Chapter 6 Fever

1.Introduction
2.Causes and mechanisms of fever
3.Febrile phases and the characteristics of thermo-metabolism
4.Functional and metabolic changes induced by febrile response
5.Pathophysiological basis of prevention and treatment for fever


thermometer

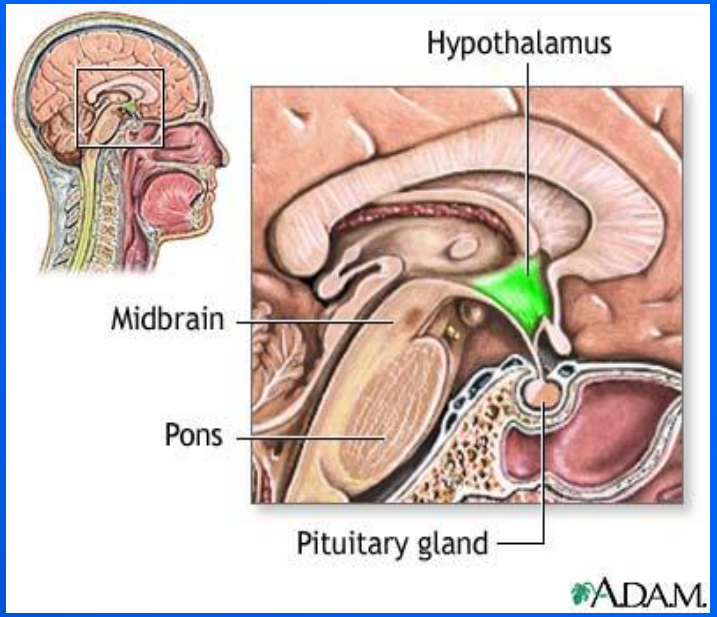
Jimin Shao (邵吉民), Ph.D.
Director and Professor, Pathophysiology
Tel: 88208209;
E-mail: shaojimin@zju.edu.cn

1. Introduction

(1)Normal body temperature

～37℃（98.6 °F）with a variation ～1°C

- Axillary 36-37 .4 °C
- Oral 36.7-37.7 °C
- Rectal 36.9-37.9 °C



（2）Regulation of normal body temperature (homeostasis)

Thermoregulatory center: mainly located in hypothalamus

Set point of hypothalamic thermostat:

- a hypothetic model for regulation of body temperature, which use the mechanic principle of thermostat of incubator to explain the process of body thermoregulation.
- The neurons in "set point" can sense the deviation of body temperature from its thermostat point and issue pulses to control the heat production and heat dissipation correspondently.

(3)Elevation of body temperature

An elevation of body temperature above the normal amplitude of daily variation(>0.5℃)

Types of body temperature elevation

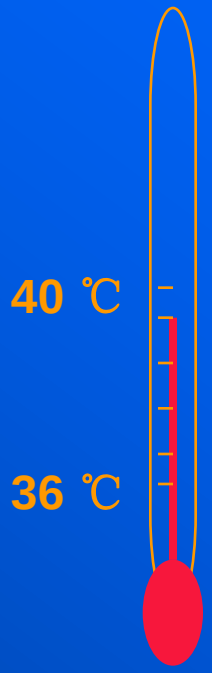
Physiological elevation

- before menstruation
- severe exercise
- stress

Pathological elevation

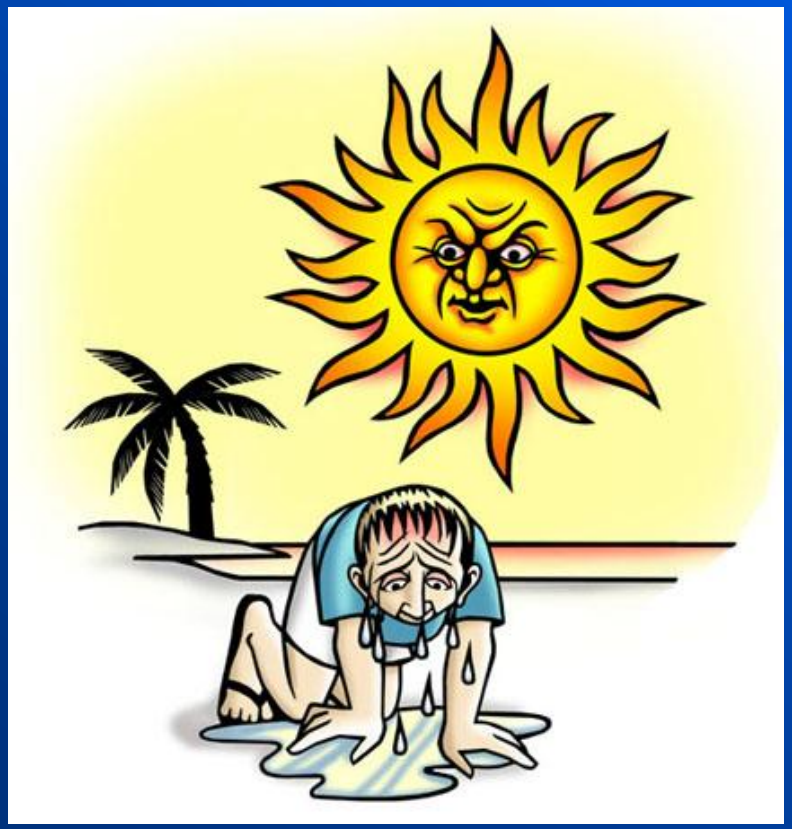
- Fever（发热）, e.g. Infection diseases
- Hyperthermia（过热）, e.g. heatstroke

An elevation of body temperature is fever?



Physiologic elevation of body temperature

A pathologic elevation of body temperature is fever?



Heatstroke

Hyperthyroidism

Central nervous system damage

hyperthermia

Fever

Fever is a complicated pathological process characterized by a regulated elevation of core body temperature that exceeds the normal daily variation (>0.5℃), in which pyrogens cause a temporary upward resetting of the hypothalamic thermostatic setpoint, inducing a complex physiologic and pathophysiologic febrile response.

- Regulated increase of body temperature above 37.5℃
- Caused by pyrogens
- Body temperature =the changed setpoint

Hyperthermia

An unregulated rise in body temperature beyond the unchanged hypothalamic thermostatic setpoint resulting from the dysfunction of body temperature center or impairment of heat production and/or heat loss mechanisms.

Causes:

- overproduction of heat
- impediment in heat loss
- dysfunction of body temperature center

Features:

- Passive increase of body temperature >0.5 °C
- Body temperature beyond the unchanged setpoint

Comparison between hyperthermia and fever

Hyperthermia	Fever
Arising from changes within the body or by changes in environment	Resulting from pyrogen
Set-point remains unchanged or damaged, or effector organs fails	Ability to regulate set-point remains intact, but is turned up at a high level functionally
Body temperature may rise to a very high level	Rise of body temperature has an upper limit
Treatment with water-alcohol bathing	Treatment with antipyretics and measures and drugs to eliminate the causes

2. Causes and mechanisms of fever

(1) Pyrogenic activator（发热激活物）
(2)Endogenous pyrogen (EP，内生致热原)
(3)Mechanisms of set point elevation caused by EP
(4)Pathogenesis of fever

(1) Pyrogenic activator

Concept of pyrogenic activator

fever-inducing substances that can activate endogenous pyrogen-generating cells to generate and release EPs.

Pyrogenic activator (exogenous pyrogen) → stimulate the cells → produce and release EPs.

Category of pyrogenic activator

- **Infectious factors: microbes and microbial products**
  - G^- bacteria: Lipopolysaccharide (LPS)/Endotoxin
  - G+bacteria: Exotoxins;Peptidoglycans,Teichoic acid(LTA)
  - Viruses
  - Other microorganisms

- **Non-infectious factors:**
  - Antigen-Antibidy complexes
  - Components of the complement cascade
  - Non-infectious inflammation-genesis irritants
  - Certain steroids: etiocholanolone(本胆烷醇酮)

(2)Endogenous pyrogen (EP)

Concept of EP

EPs are fever-inducing cytokines, such as TNF, IL-1, IL-6 and IFN, via elevating the hypothalamic thermostatic setpoint, and derived from mononuclear cells, macrophages, Kupffer cell, endothelia cells and etc, under the action of pyrogenic activators.

EP generating cells

- Monocyte
- Macrophage
- T lymphocyte
- Kupffer cells
- Endothelia cells
- Some tumor cells

Category of EPs

- Interleukin-1 (IL-1)
- Tumor necrosis factor (TNF)
- Interferon (IFN)
- Macrophage inflammatory protein-1 (MIP-1)
- Interleukin-6 (IL-6)
- Others

Endogenous Pyrogenic cytokines

EPs	Principle source	Inducers
IL-1α IL-1β	Macrophages and other cell types	LPS,TNF, Other microbial products
TNF-α	Macrophages	LPS, Other microbial products
TNF-β	Lymphocytes(T&B)	antigen, mitogen stmulation
IFN- α	Leukocytes	
IFN- β	Fibloblasts	LPS, viral infection
IFN-γ	T-lymphocytes	
IL-6	Many cell types	LPS, TNF
MIP-1α MIP-1β	Macrophages	LPS
IL-8	Many cell types	LPS, TNF, IL-1

Production and release of EP

LPS + LBP (LPS binding protein, serum)--- + sCD14
---TLR (Toll-like receptors, EP-producing cells)
--- NF- κ B---Target genes --- EP expression and release

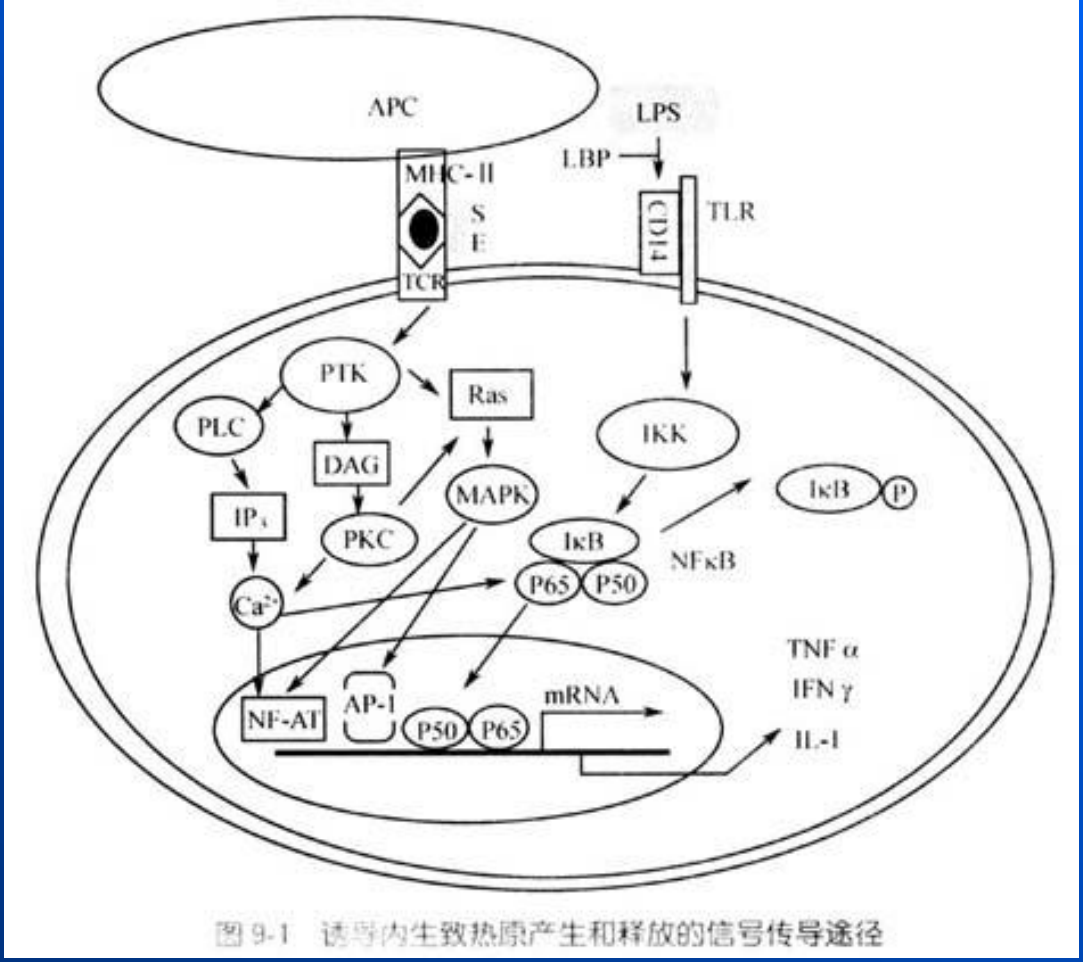


图 9-1 诱导内生致热原产生和释放的信号传导途径

(3)Mechanisms of setpoint elevation by EP

Thermoregulation center

- Positive regulation center

  Preoptic region of anterior hypothalamus(POAH，视前区-下丘脑前部)：

  Temperature-sensitive neurons

  Cold sensitive neuron

  Warm sensitive neuron

- Negative regulation center

  Medial amygdaloid nucleus (MAN，中杏仁核)

  Ventral septal area (VSA，下丘脑腹隔区)

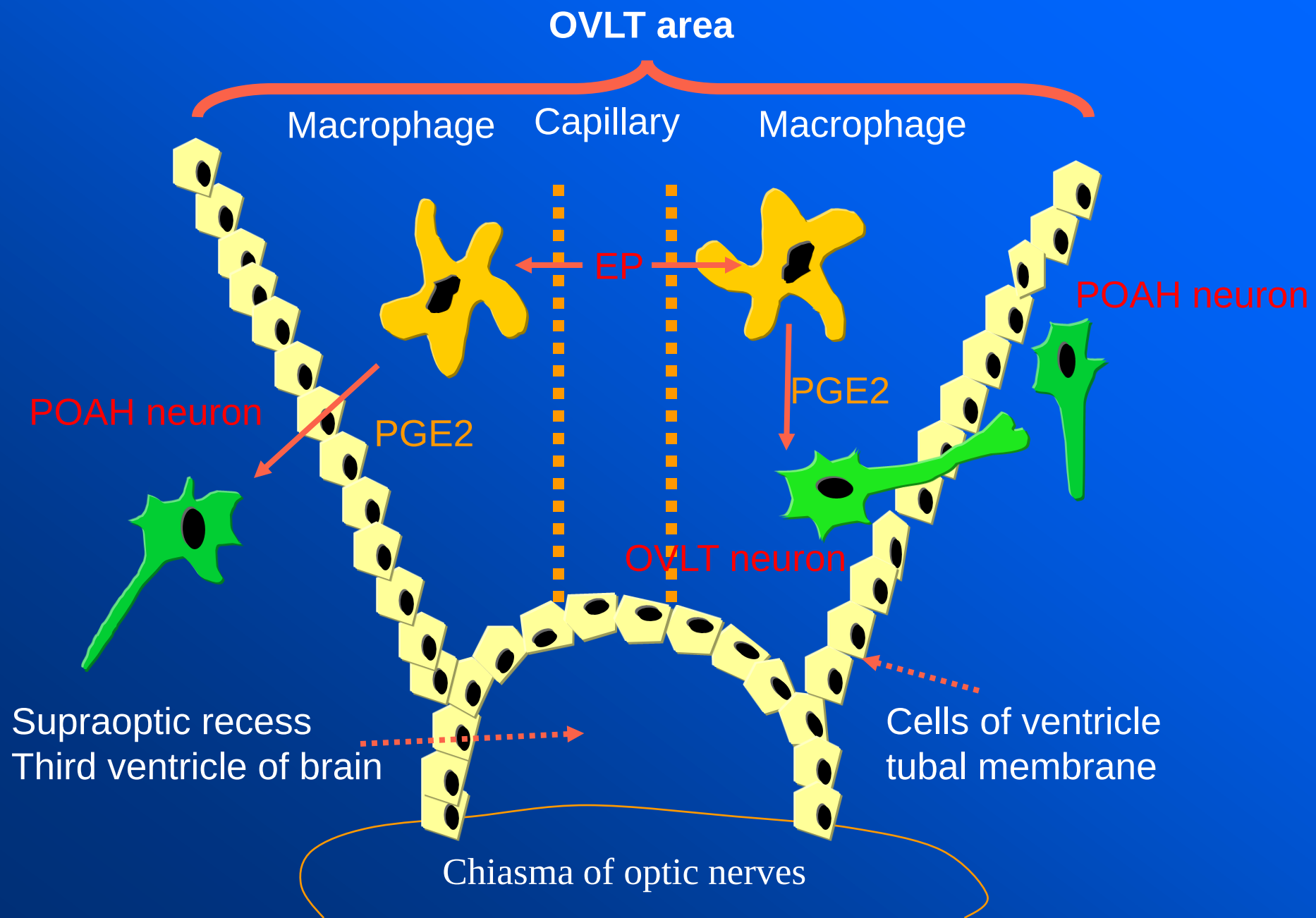
The routes for EP signals into the thermoregulatory center of hypothalamus

- Organum vasculosum laminae terminalis (OVLT，下丘脑终板血管器)
  specialized neural regions along the margins of the cerebral ventricular system that have fenestrated capillaries (almost no blood-brain-barrier)

- Blood-brain barrier

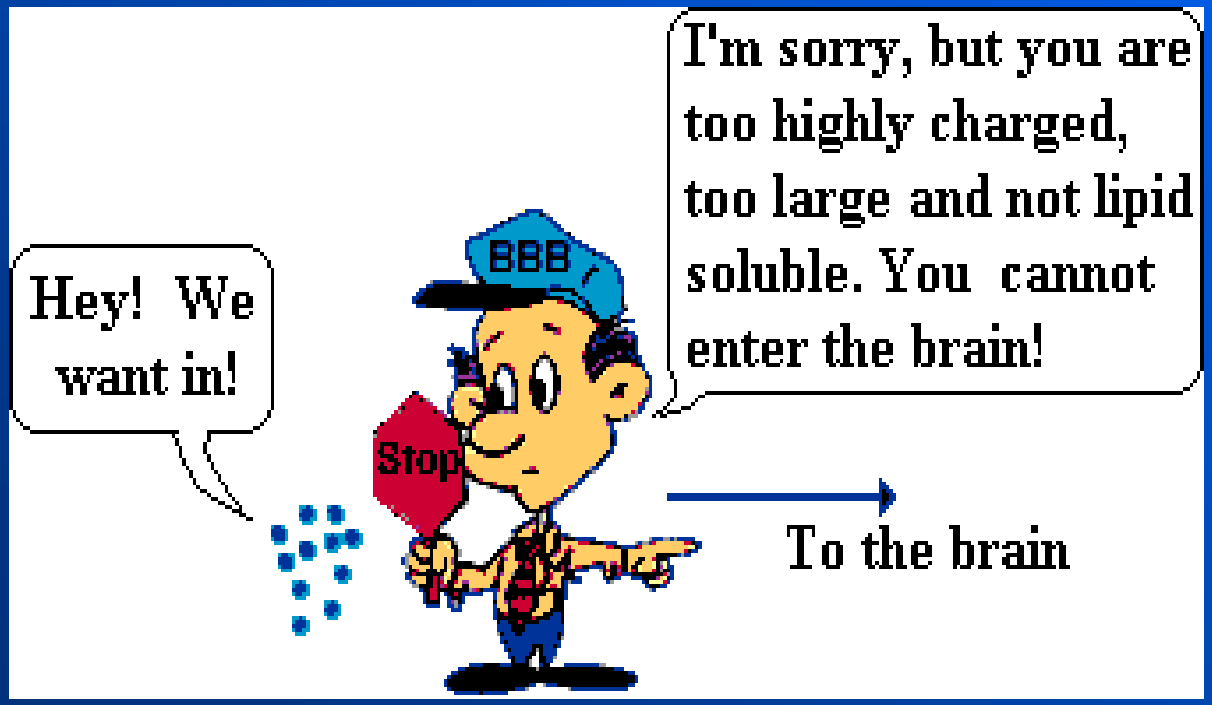
- Vagal afferent nerve fibers

The Role of OVLT in pathogenesis of fever



The BBB can be broken down by:

Hypertension: high blood pressure opens the BBB
Development: the BBB is not fully formed at birth.
Radiation: exposure to radiation can open the BBB.
Infection: exposure to infectious agents can open the BBB.



Central mediators of fever

❖The positive regulatory mediators

- ✱ Prostaglandins (PGE2)
- ✱ Corticotropin releasing hormone (CRH)
- ✱ The ratio of central Na^+/Ca^{2+}
- ✱ cAMP
- ✱ Nitric oxide (NO)

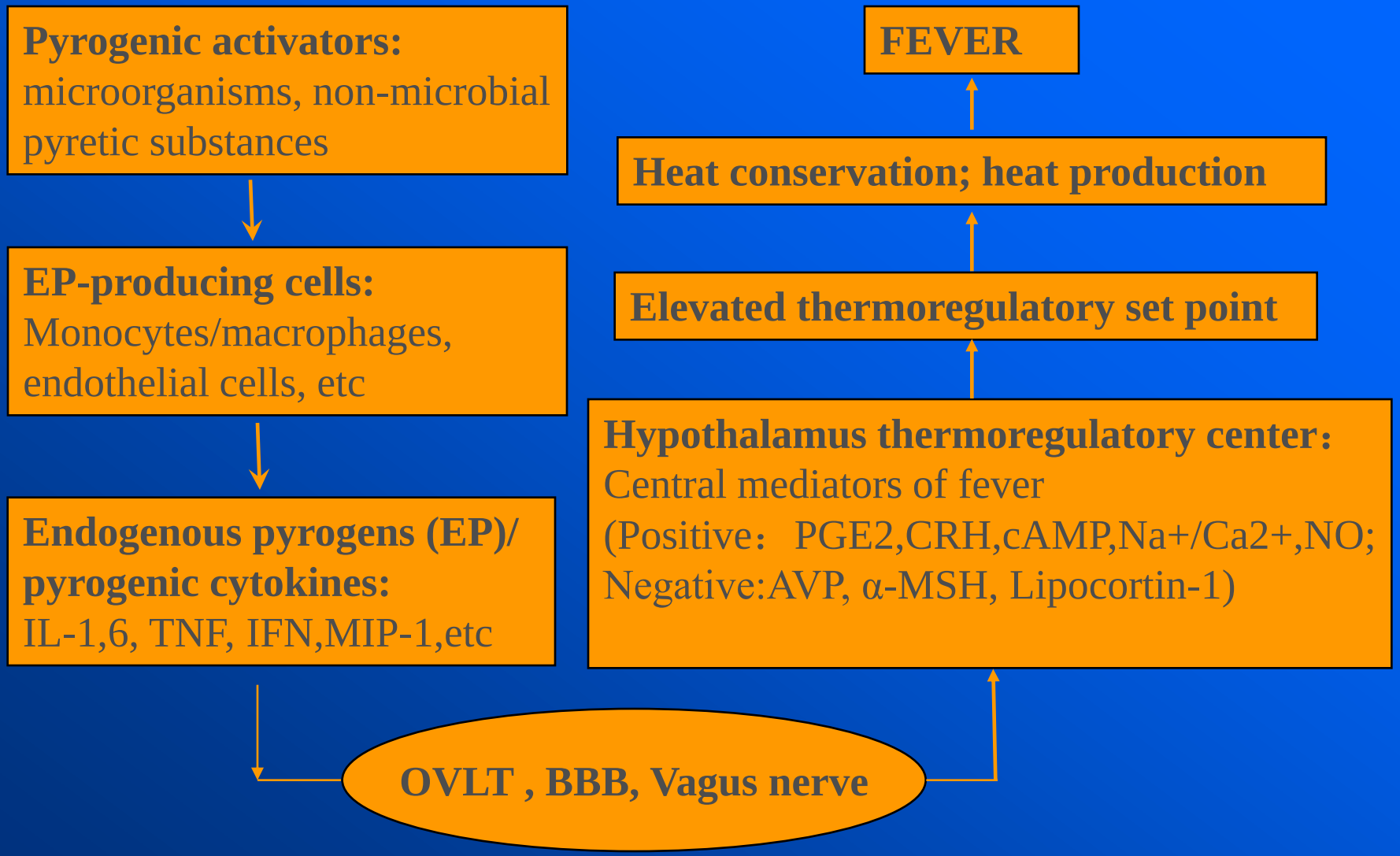
❖The negative regulatory mediators

Febrile ceiling（热限）: The febrile response is controlled within a strict limit, the upper limit almost never exceeds 41.0℃.

Endogenous cryogen: the endogenous antipyretic substances that antagonize the effects of pyrogens on thermosensitive neurons, including:

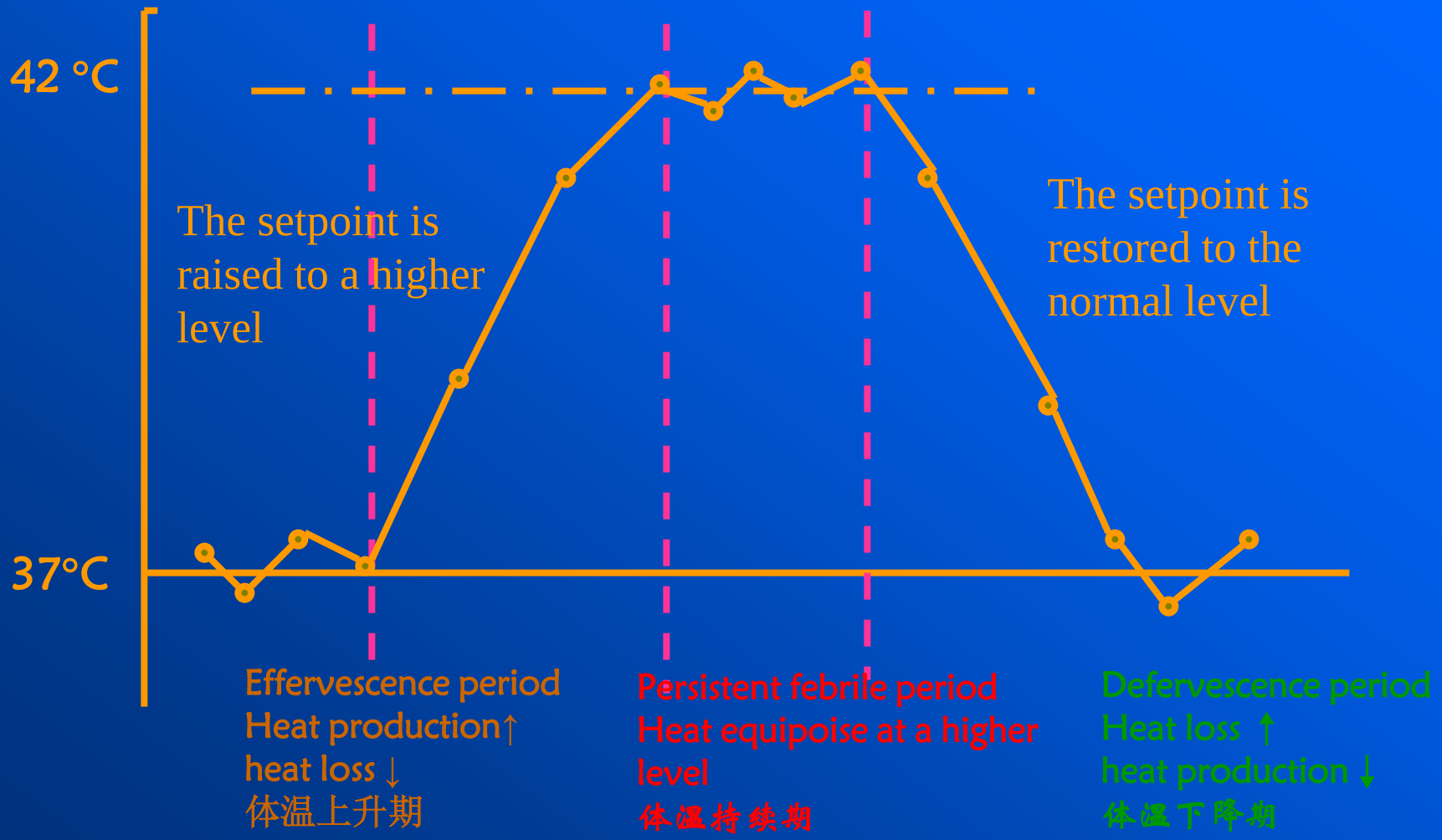
- ✱ Arginine vasopressin (AVP，精氨酸加压素)
- ✱ α-melanocyte-stimulating hormone (α-MSH，α黑素细胞刺激素)
- ✱ Lipocortin-1/Annexin A1（脂皮质蛋白-1/膜联蛋白A1）

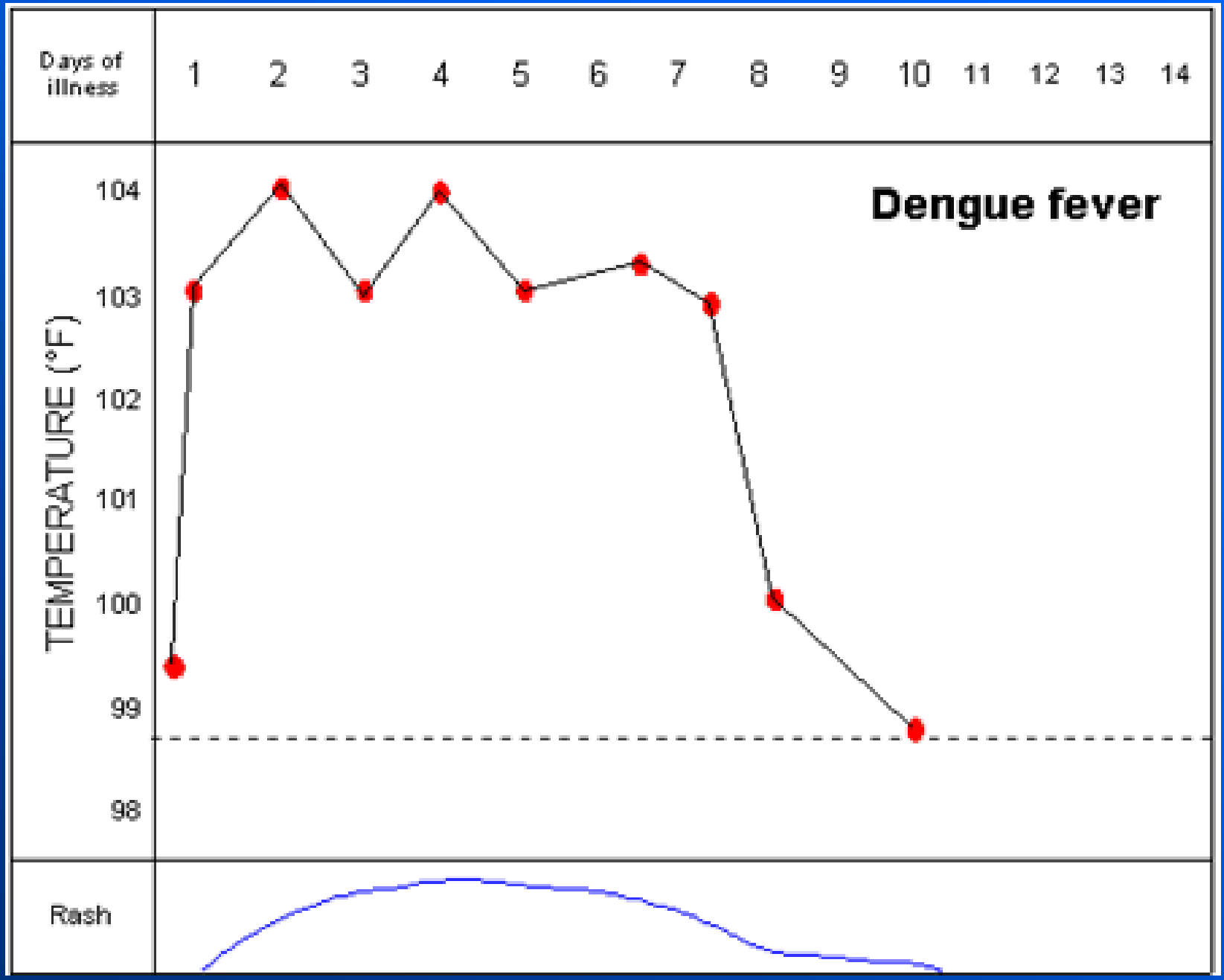
(4) Pathogenesis of fever

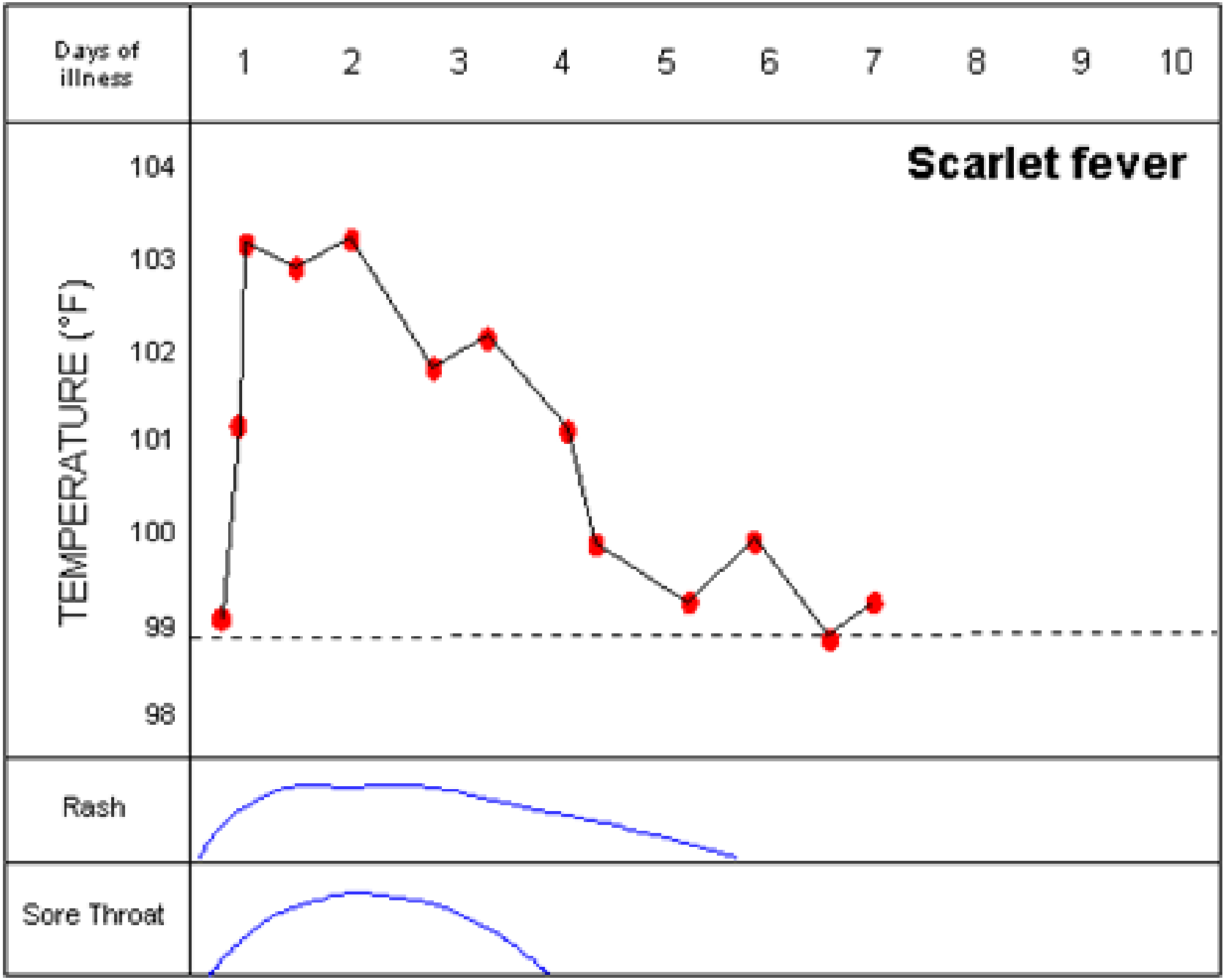


3. Febrile phases and the characteristics of thermo-metabolism

Three stages of fever (typical)




Days of illness
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Dengue fever
TEMPERATURE (°F)
104
103
102
101
100
99
98
Rash


Days of illness
1
2
3
4
5
6
7
8
9
10
Scarlet fever
TEMPERATURE (°F)
104
103
102
101
100
99
98
Rash
Sore Throat

4.Functional and metabolic changes induced by febrile response

In addition to changes of the primary disease eliciting fever, a series of functional and metabolic alterations occur during fever because of the elevated body temperature.

(1)Functional changes

- Central nervous system: excitability↑
- Cardiovascular system: beat rate↑,cardiac output↑
- Respiratory system: hyperventilation/respiratory rate ↑
- Digestive system: suppressed ↓
- Immune system: anti-infection and anti-tumor activities ↑

(2)Changes of metabolism

- Generally, the basal metabolic rate increases 13% while 1 °C elevation in body temperature.
- Consumption and catabolism of nutrients increase during fever: Carbohydrates, Lipid, Protein, Walter, Salts, Vitamines

5. Pathophysiological basis of prevention and treatment for fever

Basic principles for fever treatment

- Determine and eliminate the cause of a fever；
- Antipyretic therapy:
  High fever,
  children,
  pregnant wommen,
  patients with severe cardiopathy
- Support measures:fluid and nutrients
- Physical measures

Case study