The immune system

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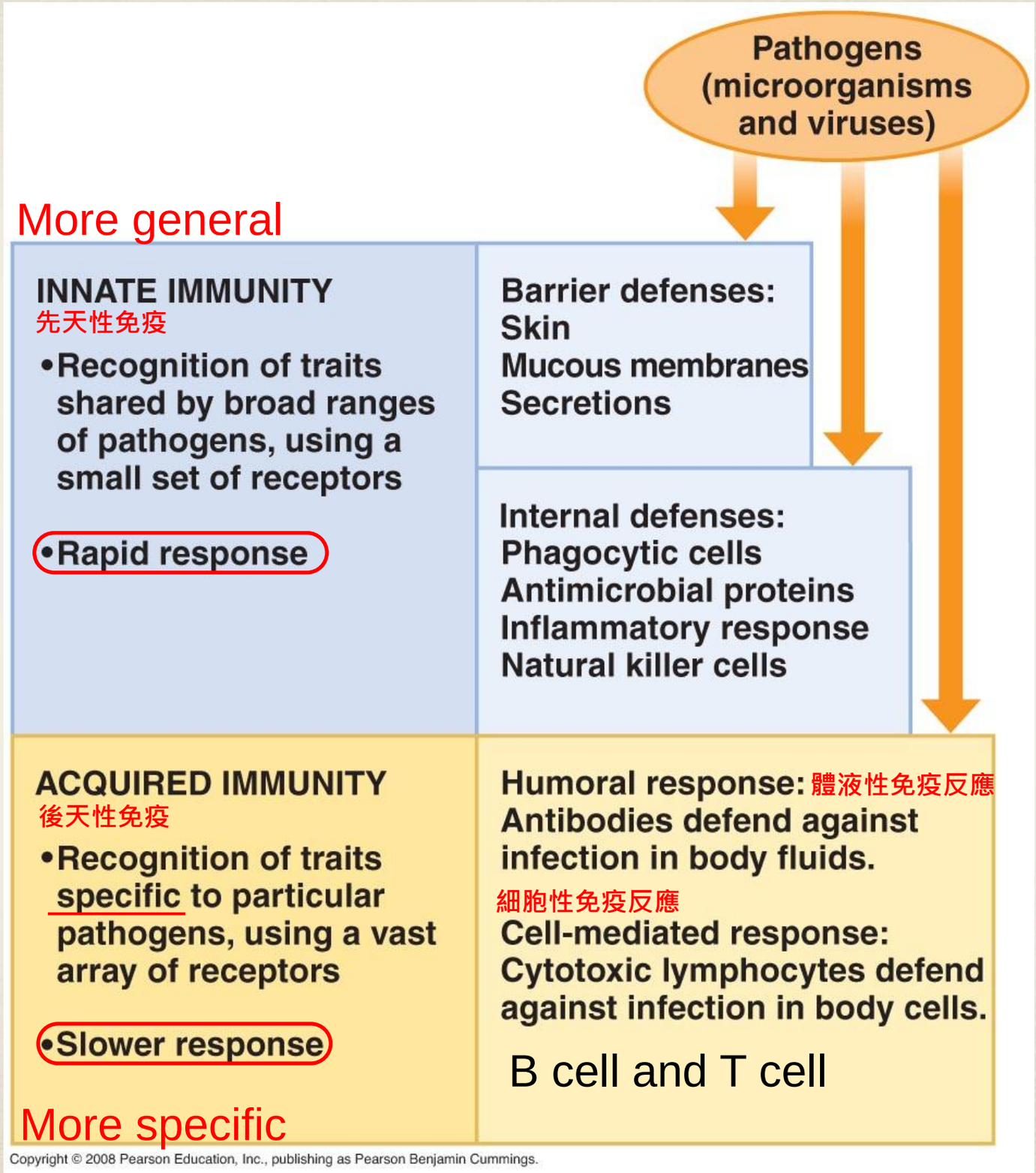
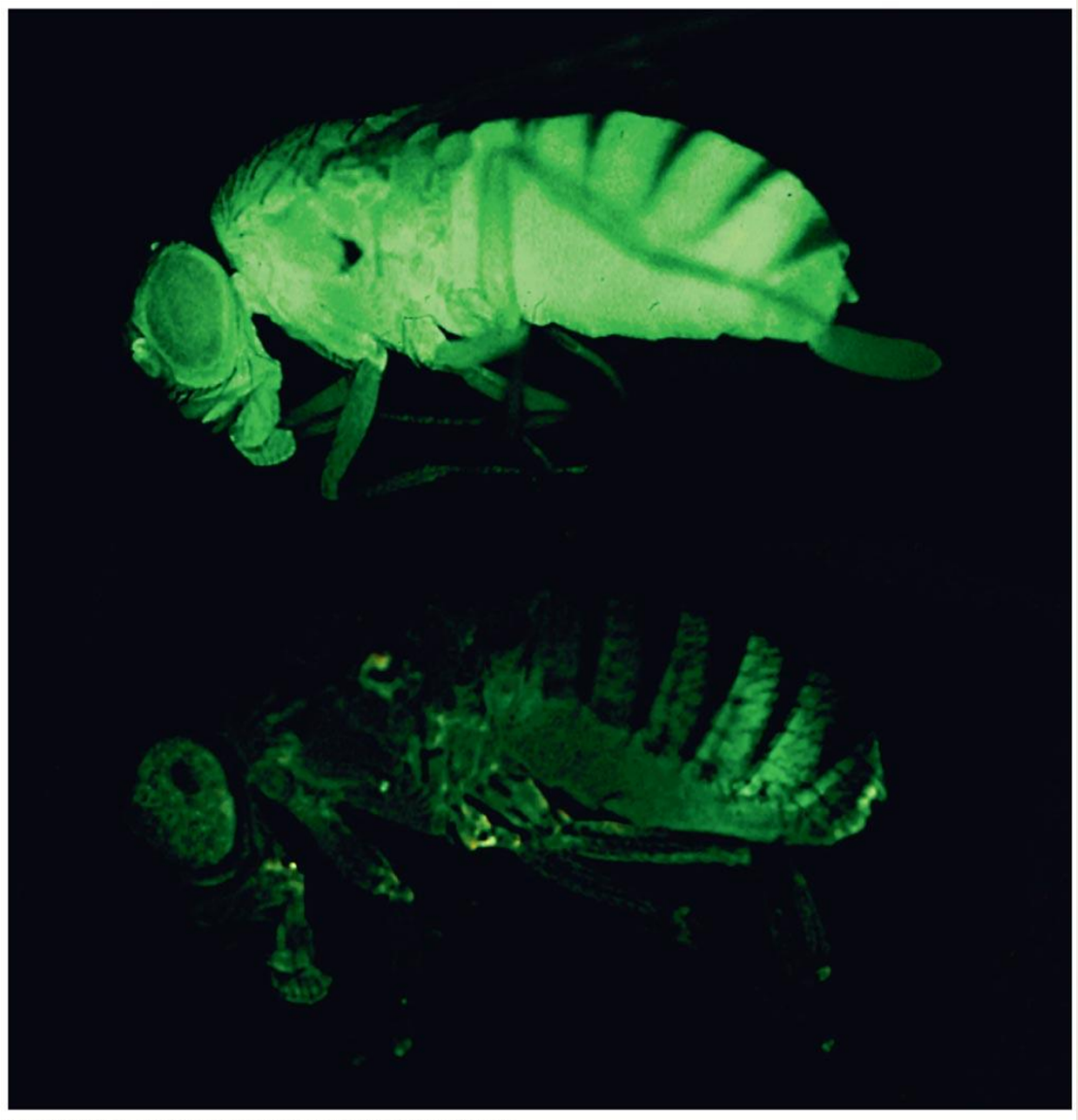
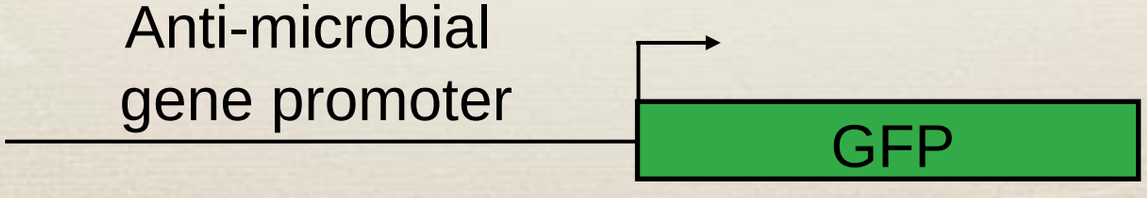
Overview of the immune response



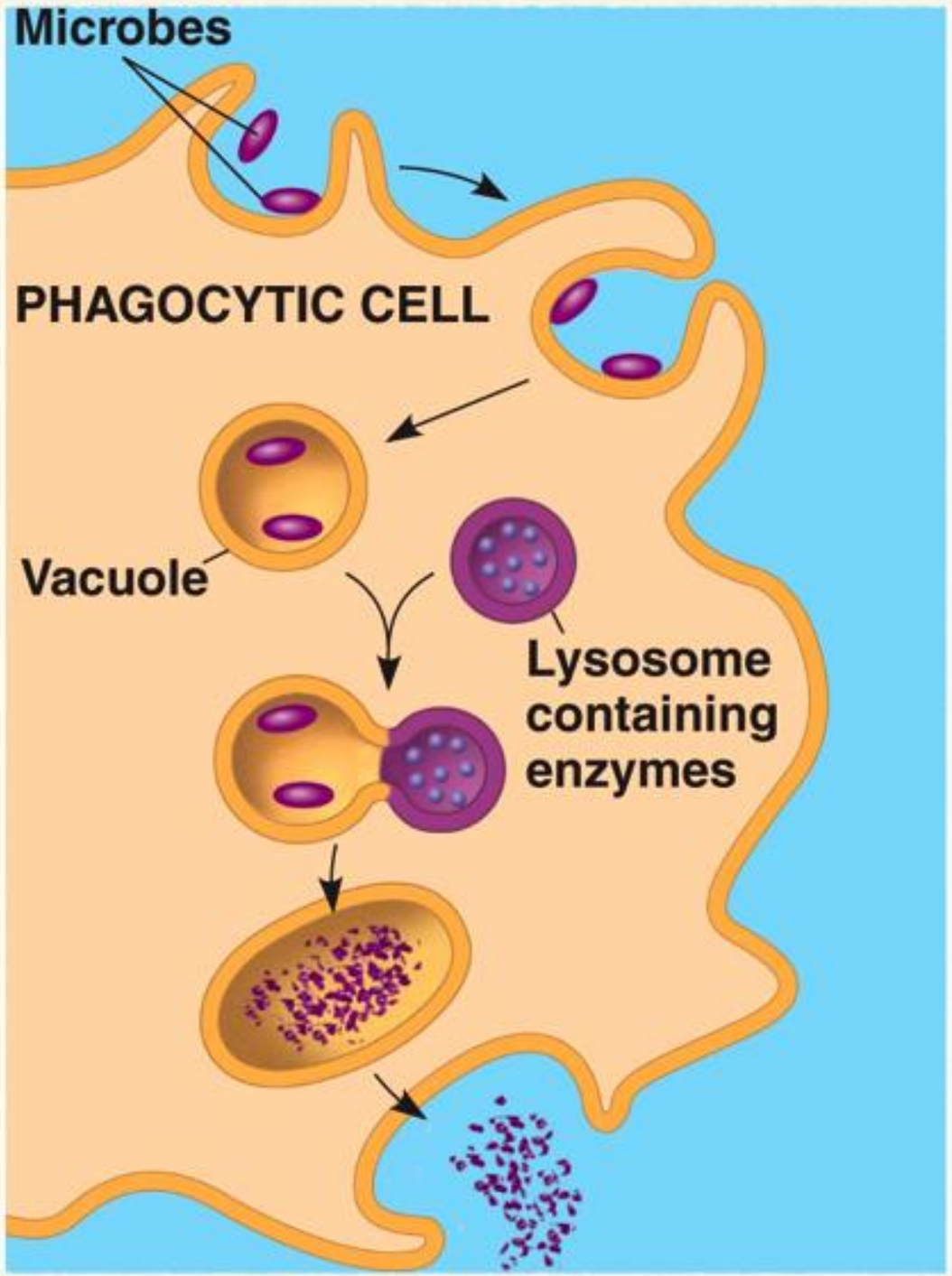
Innate immunity of invertebrate



- Fruit flies are engineered to express the GFP
- The fly on top is injected with bacteria, whereas the fly on the bottom is not infected
- Only the infected fly activates antimicrobial peptide genes, which expresses GFP leading to glows of green fluorescent light



Phagocytosis 噬菌作用

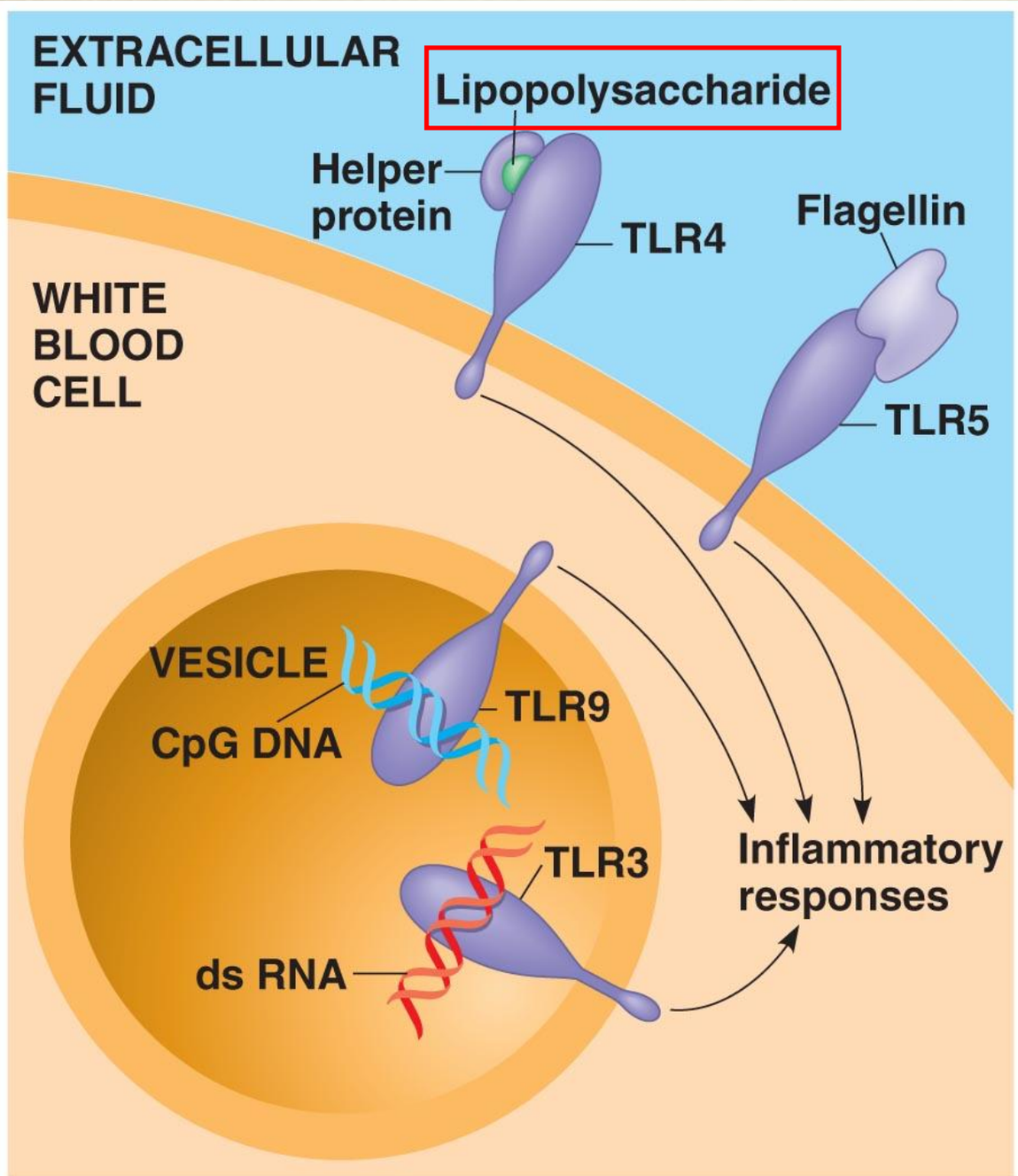


- Hemocytes (血球細胞) carried out an internal immune response called phagocytosis, which ingests and digests bacteria and other foreign substances
- Hemocytes also secret anti-microbial peptides that kill or inactivate microbes by disrupting their plasma membranes

Vertebrate innate immunity

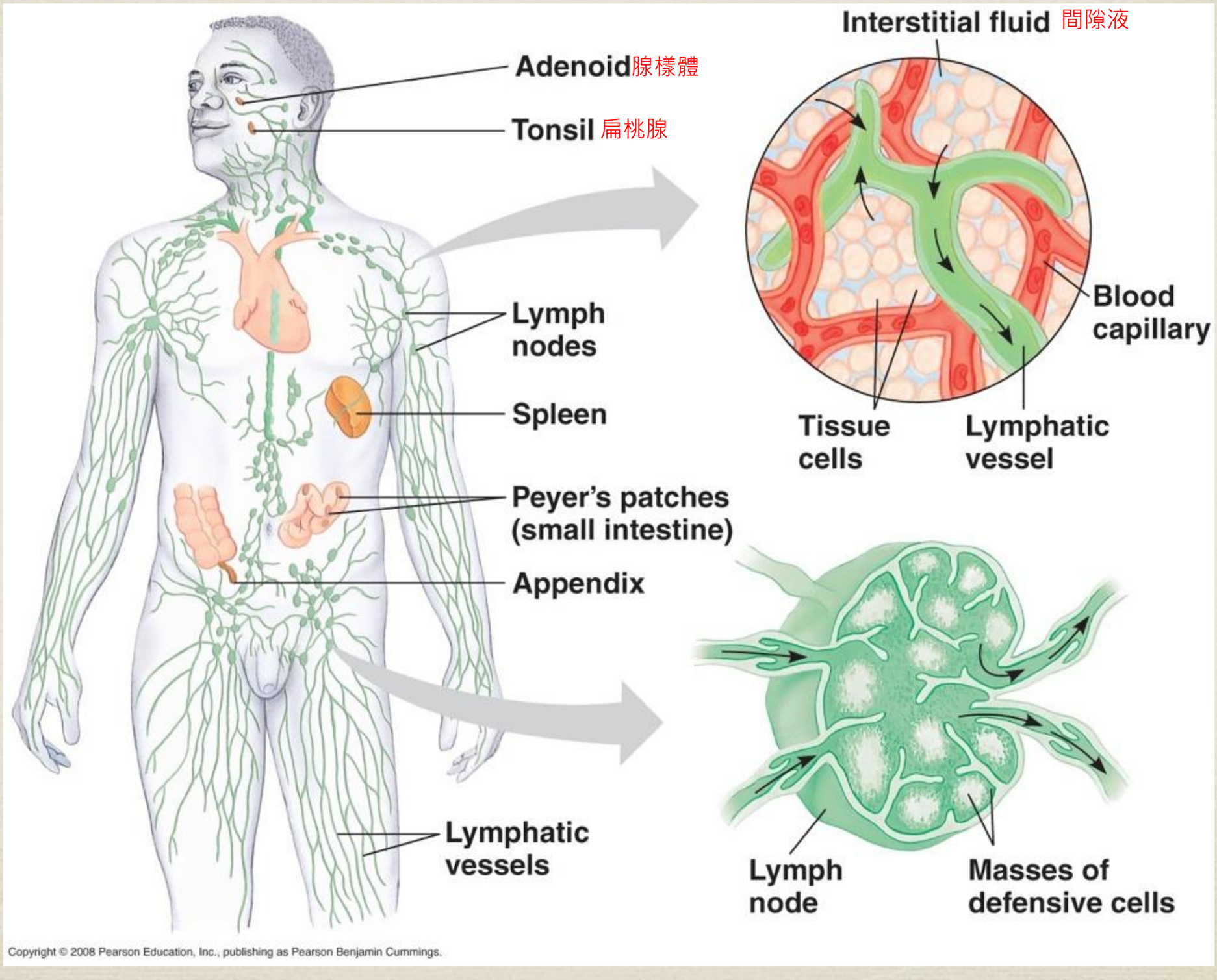
- Barrier defense
  - skin (epithlial cells)
  - mucous membrane (produce mucus)
  - lysozme (溶菌酶) in syliva and tears
  - body secretion creates an acidic environments
- Phagocytosis (吞噬作用)
- Anti-microbial peptides (抗菌胜肽)
- Inflammatory response (發炎反應)
- Natural killer cells (自然殺手細胞)

Vertebrate innate immunity



- Phagocytic white blood cells (leukocytes) uses cell surface receptor (TLR) recognizes fragments of a particular set of pathogens
- Recognition by a TLR triggers a series of internal defenses, beginning with phagocytosis
- Mammalian phagocytotic cells involve neutrophils (嗜中性白細胞) and macrophages (巨噬細胞)

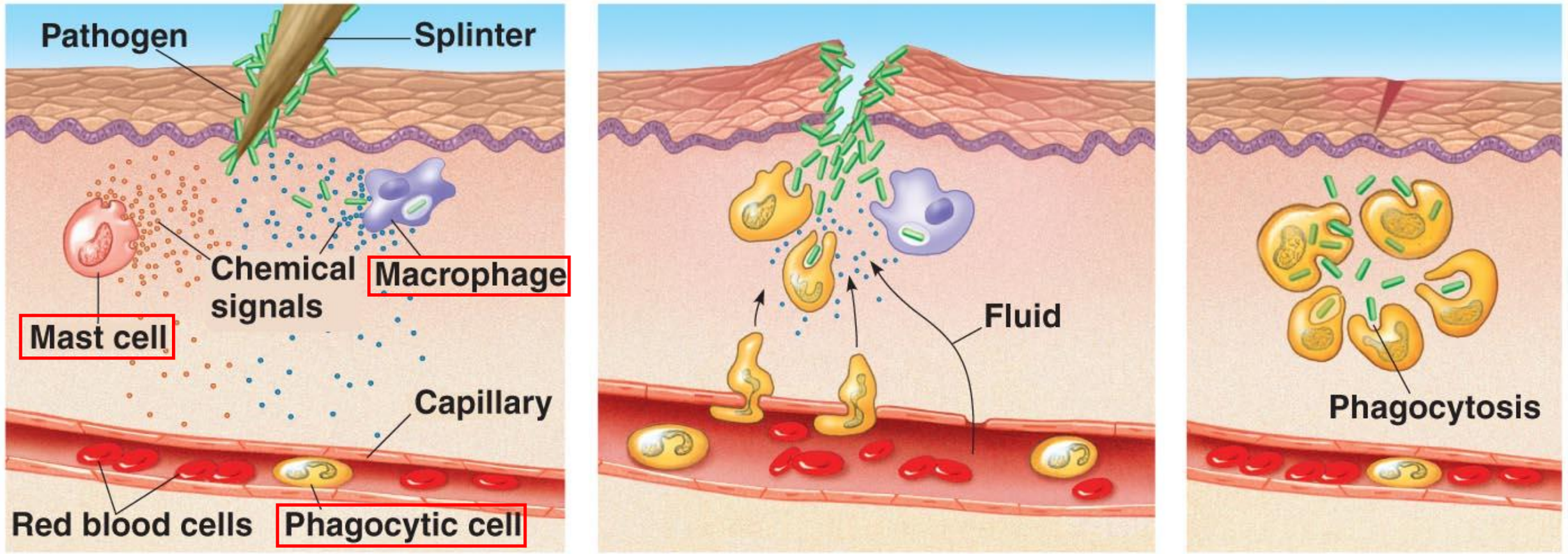
The human lymphatic system



Antimicrobial peptides and proteins

- Complement proteins (補體蛋白) damage pathogens by disrupting membrane integrity
- Interferons (干擾素) are unique to vertebrate immune system
  - defense against viral infection
  - secreted by virus-infected cells, which induce uninfected cells to produce substance to inhibit viral production
  - Some leukocytes secrete a different type of interferon that activates macrophages
  - mass-produced by recombinant DNA technology for treating certain viral infections

The inflammatory response



Mast cells (肥大細胞) secrete inflammatory signal that triggers blood vesicle dilation

Increased vessel permeability allows phagocytic cells (噬菌細胞) to enter injured tissue and helps deliver antimicrobial peptides

Formation Pus (膿) containing leukocyte, dead microbes and cell debris

- Activated macrophages release additional signals that promote blood flow to site of injury, causing the redness and heat typical of inflammation
- Fluid leak from blood into neighboring cells result in the characteristic swelling

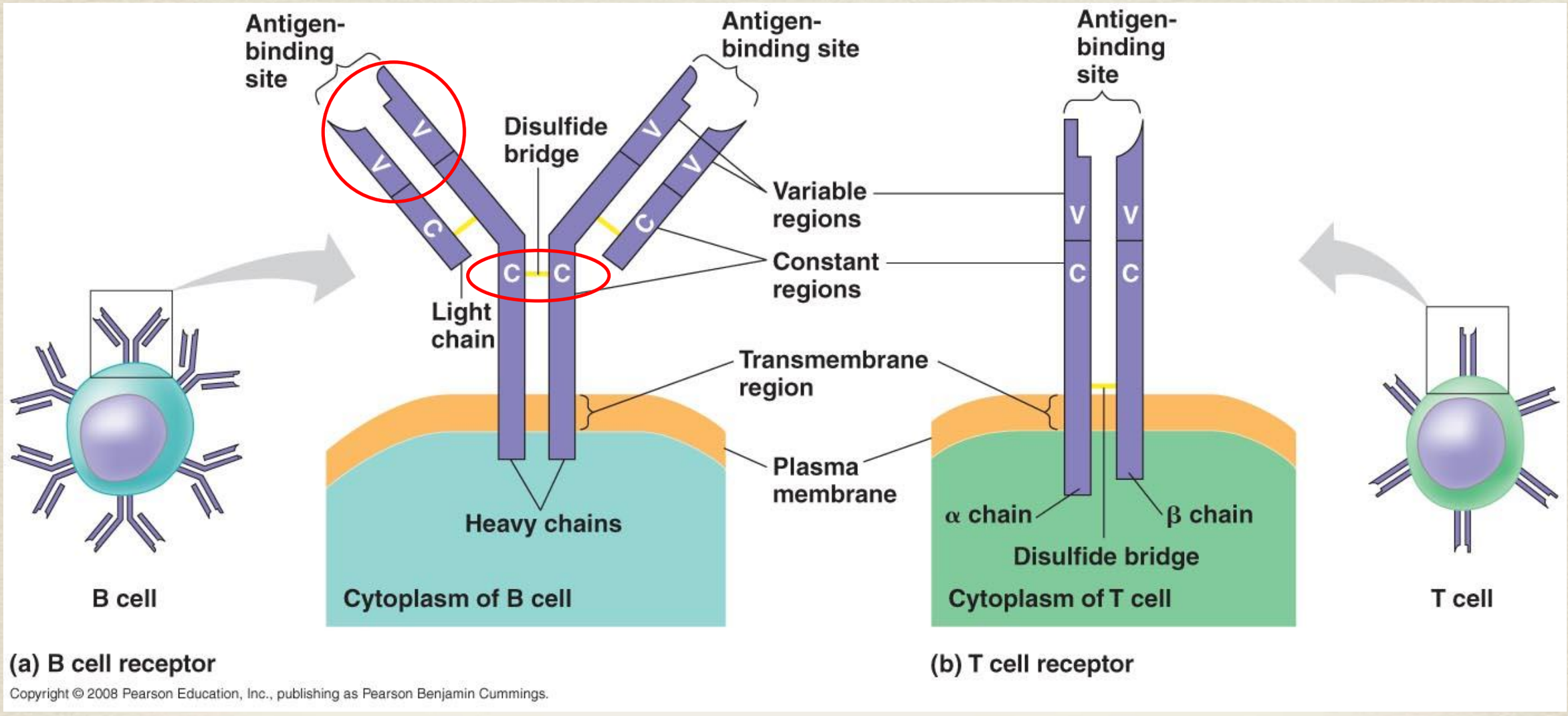
Natural killer (NK) cells

- NK cells recognise and eliminate certain diseased cells in vertebrates
- Following viral infection or conversion to a cancerous state, cells stop express surface protein called class I MHC molecule
- The NK cells recognize such cells and release chemical leading to cell death, inhibiting further spread of virus or cancer

Acquired immunity (後天性免疫)

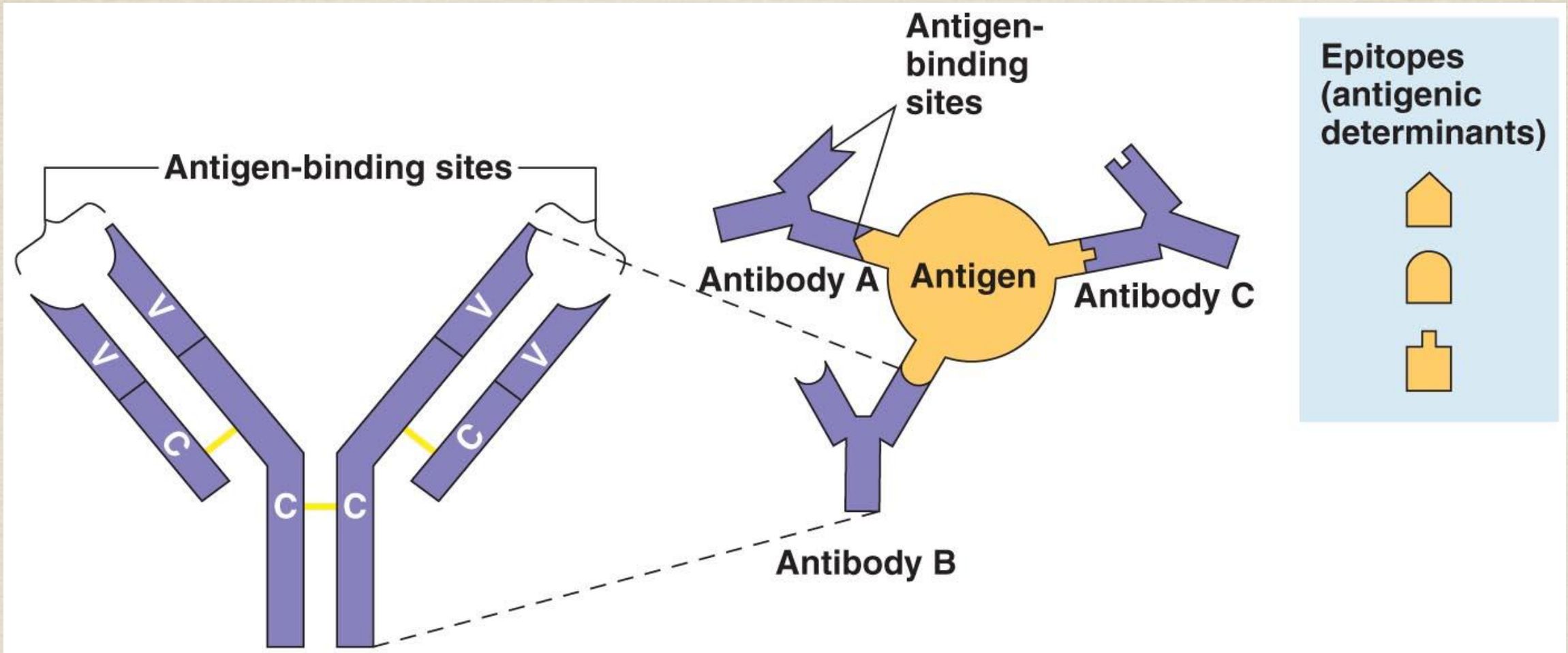
- Mediated by lymphocytes including B cells (matured in bone marrow) and T cells (matured in thymus 胸腺)
- Both types of cells contribute to immunological memory, an enhanced response to a foreign molecules encountered previously
- After infection, signals from phagocytic cells carrying out innate immune response activates lymphocyte, setting stage for the slower-developing acquired immune response
- the phagocytic cells secrete cytokines (細胞激素) to help recruit and activate lymphocytes

Antigen receptors on lymphocytes



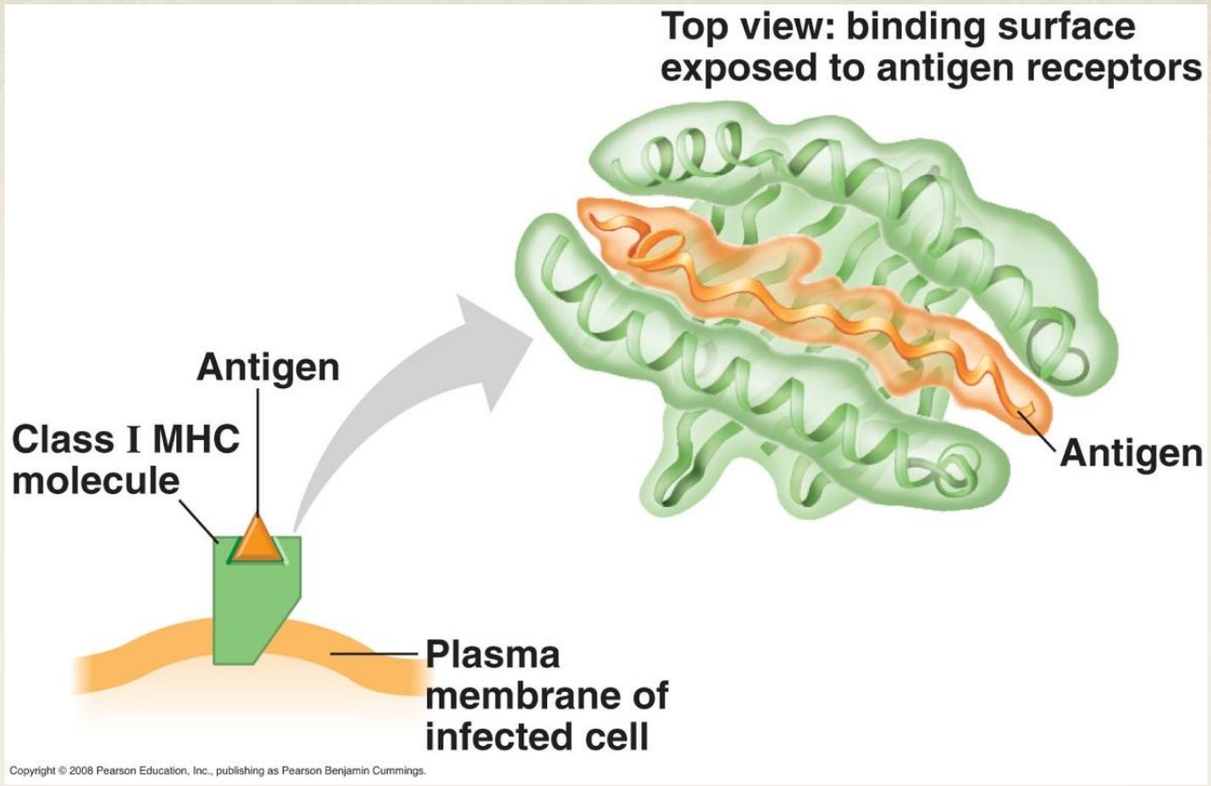
- Each B and T cells has surface receptors, which can recognise and bind a particular foreign molecules (antigen)
- There are millions of lymphocytes in the body that differ in their surface receptors

Antibody



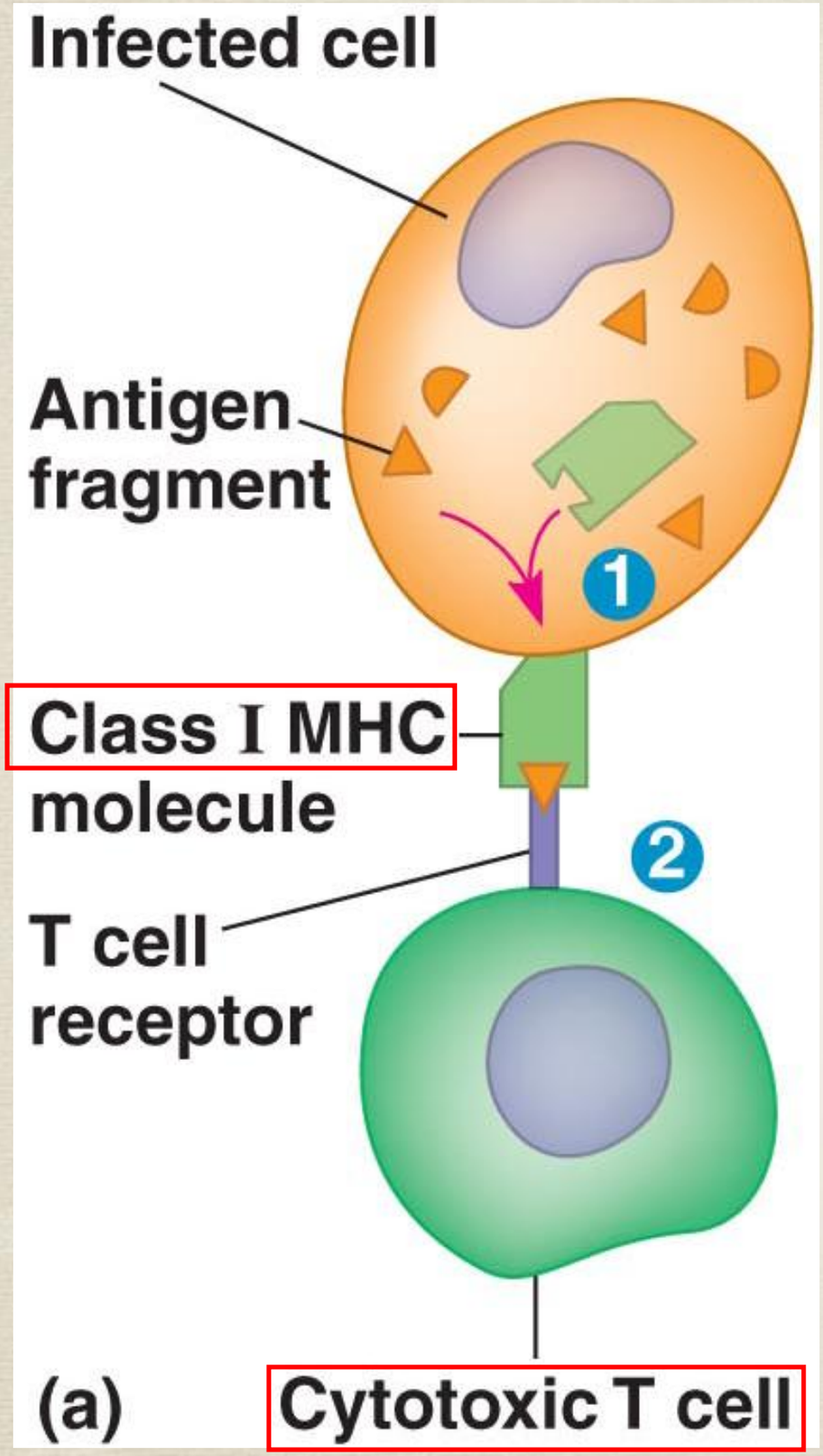
- B cells sometimes produce plasma cells that secrete a soluble form of the antigen receptor, called antibody
- Antibodies recognise just a small accessible portion of an antigen, called epitope or antigenic determinant
- A single antigen has several different epitopes

Antigen presentation by an MHC molecule



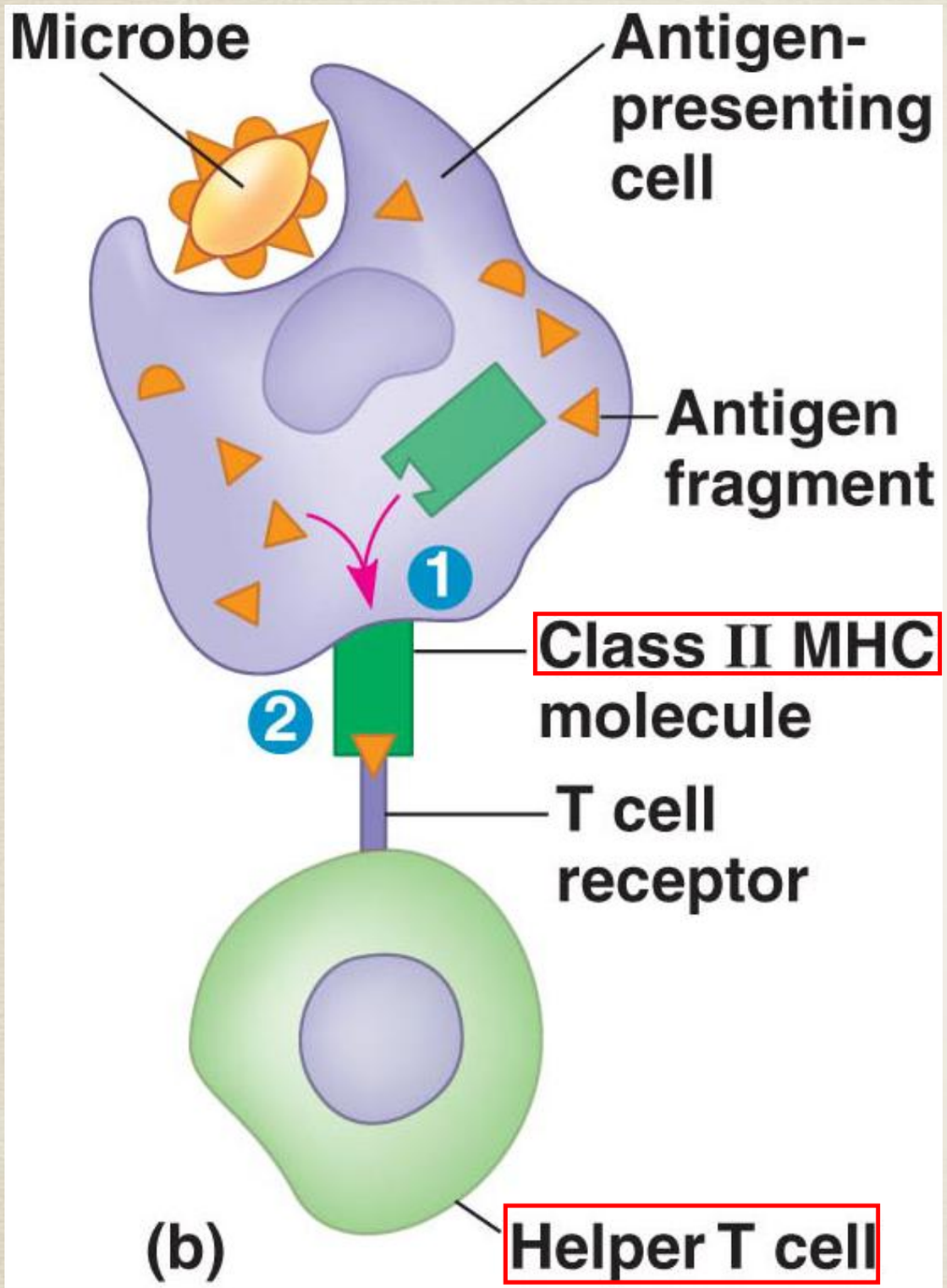
- T cells receptors only bind to antigen fragment that are presented on the surface of host cells
- Each of the gene in a group called major histocompatibility complex (MHC) produces a host cell protein that can present an antigen fragment to T cell receptors
- The interaction of an antigen fragment presented by an MHC molecule with a T cell receptor is a central event in acquired immunity

Class I MHC molecules



- Class I MHC are found on almost all cell types
- A fragment of foreign protein inside the cell associates with MHC is transported to the cell surface
- Class I MHC displaying bound peptide antigens are recognised by T cell receptor on cytotoxic T cells

Class II MHC molecules

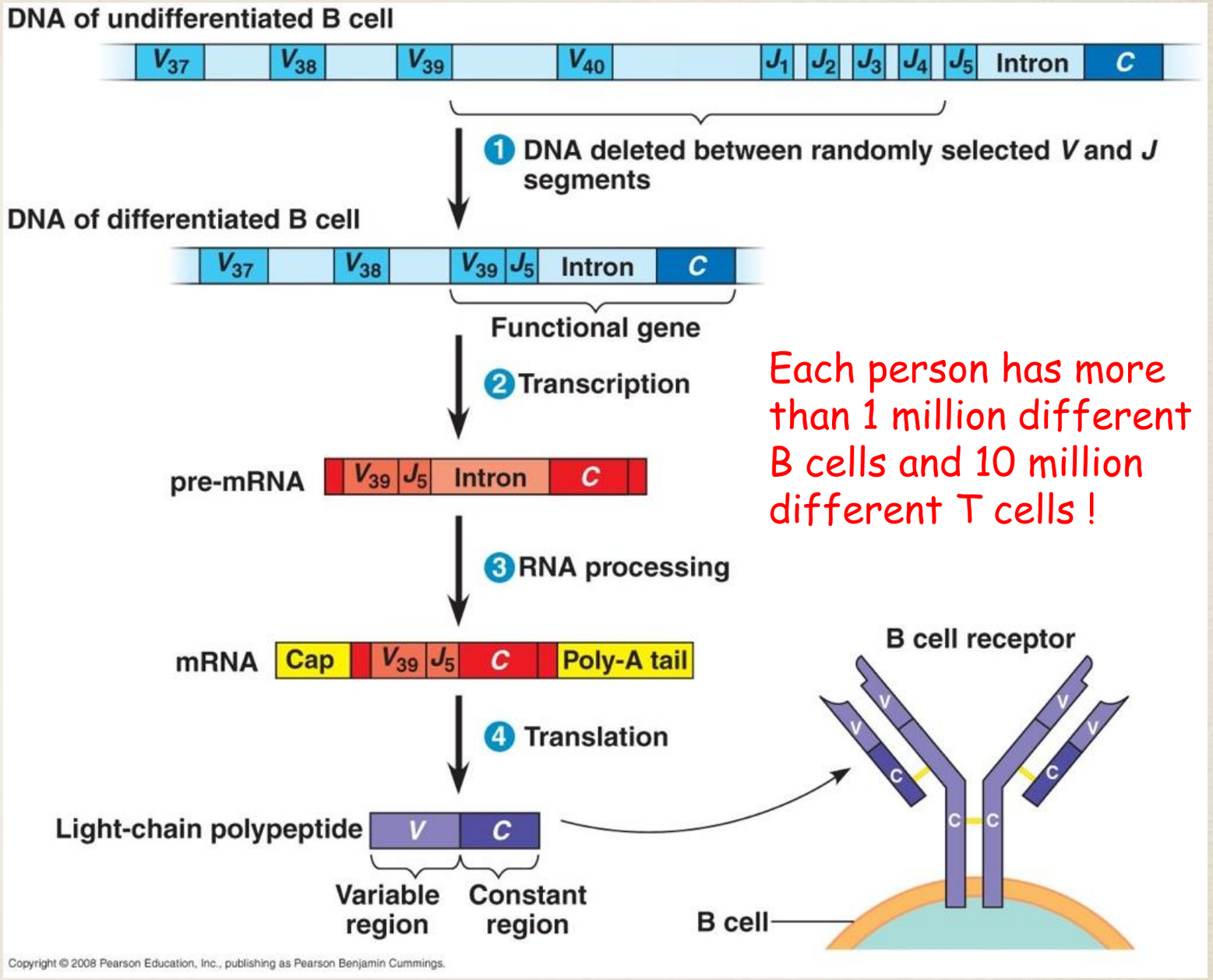


- Class II MHC are expressed in antigen-presenting cells, including dendritic cells (樹突細胞), macrophages and B cells
- Class II MHC typically bind peptide derived from foreign materials that have been internalized and fragmented via phagocytosis or endocytosis
- The antigen-presenting cells display antigen for recognition by cytotoxic and helper T cells

Generation of lymphocyte diversity

The light chain of a receptor is assembled from 3 pieces: variable (V), joining (J) and constant (C) segments

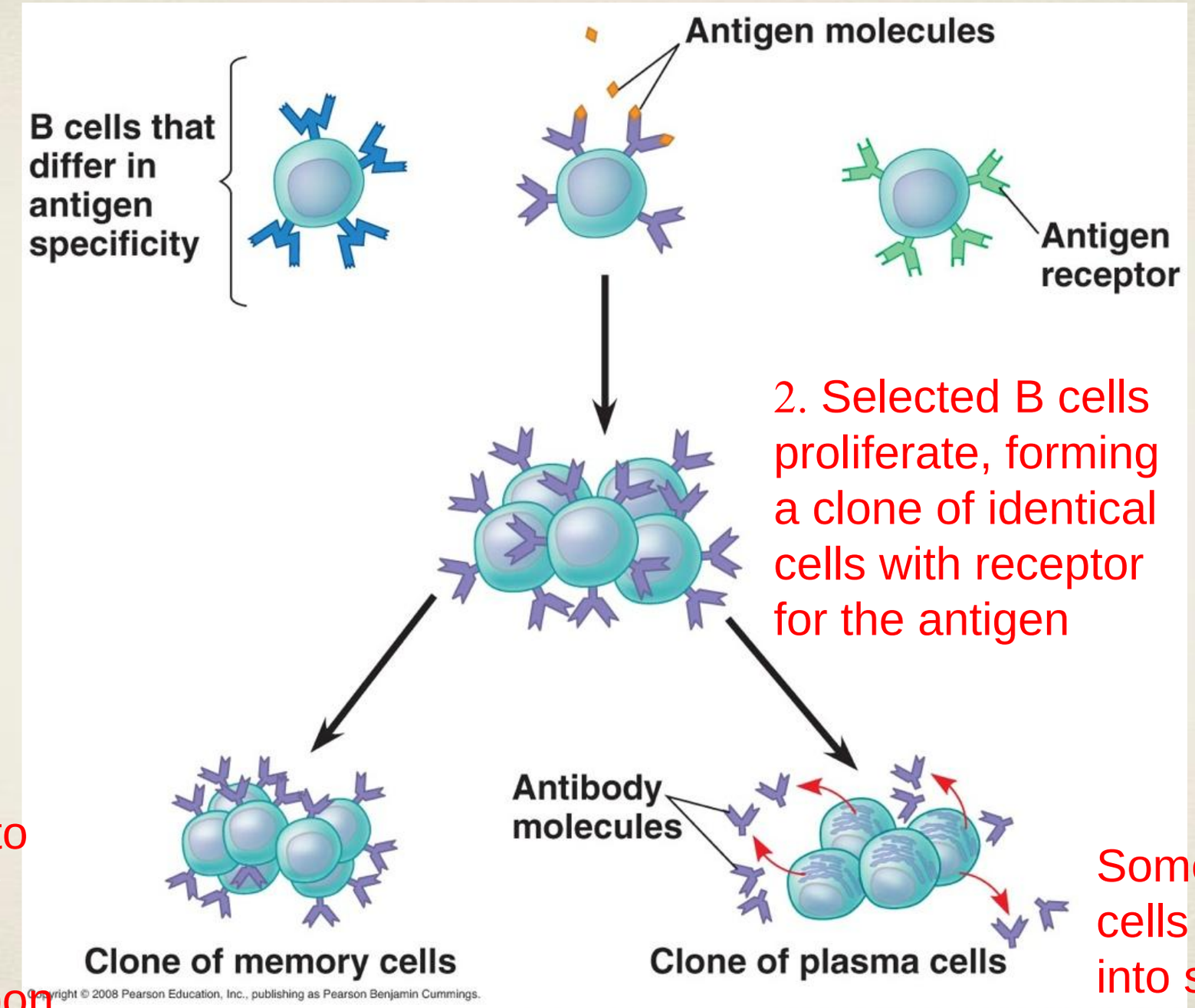
DNA sequence reveal that the light chain gene contains a single C segment, 5 J gene segments and 40 V gene segments, which could produce 200 different molecules



Each person has more than 1 million different B cells and 10 million different T cells !

Amplifying lymphocytes by clonal selection

1. Antigen binds to the receptor

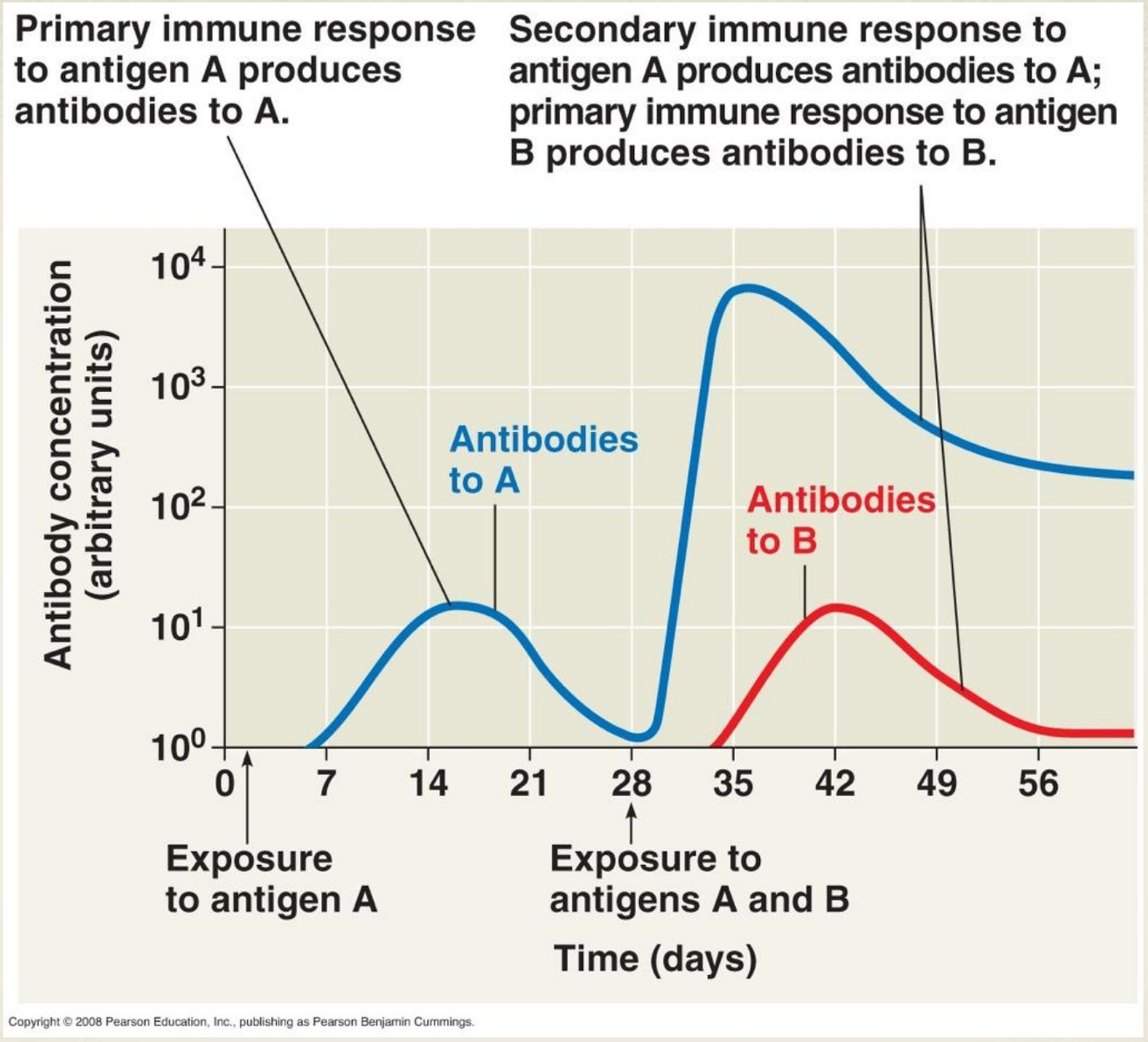


2. Selected B cells proliferate, forming a clone of identical cells with receptor for the antigen

Some proliferating cells developed into long-lived memory cells that can respond rapidly upon subsequent exposure to the same antigen

Some proliferating cells developed into short-lived plasma cells that secrete antibody

The specificity of immunological memory

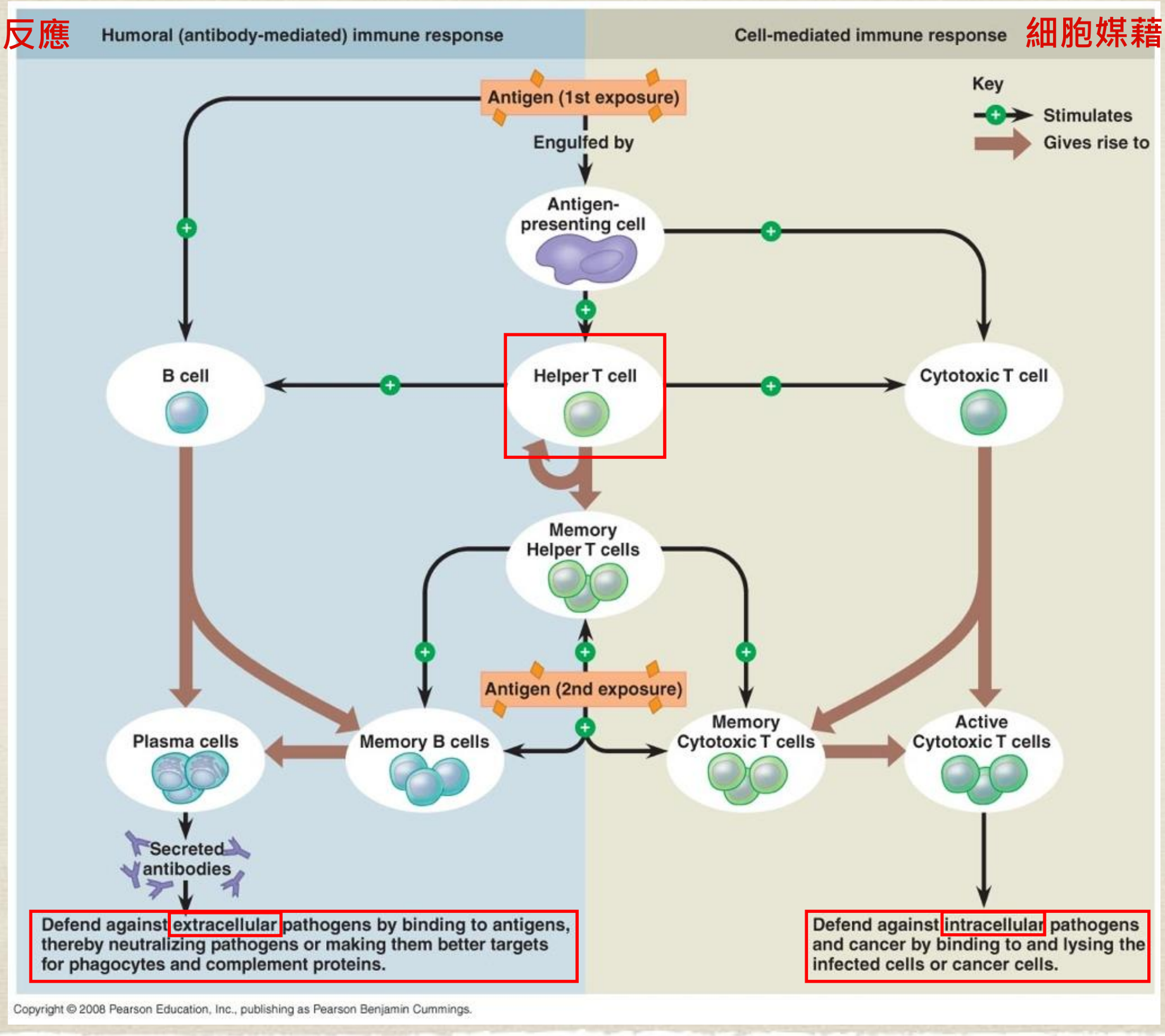


- Long-lived memory cells generated in the primary response to antigen A produce an enhanced secondary response to the same antigen but don't affect primary response to antigen B
- The secondary response is quicker and stronger

An overview of the acquired immune response

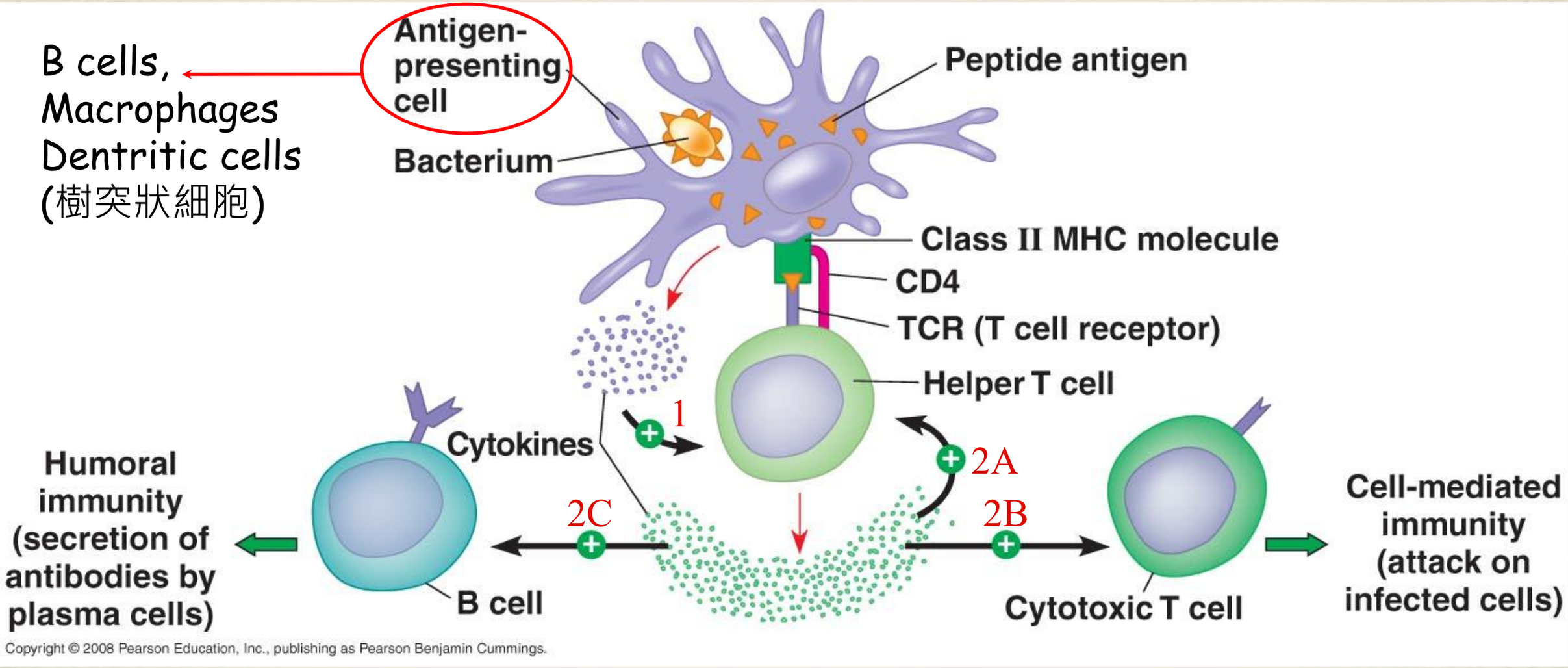
體液性免疫反應 Humoral (antibody-mediated) immune response

Cell-mediated immune response 細胞媒藉性免疫反應



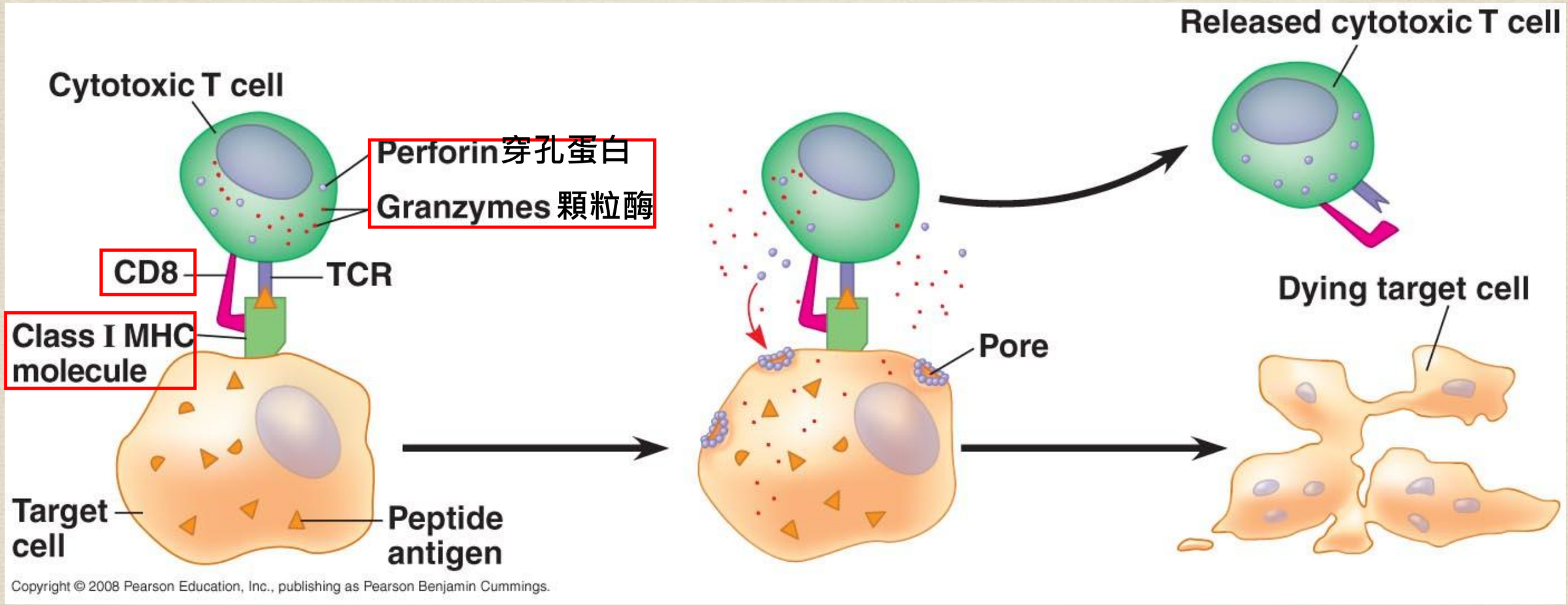
The central role of helper T cells

B cells,
Macrophages
Dentritic cells
(樹突狀細胞)



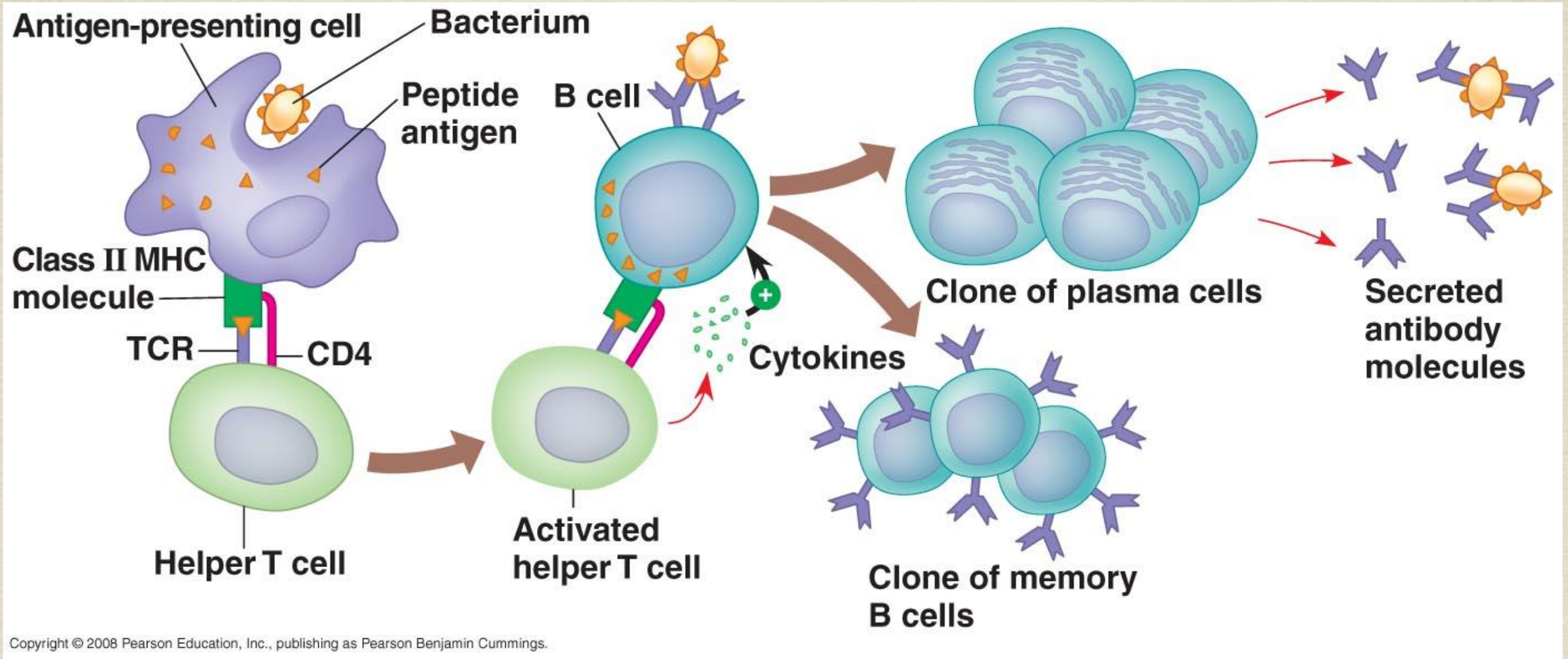
- Dendritic cells are important in triggering a primary immune response, whereas B cells mediate humoral response

The killing action of cytotoxic T cells



- The activated cytotoxic T cell binds to a class I MHC complex on a target cell with the aid of CD8
- Activated cytotoxic T cells release perforin that make pores in the target cell's membrane and enzymes promoting apoptosis leading to cell death

B cell activation in the humoral immune response



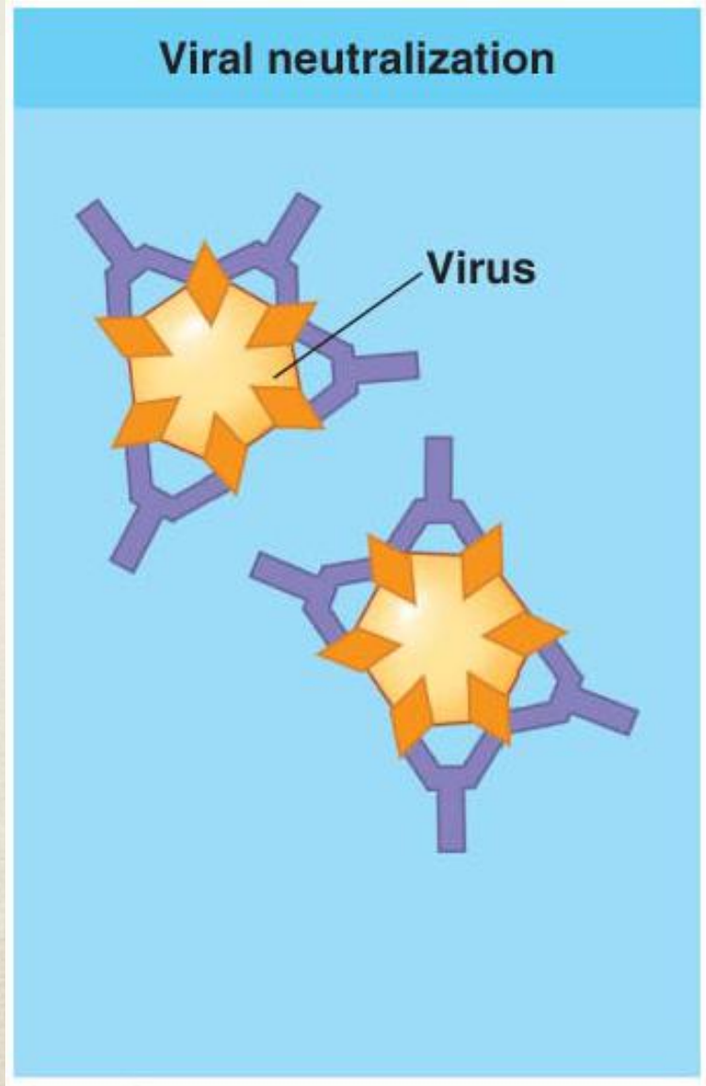
The interaction between TCR/CD4 in helper T cells and antigen/MHC complex activate helper T cells

B cells with MHC II antigen complex bind to activated T cells, which release cytokine to activate the B cells

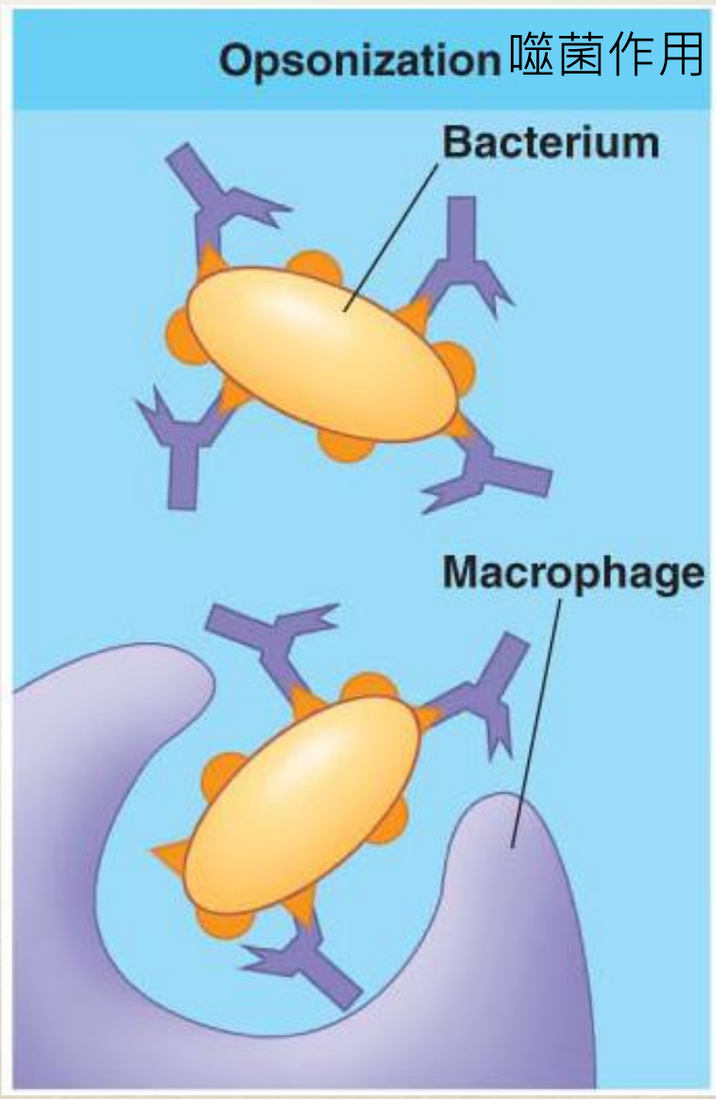
Activated B cells proliferate and differentiate into plasma cells and memory B cells

The role of antibodies in immunity

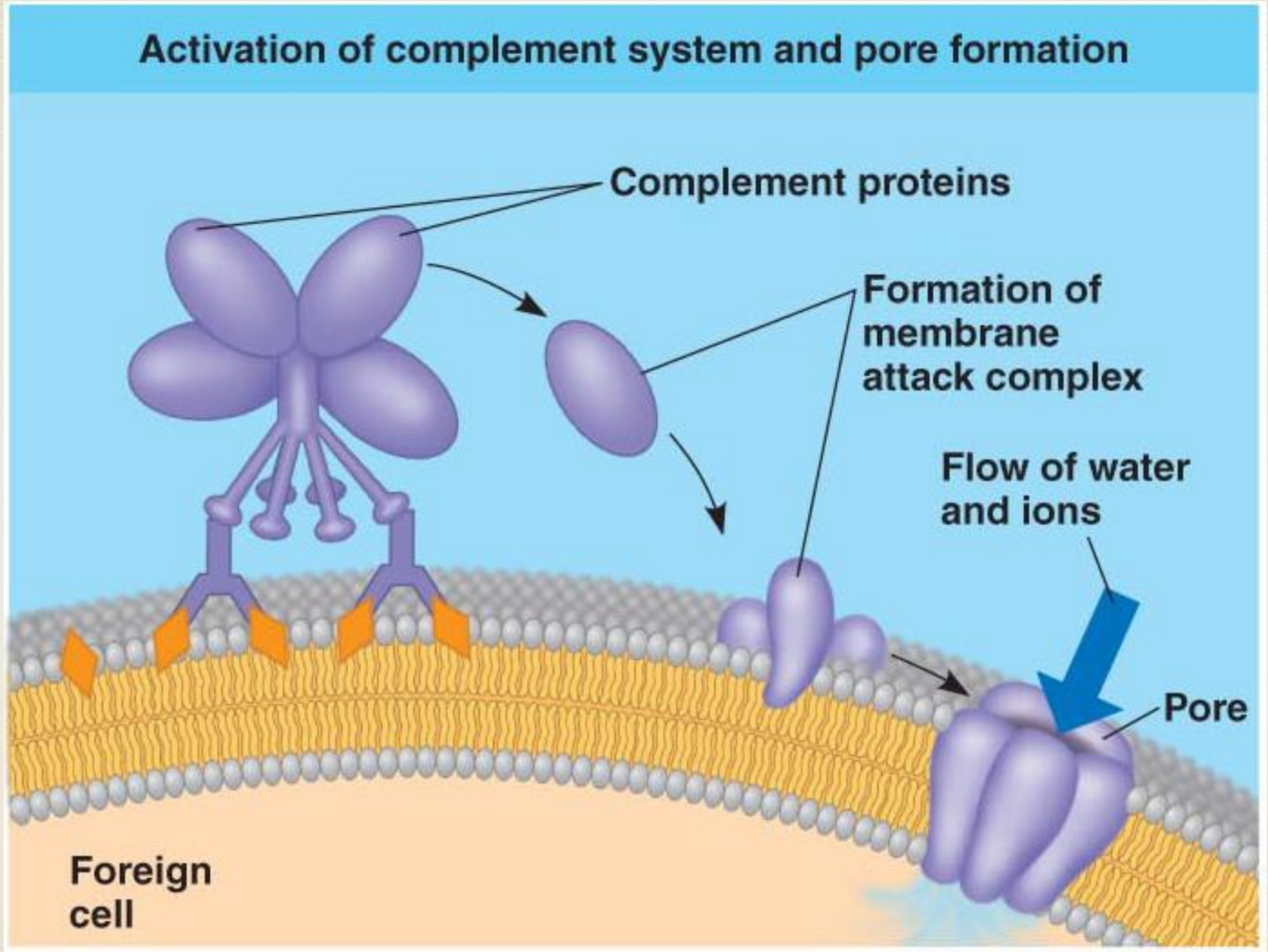
Antibody bound to antigens on the surface of a virus neutralise it by blocking its ability to bind to a host cell



Binding of antibody to antigen on the surface of bacteria promotes phagocytosis by macrophages



Activation of complement system



Binding of antibody to antigen on surface of foreign cell activates the complement system

Following activation, membrane attack complex form pores, leading to cell swell and lysis

Active and passive immunisation

- Active immunity: in response to infection, clones of memory cells form
- Passive immunity: the antibodies provided by the mother to protect against microbes that have never infected the newborn
- Vaccination: both active and passive immunity can be induced artificially by immunisation, which enhance the immune response

- Vaccine can be made from many resources to induce primary immune response
- An encounter of the pathogen from which the vaccine is derived triggers a rapid and strong secondary response

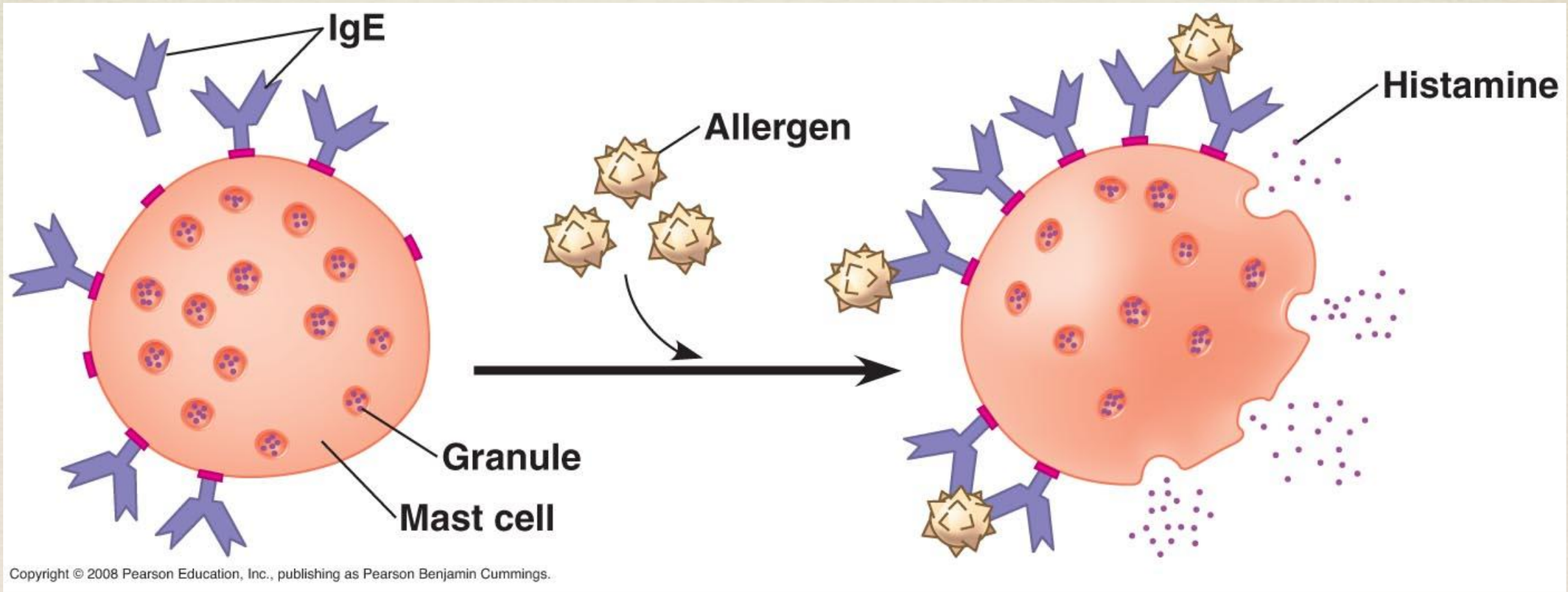
Autoimmune diseases (自體免疫) and immunodeficiency (免疫缺乏)

• Autoimmune disease: the immune system turns against particular molecules of the body (loss of self-tolerance)
- systemic lupus erythematosus (紅斑性狼瘡)
- rheumatoid arthritis (類風濕性關節炎)
- multiple sclerosis (多發性硬化症)

• Immunodeficiency is a disorder in which the ability of an immune system to protect against pathogens is defective
-AIDS caused by HIV, which both escapes and attacks acquired immune system
- HIV persists are helped by antigenic variation and latency

•The immune system is suppressed by certain cancer
- Hodgkin's lymphoma (霍奇金病淋巴瘤)

Disruptions in immune system - allergies



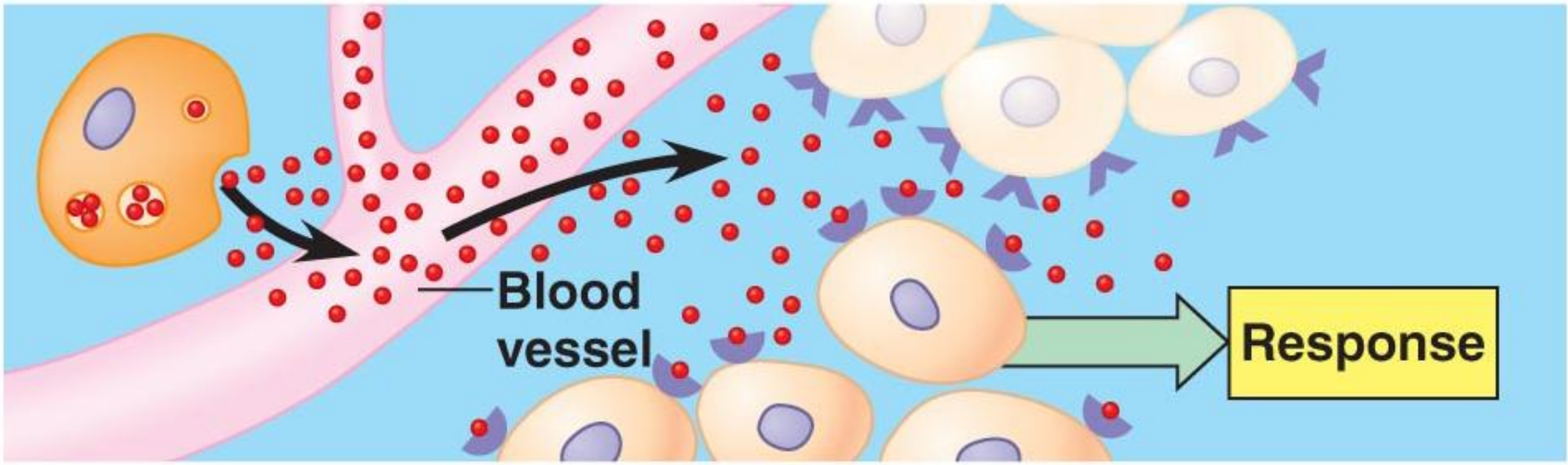
IgE antibody produced in response to initial exposure to an allergen bind to the receptor on mast cells

On exposure to the same allergen, IgE on the surface of mast cells recognise and bind allergen

Degranulation of the cell releases histamine and other chemicals, leading to allergy symptom

Hormones and the endocrine system

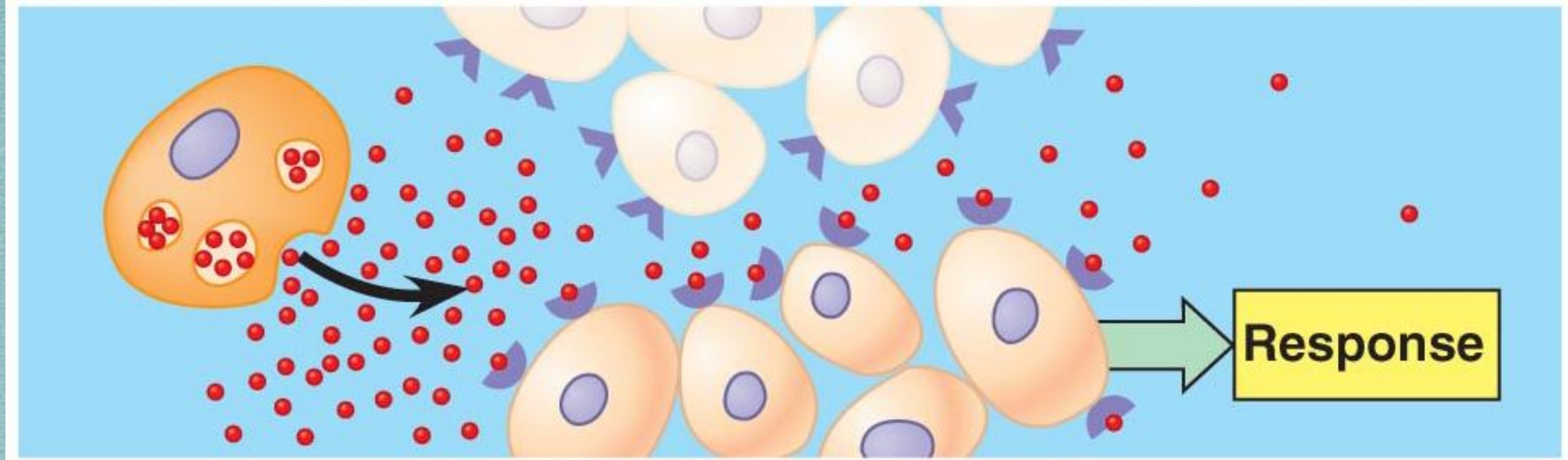
Intracellular communication by endocrine signaling



- Hormones
- maintain hemeostasis (體內動態平衡),
- mediate stress response (逆境反應) to environmental stumuli
- regulating growth development and reproduction

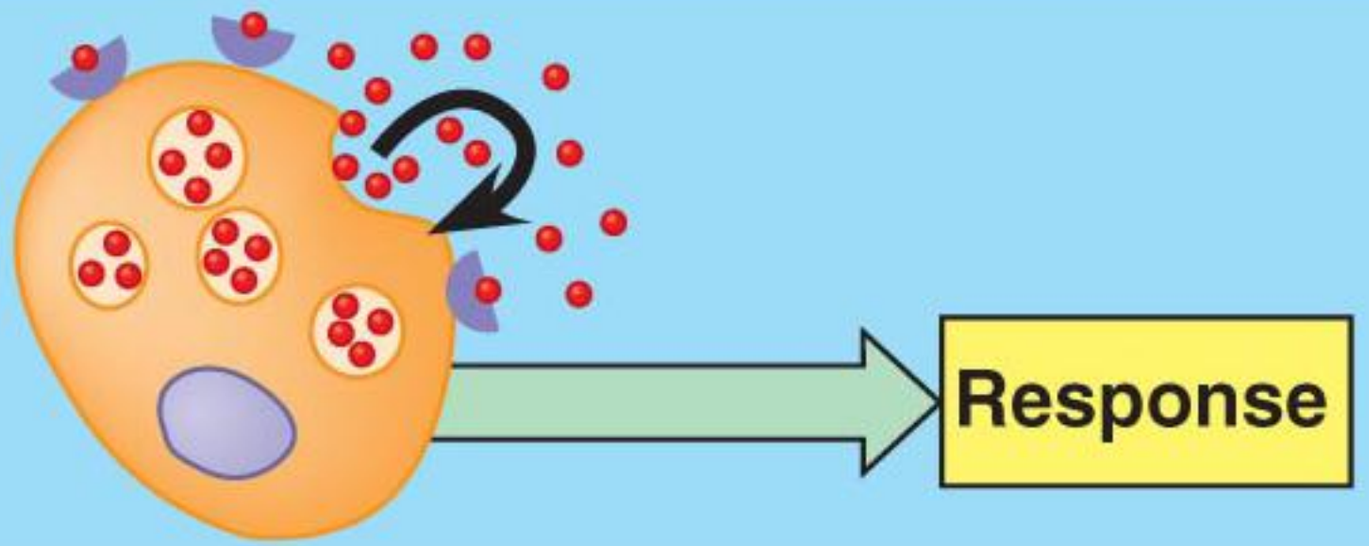
- In endocrine signaling, endocrine cells secreted hormones (激素) diffuse into the bloodstream and trigger responses in target cells anywhere in the body

Local regulators



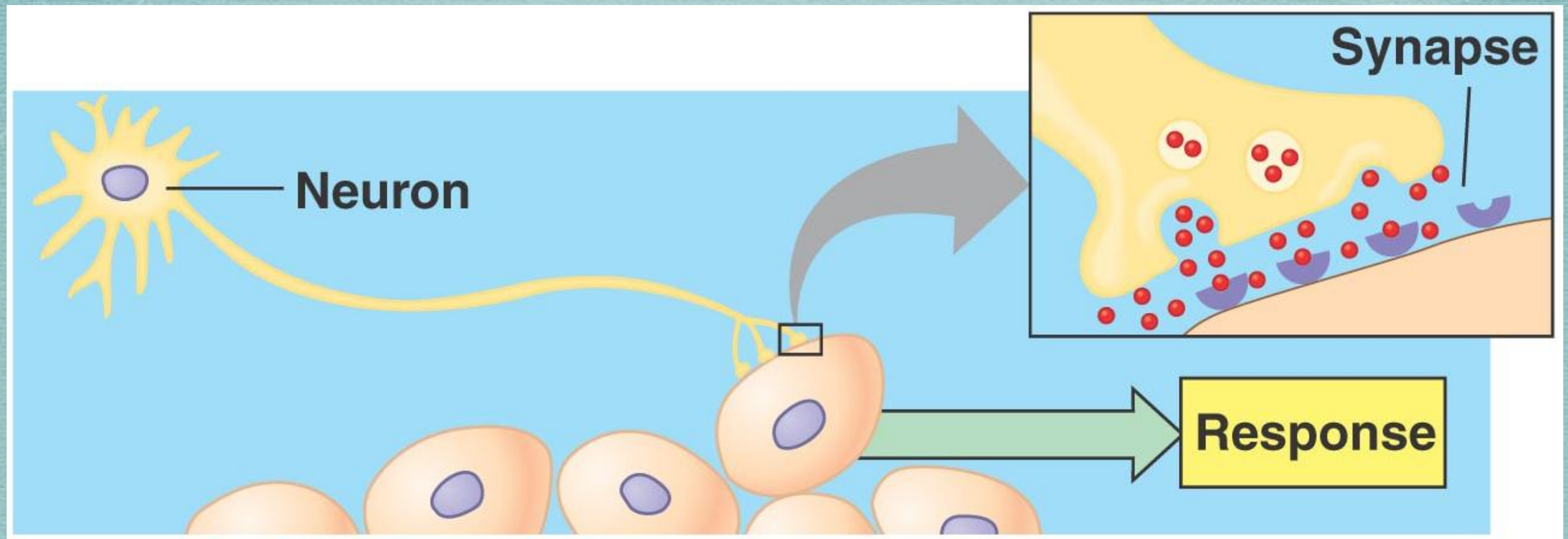
- Many types of cells produce local regulators, secreted molecules that act over short distance and reach their target cells only by diffusion
- Local regulators function in paracrine (旁分泌) and autocrine (自分泌) signaling
- In paracrine signaling, secreted molecules diffuse locally and trigger a response in neighboring cells

Autocrine signaling



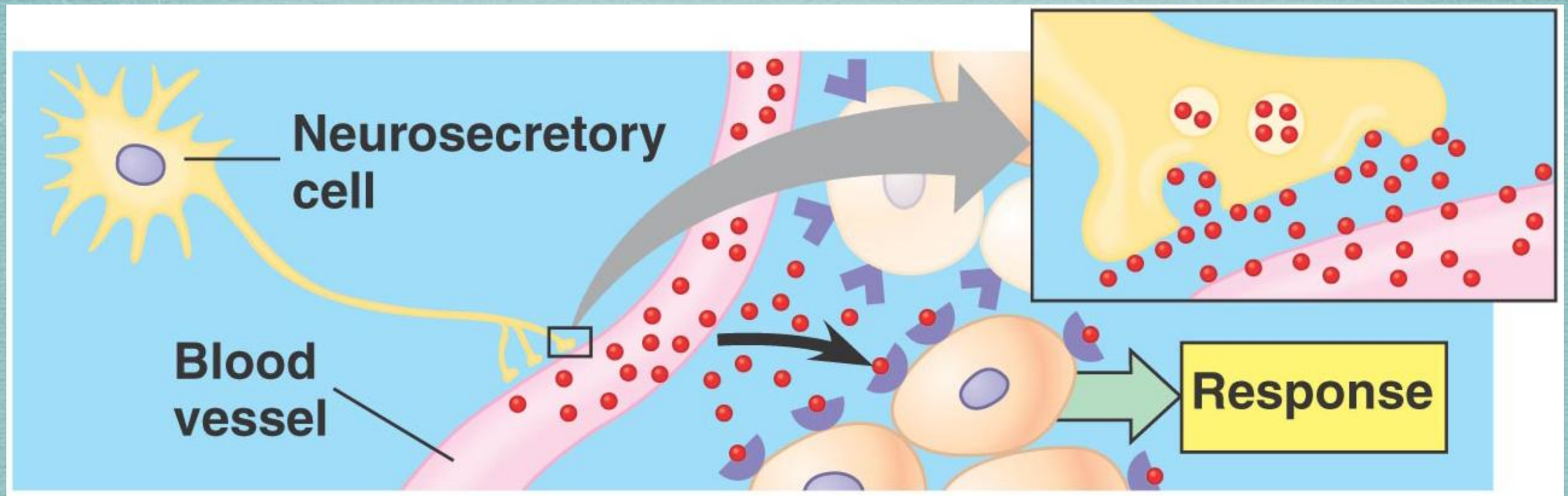
- In autocrine signaling, the secreted molecules act on the secreting cell itself
- Some secreted molecules have both paracrine and autocrine activity
- Local regulators
  - cytokines
  - growth factors
  - nitric oxide (promotes vasodilation)
  - prostaglandins (aspirin and ibuprofen inhibit PG synthesis and used as anti-inflammatory drugs)

Synaptic signaling



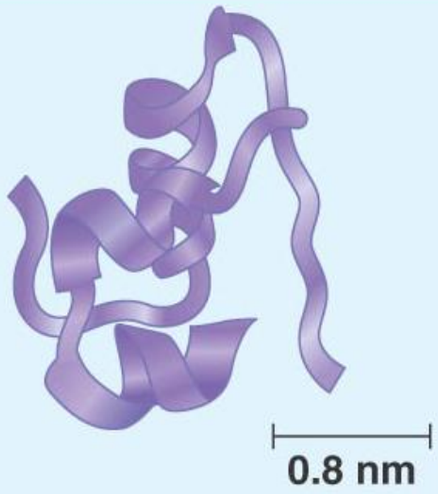
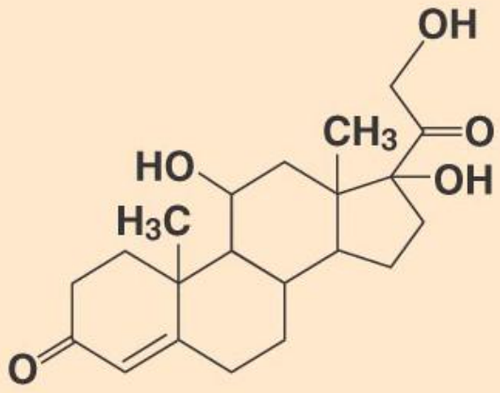
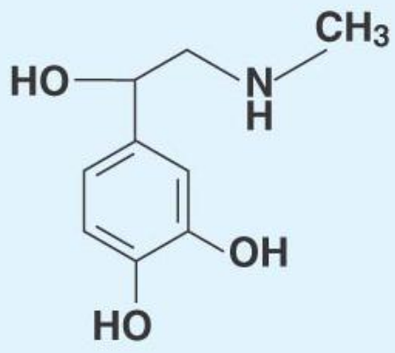
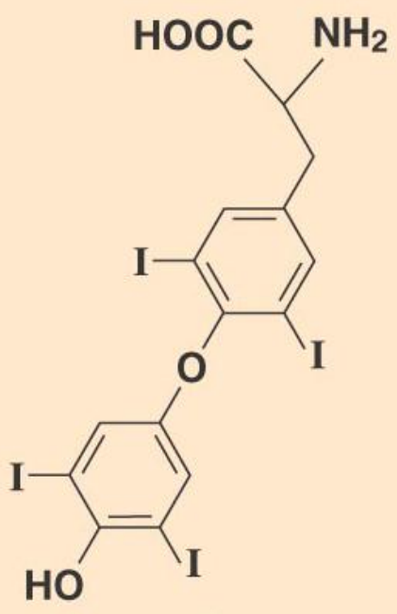
- Neurons communicate with target cells in other neurons and muscles at specialized junctions known as synapses (突觸)
- At many synapses, neurons secrete molecules called neurotransmitters (神經傳導物質) that bind receptors on nearby target cells
- Neurotransmitters play essential roles in sensation, learning, memory, cognition (認知) and movement

Neuroendocrine signaling



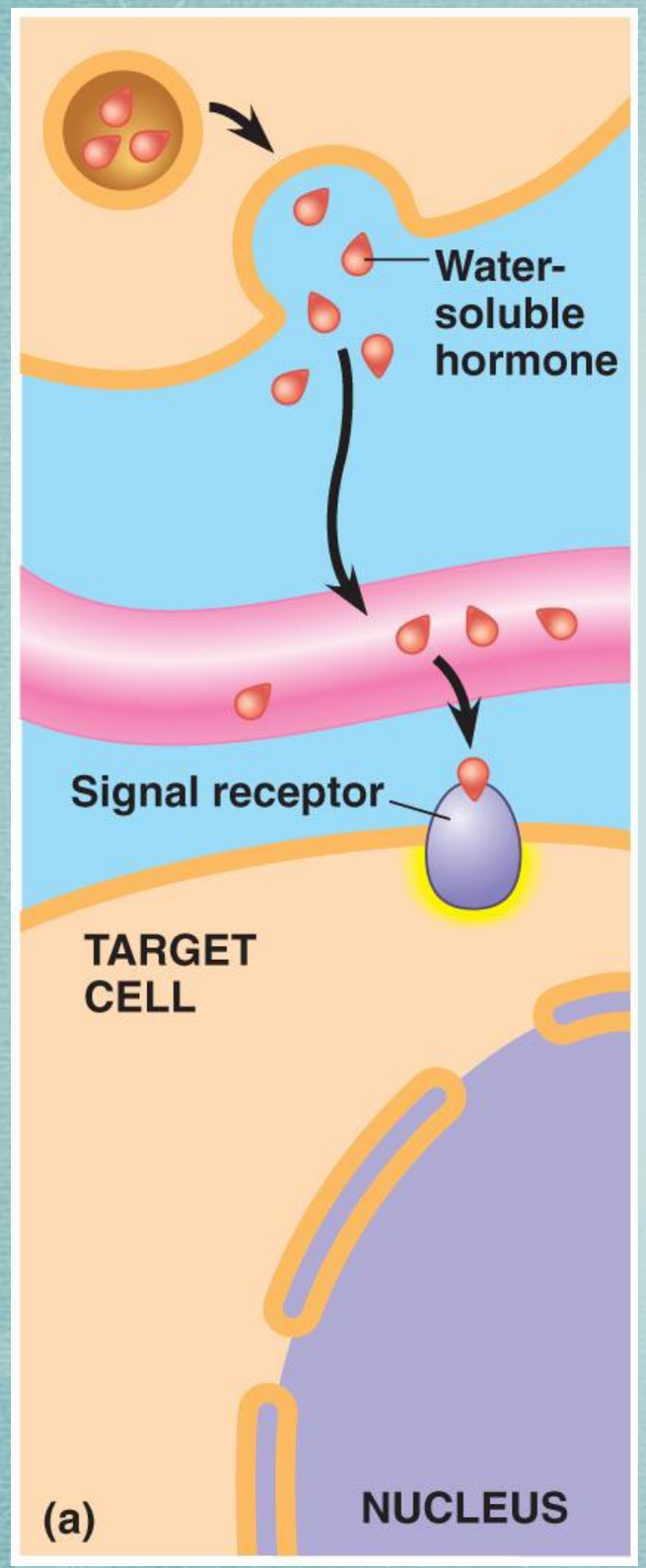
- In neuroendocrine signaling, neurosecretory cells secrete molecules that diffuse from nerve cell endings into the blood stream
- These molecules are neurohormones, which travel through the bloodstream to reach target cells anywhere in the body

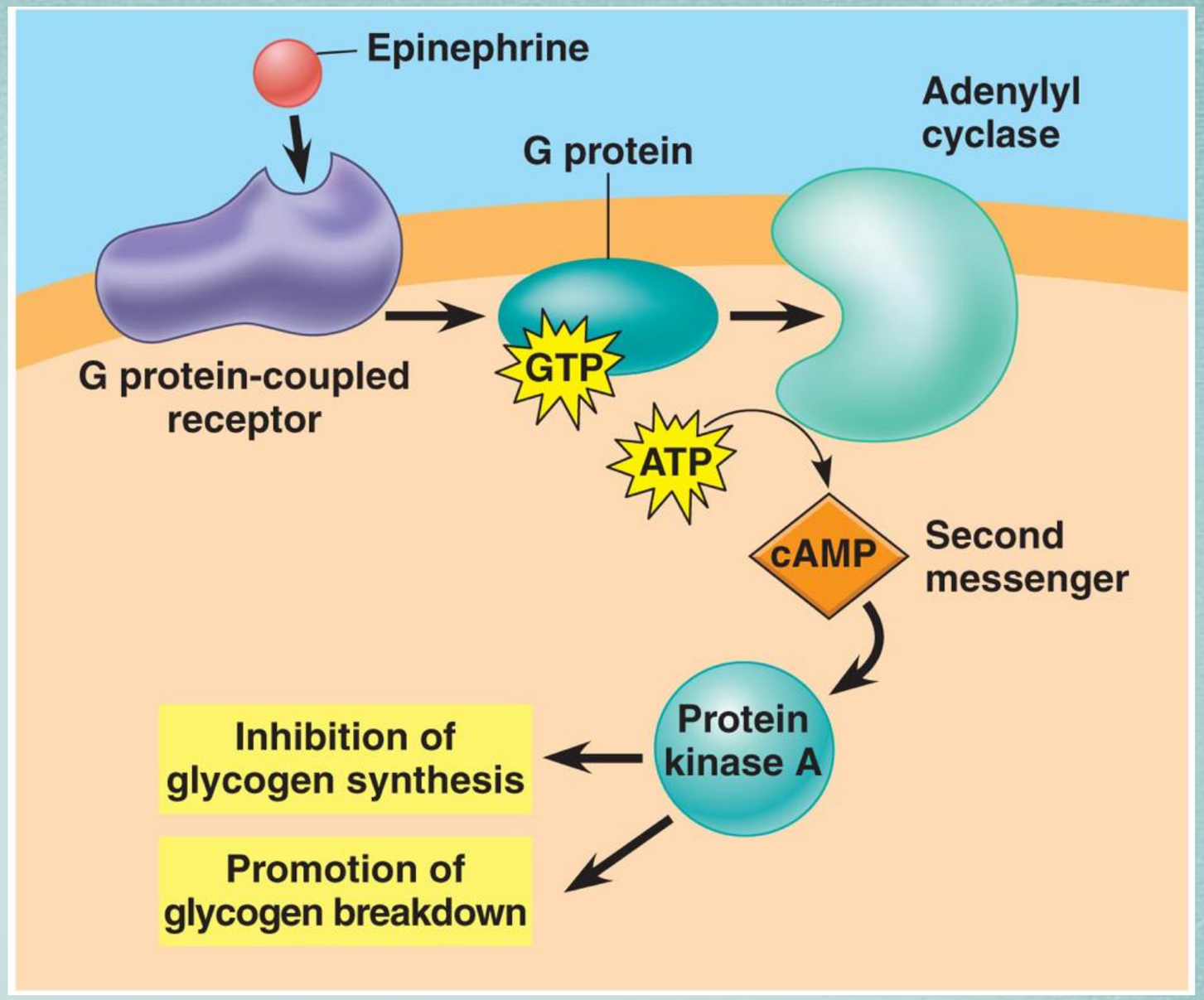
Hormones differ in form and solubility

Water-soluble	Lipid-soluble
 Polypeptide: Insulin	 Steroid: Cortisol
 Amine: Epinephrine	 Amine: Thyroxine

- Based on their structure and synthetic pathways, hormones are divided into polypeptides, amines and steroid hormones (類固醇激素)
- They differ in solubility in aqueous and lipid-rich environments
- Polypeptides and many amine hormones are water-soluble and they cannot pass through the plasma membrane of cells
- Steroid hormones and other non-polar hormones are lipid-soluble and can pass through cell membrane

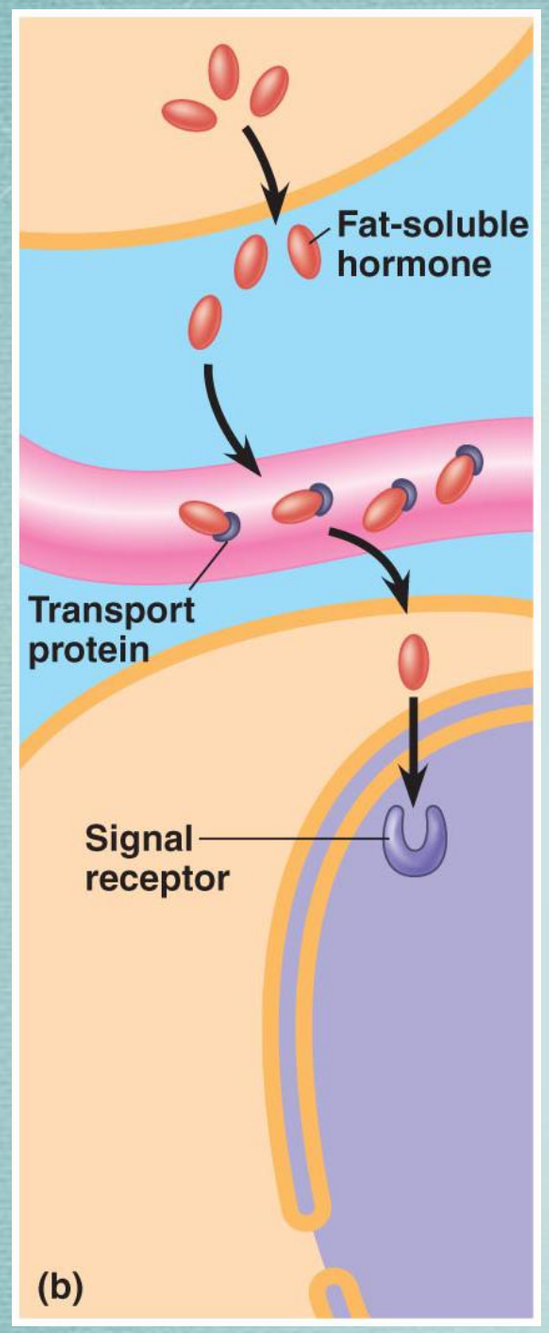
Receptor location varies with hormone

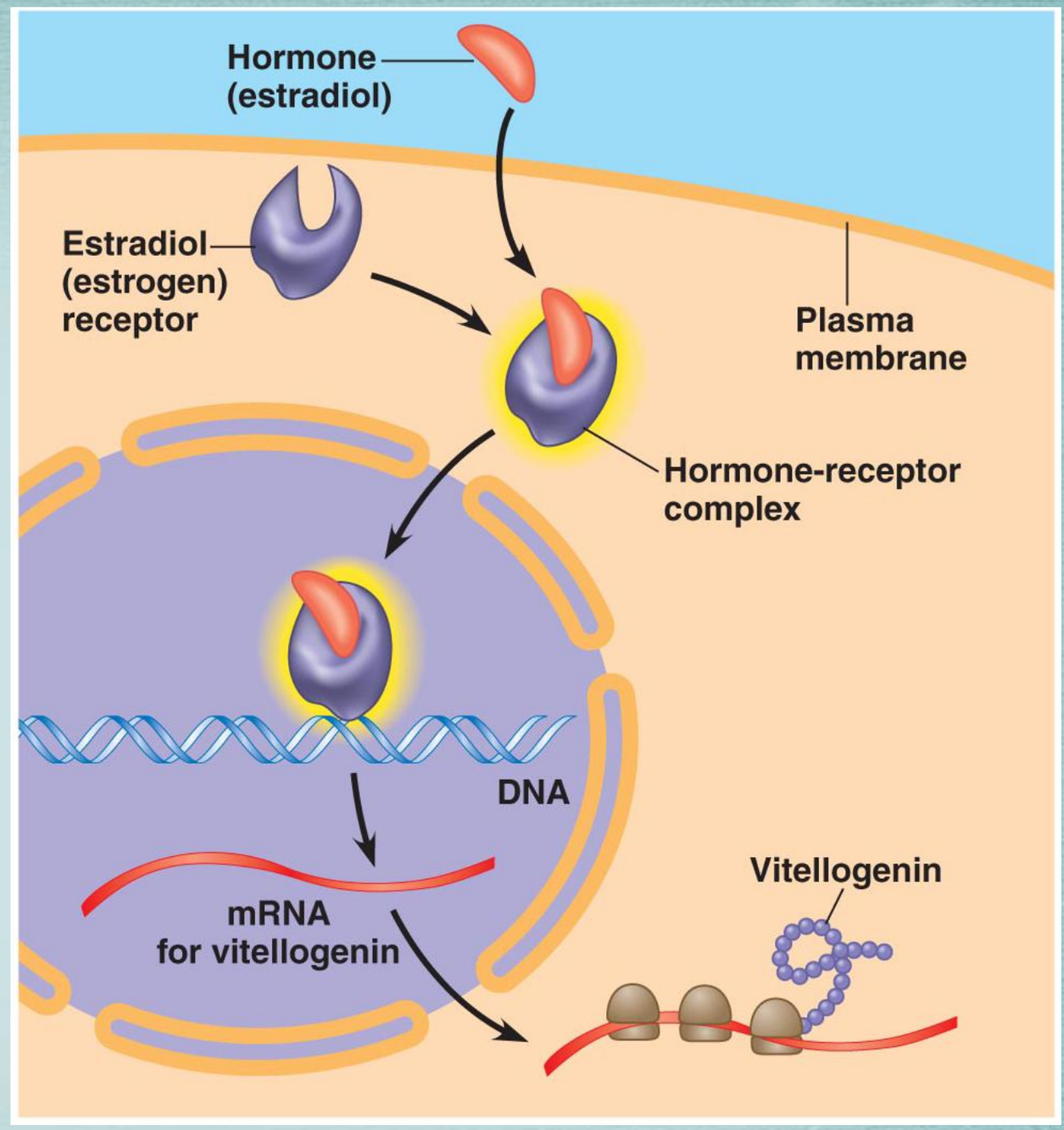




- Water soluble hormone binds to receptor protein on the surface of a target cell
- This interaction triggers signal transduction leading to change in cytoplasmic function or gene expression in the nucleus

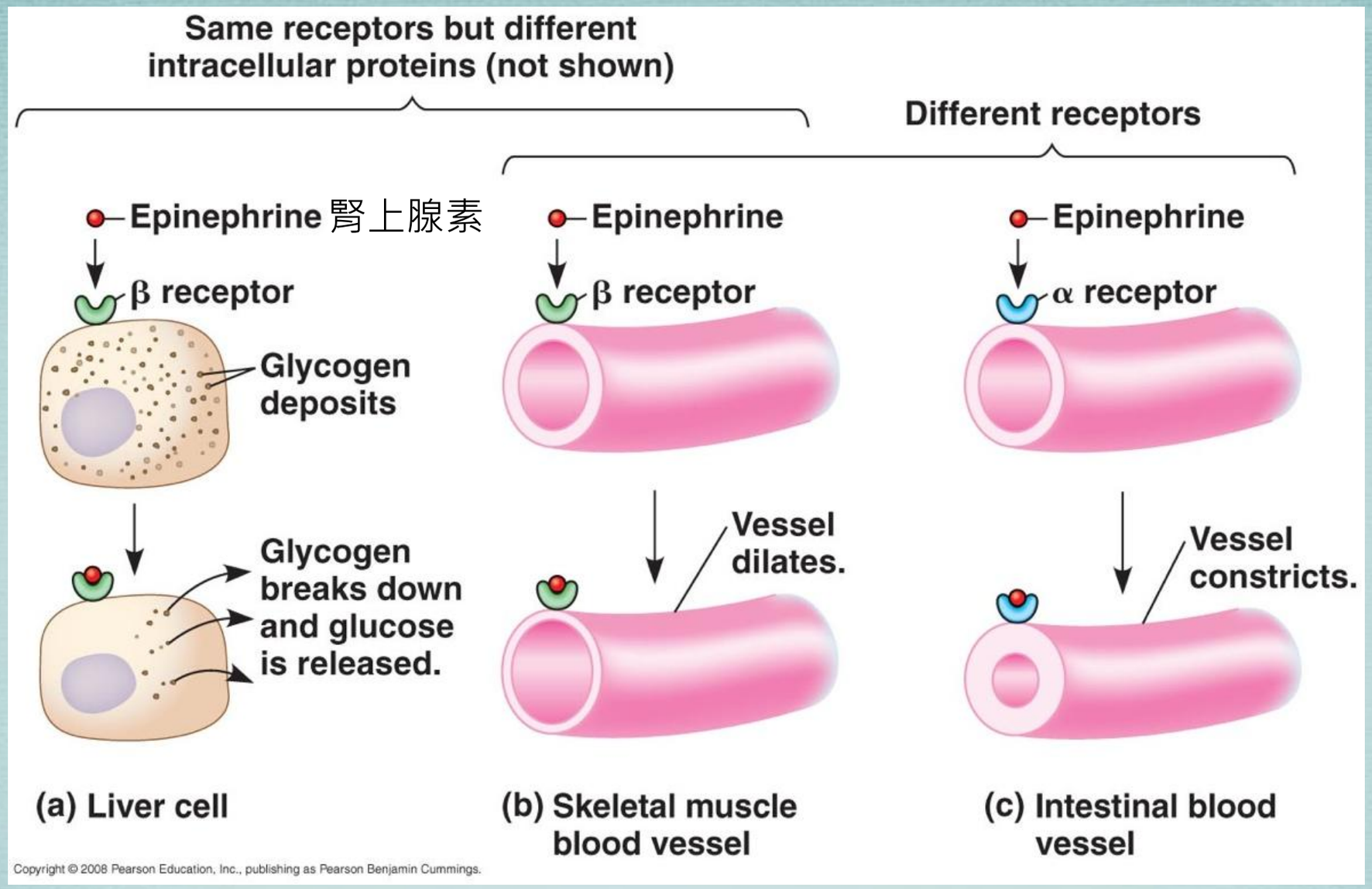
Steroid hormone receptors regulate gene expression





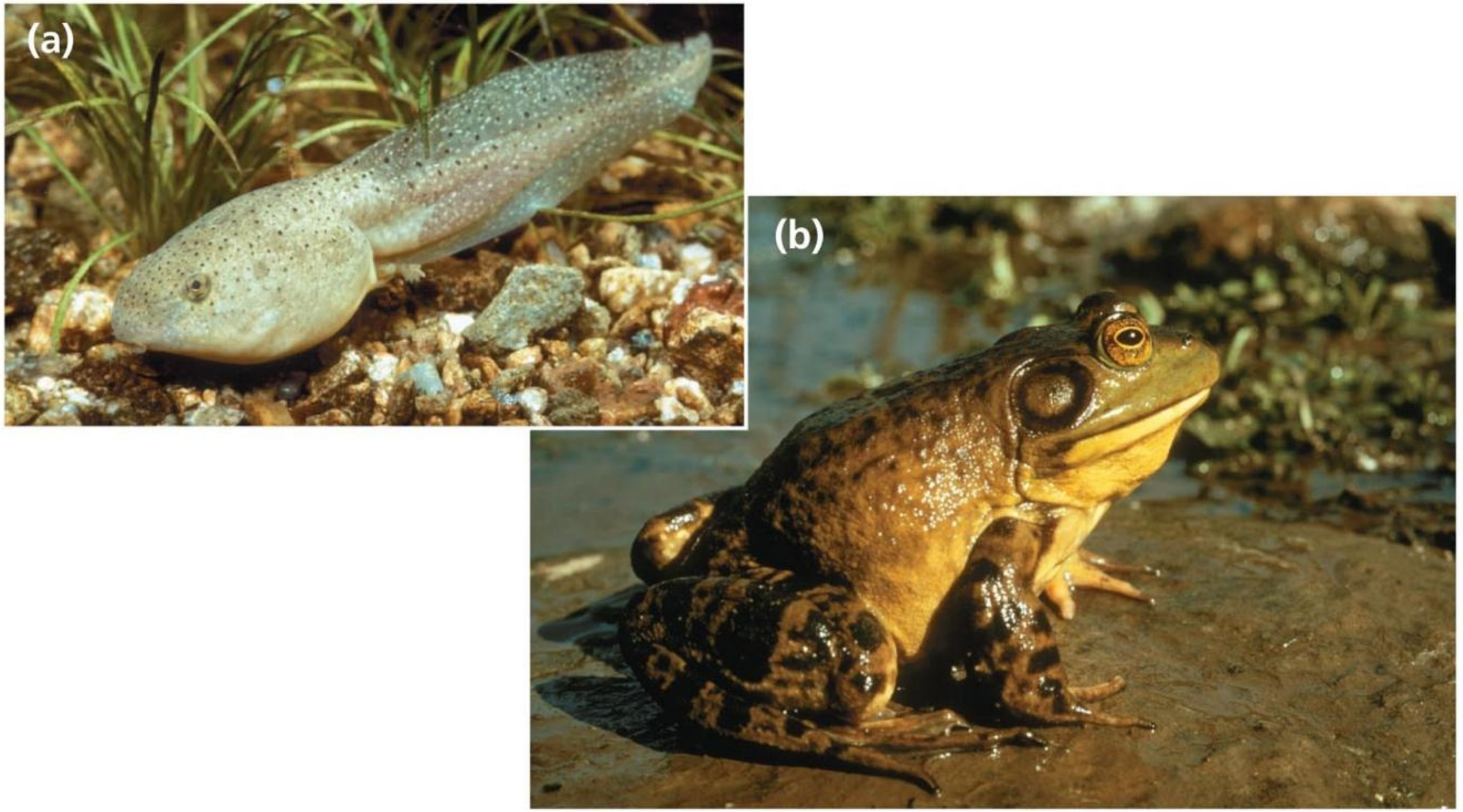
- Lipid soluble hormone penetrates target cell's membrane and binds to an intra-cellular receptor either in the cytoplasm or nucleus
- The signal receptor complex acts as a transcription factor, typically activating gene expression

One hormone with multiple effects



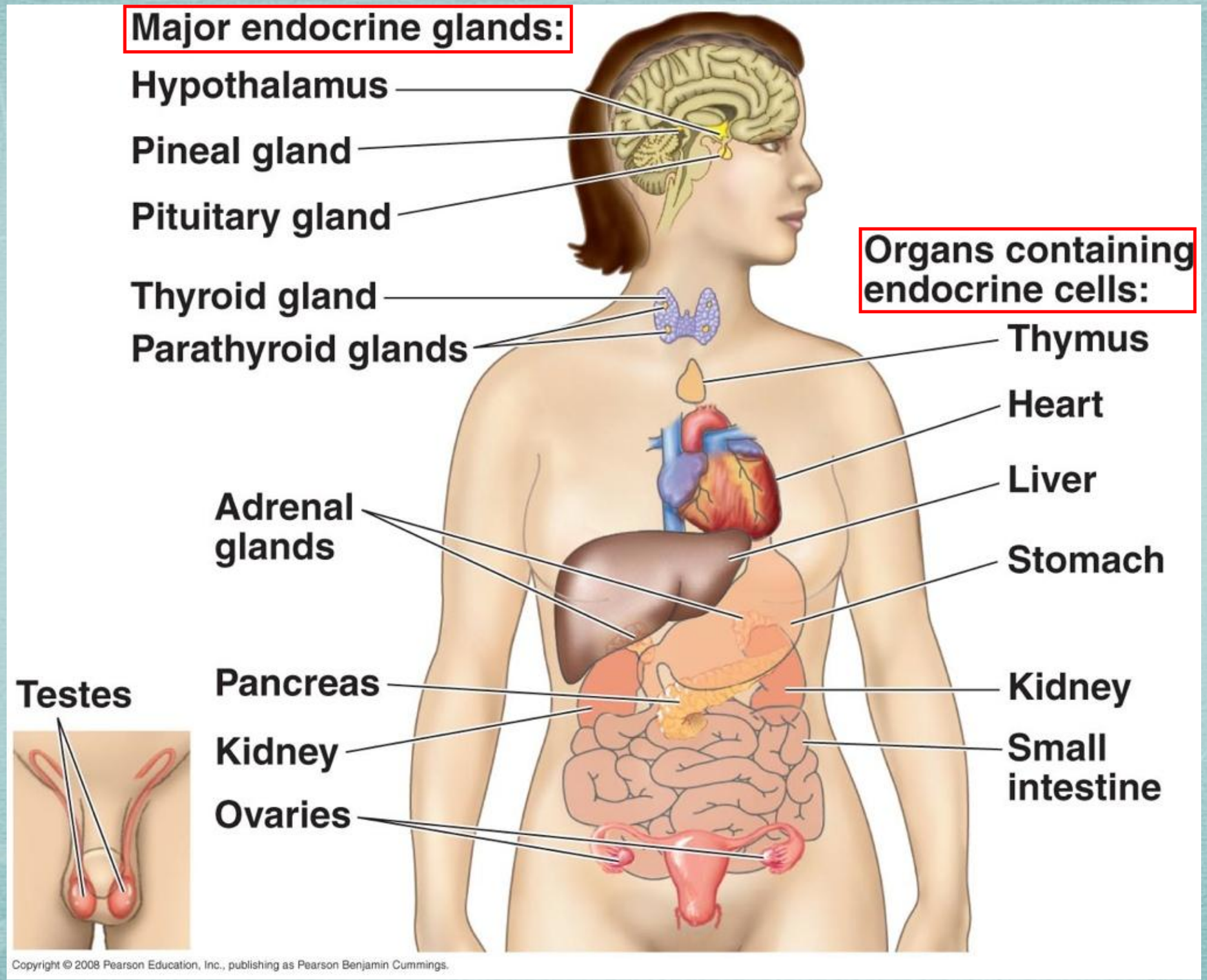
- Hormone produces different responses in different target cells
- Target cells with the same receptor exhibit different responses if they have different signal transduction pathways or effector proteins
- Responses of target cells may also differ if they have different receptors for the same hormone

Specialized role of hormone in frog metamorphosis

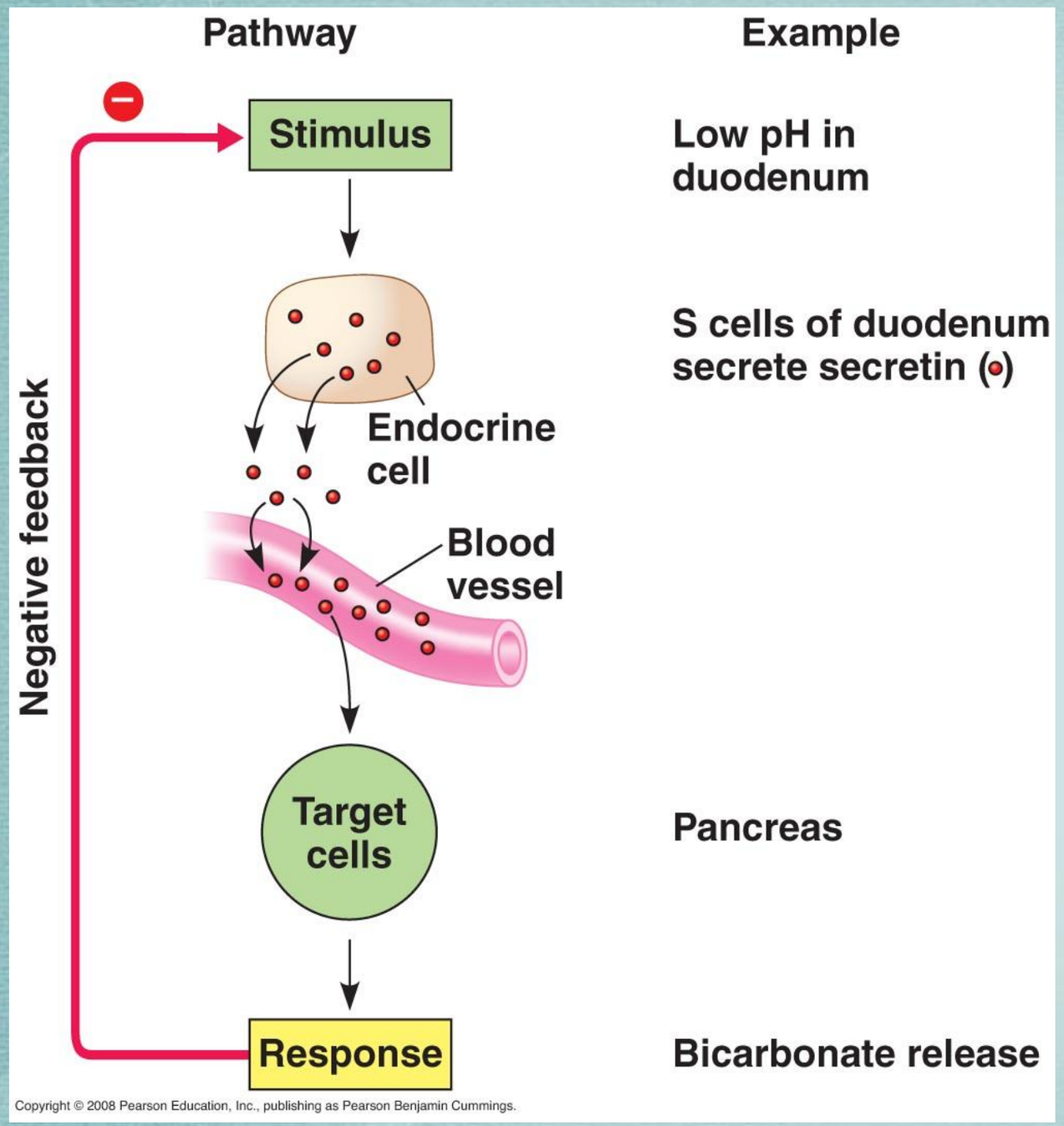


- In some cases, a given hormone has different effects in different species
- Thyroxine (甲狀腺素) produced by thyroid gland regulates metabolism in human and other vertebrates, whereas it stimulates resorption of the tadpole's tail as the frog develops into its adult form

Major human endocrine glands and tissues

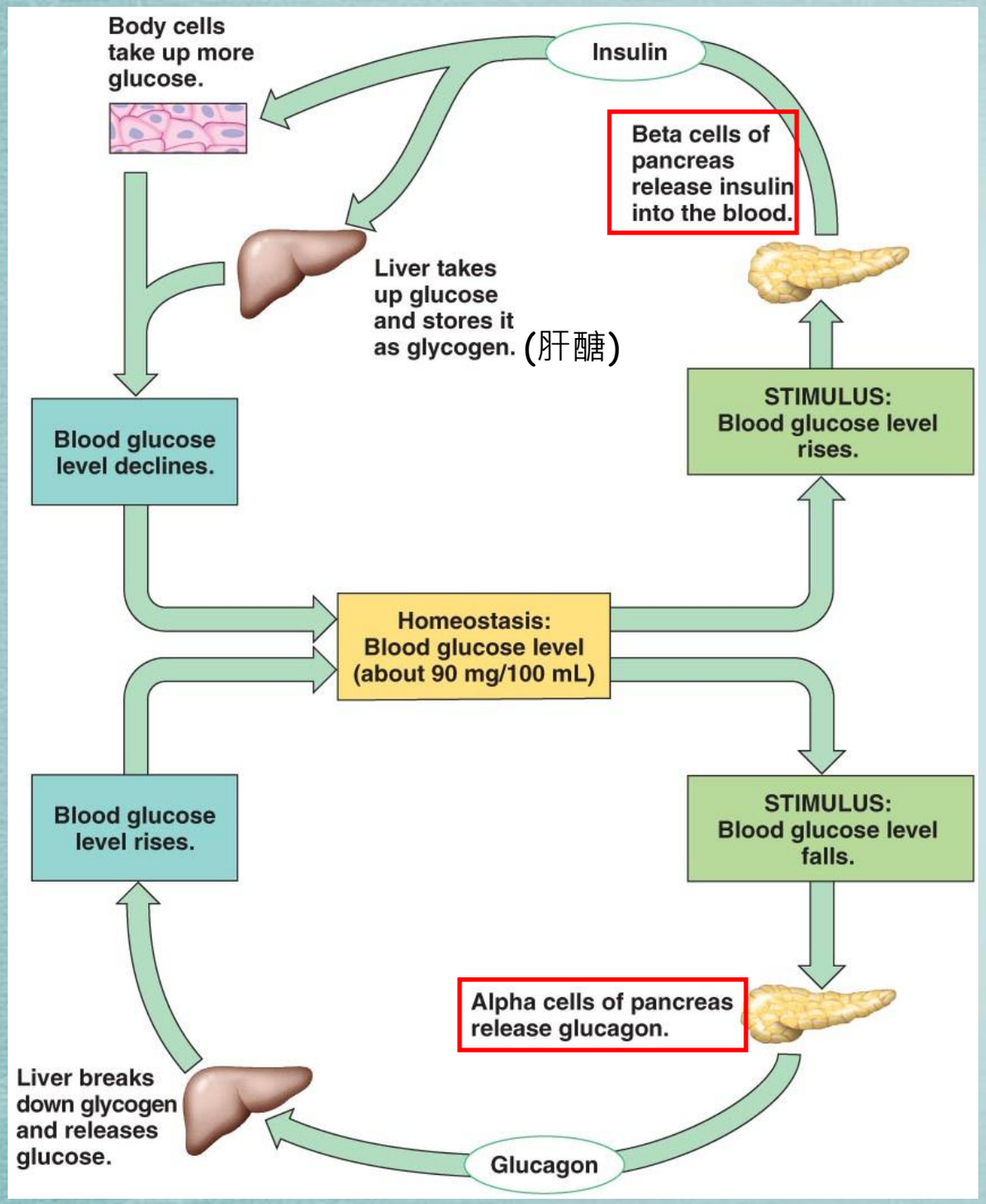


Simple hormone pathways



- The stimulus causes endocrine cells to secrete a hormone
- Upon reaching its target cell via bloodstream, the hormone binds to its receptor, triggering signal transduction that results in a specific response
- A negative feedback (負回饋) is a loop in which the response reduces the initial stimulus, which prevents excessive pathway activity

Maintenance of glucose homeostasis



- Two antagonistic (頡抗作用) hormones, insulin (胰島素) and glucagon (升糖素), which regulate the concentration of glucose in the blood (90 mg/100 ml)
- When blood glucose rises, releases of insulin triggers uptake of glucose from the blood, decreasing the blood glucose concentration
- When blood glucose drops, the release of glucagon promotes the release of glucose into the blood

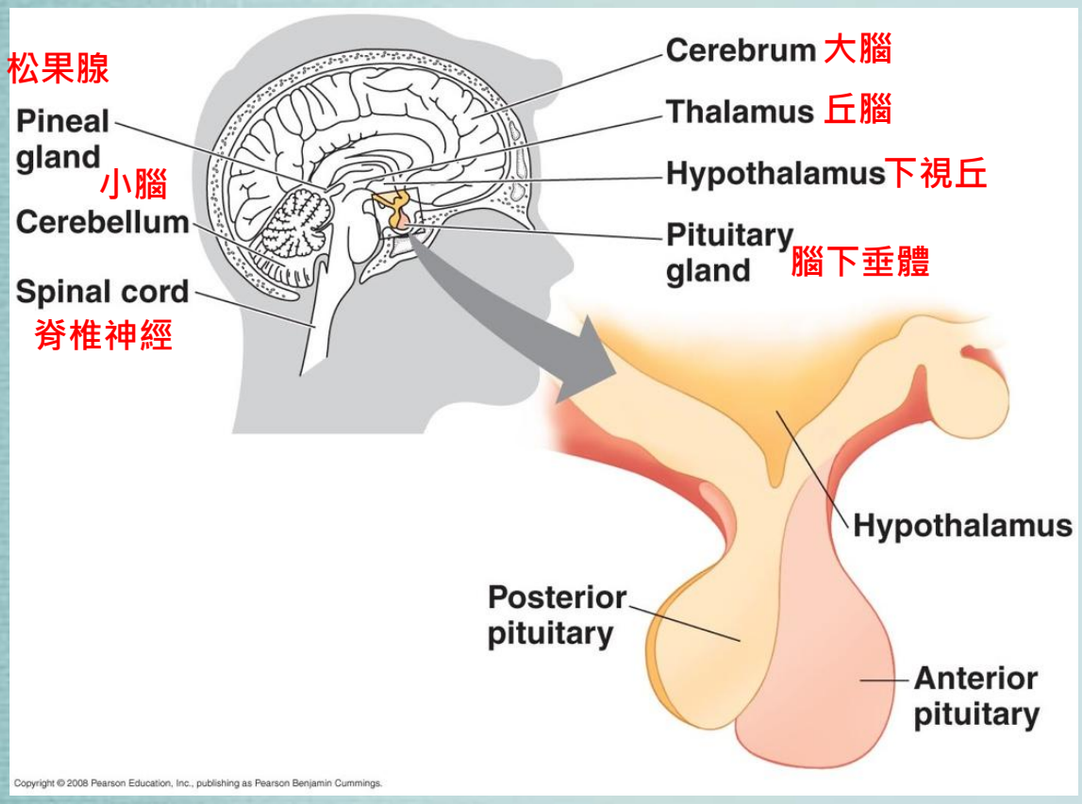
Perturbations of glucose homeostasis

- A disruption of glucose homeostasis causes diabetes mellitus, which refers to the presence of sugar in urine

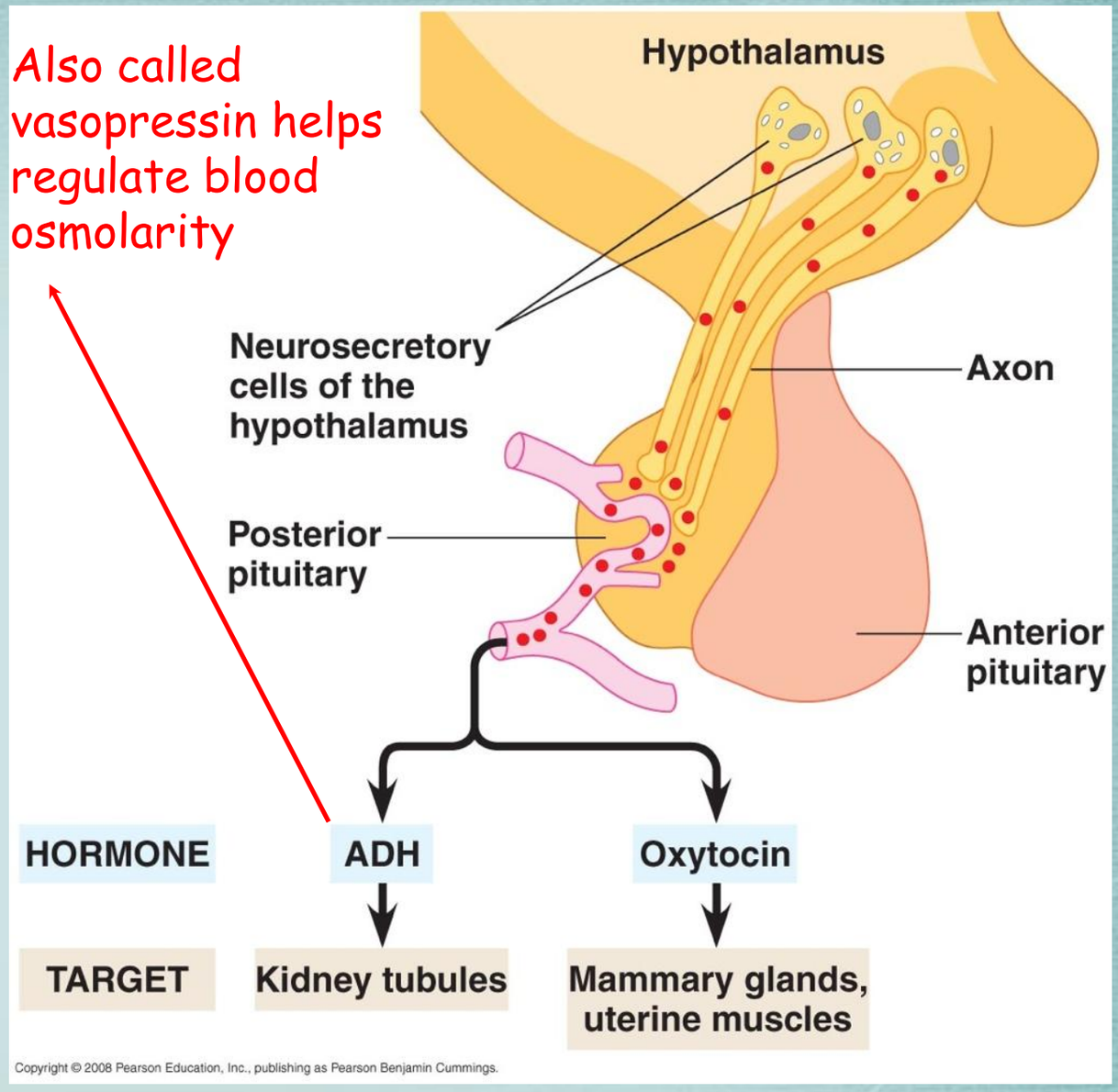
  - Insulin-dependent diabetes (Type I), is an autoimmune disorder, in which immune system destroys beta-cells that produce insulin
  - Insulin-independent diabetes (Type II), is characterised by failure of target cells to respond normally to insulin
  - More than 90% of people with diabetes have type II, a multifactorial disorder contributed by genetic components and environmental factors

Endocrine and nervous system in vertebrate brain

The hypothalamus (下視丘) plays a central role in integrating the endocrine and nervous systems

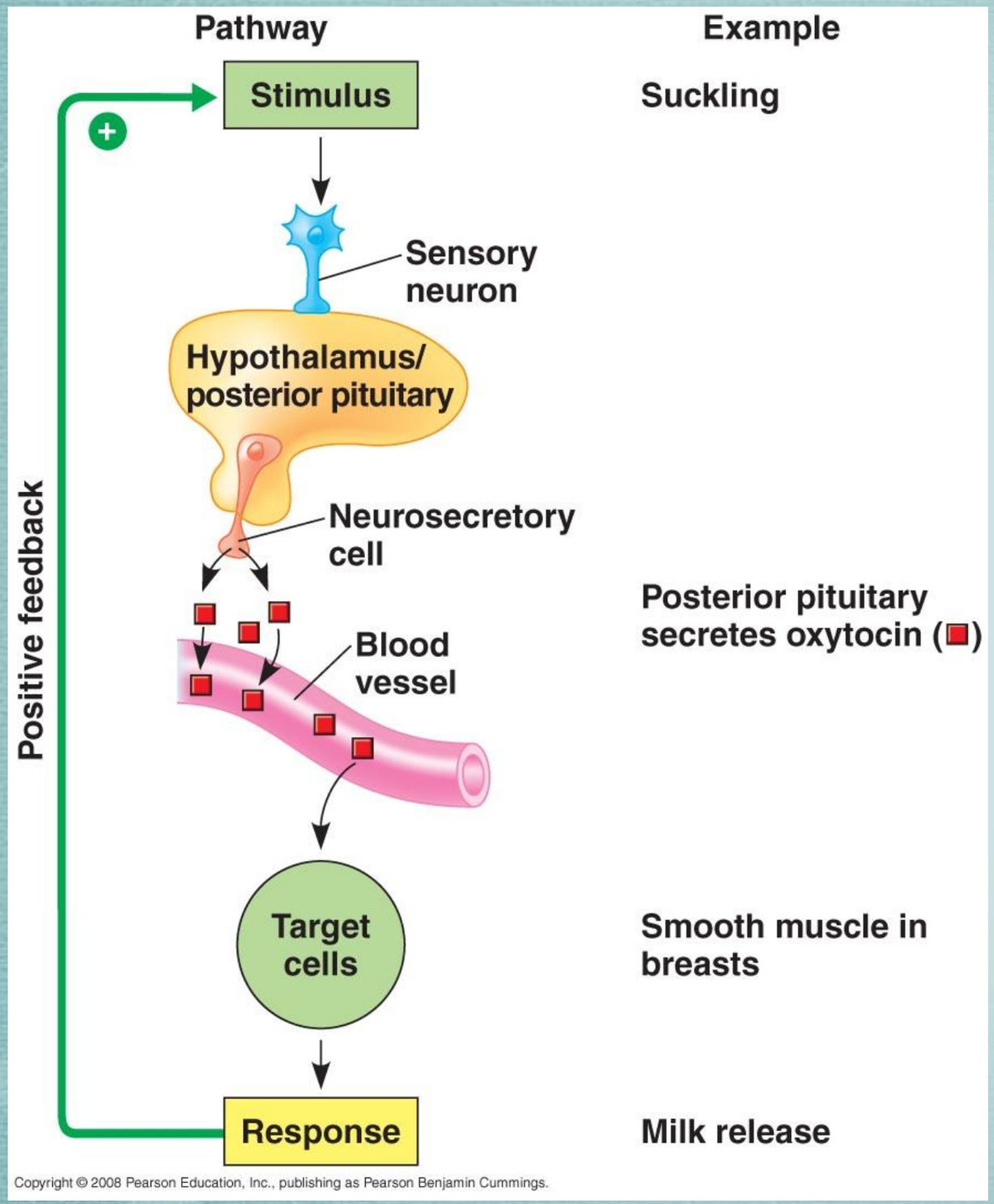


Signals from hypothalamus travel to the pituitary gland, which contain two glands, the posterior and anterior pituitary



The posterior pituitary, or neuro-hypophysis (神經垂體), is an extension of the hypothalamus and it stores and secretes oxytocin (催產素) and antidiuretic hormone (ADH; 抗利尿激素)

A positive feedback neurohormone pathway



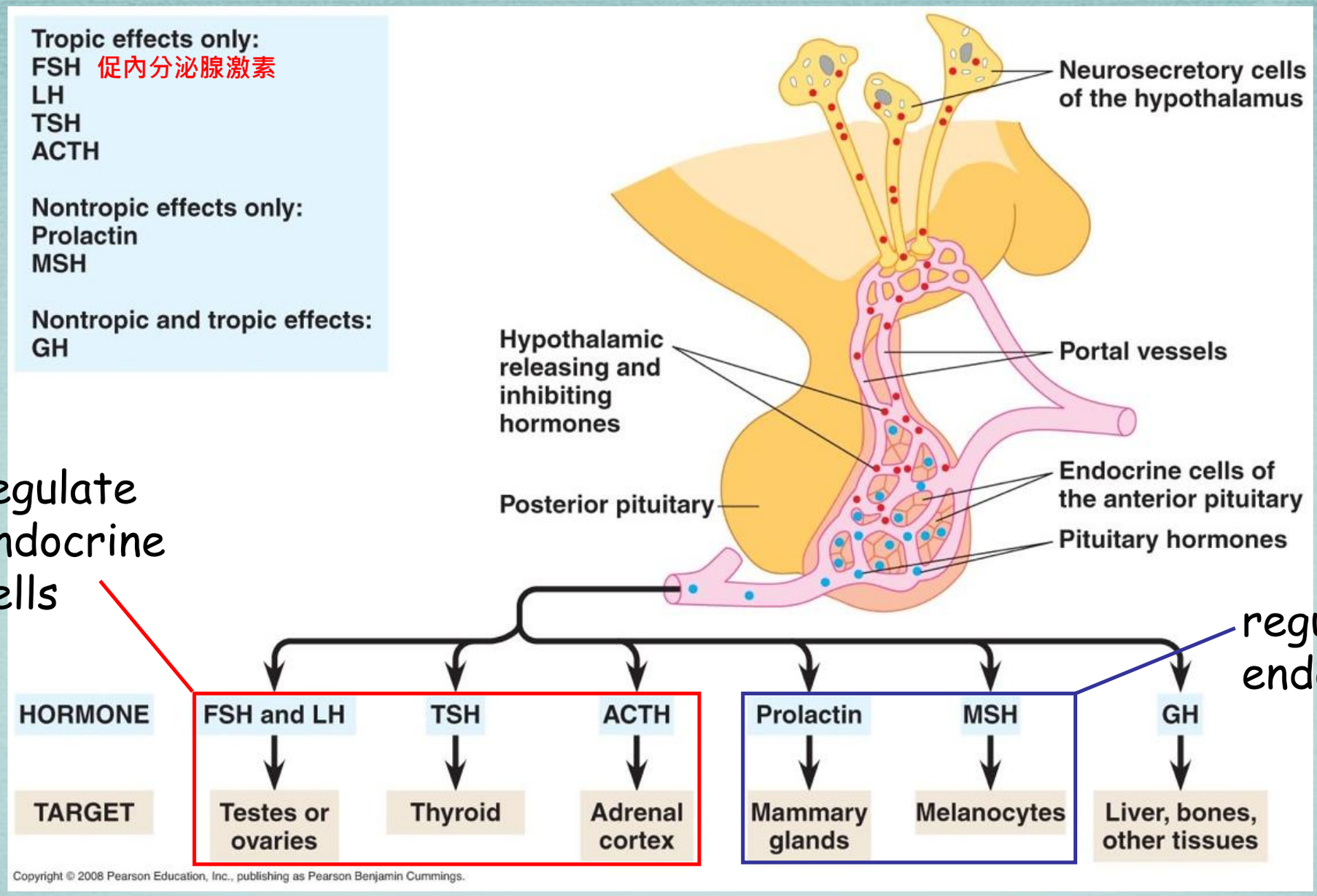
- One function of oxytocin is to regulate milk release during nursing
- The oxytocin pathway provides an example of positive feedback (正回饋) mechanism, which reinforces the stimulus leading to an even greater response
- Oxytocin induces target cells in the uterine muscle to contract, which drives the birth process to completion
- Oxytocin also functions in regulating mood and sexual arousal (性衝動) in both females and males

Production and release of anterior pituitary hormones

Tropic effects only:
FSH 促内分泌腺激素
LH
TSH
ACTH

Nontropic effects only:
Prolactin
MSH

Nontropic and tropic effects:
GH



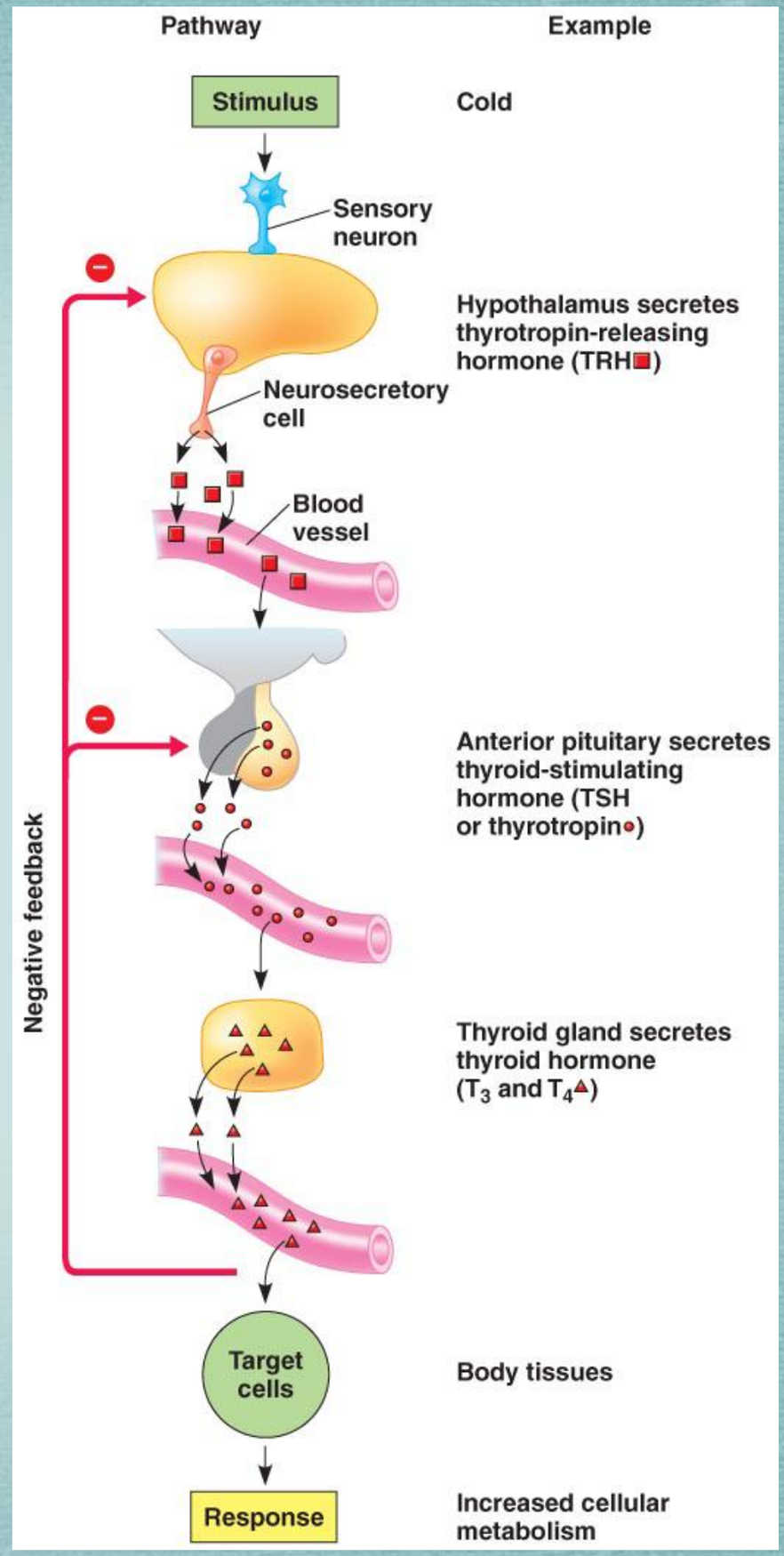
regulate endocrine cells

regulate non-endocrine cells

- The anterior pituitary synthesizes and secretes many different hormones and is itself regulated by hypothalamic hormones
- Each hypothalamic hormone is either a releasing hormone or an inhibiting hormone

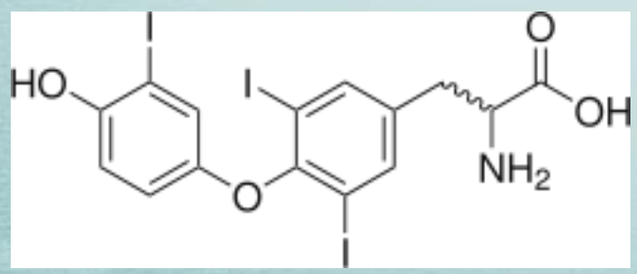
A hormone cascade pathway

Set of hormones from the hypothalamus, the anterior pituitary and a target endocrine gland are organised into a hormone cascade pathway

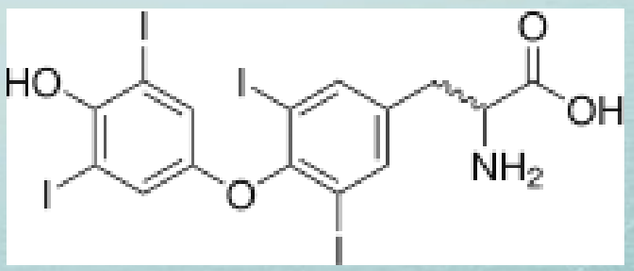


Thyroid hormone (甲狀腺激素) controls metabolism and development

- TH contains a pair of similar hormones, T3 (Triiodothyronine) and T4 (thyroxine), both derived from tyrosine
- Hyper-thyroidism: excessive secretion of TH can lead to severe symptoms, including high body temperature, profuse sweating, weight loss and high blood pressure
- Hypothyroidism, a condition of too little thyroid function can produce symptoms such as weight gain, lethargy and intolerance to cold

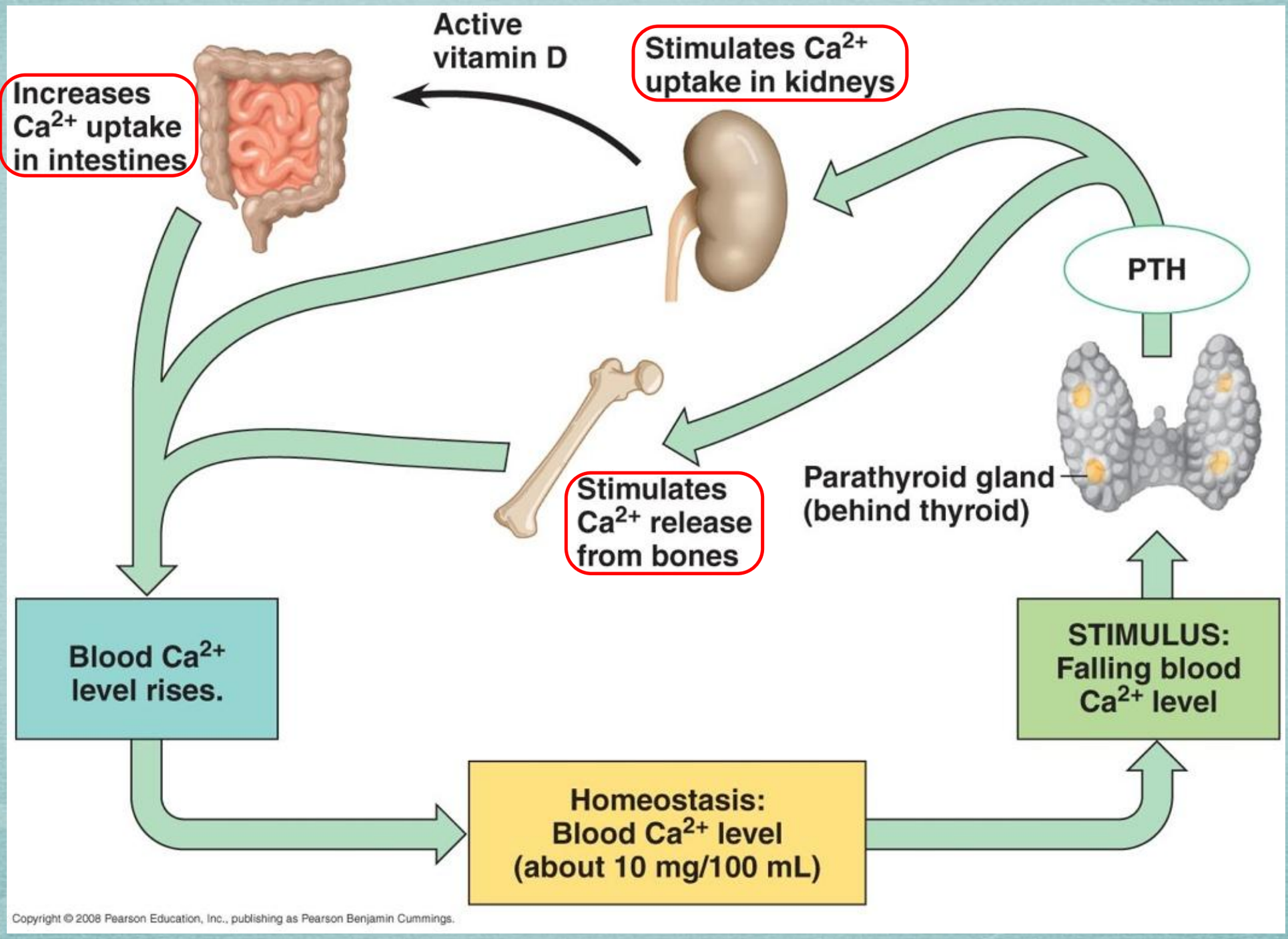


T3

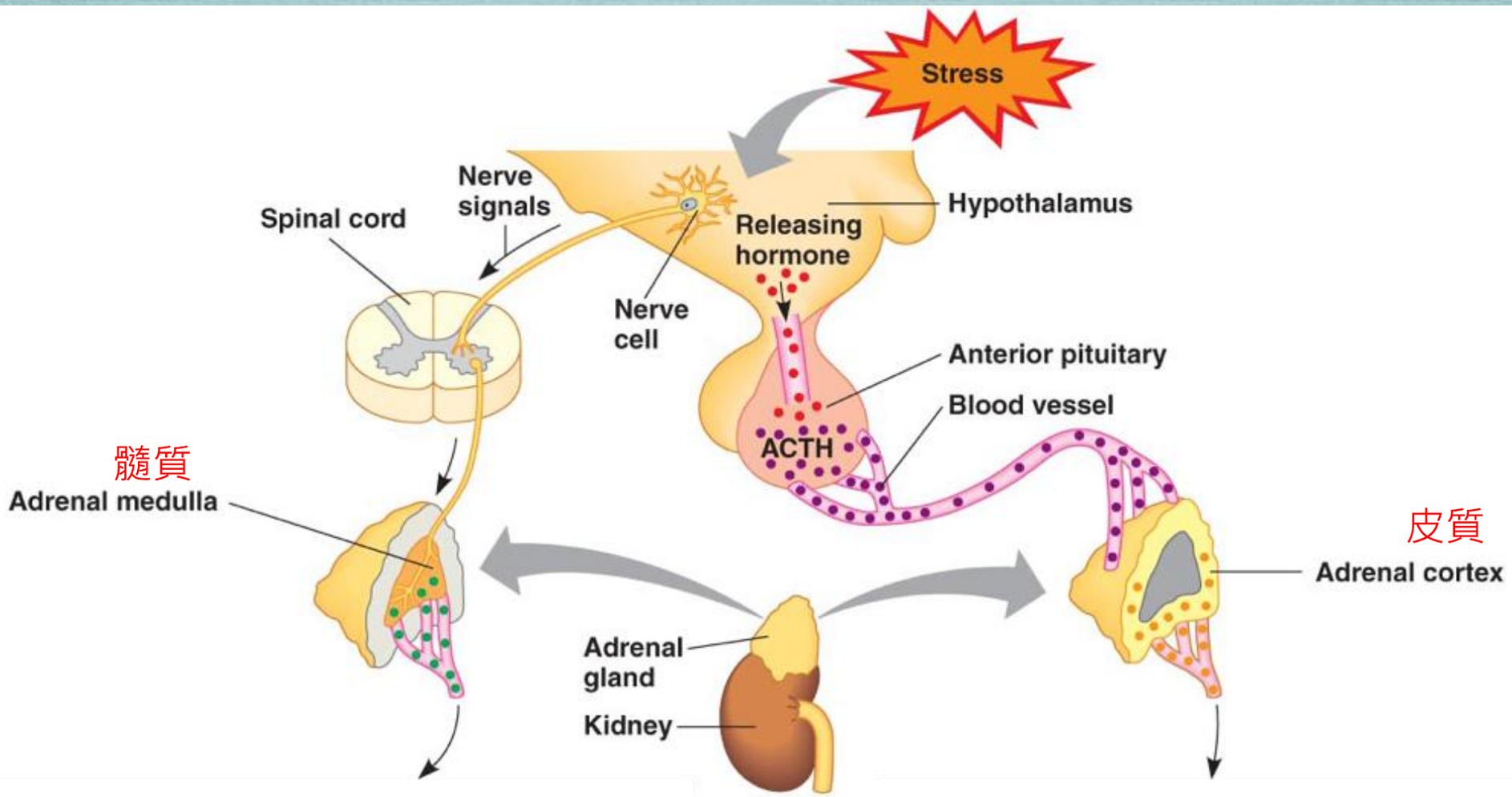


T4

Parathyroid hormone and vitamine D control blood calcium



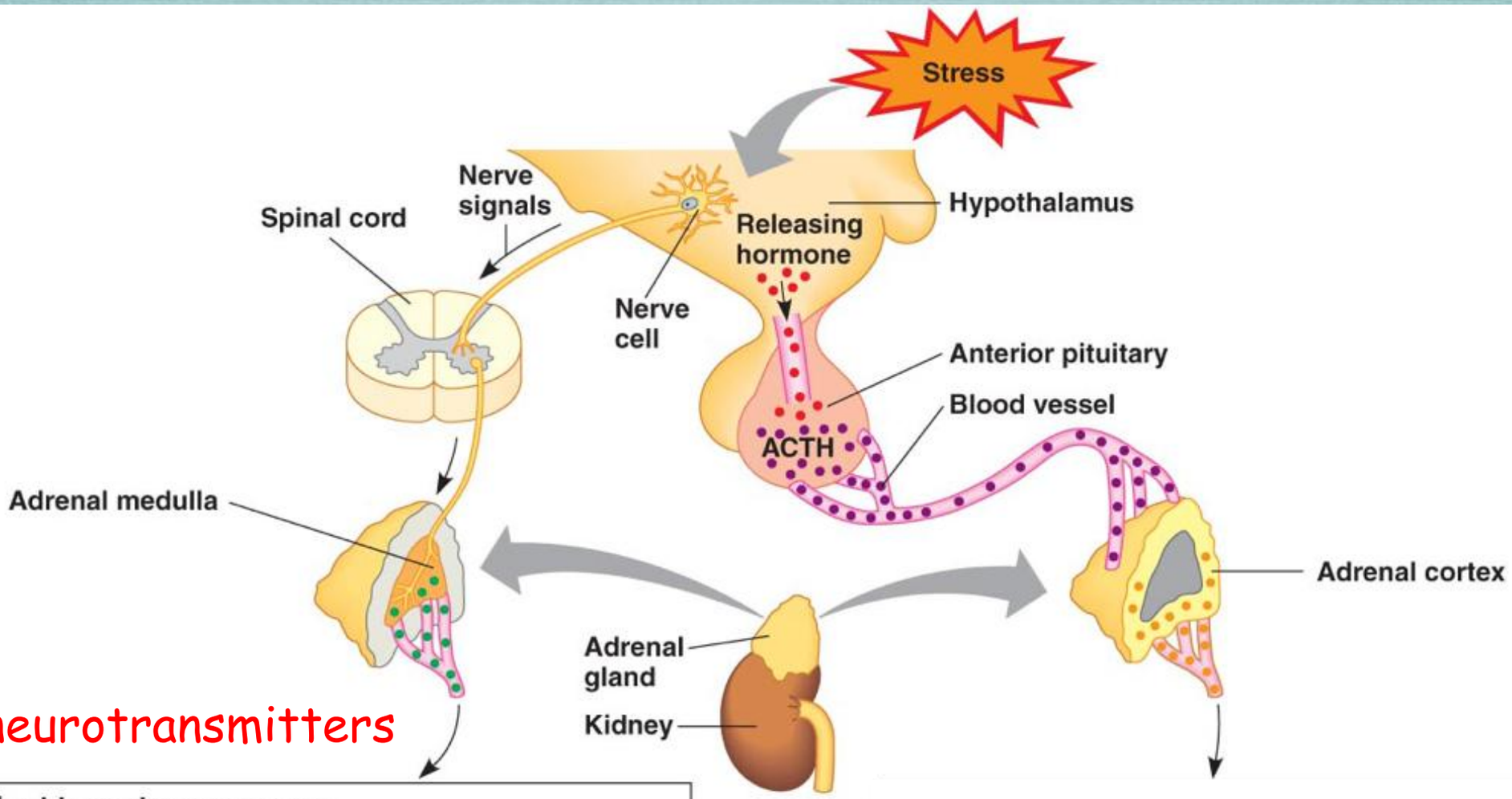
Adrenal hormone: response to stress



contains secretory cells

contains endocrine cells

Hormones from adrenal medulla

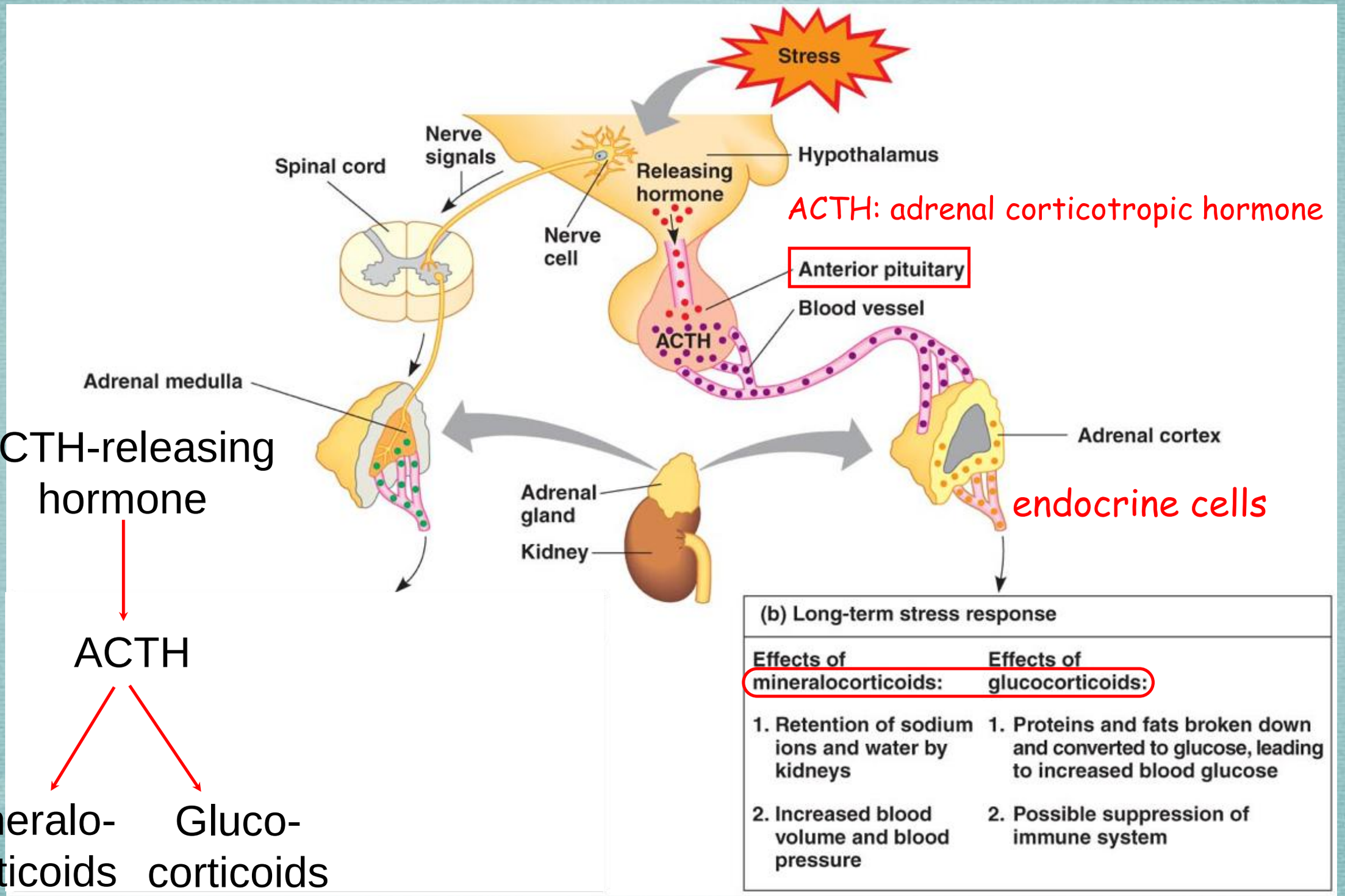


neurotransmitters

(a) Short-term stress response
Effects of epinephrine and norepinephrine:
1. Glycogen broken down to glucose; increased blood glucose 2. Increased blood pressure 3. Increased breathing rate 4. Increased metabolic rate 5. Change in blood flow patterns, leading to increased alertness and decreased digestive, excretory, and reproductive system activity

In response to a stressful stimulus, nerve impulses from the hypothalamus travel to the adrenal medulla, where they trigger the release of catecholamines and each function as neurotransmitters in different neurohormone pathways

A hormone cascade pathway to adrenal cortex



ACTH: adrenal corticotropic hormone

endocrine cells

ACTH-releasing hormone

ACTH

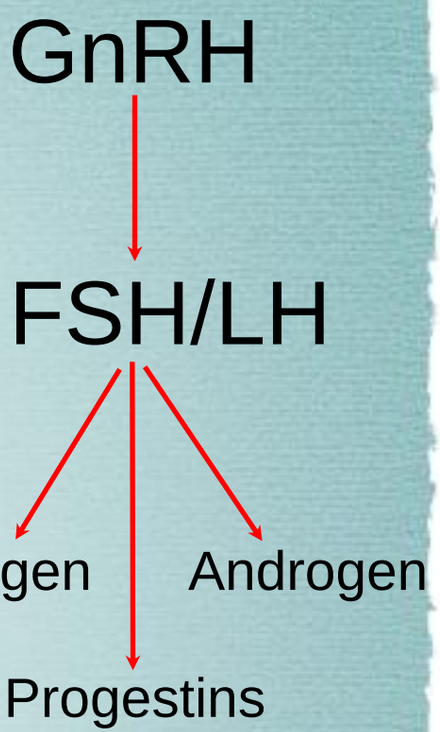
Mineralo-corticoids

Gluco-corticoids

(b) Long-term stress response	
Effects of mineralocorticoids:	Effects of glucocorticoids:
1. Retention of sodium ions and water by kidneys	1. Proteins and fats broken down and converted to glucose, leading to increased blood glucose
2. Increased blood volume and blood pressure	2. Possible suppression of immune system

Gonadal sex hormones

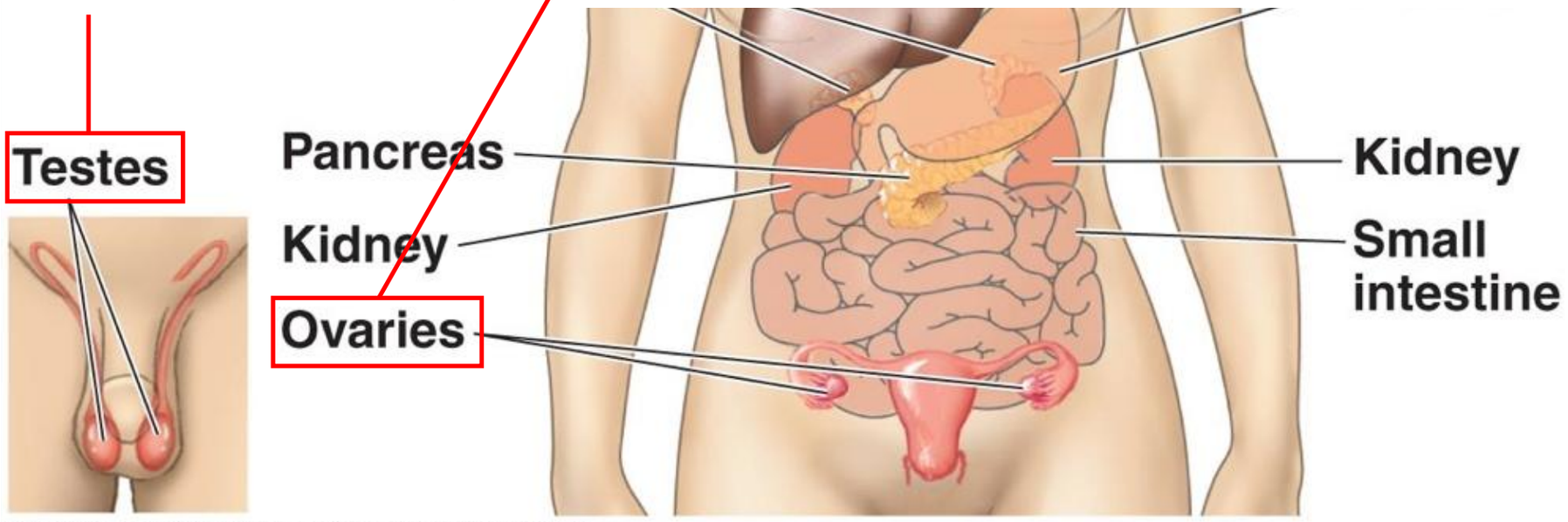
- Estrogens (雌性激素), progestins (黃體激素) and androgens (男性荷爾蒙) are composed of hormone cascade pathways, synthesis of which is controlled by gonadotropins (促性腺激素; FSH and LH) from the anterior pituitary gland
- FSH and LH secretion is in turn controlled by a releasing hormone from the hypothalamus GnRH (gonadotropin-releasing hormone)



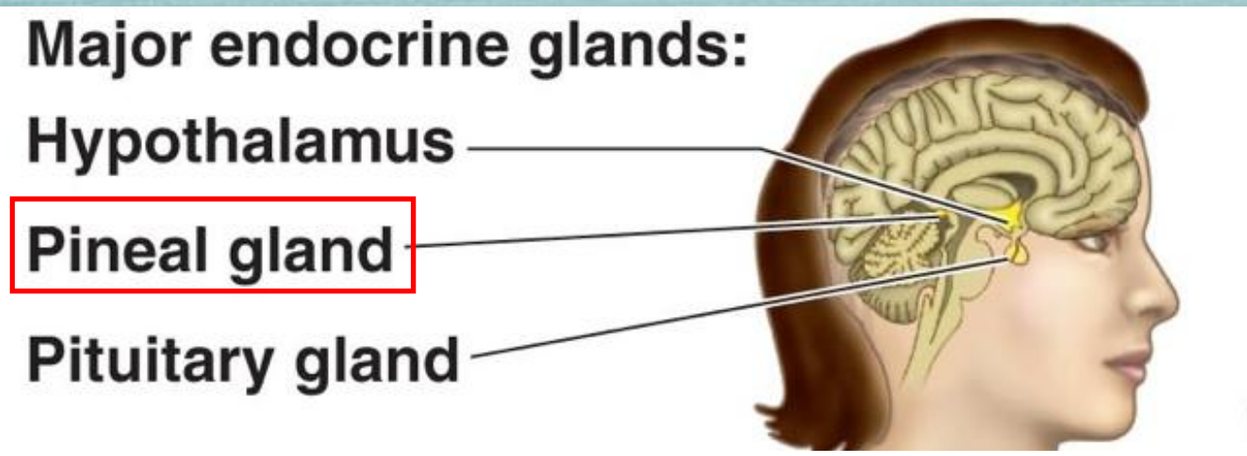
Estrogens (estradiol; 女性雌二醇)

Progestins (progesterone; 黃體酮)

Androgens (e.g. testosterone; 睪固酮)



Pineal gland and melatonin



- Pineal gland (松果體) synthesis and secrete melatonin (退黑激素)
- Pineal gland contains light-sensitive cells or has nervous connection from the eyes that control its secretory activity
- although melatonin affects skin pigmentation, its primary functions relate to biological rhythms (節奏;韻律)
- Melatonin regulates functions related to light and to seasons marked by changes in day length
- The main target of melatonin is a group of neuron in the hypothalamus called suprachiasmatic nucleus (SCN), which function as biological clock
- Melatonin seems to decrease the activity of the SCN