




The Pathogenesis of Fever

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**Humanity has but three great enemies:
fever, famine, and war. Of these, by far the
greatest, by far the most terrible, is fever.**

— *Sir William Osler*



Outline

- History
- Definitions of Fever
- Thermoregulation
- Mechanisms of Fever Induction
- Therapy

History I

- Hippocrates believed that fever resulted from an imbalance in four humors: yellow bile, black bile, blood, and phlegm
- Wunderlich in 1868 observed over 1 million temperatures over a 16-year period
 - Temperature $>38^{\circ}\text{C}$ suspicious
 - Normal temperature between 36.3°C and 37.5°C
 - Trough at dawn, peak in evening
 - Elderly have temperature 0.5°C lower

History II

- Welch hypothesized in 1888 that microbes produced fevers by acting directly on the brain
- 1950s endogenous pyrogens were discovered
- Additional advances made in understanding fever in past decade

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graph TD; A[↑ Temperature] --> B[Fever]; A --> C[Hyperthermia]
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↑ Temperature

Fever

Hyperthermia

Fever

- One of array of host defense responses to invasion of body by microbes
- Fever is a healing response
- Arises from complex sequence of interactions among soluble factors and host cells
- Initiated in periphery and transmitted to brain to modulate fever response
- Response both propyretic and antipyretic

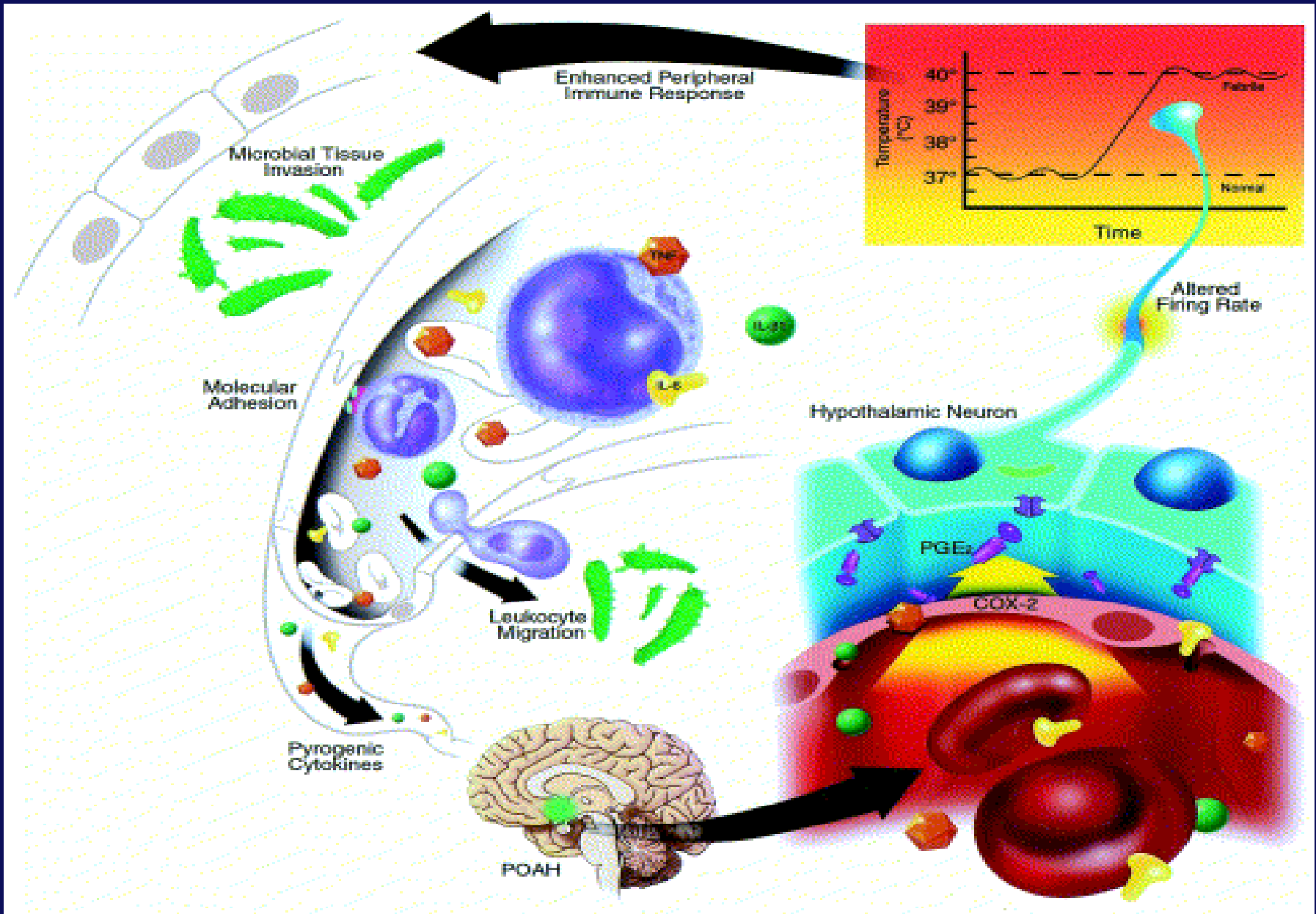
Hyperthermia

- Unregulated T rise above the set point
- Pathologic condition that reflects an imbalance between heat-generating & heat-dissipating mechanisms
- Exertional, passive (sauna), meds, volume depletion, high ambient T
- Subjects choose cool environments

Fever

- Unlike hyperthermia, fever rarely exceeds 107.6°F (42°C)
- If $T > 107.6^\circ\text{F}$, thermoregulatory failure (hyperthermia)
 - Volume depletion
 - Anticholinergic meds
 - Overdressed
 - NMS, etc

NMS = neuroleptic malignant syndrome.



Aronoff DM, et al. *Am J Med.* 2001;111:304-315.

Acute Phase Responses

■ Increases in

- Elevated core temp
- ACTH, GH, AVP
- Neutrophils
- Sympathetic activity
- Muscle proteolysis
- Lipogenesis
- CRP, C, fibrinogen

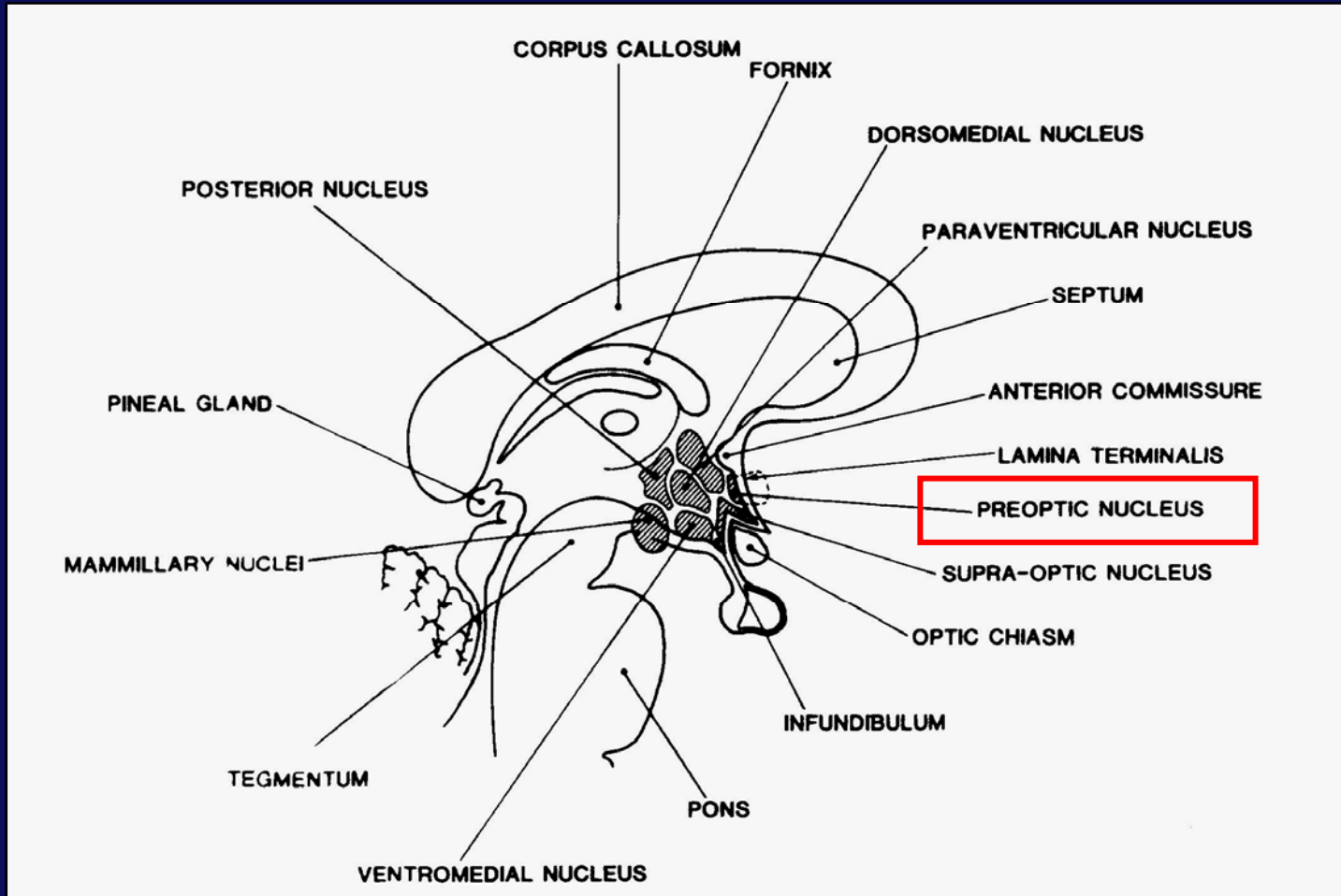
■ Decreases in

- TSH
- Erythropoiesis
- Albumin, transferrin
- Bone substance
- Gluconeogenesis

Thermoregulation

- Thermoregulatory center in preoptic area of the anterior hypothalamus (POAH)
- Body temperature is circadian
 - 97.0°F - 99.3°F (36.1°C - 37.4°C)
- Lowest in early AM; highest at 4-6 PM
- Fluctuation is also seen with illness

POAH: Preoptic Area of the Anterior Hypothalamus

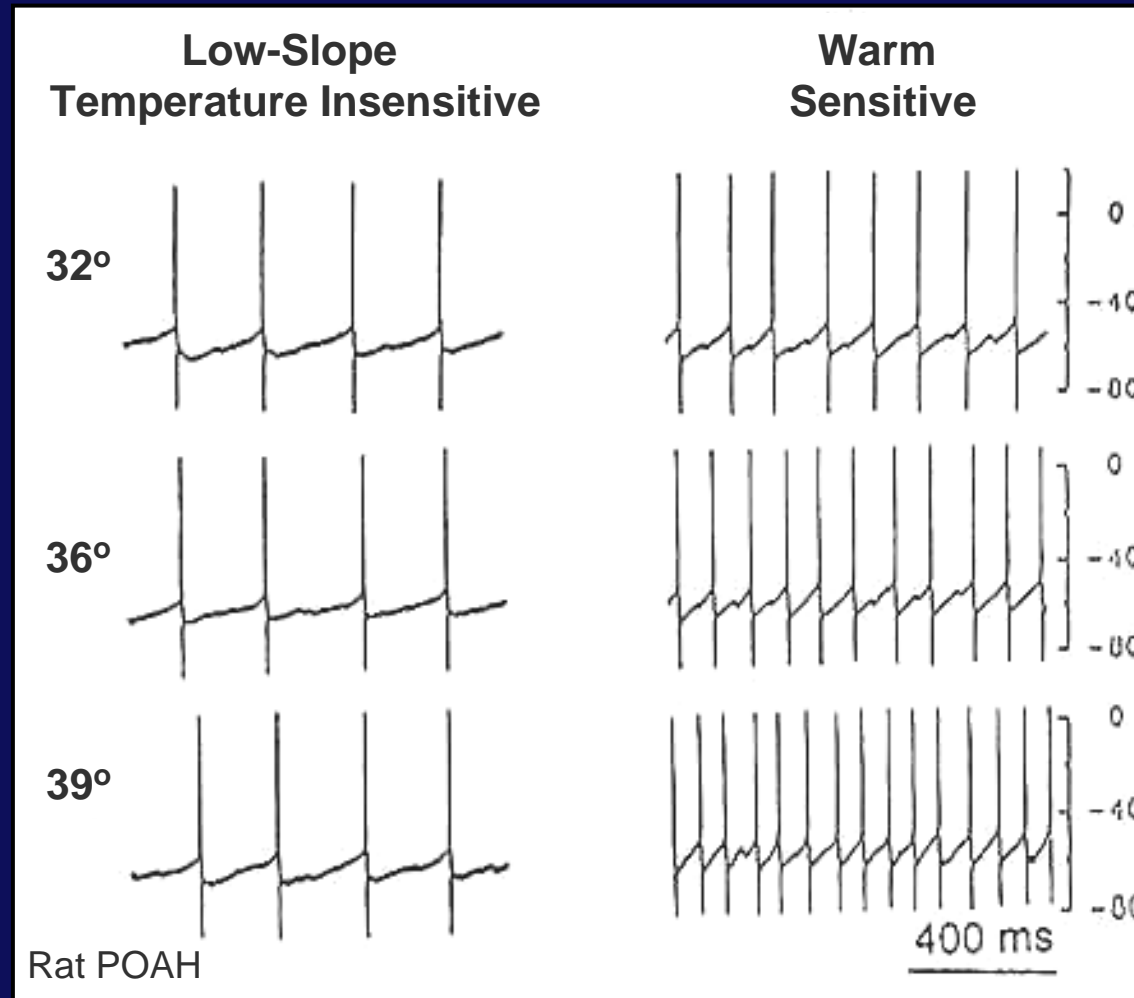


Cooper KE. *Fever and Antipyresis: the Role of the Nervous System*. New York, NY: Cambridge University Press; 1995:145.

Neurons in the POAH are Both Temperature-Sensitive and Temperature Insensitive

- Firing rates depend upon afferent T signals
 - Skin
 - Viscera
 - Blood/Brain
- The majority of the POAH neurons are temperature insensitive

T Insensitive and Temperature Sensitive Neurons



Warm Ambient Temp

Skin

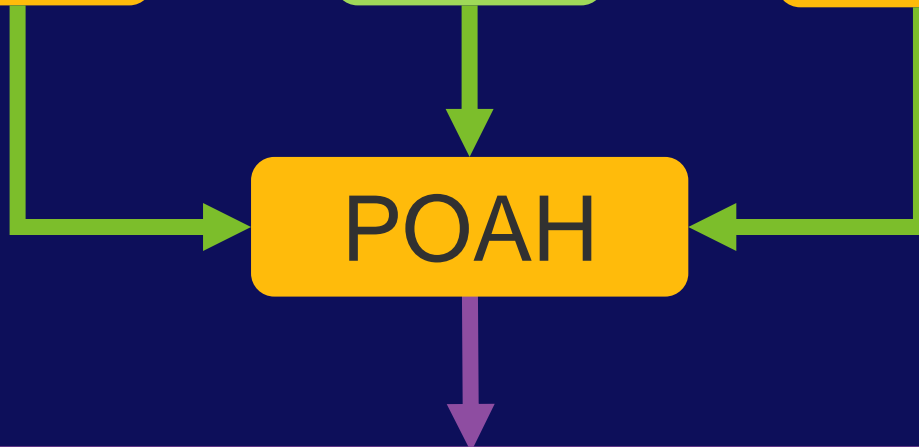
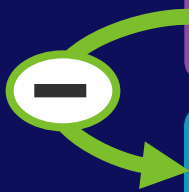
Core

Brain

POAH

↑ Firing warm-sensitive neurons

↓ Firing cold-sensitive neurons



The Warm Response

↓ Heat production
↑ Heat loss

Behavioral changes

Seek cool environment

Subtract clothes

↓ Physical activity

Physiological changes

Sweating

Cutaneous vasodilatation

Cold Ambient Temp

Skin

Core

Brain

POAH

↓ Firing warm-sensitive neurons

↑ Firing cold-sensitive neurons

The Cold Response

↓ Heat loss
↑ Heat production

Behavioral changes

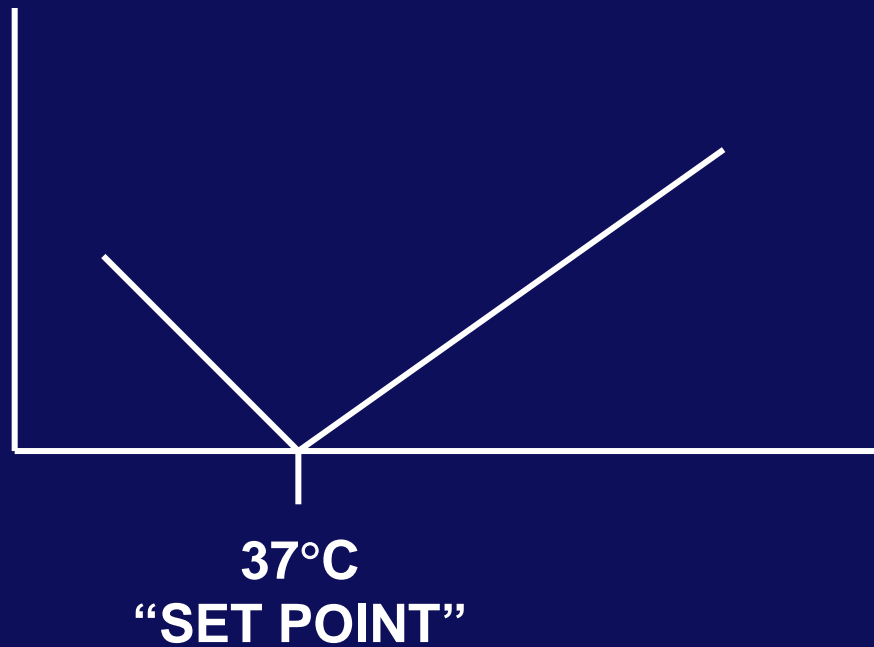
Seek warm environment
Add clothes
↑ Physical activity

Physiological changes

Shivering
Nonshivering thermogenesis
BAT
Thyroxine
Catecholamines
Cutaneous vasoconstriction

Thermoregulation

Whole Body
Heat Production
& Heat Loss



Elevated Temperature

Early AM

$$T_o \geq 99.0^\circ\text{F} (37.2^\circ\text{C})$$

Any time

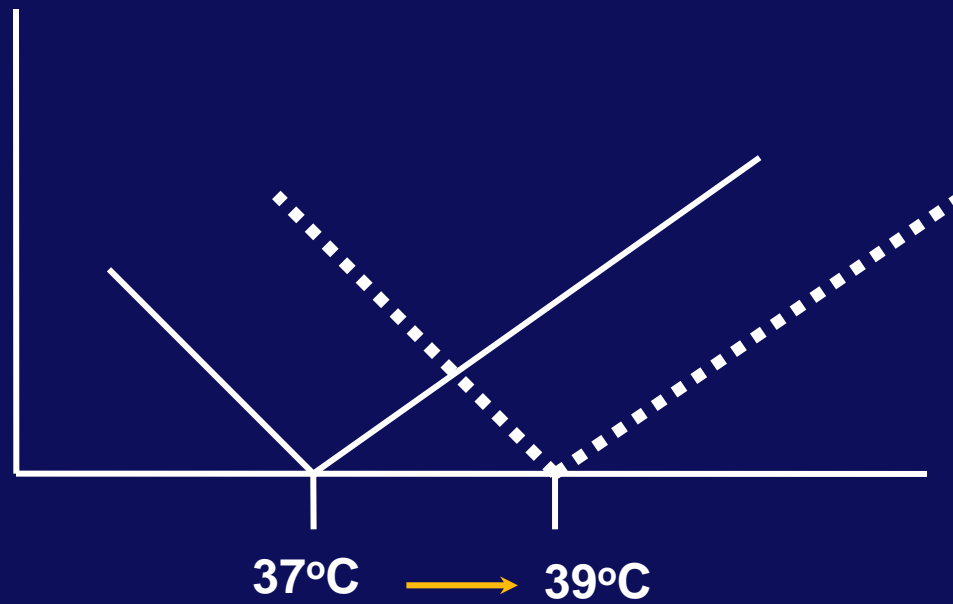
$$T_o \geq 100.0^\circ\text{F} (37.8^\circ\text{C})$$

Fever

- Controlled temperature ↑ in response to an elevated hypothalamic set point
 - Heat generation favored over heat loss until new set point reached
 - Febrile hosts prefer warm environments to facilitate heat conservation
 - Increase heat production by shivering, cutaneous vasoconstriction, no sweating

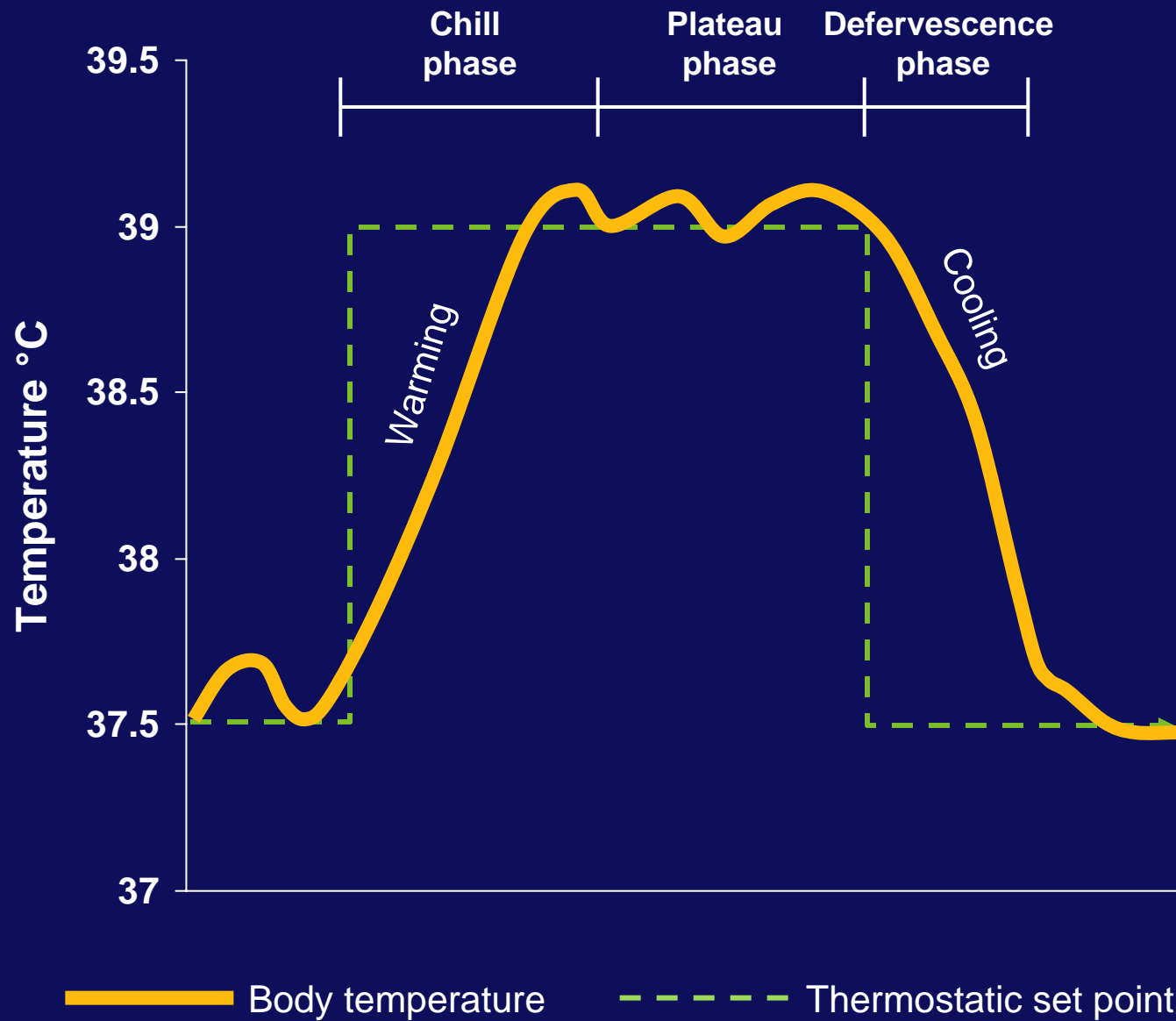
Fever

Whole Body
Heat Production
& Heat Loss



NEW SET POINT

Thermoregulation occurs normally



Modified from Fenella C. *Nurs Stand.* 1997;12:40-43.

Measurement of Fever

- In clinical practice, core temperature is best measured by rectal thermometer
- Usually rectal 1° > oral; 2° to 2.5° > axillary
- Electronic thermometers often adequate
- Skin temperature measurements and infrared thermometers are less reliable

Effects of Fever

■ Beneficial

- Impair organisms
- Increased Fe+ needs
- Increased PMNs
- Increased ingestion
- Increased interferon
- Improved survival in animals early in infection

■ Detrimental

- High fever impairs PMNs
- Increased mortality in septic shock
- Decreased survival in animals late in infection
- Imposes cardiac stresses
- Neurologic symptoms
- Causes discomfort

PMN = polymorphonuclear leukocyte.

Host-Microbial Interactions

- Exogenous pyrogens (microbes) stimulate local release of endogenous pyrogens (cytokines)
- Pyrogenic cytokines = directly provoke febrile response
 - IL-1 β , TNF & IL-6

IL = interleukin; TNF = tumor necrosis factor.

Sources of Pyrogenic Cytokines

Monocytes/Macrophages

Dendritic cells

- PMNs
- Endothelial cells
- Etc



**Antigen presenting cells
(APCs)**

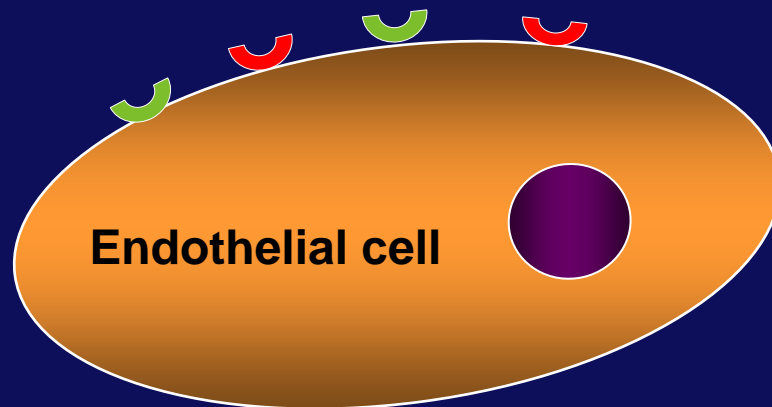
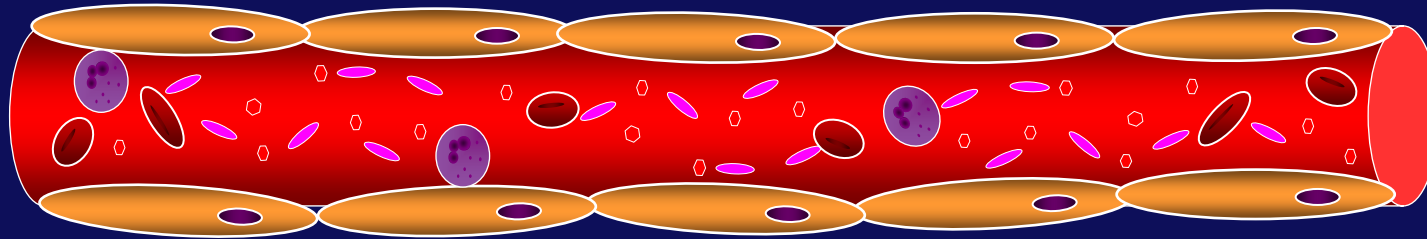
Sources of Pyrogenic Cytokines

- Microbes activate APCs via
 - Toll-like receptors (TLRs 1-10)
 - Endocytic pattern-recognition receptors
 - M ϕ mannose receptor
 - MHC_{II}-T cell receptor (superantigens)

How Does Cytokinememia Modulate Hypothalamic Neurons?

- Access problem: cytokines do not cross BBB well
- Answer: brain endothelial cells act as signal transducer to neurons

Cytokines & Germs Stimulate Endothelial Cells



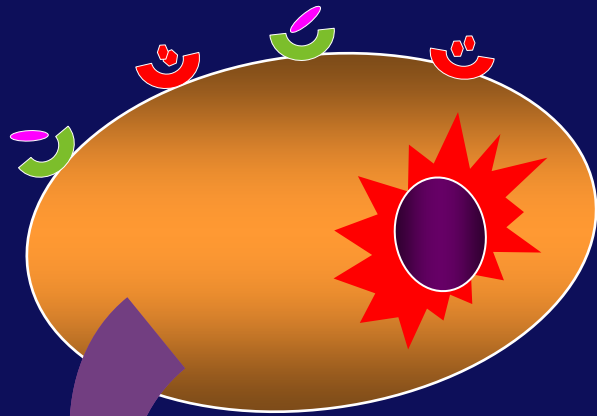
IL-1 β signals via IL-1R₁

TNF signals via p55

IL-6 signals via IL-6R/gp130

Bugs signal via TLRs

Endothelial PGE₂ Production



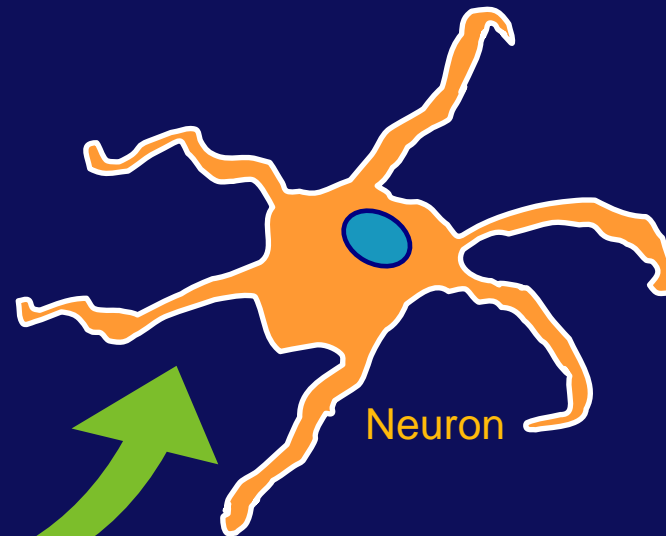
↑↑ Expression & Activity

cPLA₂: cytosolic phospholipase

COX-2: cyclooxygenase-2

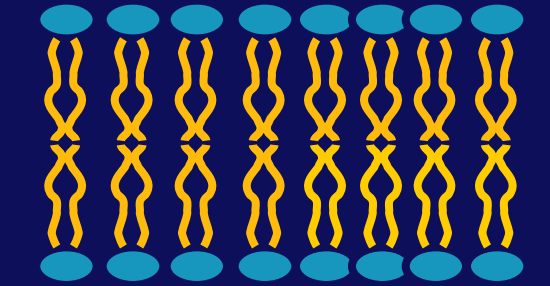
mPGES: microsomal PGE
synthase

PGE₂



Neuron

PGE₂ Synthesis



Membrane phospholipids

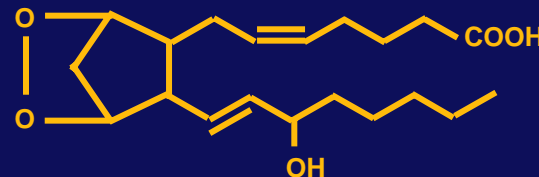
cPLA₂



Arachidonic acid

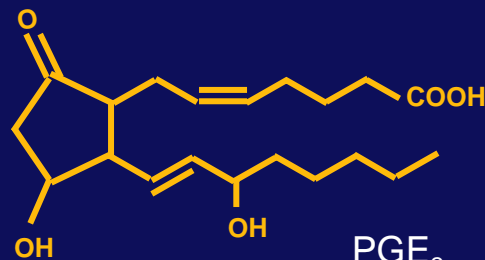
2 O₂

COX-2



PGH₂

mPGES



PGE₂

The Role of PGE₂ in Fever

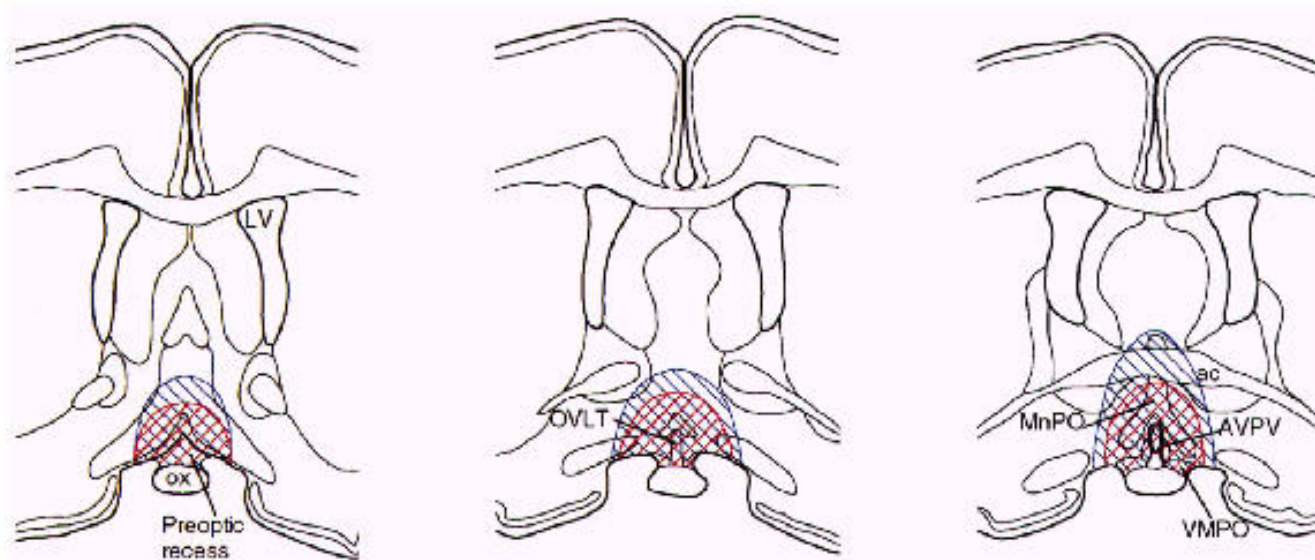
- 1970: Milton and Wendlandt
 - ICV PGE₁ induces fever in cats
- 1971: Vane
 - Antipyretics inhibit PGE production
- 1972: Feldberg et al
 - Fever associated with ↑CSF [PGE₂]
- 1975: Veale and Cooper
 - POAH very sensitive to PGE injection

ICV = intracerebroventricular.

Cooper KE. *Fever and Antipyresis: the Role of the Nervous System*. New York, NY: Cambridge University Press; 1995.

The POAH & PGE₂ Action

Rat Brain

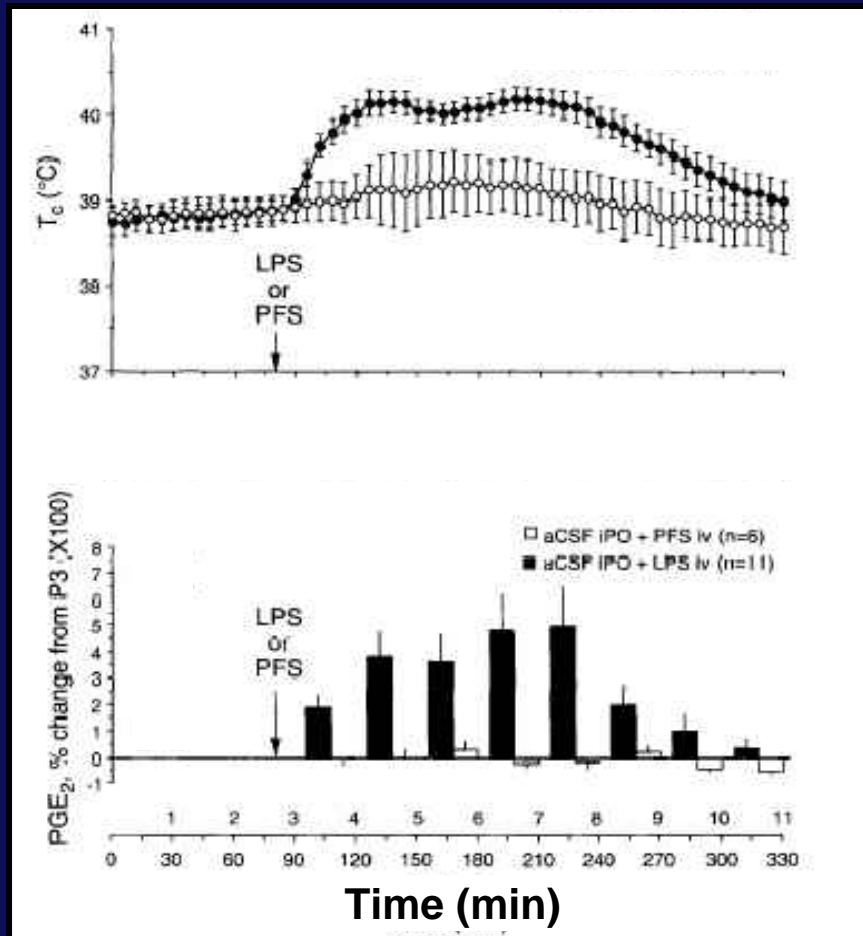


 PGE₂ injection → fever

 NSAID blocks fever to IV endotoxin
(POAH is site of PGE₂ synthesis)

Preoptic PGE₂ Levels Rise & Fall With Fever

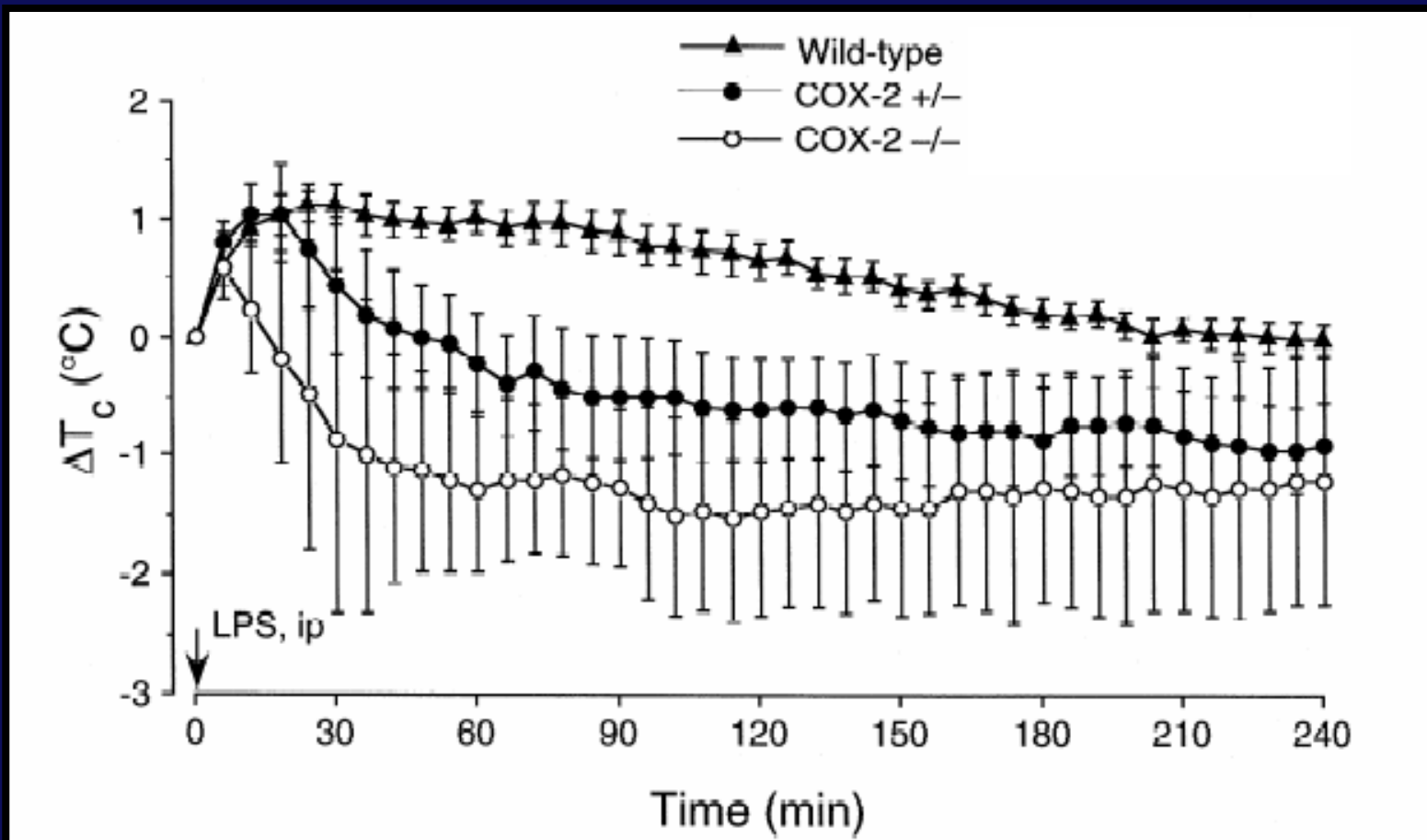
TEMP (°C)



Δ PGE₂

- Guinea pig model
- IV LPS pyrogen
- PGE₂ measured by microdialysis

Febrile Response to Lipopolysaccharide (LPS) in COX-2^{-/-}



PGE₂-EP₃ coupling



↓ cAMP



↓ Firing warm-sensitive neurons



Derepression

↑ Firing cold-sensitive neurons



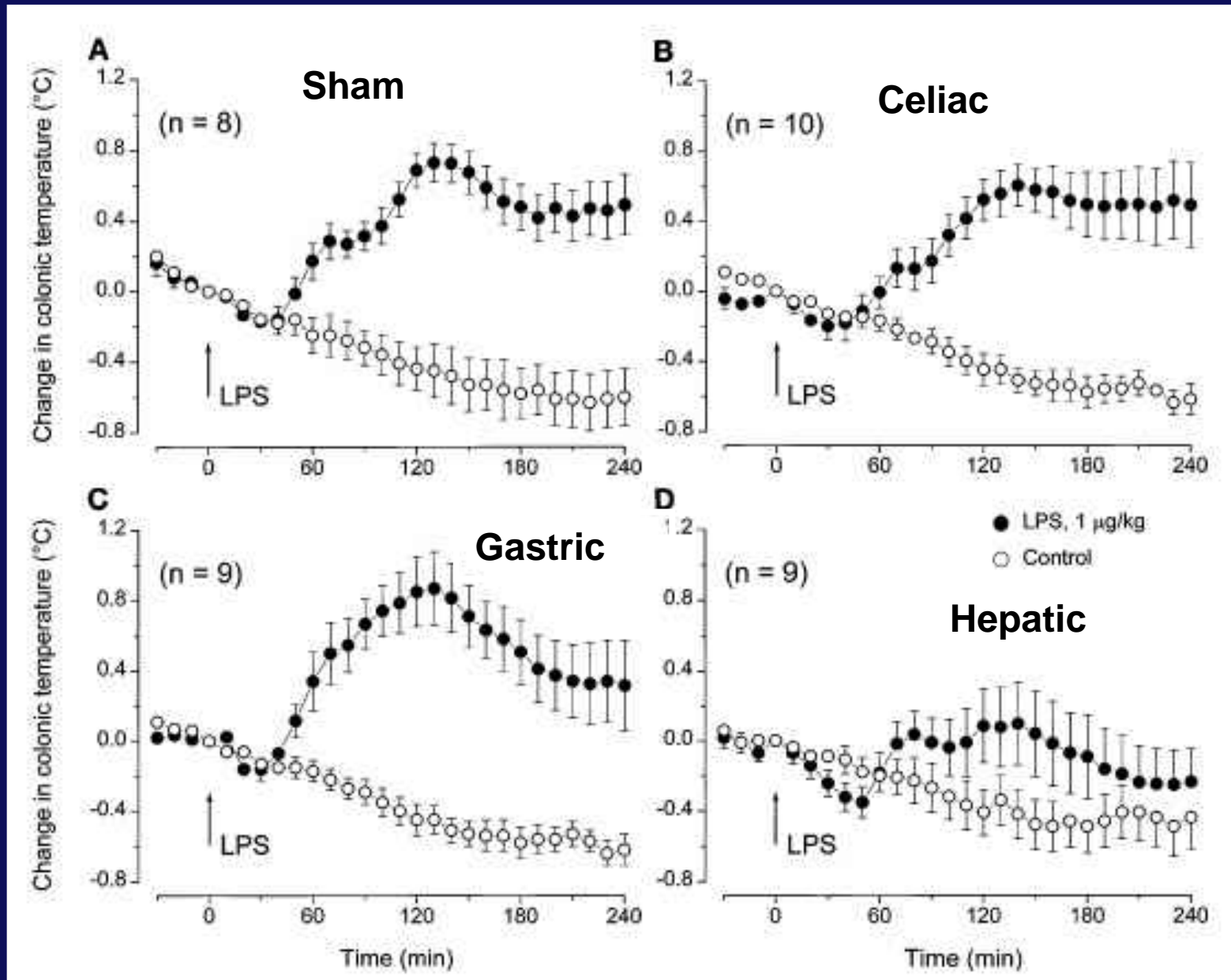
↑ Heat production
↓ Heat loss



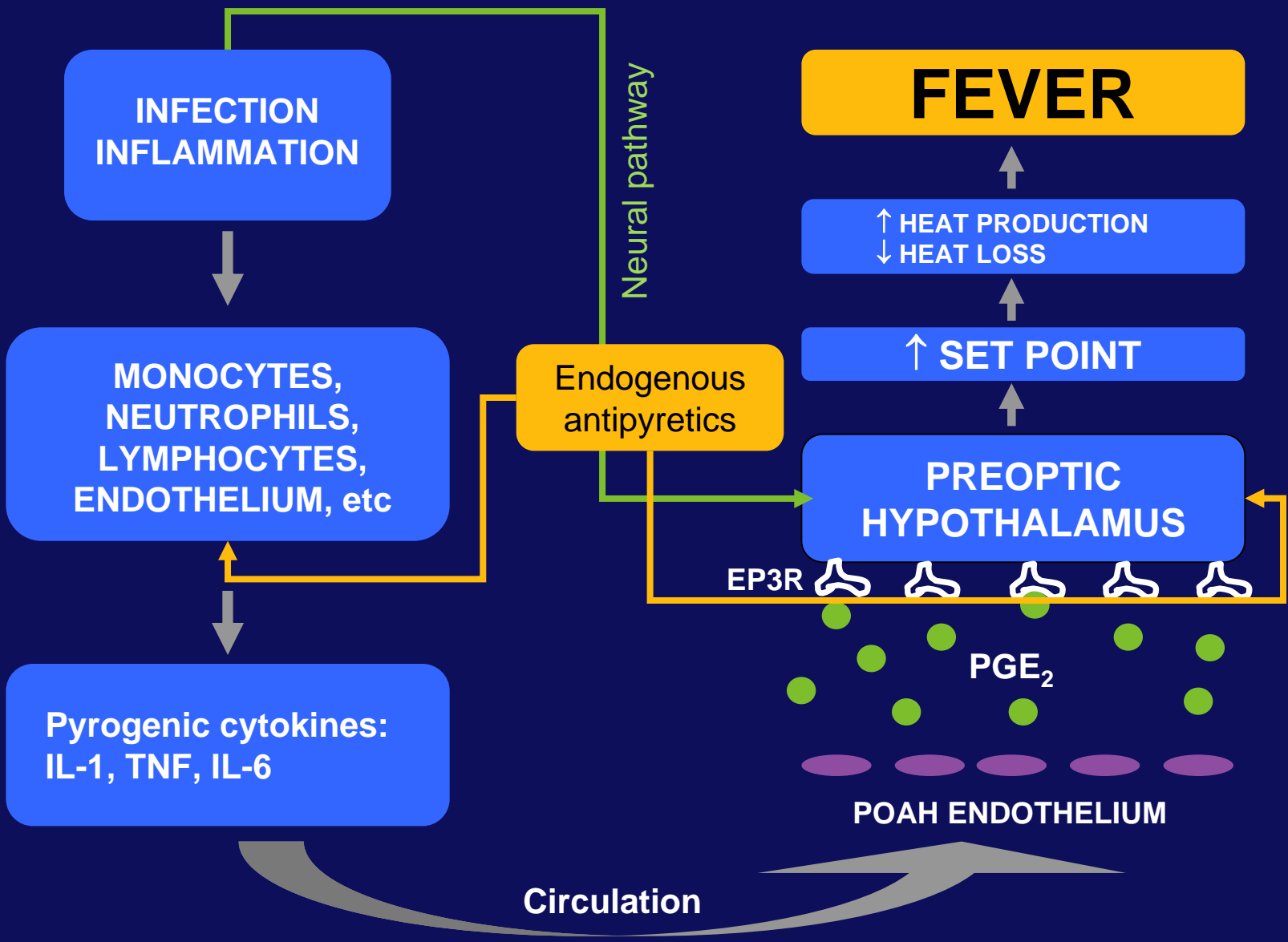
Fever

Role of Vagus Nerve in Fever

- Hepatic branch of the vagus nerve transduces inflammatory messages to the CNS
- Abdominal vagotomy
 - Blocks CNS activation by endotoxin
 - Attenuates fever from “low-dose” LPS
 - Prevents sickness behavior and HPA activation by LPS, IL1- β



Simons CT, et al. *Am J Physiol.* 1998;275:R63-R68.



Adapted from Dinarello CA, et al. *Curr Biol.* 1999;9:R147-R150.



Limiting the Febrile Response

Endogenous Antipyretics

- Substances that limit the height and duration of the febrile response
- Act at peripheral sites of inflammation & central sites of thermoregulation

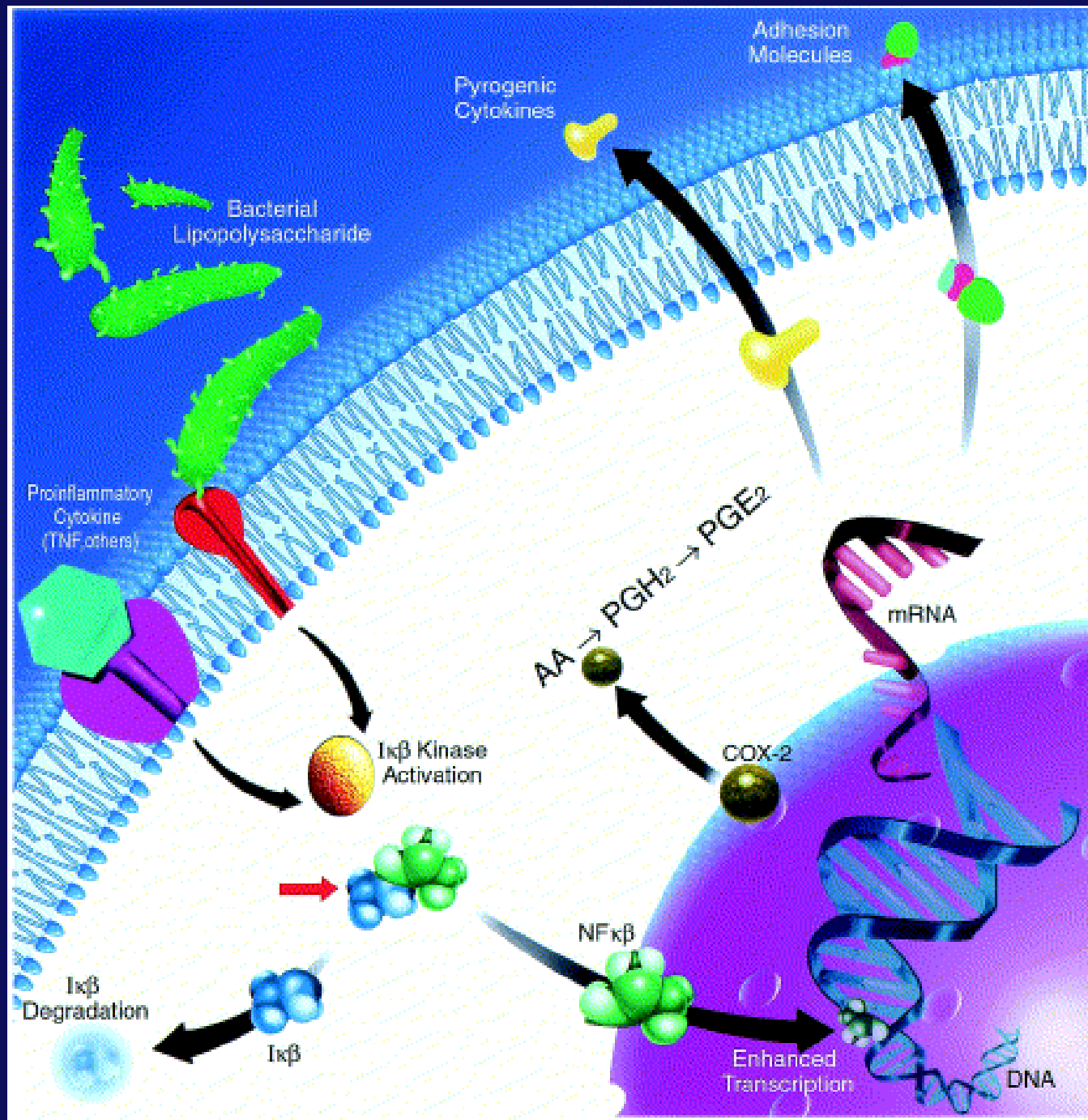
Endogenous Antipyretics

Class & Agent	Site of Action	Mechanism
Steroid hormones, Glucocorticoids	CNS	?, via type II GR
Neuropeptides/hormones Arginine vasopressin Melanocortins (ACTH, α -MSH, γ -MSH)	CNS CNS Adrenal Cortex	?, via V1R ?, via MC3/MC4 R ACTH: MC2 R
Cytokines TNF- α IL-10	Peripheral Unknown	? ↓ Pyrogenic cytokine release
Other Lipocortin-1 Epoxyeicosanoids	Unknown CNS	? ?

Adapted from Tatro JB. *Clin Infect Dis.* 2000;31(suppl 5):S190-S201; Kozak W, et al. *Am J Physiol.* 2000;279:R455-R460.

Decision to Treat Fever

- No compelling reason to treat all fevers
- Treat if subject is uncomfortable
- Patients who are critically ill should be maintained euthermic, if possible
- High fever causes dehydration, increases risk of cardiopulmonary failure, and is associated with metabolic and neurologic complications



CENTRAL

PERIPHERAL



↓PGE₂

↑Endogenous antipyretics



↓Pyrogenic cytokines

↓Adhesion molecules

↑Anti-inflammatory molecules

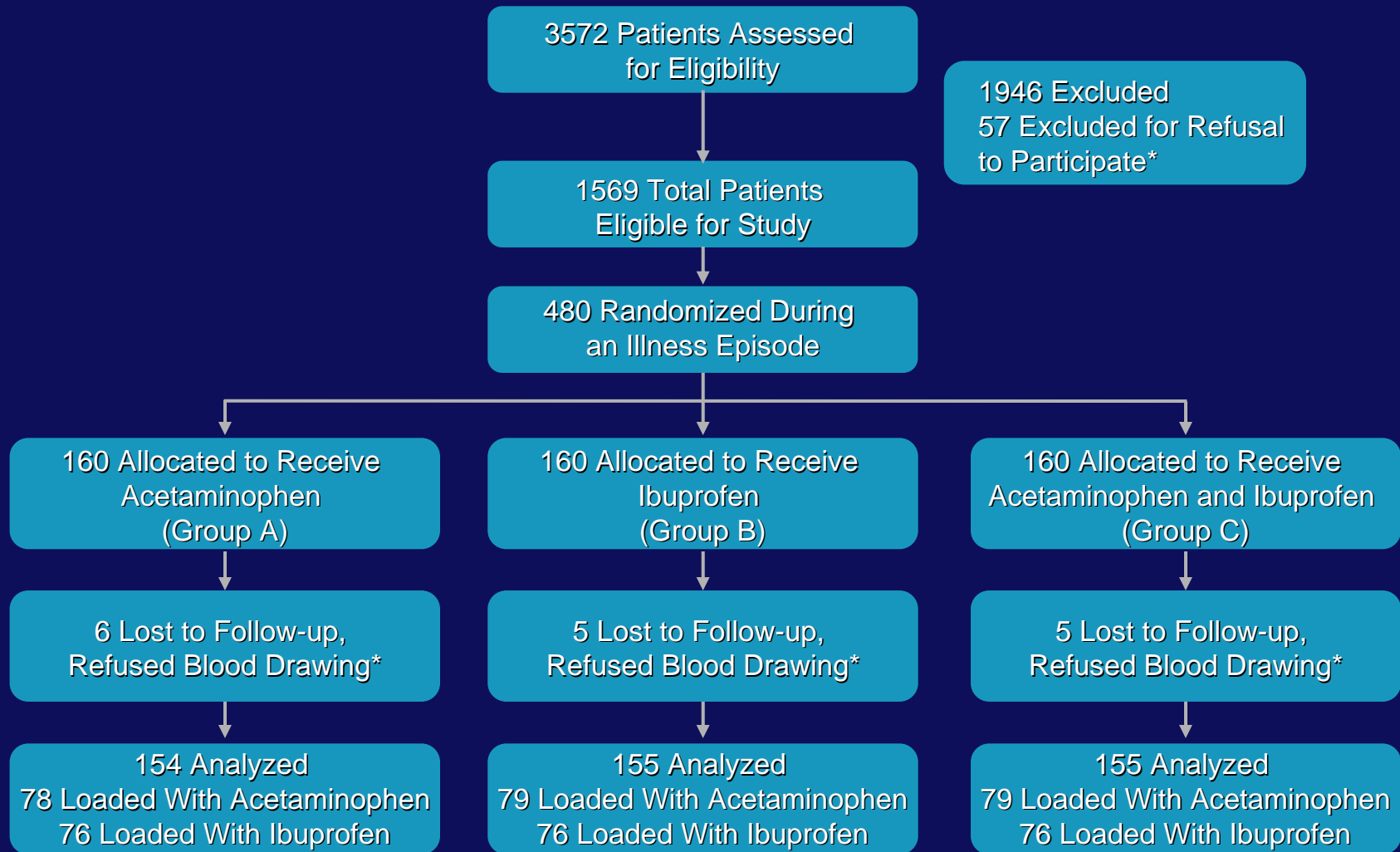


Antipyretic Treatment in Young Children With Fever

*Acetaminophen, Ibuprofen, or Both Alternating in a
Randomized, Double-blind Study*

E. Michael Sarrell, MD, Eliahu Wielunsky, MD, Herman Avner Cohen, MD

Flow Chart of Study



Comparison of Treatment Groups

Table 1. Background Variables of Study Sample by Group

Variable	Acetaminophen (Group A) (n = 154)	Ibuprofen (Group B) (n = 155)	Acetaminophen and Ibuprofen (Group C) (n = 155)	P Value
Age, mo (SD)	18.6 (8.72)	19.5 (9.09)	19.3 (9.29)	.64
Sex, No. (%)				
Male	71 (46)	73 (40)	62 (38)	.40
Female	83 (54)	82 (60)	93 (62)	
Parental status, No. (%)				
2 Parents	128 (83)	131 (85)	133 (86)	.81
1 Parent	26 (17)	24 (15)	22 (14)	
Other siblings, No. (%)	117 (76)	113 (73)	114 (74)	.81
Prenatal or neonatal complications, No. (%)	22 (14)	13 (8)	17 (11)	.26
Smoking at home, No. (%)				
None	135 (88)	140 (90)	127 (82)	.09
Occasional	19 (12)	15 (10)	28 (18)	
Initial medical illness associated with fever, No. (%)				
URI	66 (43)	81 (52)	80 (51)	.70
AOM	16 (10)	13 (8)	17 (11)	
Pharyngitis	10 (7)	7 (5)	3 (2)	
Bronchiolitis	8 (5)	7 (5)	9 (6)	
Gastroenteritis	7 (5)	7 (5)	6 (4)	
Viral illness	47 (30)	40 (25)	40 (26)	

AOM = acute otitis media; URI = upper respiratory tract infection.

Response to Therapy 1

Table 2. Primary Outcome Measures of Treatment by Group

Outcome	Acetaminophen (Group A), % ± SD (95% CI) (n = 154)	Ibuprofen (Group B), % ± SD (95% CI) (n = 155)	Acetaminophen and Ibuprofen (Group C), % ± SD (95% CI) (n = 155)	P Value
Fever				
Admission	40.74 ± 1.01 (40.58-40.90)	40.58 ± 1.02 (40.42-40.74)	40.71 ± 0.93 (40.56-40.86)	.31
Day 1	40.55 ± 1.31 (40.34-40.76)	40.6 ± 1.46 (40.37-40.83)	39.64 ± 1.17 (39.45-39.82)	<.001
Day 2	39.74 ± 1.37 (39.51-39.95)	39.66 ± 1.48 (39.42-39.89)	38.78 ± 0.87 (38.64-38.92)	<.001
Day 3	39.34 ± 1.19 (39.15-39.53)	39.64 ± 1.46 (39.41-39.87)	38.54 ± 0.74 (38.42-38.66)	<.001
NCCPC				
Admission	18.30 ± 1.67 (18.03-18.56)	19.00 ± 1.27 (18.80-19.20)	19.46 ± 2.40 (19.08-19.84)	<.001
NCCPC day 1	11.77 ± 2.64 (11.35-12.19)	11.48 ± 2.58 (11.07-11.89)	9.26 ± 2.49 (8.86-9.65)	<.001
NCCPC day 2	8.87 ± 2.54 (8.47-9.27)	8.83 ± 2.67 (8.40-9.25)	5.09 ± 2.78 (4.65-5.53)	<.001
NCCPC day 3	7.66 ± 2.96 (7.19-8.13)	7.96 ± 2.71 (7.53-8.39)	4.18 ± 2.74 (3.75-4.62)	<.001
Medication				
Day 1	4.33 ± 0.85 (4.20-4.47)	2.99 ± 0.11 (2.97-3.01)	2.57 ± 0.88 (2.43-2.71)	<.001
Day 2	3.84 ± 0.73 (3.73-3.96)	2.92 ± 0.27 (2.88-2.96)	1.99 ± 0.58 (1.89-2.08)	<.001
Day 3	2.90 ± 0.73 (2.79-3.02)	2.84 ± 0.46 (2.77-2.92)	1.48 ± 0.71 (1.37-1.59)	<.001

CI = confidence interval; NCCPC = Noncommunicating Children's Pain Checklist.

Response to Therapy 2

Table 3. Secondary Outcome Measures and Follow-up by Group

Outcome	Acetaminophen (Group A) (n = 154)	Ibuprofen (Group B) (n = 155)	Acetaminophen and Ibuprofen (Group C) (n = 155)	P Value
Fever recurrence, No. (%)				
At 5 d	33 (21)	27 (17)	15 (10)	.02
At 10 d	18 (12)	19 (12)	14 (9)	.62
Absent from day care, d, No. \pm SD (95% CI)	2.64 \pm 0.58 (2.55-2.74)	2.58 \pm 0.61 (2.48-2.68)	1.76 \pm 0.69 (1.66-1.87)	<.001
Patients visiting emergency department, No. (%)	21 (14)	20 (13)	16 (10)	.65
Patients with abnormal renal laboratory values, No. (%)*				
Acute stage	5 (3.3)	4 (3.8)	5 (3.2)	.93
Follow-up	0	0	0	NA
Patients with abnormal liver laboratory values, No. (%)†				
Acute stage	4 (2.6)	2 (1.3)	2 (1.3)	.60
Follow-up	0	0	0	NA

NA = Not applicable.

*Blood urea nitrogen level of 18 mg/dL or higher (≥ 6.4 $\mu\text{mol/L}$), or serum creatinine level of 0.9 mg/dL or higher (≥ 68.6 $\mu\text{mol/L}$).

† γ -Glutamyltransferase, serum glutamic oxaloacetic transaminase, or serum glutamate pyruvate transaminase level of 20 U/L or higher, or total serum bilirubin level of 1 mg/dL or higher (≥ 17 $\mu\text{mol/L}$).

Conclusions

- Fever is a controlled $T \uparrow$ in response to an elevated “set point” in the hypothalamus
- It is a highly regulated response involving cytokines, endogenous antipyretics & PGE_2
- Our current model is becoming more complex



**Fever is Nature's engine which she
brings into the field to remove her Enemy.**

— *Thomas Sydenham*
(1624-1689)