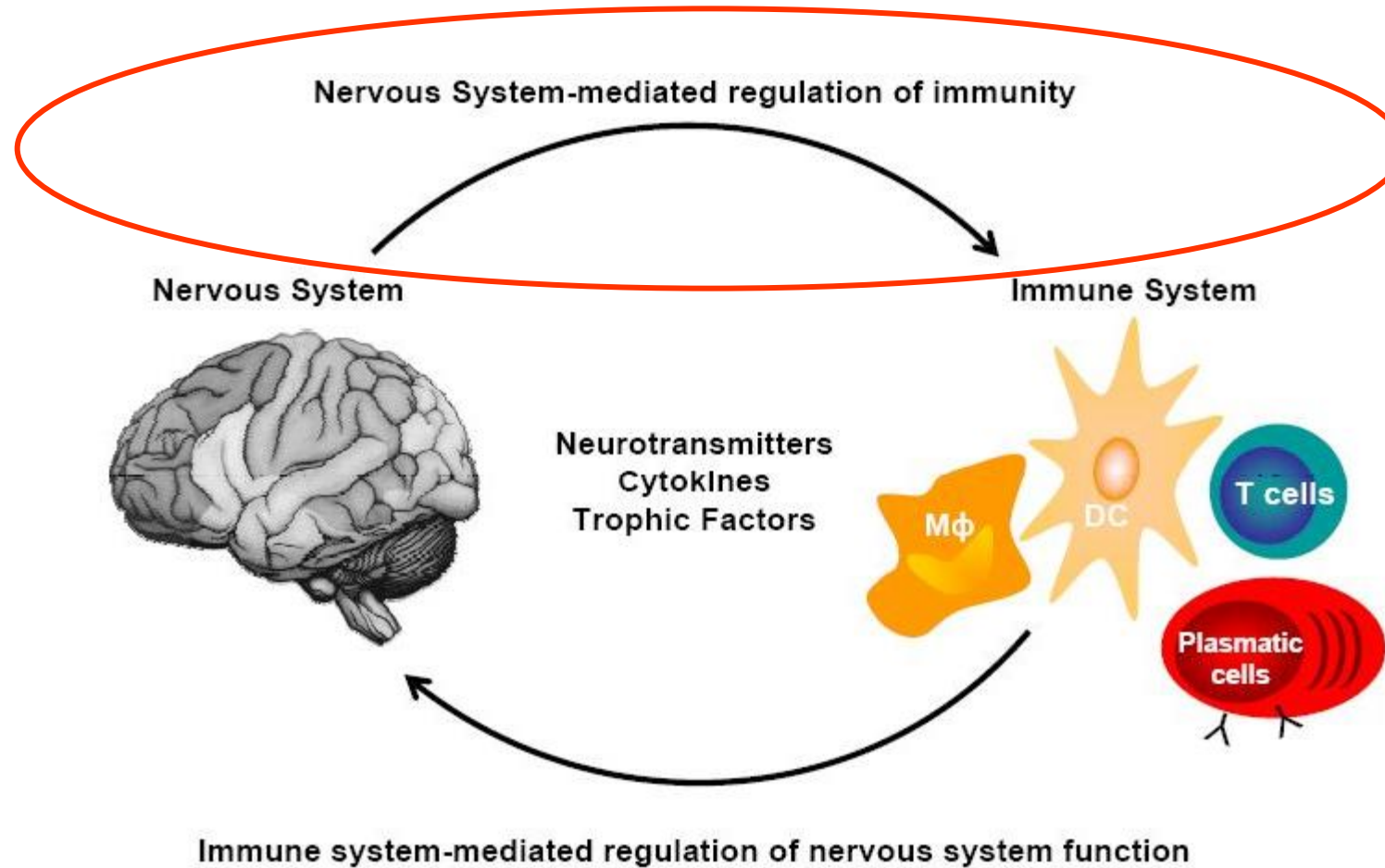
Immune System



# The Body's Two Supersystems



# The Body's Two Supersystems



How did a straight neuroscientist  
get involved in this minefield?

# Ulrich Dirnagl



# CENTRAL NERVOUS SYSTEM INJURY-INDUCED IMMUNE DEFICIENCY SYNDROME

*Christian Meisel<sup>\*</sup>, Jan M. Schwab<sup>†§||</sup>, Konstantin Prass<sup>§</sup>,  
Andreas Meisel<sup>§</sup> and Ulrich Dirnagl<sup>§</sup>*

Abstract | Infections are a leading cause of morbidity and mortality in patients with acute CNS injury. It has recently become clear that CNS injury significantly increases susceptibility to infection by brain-specific mechanisms: CNS injury induces a disturbance of the normally well balanced interplay between the immune system and the CNS. As a result, CNS injury leads to secondary immunodeficiency — CNS injury-induced immunodepression (CIDS) — and infection. CIDS might serve as a model for the study of the mechanisms and mediators of brain control over immunity. More importantly, understanding CIDS will allow us to work on developing effective therapeutic strategies, with which the outcome after CNS damage by a host of diseases could be improved by eliminating a major determinant of poor recovery.

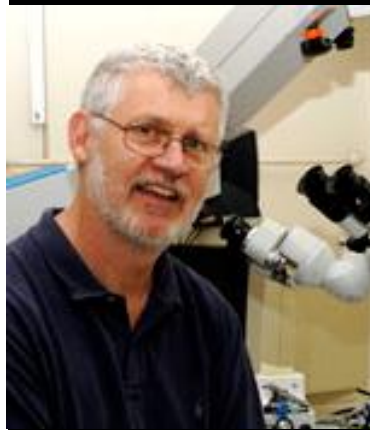
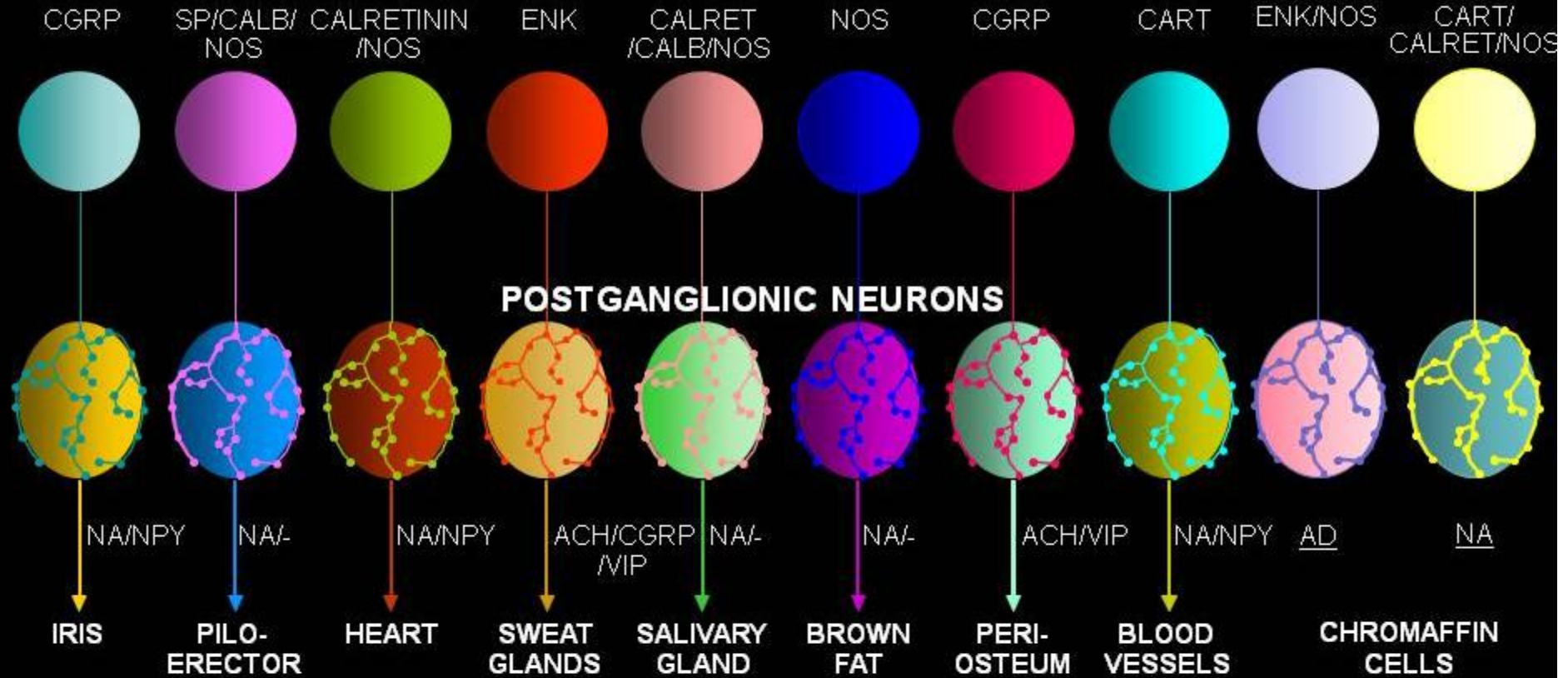


**Robin M. McAllen**

# Sympathetic classes

- Muscle Sympathetic (VC +?)
- Skin vasoconstrictor x 2+
- Skin vasodilator
- Heart x 3+?
- Sudomotor
- Pilomotor
- Renal x 2+
- Visceral vasoconstrictor x?
- Gut motility regulator x 2+
- Gut secretion inhibitor
- Bronchodilator
- Nasal vasoconstrictor
- Salivary gland
- Pupillodilator
- Levator palpebri
- Bladder detrusor, sphincter
- Genital vasoconstrictor
- Vas deferens
- Lipomotor white
- Lipomotor BAT
- Adrenal NE
- Adrenal E
- Etc.

## PREGANGLIONIC NEURONS



Courtesy of  
Colin Anderson

# Sympathetic classes

- Muscle Sympathetic (VC +?)
- Skin vasoconstrictor x 2+
- Skin vasodilator
- Heart x 3+?
- Sudomotor
- Pilomotor
- Renal x 2+
- Visceral vasoconstrictor x?
- Gut motility regulator x 2+
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- Etc.

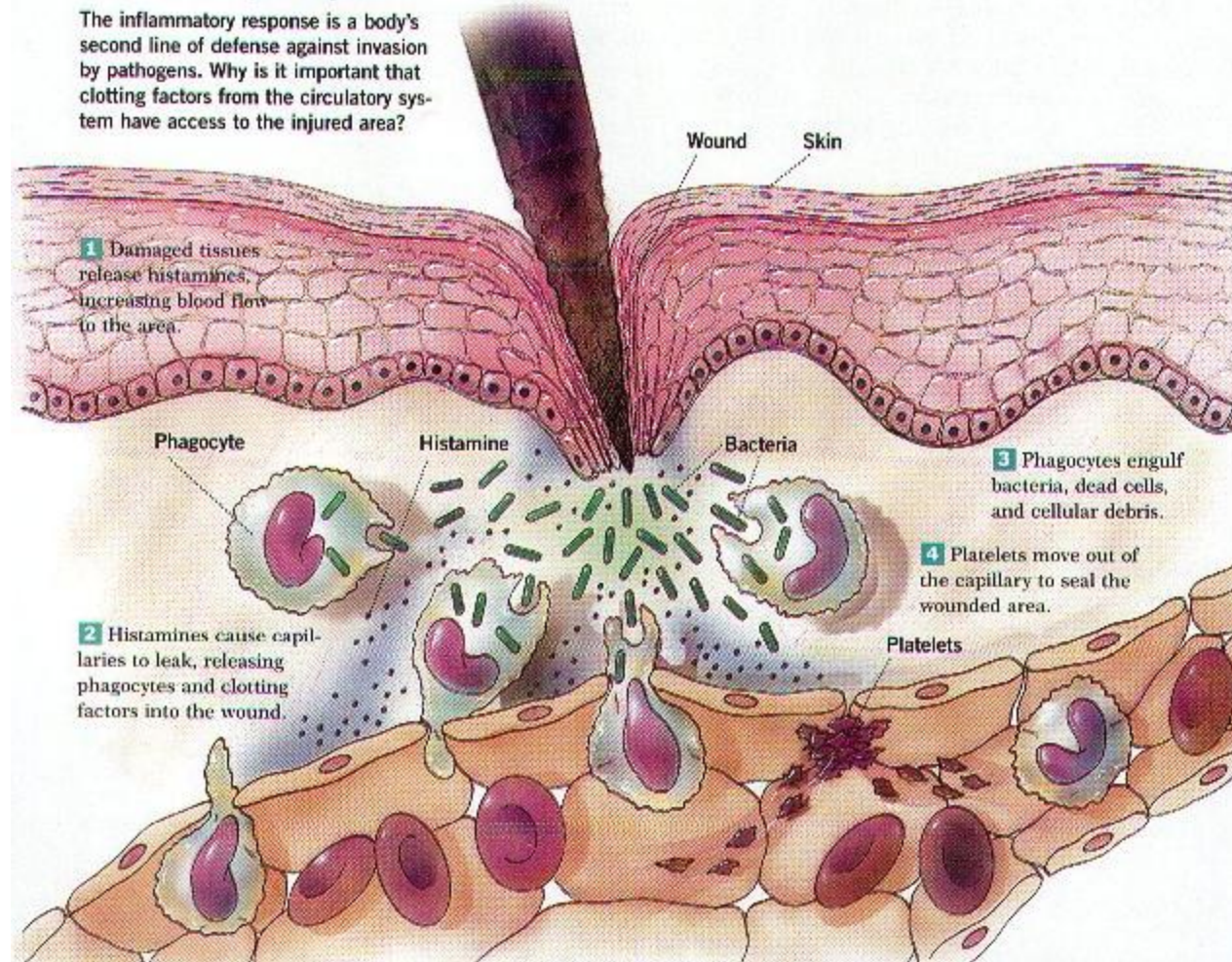
# Sympathetic classes

- Muscle Sympathetic (VC +?)
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- Visceral vasoconstrictor x?
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- Gut secretion inhibitor
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- Levator palpebri
- Bladder detrusor, sphincter
- Genital vasoconstrictor
- Vas deferens
- Lipomotor white
- Lipomotor BAT
- Adrenal NE
- Adrenal E
- Etc.
- **Immunomodulator ?**

Inflammation – the first stage of innate immunity

## Steps of the Inflammatory Response

The inflammatory response is a body's second line of defense against invasion by pathogens. Why is it important that clotting factors from the circulatory system have access to the injured area?



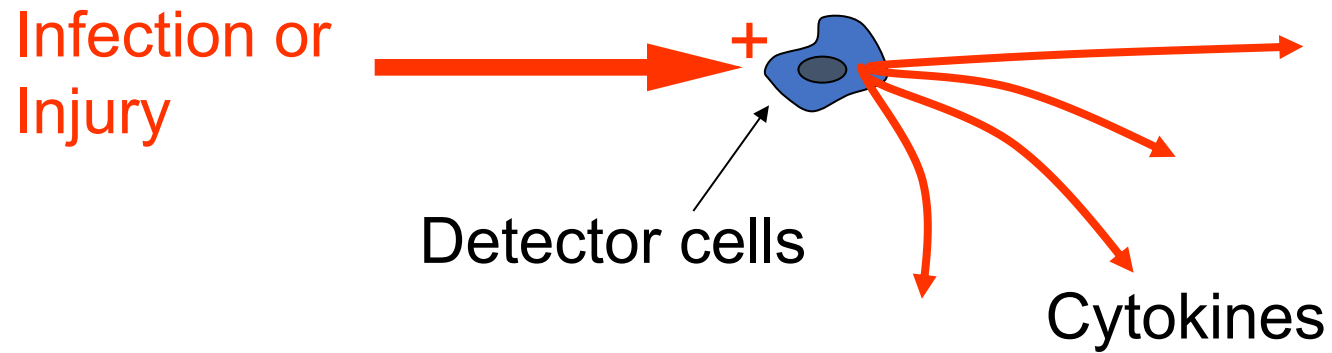
# Inflammation – the first stage of innate immunity

Infection or  
Injury 

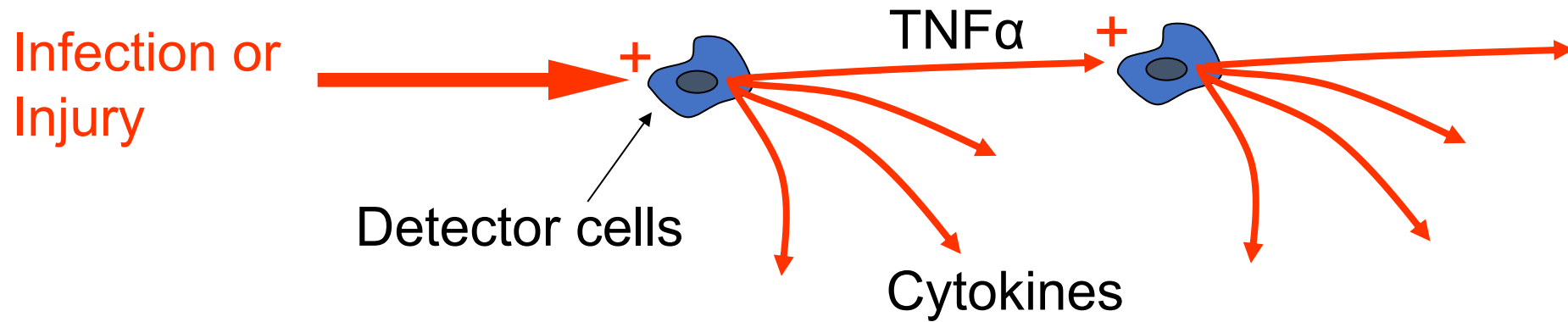
# Inflammation – the first stage of innate immunity



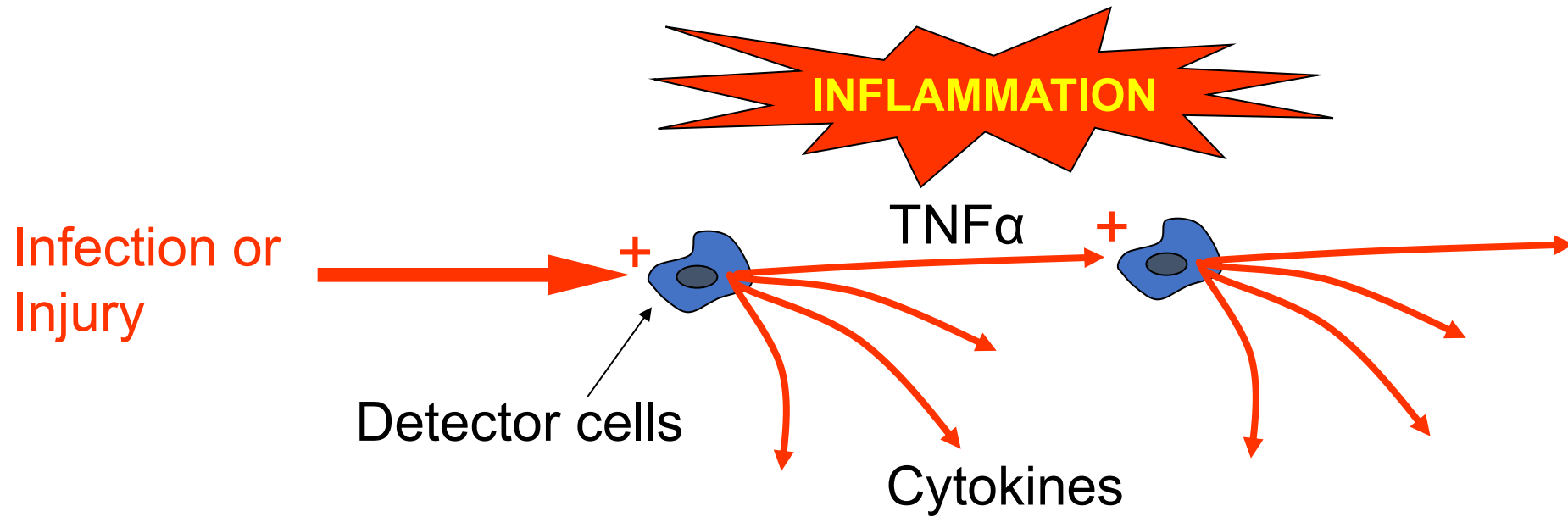
# Inflammation – the first stage of innate immunity



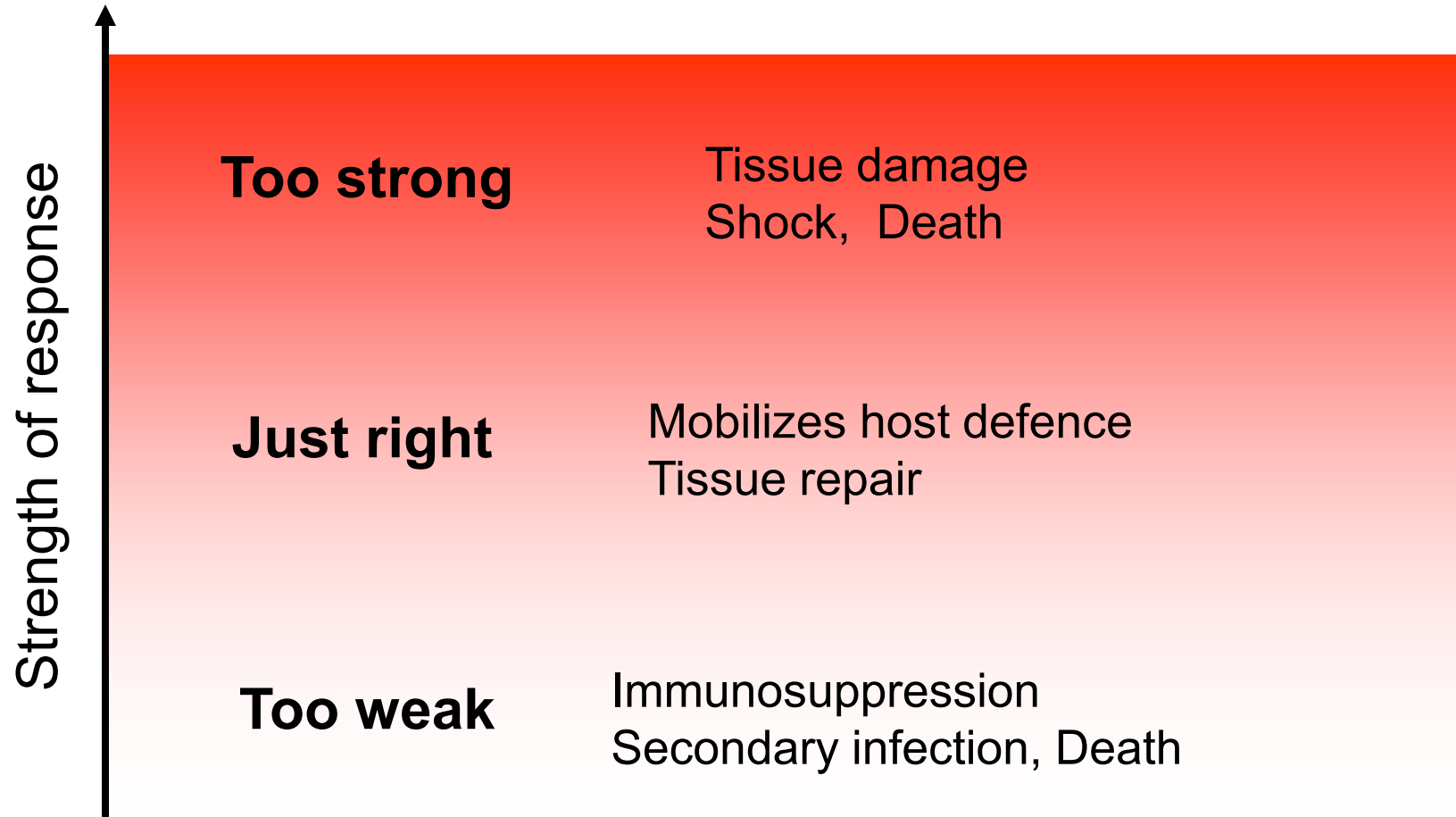
# Inflammation – the first stage of innate immunity



# Inflammation – the first stage of innate immunity



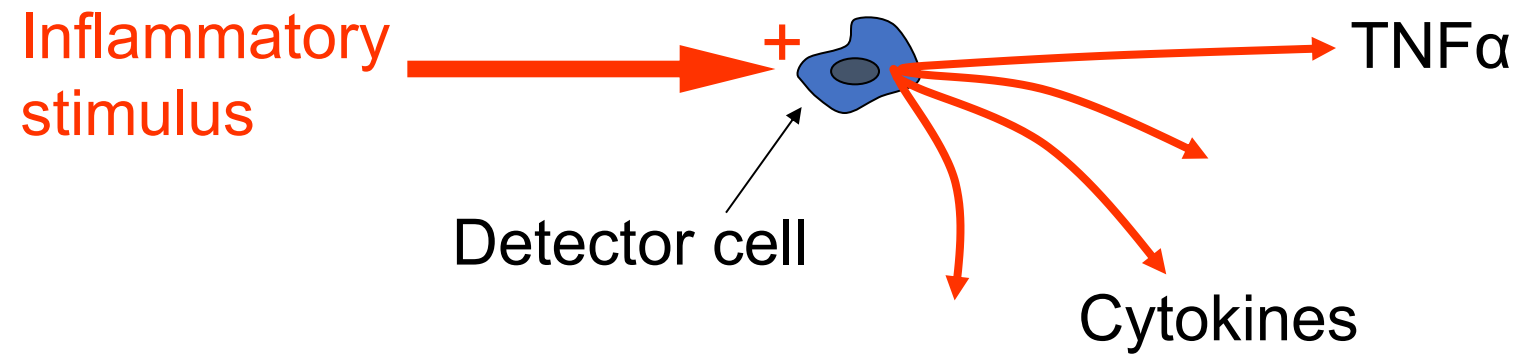
# Inflammation



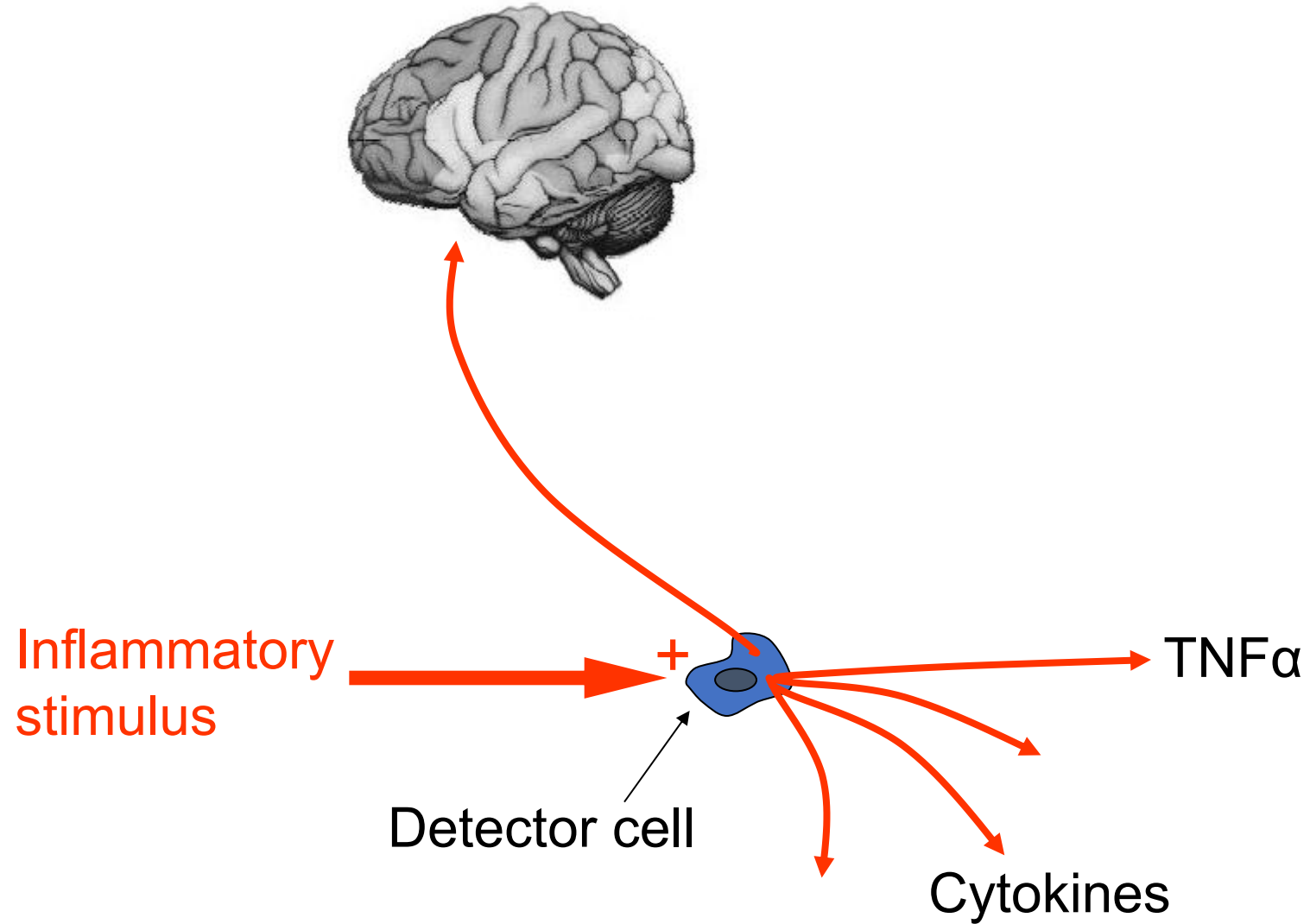
# The Inflammatory Reflex



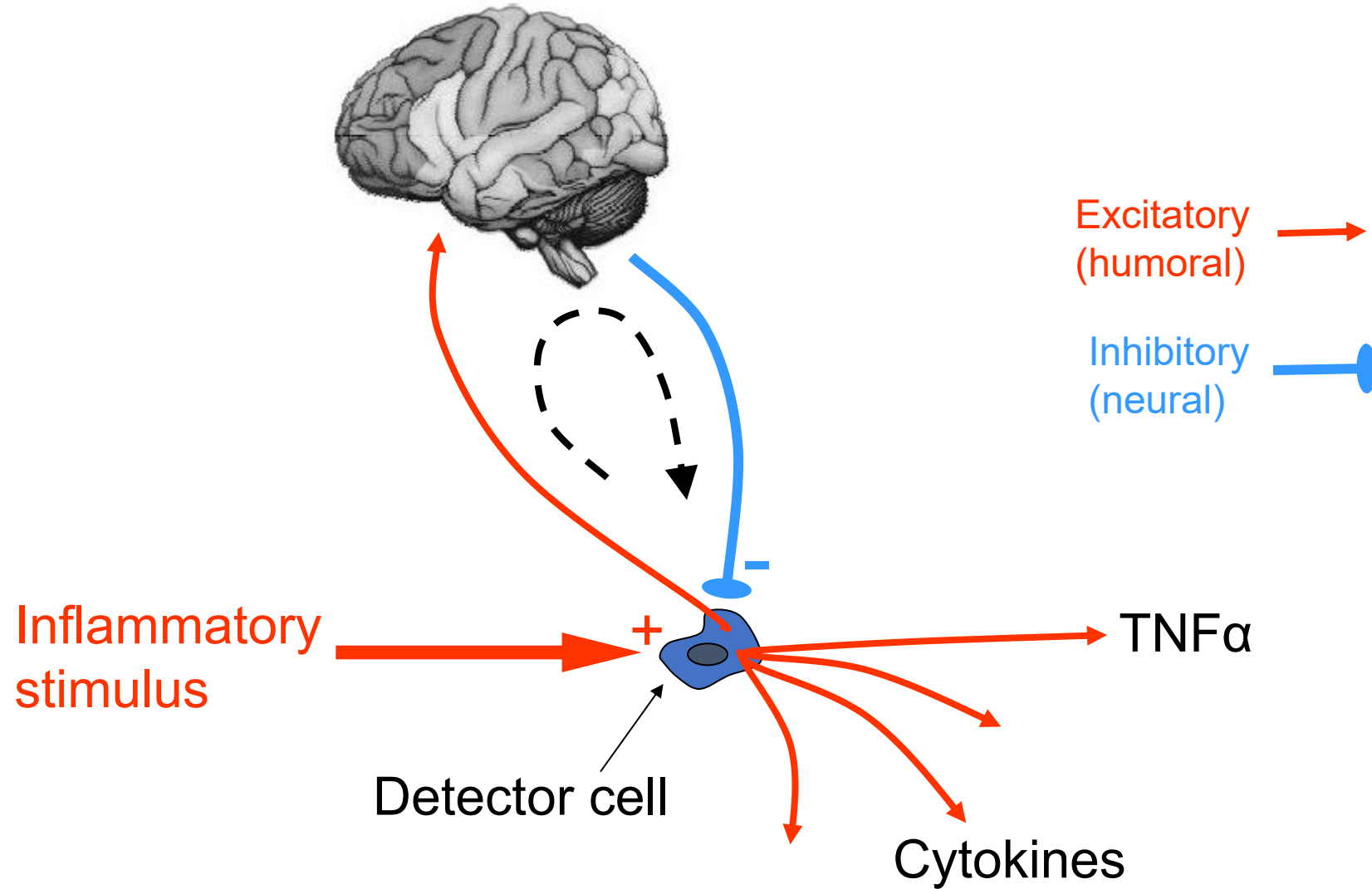
# The Inflammatory Reflex



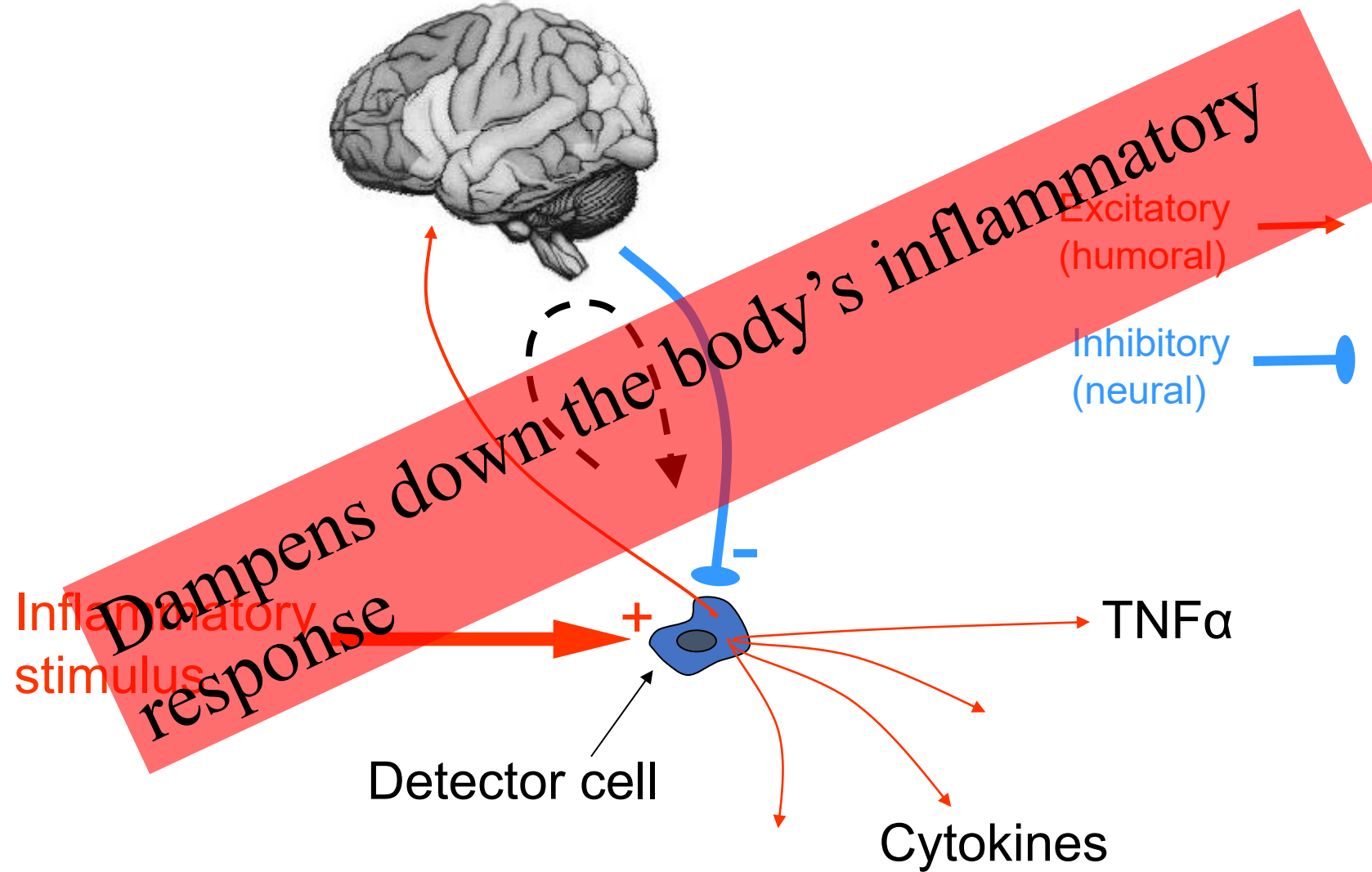
# The Inflammatory Reflex



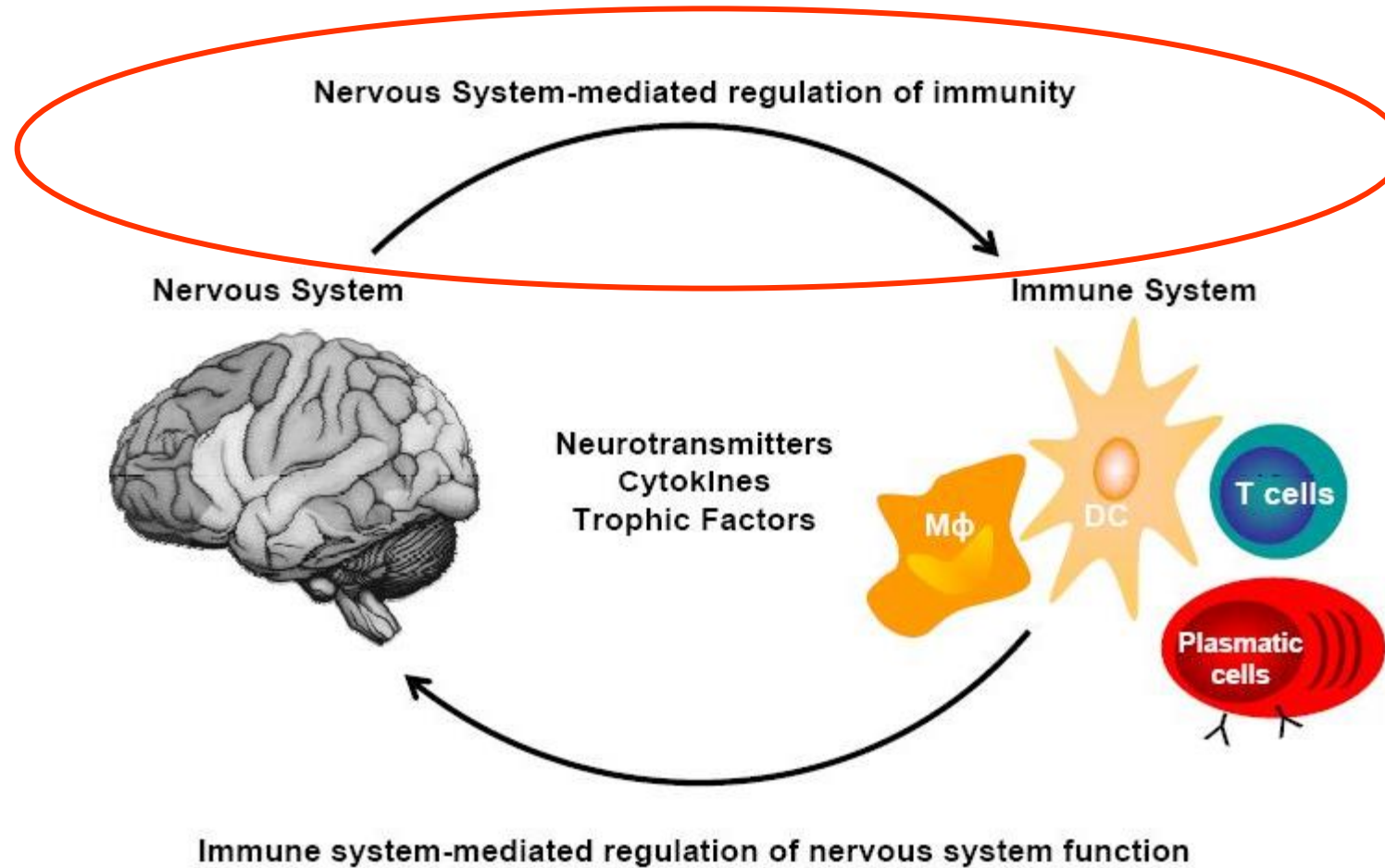
# The Inflammatory Reflex



# The Inflammatory Reflex



# What is the pathway?



# Nature 2002: An influential review

(>1700 citations)

**insight review articles**

## The inflammatory reflex

Kevin J. Tracey

Laboratory of Biomedical Science, North Shore-LIJ Research Institute, 350 Community Drive, Manhasset, New York 11030, USA  
(e-mail: kjtracey@sprynet.com)



**Inflammation is a local, protective response to microbial invasion or injury. It must be fine-tuned and regulated precisely, because deficiencies or excesses of the inflammatory response cause morbidity and shorten lifespan. The discovery that cholinergic neurons inhibit acute inflammation has qualitatively expanded our understanding of how the nervous system modulates immune responses. The nervous system reflexively regulates the inflammatory response in real time, just as it controls heart rate and other vital functions. The opportunity now exists to apply this insight to the treatment of inflammation through selective and reversible 'hard-wired' neural systems.**

*"The mind has great influence over the body, and maladies often have their origin there." Molière (1622–1673).*

**S**urvival is impossible without vigilant defence against attack and injury. The innate immune system continuously surveys the body for the presence of invaders. When it encounters an attack, it involuntarily sets in motion a discrete, localized inflammatory response to thwart most pathogenic threats. The magnitude of the inflammatory response is crucial: insufficient responses result in immunodeficiency, which can lead to infection and cancer; excessive responses cause morbidity and mortality in diseases such as rheumatoid arthritis, Crohn's disease, atherosclerosis, diabetes, Alzheimer's disease, multiple sclerosis, and cerebral and myocardial ischaemia. If inflammation spreads into the bloodstream, as occurs in septic shock syndrome, sepsis, meningitis and severe trauma, the inflammatory responses can be more

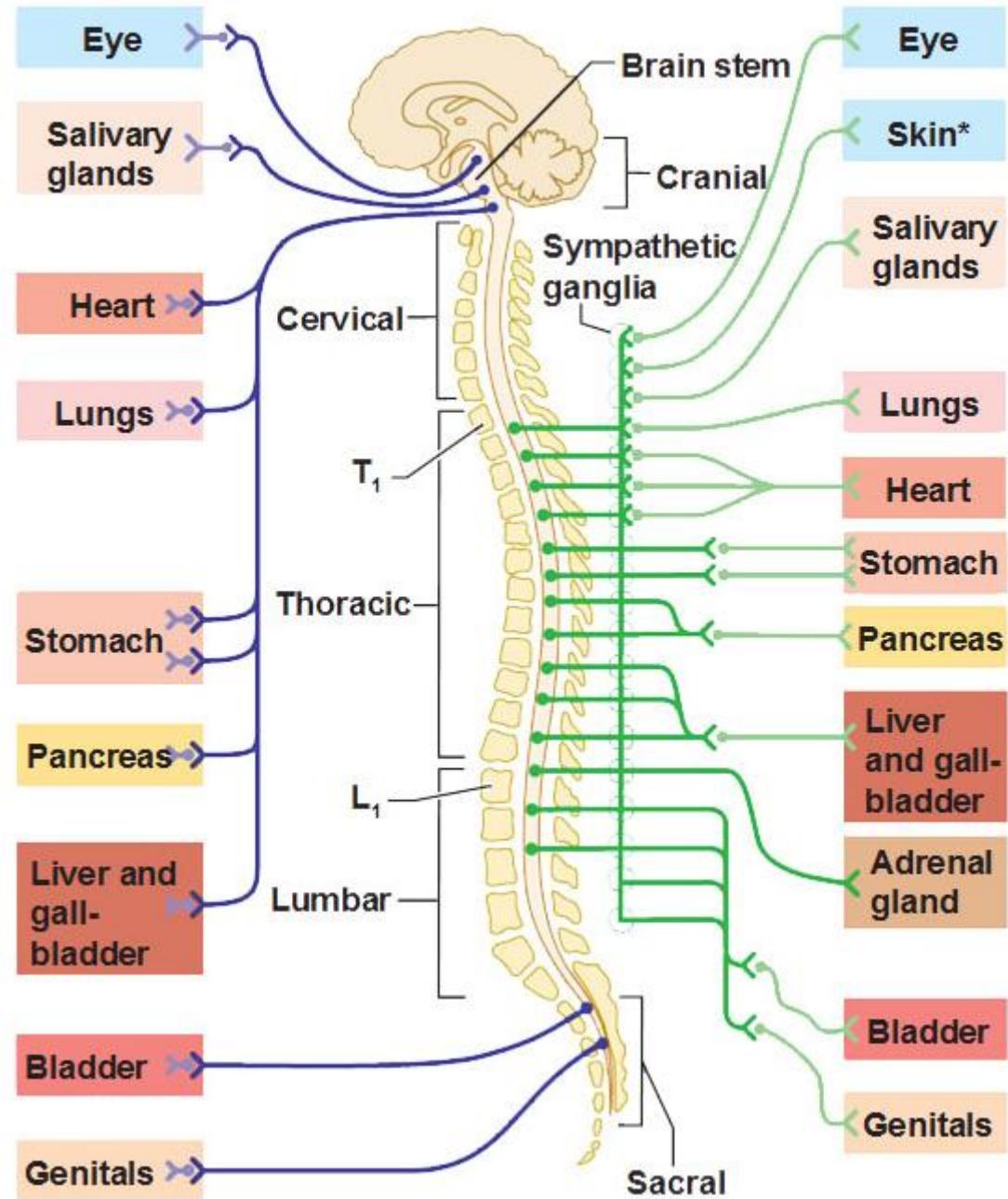
decrease their heart rate by increasing parasympathetic outflow.

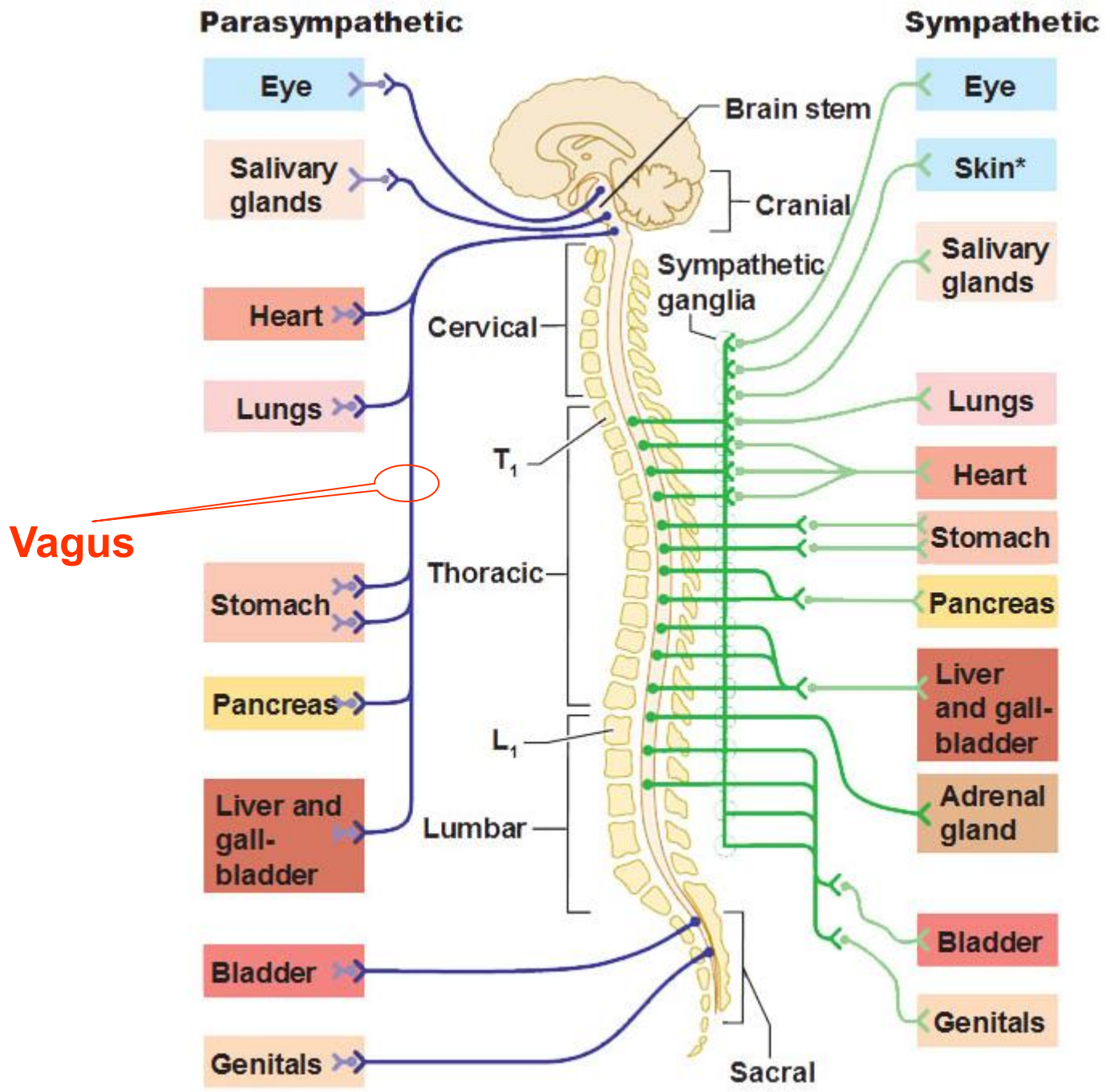
Recent insights have identified a basic neural pathway that reflexively monitors and adjusts the inflammatory response. Inflammatory stimuli activate sensory pathways that relay information to the hypothalamus. Like a knee-jerk reflex, in which the stretching of a patellar tendon elicits a rapidly opposing motor action, inflammatory input activates an anti-inflammatory response that is fast and subconscious. This prevents spillage of inflammatory products into the circulation. The nervous system integrates the inflammatory response: it gathers information about invasive events from several local sites, mobilizes defences and creates memory to improve chances for survival.

Here I review evidence showing that the neural control of acute inflammation is reflexive, directly interconnected and

**Parasympathetic**

**Sympathetic**

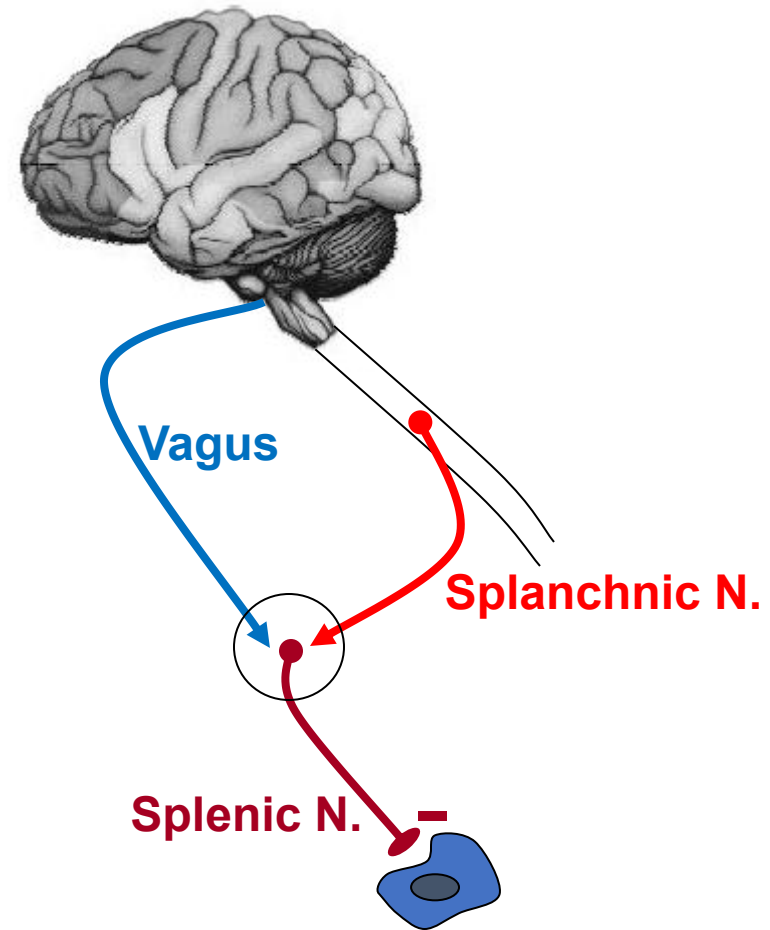




# Cytokine experiments:

Which neural pathways suppress inflammatory cytokine release? (measure TNF $\alpha$ )

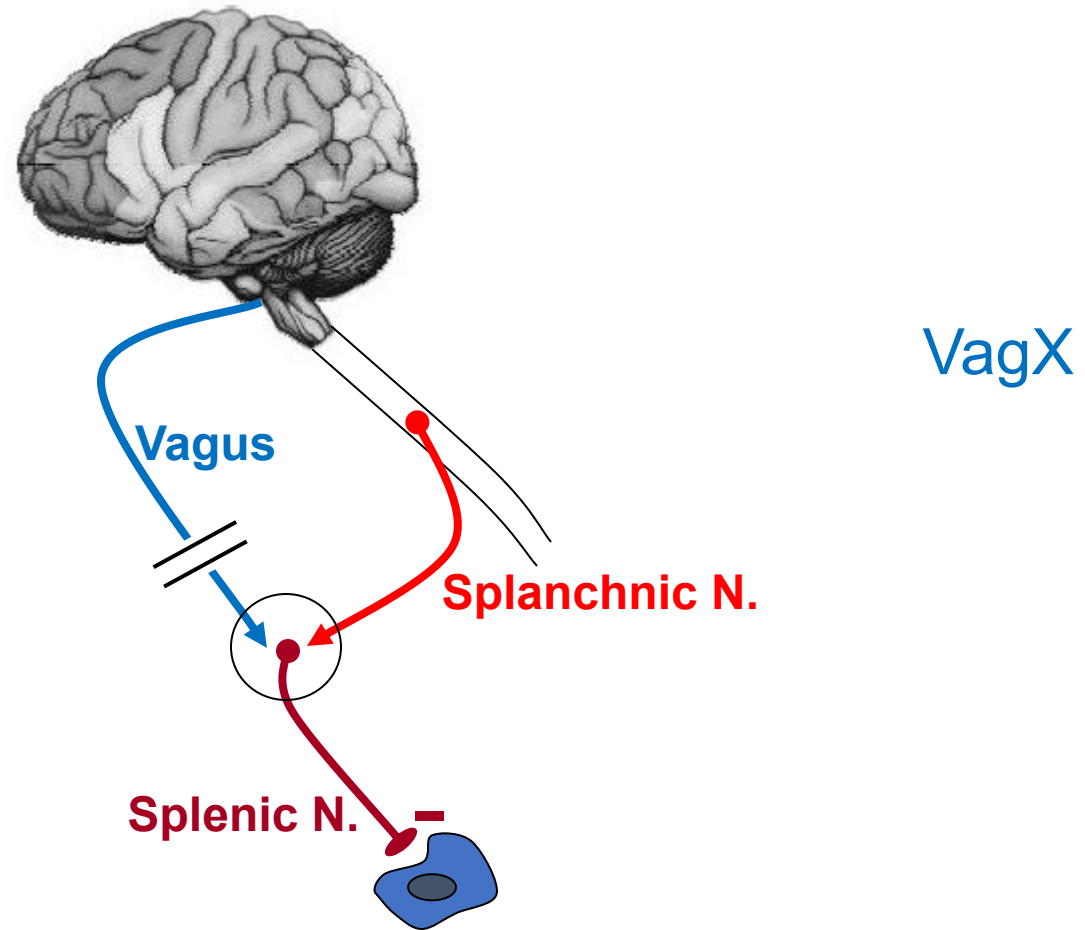
# Inflammatory Reflex Pathway



Sham

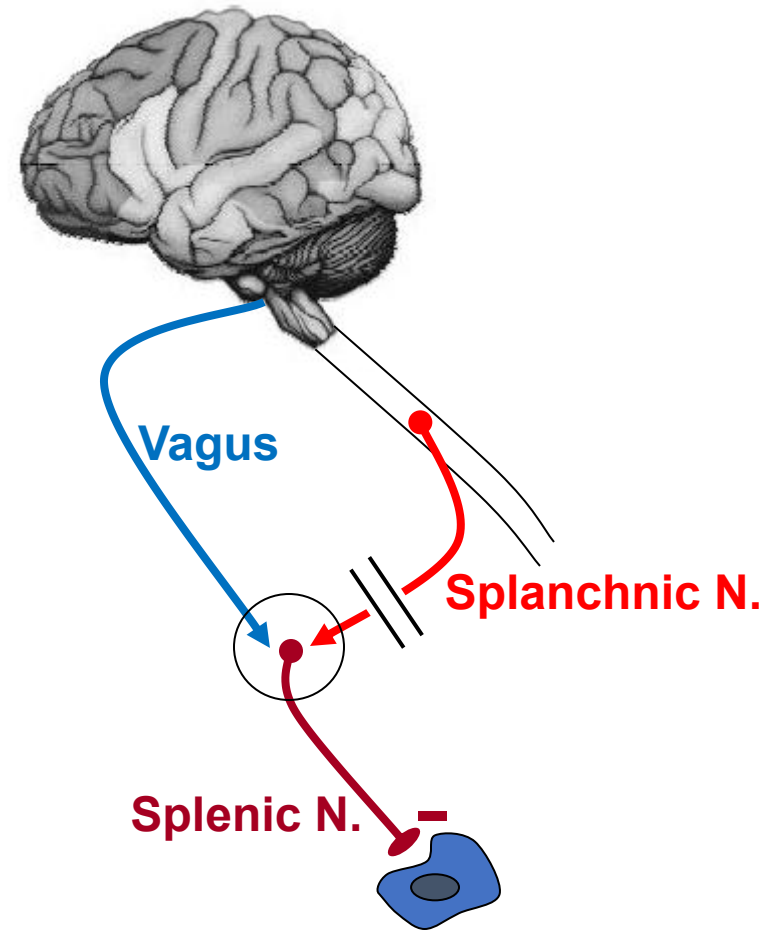
TNF $\alpha$  experiments

# Inflammatory Reflex Pathway



TNF $\alpha$  experiments

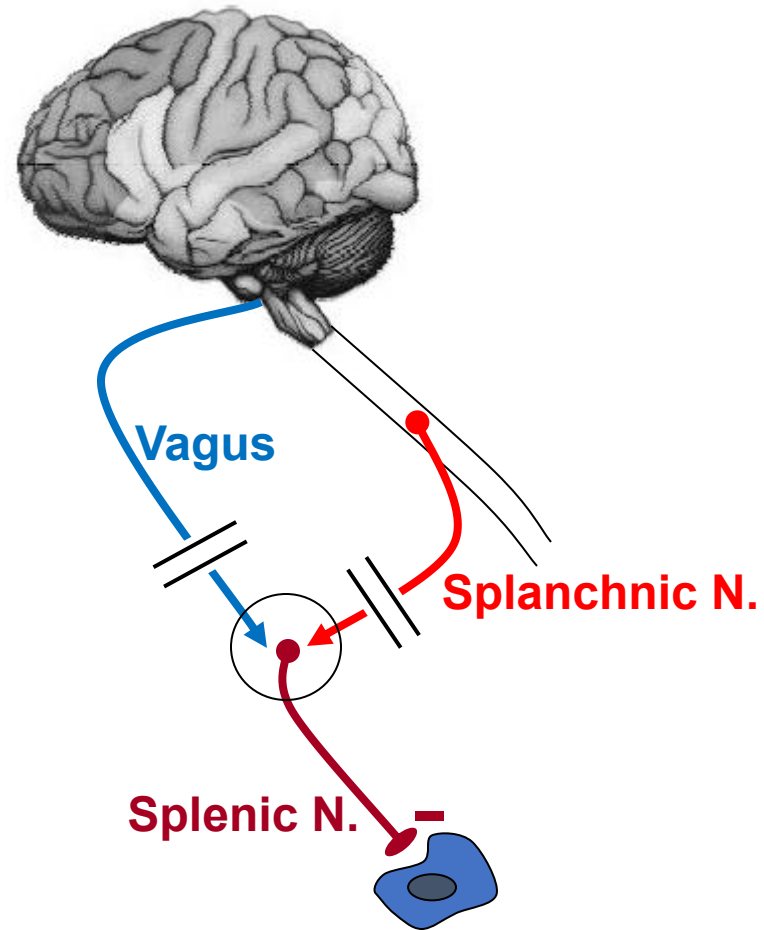
# Inflammatory Reflex Pathway



SplancX

TNF $\alpha$  experiments

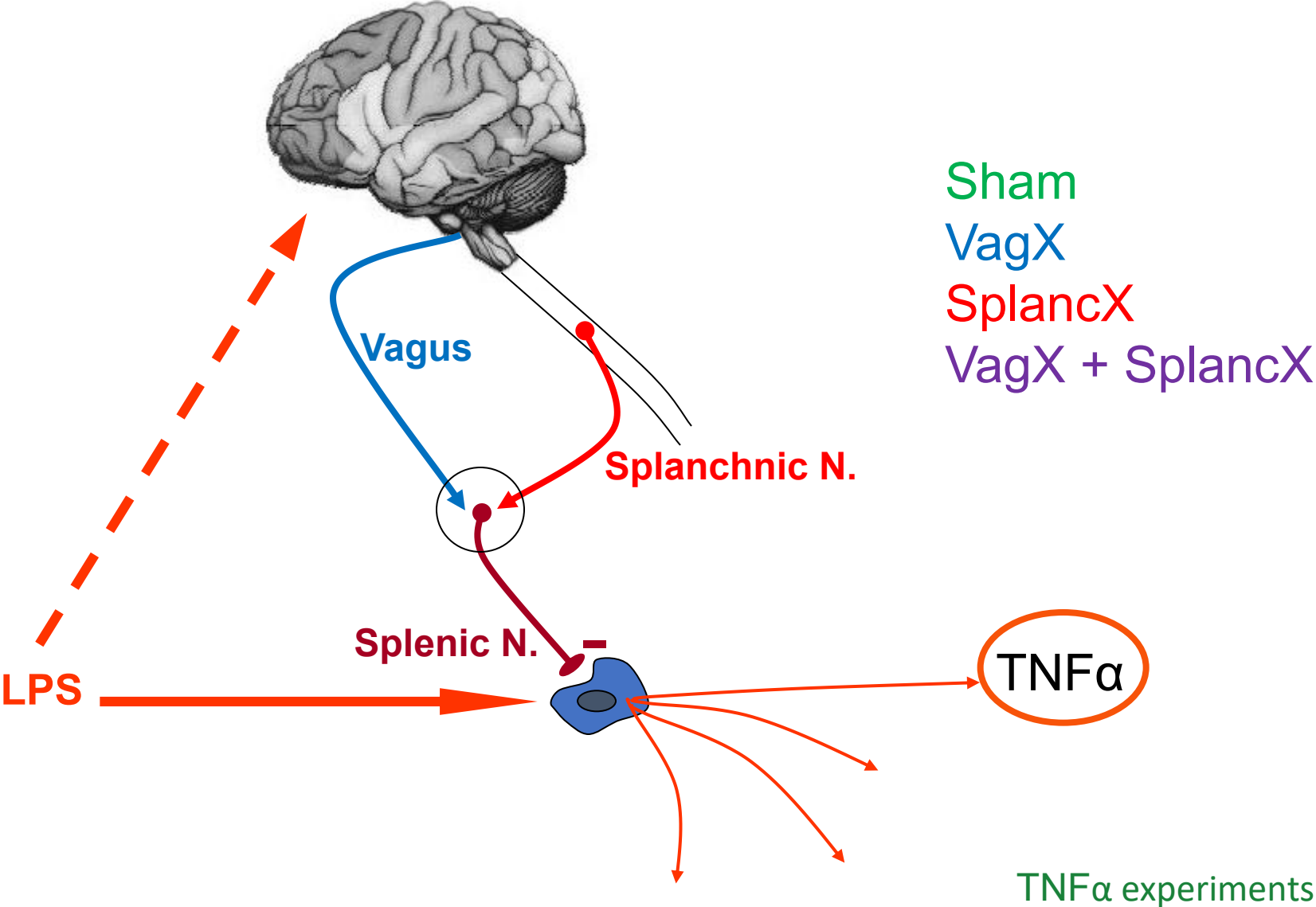
# Inflammatory Reflex Pathway



VagX + SplancX

TNF $\alpha$  experiments

# Inflammatory Reflex Pathway



Plasma TNF $\alpha$   
pg/ml

2500  
2000  
1500  
1000  
500  
0

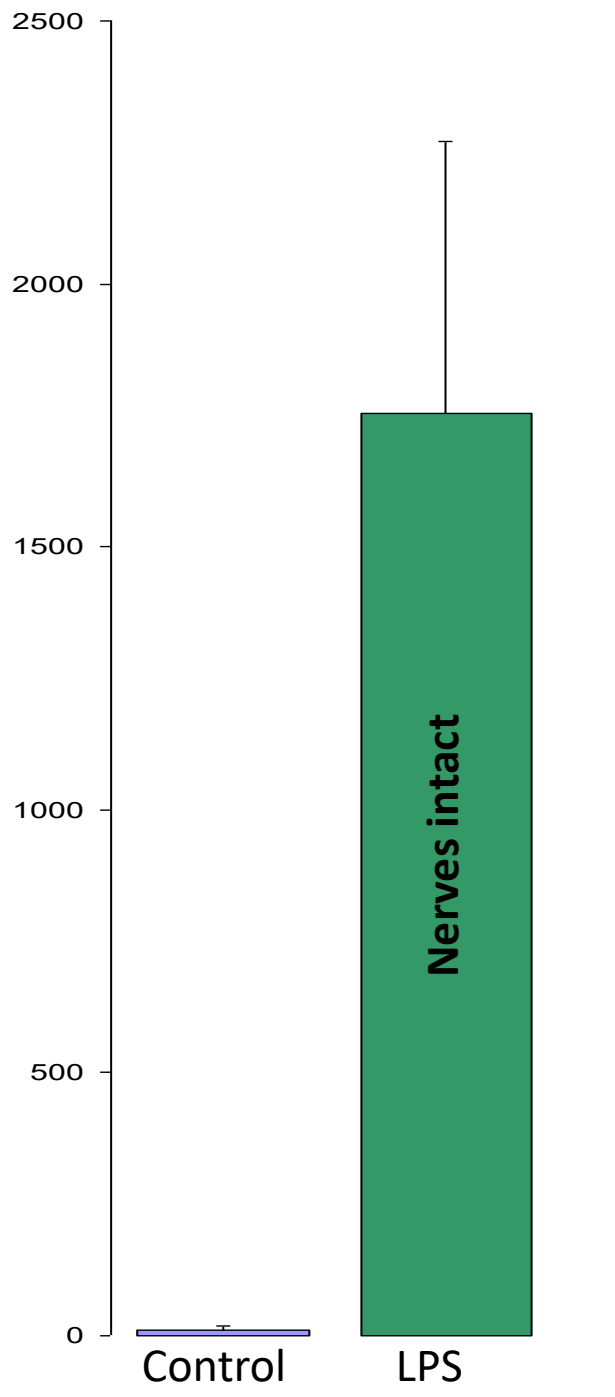
Plasma TNF $\alpha$   
pg/ml

2500  
2000  
1500  
1000  
500  
0

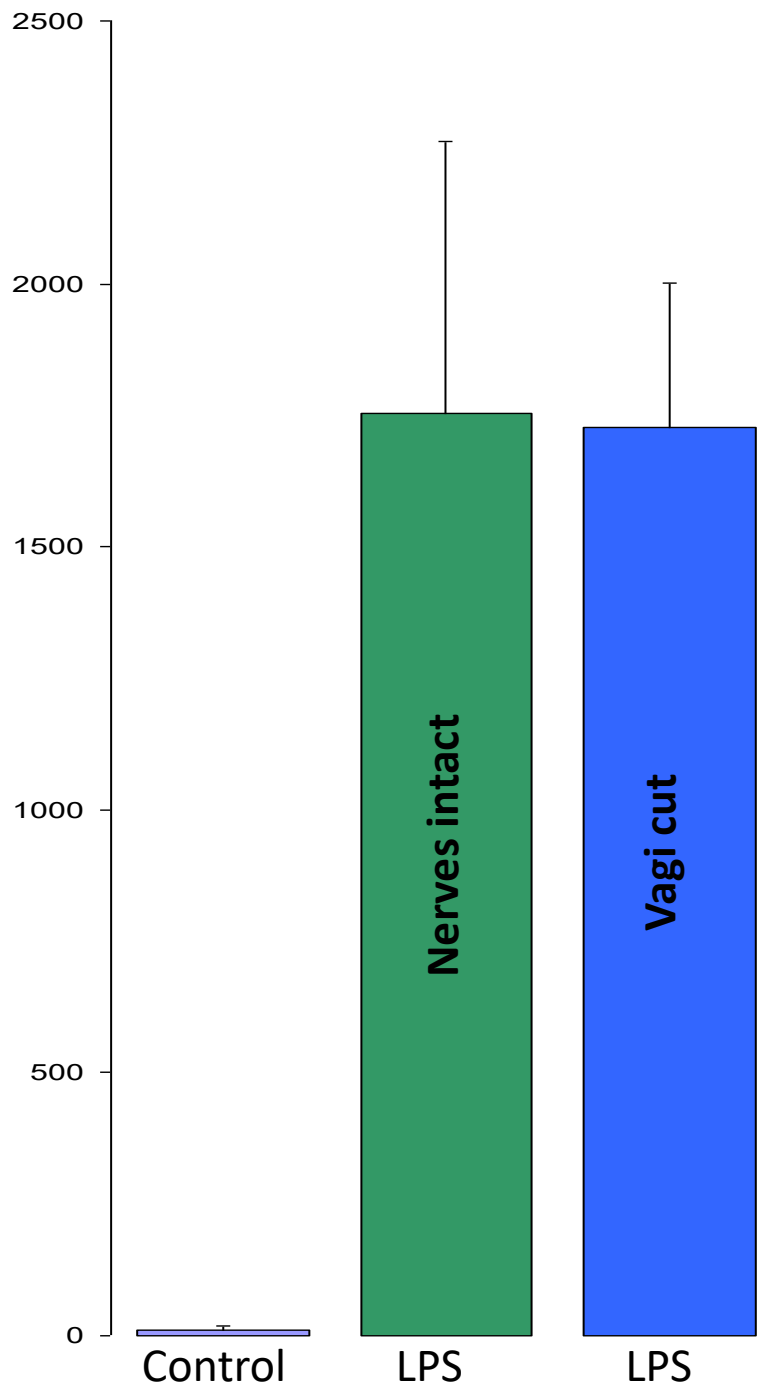
Control



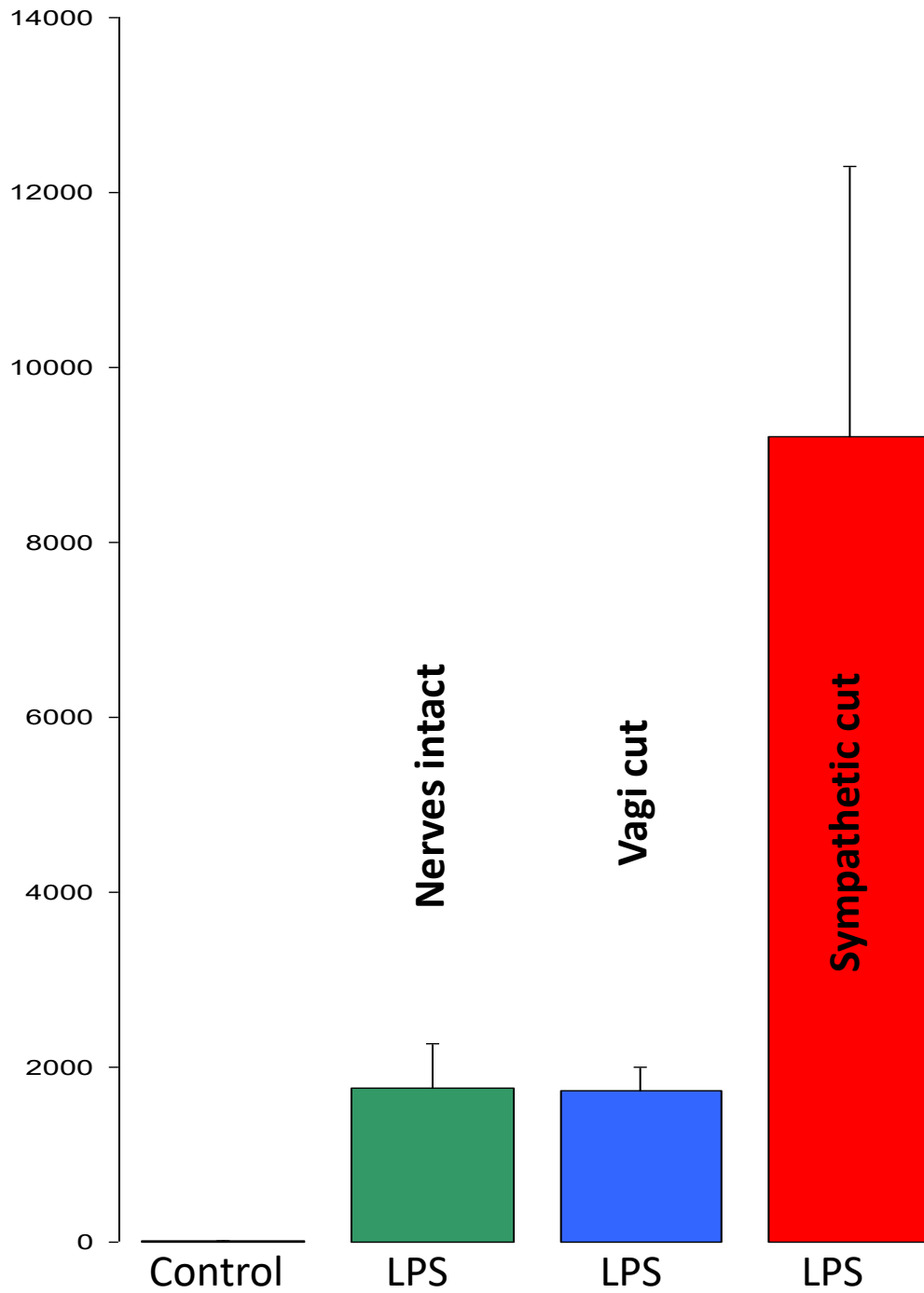
Plasma TNF $\alpha$   
pg/ml



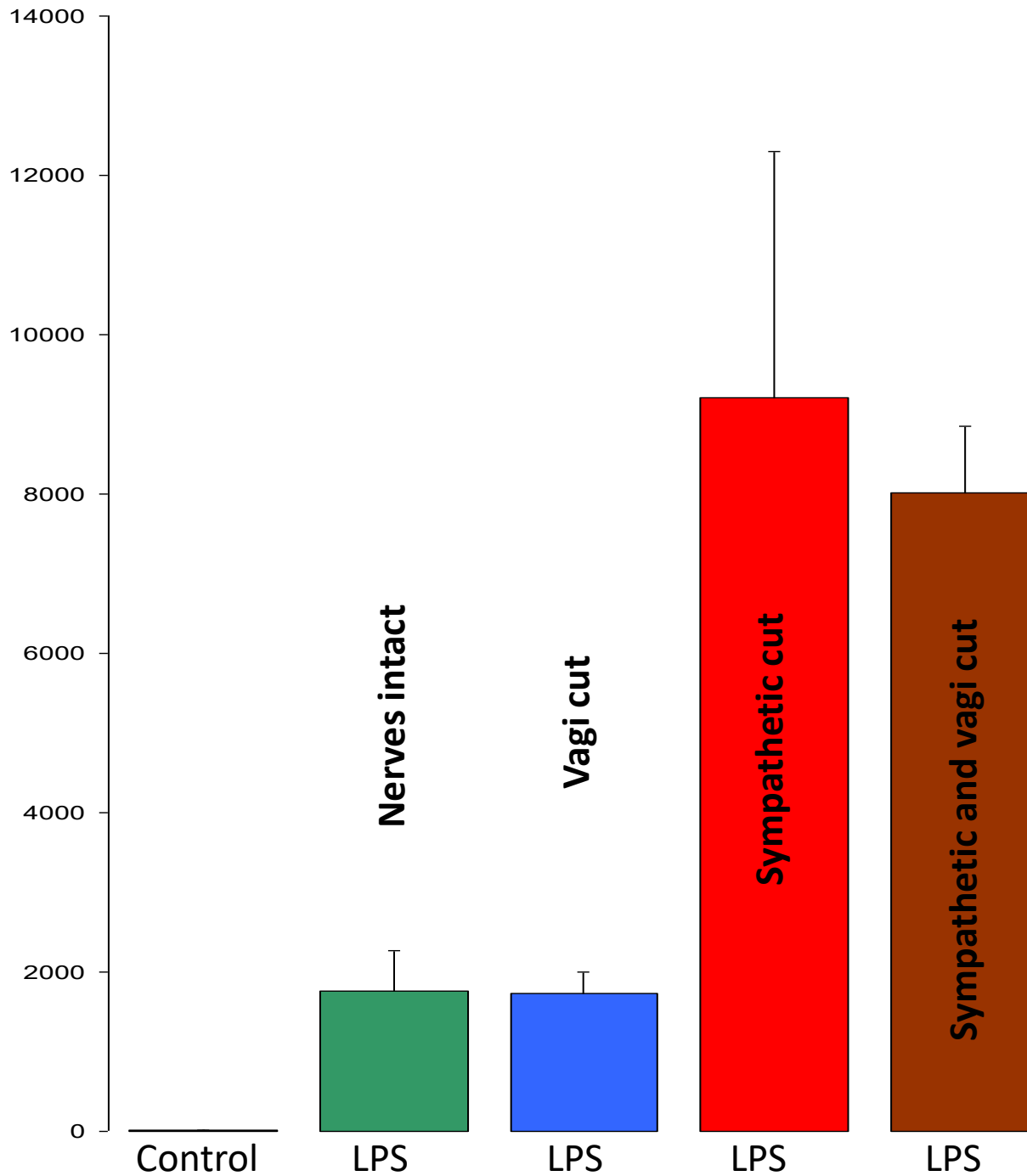
Plasma TNF $\alpha$   
pg/ml



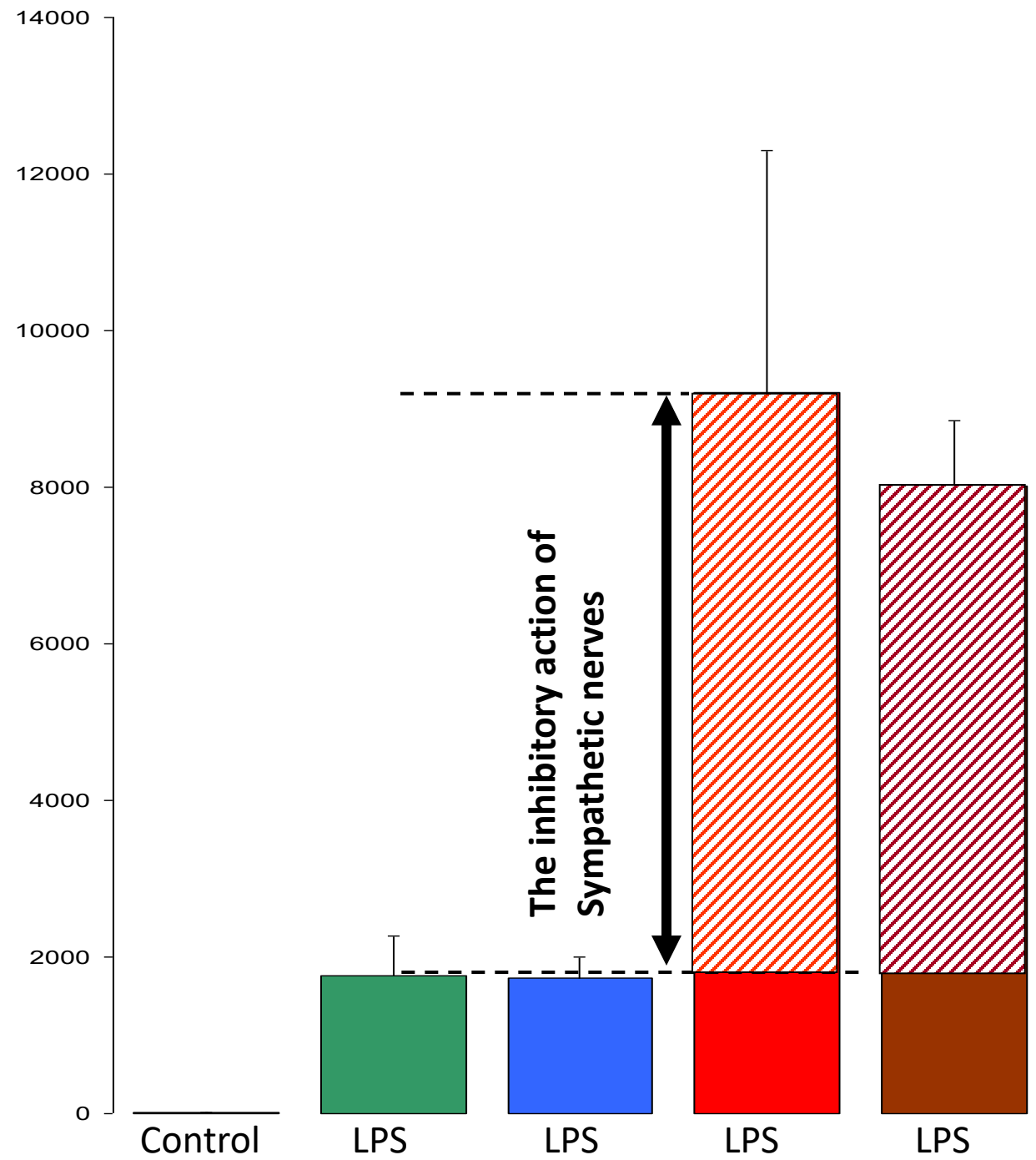
Plasma TNF $\alpha$   
pg/ml

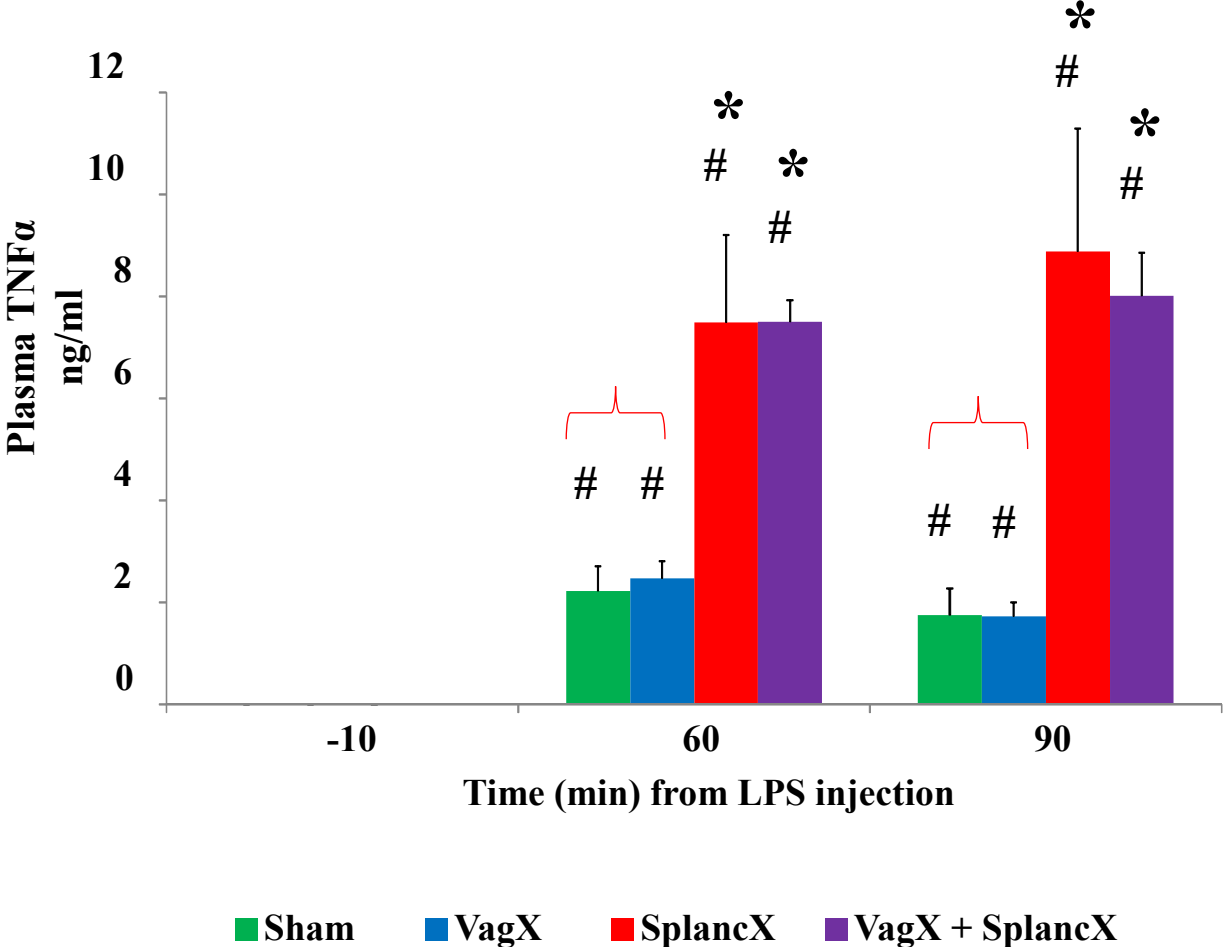


Plasma TNF $\alpha$   
pg/ml



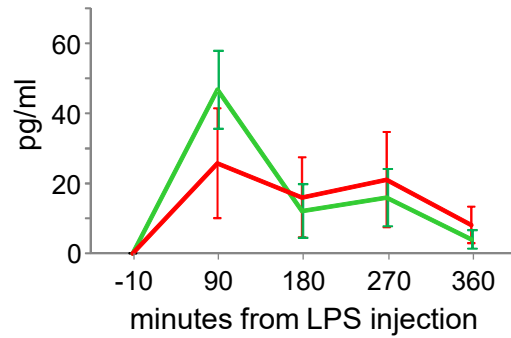
Plasma TNF $\alpha$   
pg/ml



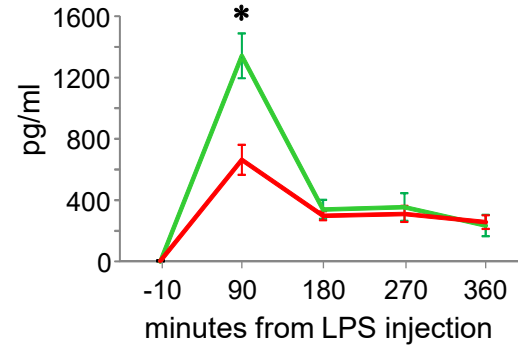


TNFα experiments

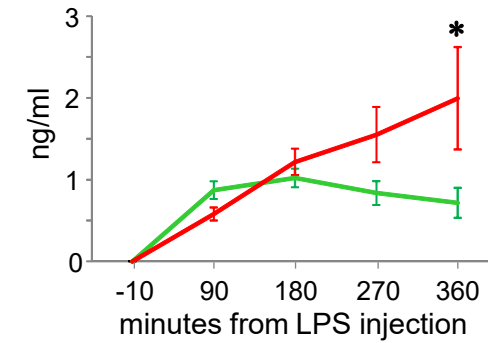
**Plasma IL-1 $\alpha$**



**Plasma IL-1 $\beta$**

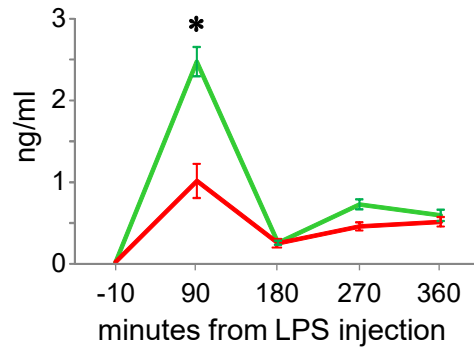


**Plasma IL-6**

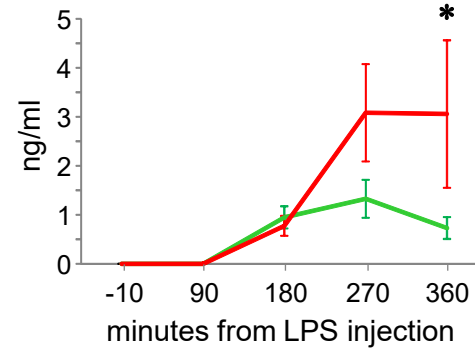


— sham  
— splancx

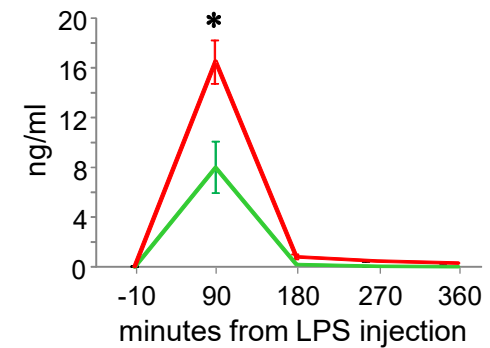
**Plasma IL-10  
(anti-inflammatory)**



**Plasma IFN- $\gamma$**



**Plasma TNF $\alpha$**




# Interpretation

The neural signals that damp down the release of  $\text{TNF}\alpha$  into the blood stream travel in sympathetic nerves, not the vagus

RESEARCH ARTICLE | *Neural control*

Anti-inflammatory reflex action of splanchnic sympathetic nerves is distributed across abdominal organs

Daive Martelli,<sup>1,2</sup> David G. S. Farmer,<sup>1</sup> Michael J. McKinley,<sup>1,2,3</sup>  Song T. Yao,<sup>1,4</sup> and Robin M. McAllen<sup>1</sup>

<sup>1</sup>Florey Institute of Neuroscience and Mental Health, Parkville, Victoria; <sup>2</sup>Neuromotor Science, University of Bologna, Bologna, Italy; <sup>3</sup>Department of Psychology, Victoria, Australia; and <sup>4</sup>Florey Department of Neuroscience and Mental Health, Victoria, Australia

