Vert Phys PCB3743

Autonomic Nervous System 2
Fox Chapter 9 part 2

Pharmacology and Disorders

Examples of Autonomic Nervous System

- Pupil dilation & contraction
- Sweating
- Horner's Syndrome
- Organophosphate Poisoning

Central Regulation of Autonomic Nervous System

- brainstem
- hypothalamus
- *example: Thermoregulation & Fever*

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Pupil Dilation & Constriction
Light via optic nerve (II) stimulates parasympathetic nerve (III) to constrict pupillary sphincter muscle (ACh muscarinic receptors)
Blocked by atropine -> pupil dilation
Sympathetic nerves cause dilation of pupil by stimulating pupillary dilator muscle (NE beta-adrenergic receptors)
Cocaine -> enhanced NE levels -> enhanced dilation

Hidrosis (sweating)
Sympathetic postganglionic neurons synapse onto sweat glands in the skin
Sympathetic neurons release **ACh** (**not NE**) to stimulate sweating
Hyperhidrosis - excessive sweating -- treated with anticholinergics, botulin toxin (botox) that blocks ACh release, or **sympathectomy** (cutting sympathetic nerves)

Horner's Syndrome
Damage to sympathetic nerves on one side of neck
Unilateral (one-sided) constriction of pupil, anhydrosis (lack of sweat), flushing

Organophosphates
insecticides that block cholinesterase enzyme -> enhanced ACh neurotransmission at all synapses
Treated with atropine to block effects of elevated ACh

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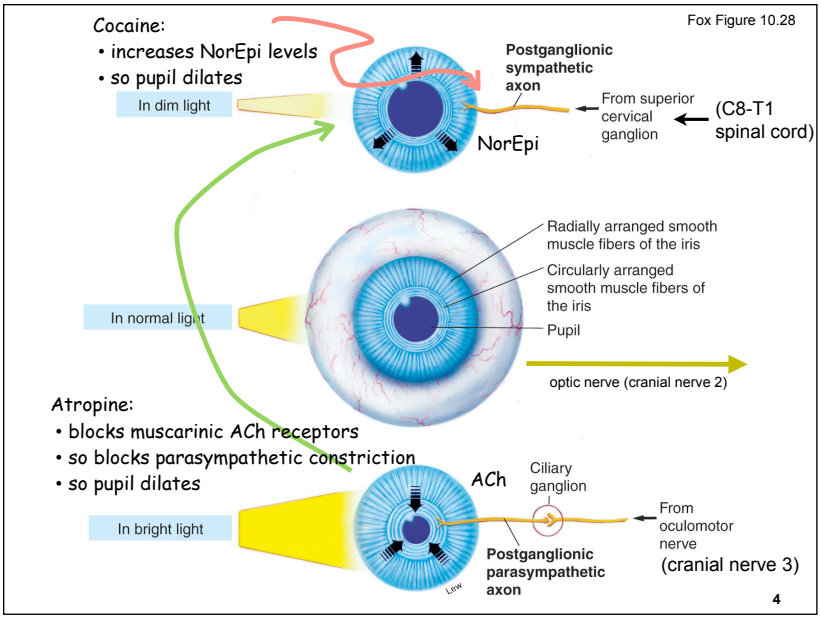
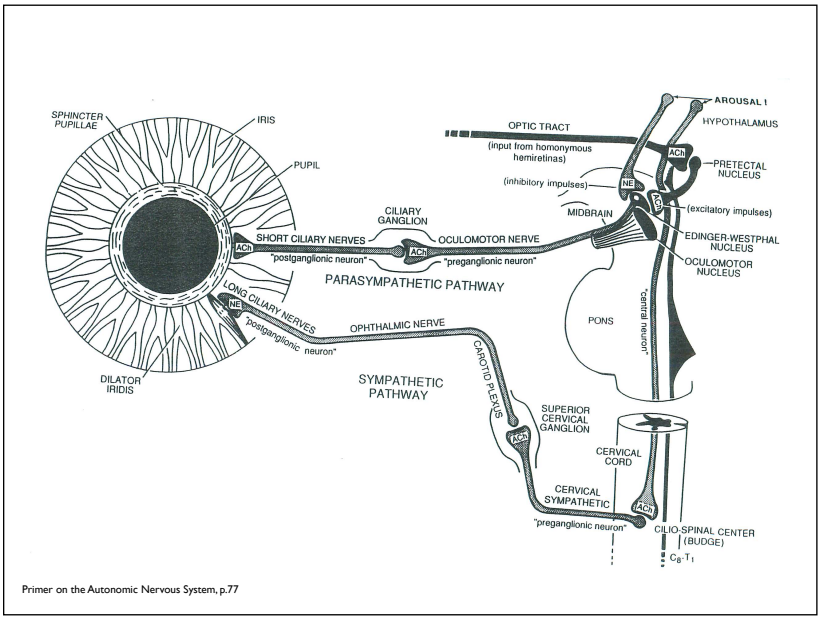

Fox Figure 10.28
Cocaine:
• increases NorEpi levels
• so pupil dilates
In dim light
Postganglionic sympathetic axon
From superior cervical ganglion
(C8-T1 spinal cord)
NorEpi
Radially arranged smooth muscle fibers of the iris
Circularly arranged smooth muscle fibers of the iris
Pupil
In normal light
optic nerve (cranial nerve 2)
Atropine:
• blocks muscarinic ACh receptors
• so blocks parasympathetic constriction
• so pupil dilates
ACh
Ciliary ganglion
In bright light
From oculomotor nerve
(cranial nerve 3)
Postganglionic parasympathetic axon
4


SPHINCTER PUPILLAE
IRIS
PUPIL
DILATOR IRIDIS
CILIARY GANGLION
SHORT CILIARY NERVES
"postganglionic neuron"
OCULOMOTOR NERVE
"preganglionic neuron"
PARASYMPATHETIC PATHWAY
LONG CILIARY NERVES
"postganglionic neuron"
OPHTHALMIC NERVE
SYMPATHETIC PATHWAY
CAROTID PLEXUS
SUPERIOR CERVICAL GANGLION
CERVICAL CORD
CERVICAL SYMPATHETIC
"preganglionic neuron"
CILIO-SPINAL CENTER (BUDGE)
C8-T1
PONS
"central neuron"
OPTIC TRACT
(input from homonymous hemiretinas)
(inhibitory impulses)
MIDBRAIN
(excitatory impulses)
AROUSAL
HYPOTHALAMUS
PRETECTAL NUCLEUS
EDINGER-WESTPHAL NUCLEUS
OCULOMOTOR NUCLEUS
ACh
NE
Primer on the Autonomic Nervous System, p.77

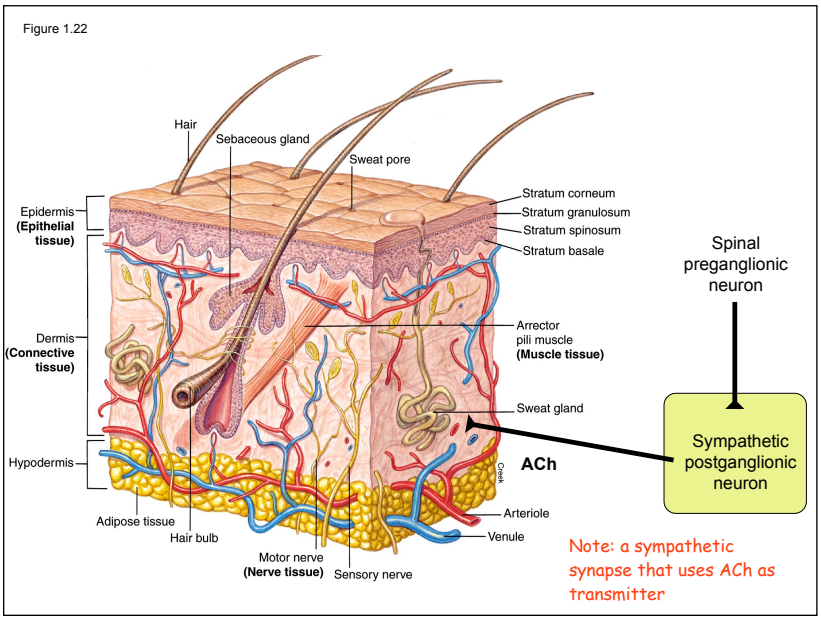
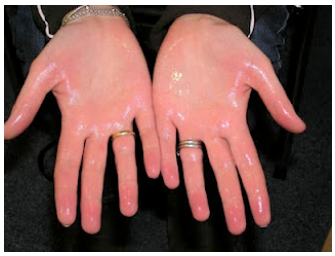
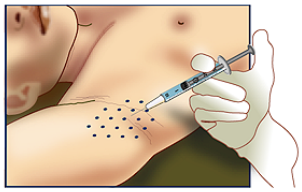


Figure 1.22
Hair
Sebaceous gland
Sweat pore
Epidermis (Epithelial tissue)
Dermis (Connective tissue)
Hypodermis
Stratum corneum
Stratum granulosum
Stratum spinosum
Stratum basale
Arrector pili muscle (Muscle tissue)
Sweat gland
Adipose tissue
Hair bulb
Motor nerve (Nerve tissue)
Sensory nerve
Arteriole
Venule
Spinal preganglionic neuron
Sympathetic postganglionic neuron
ACh
Note: a sympathetic synapse that uses ACh as transmitter

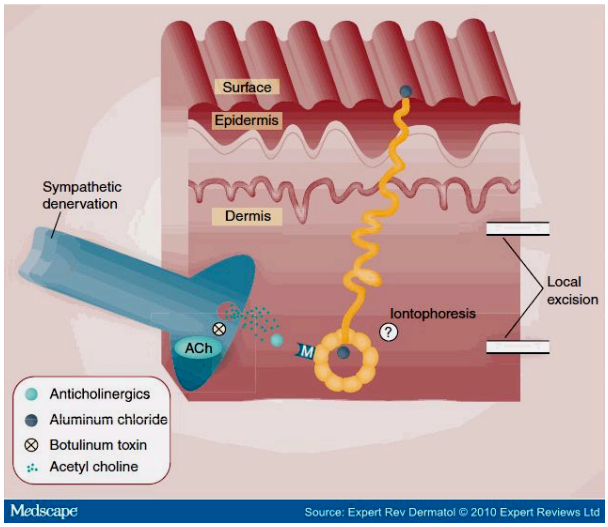
Hyperhidrosis - Excessive sweating





Botox injections

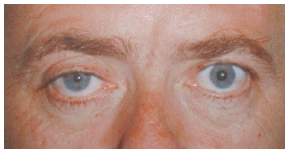
Sweating and Hyperhidrosis



Horner's Syndrome

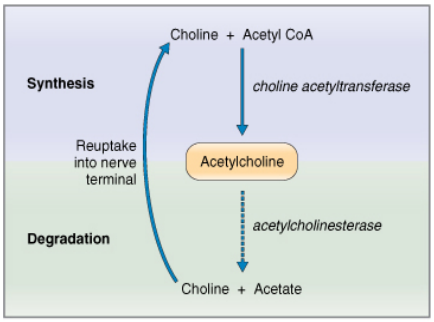
Loss of sympathetic innervation of the eye and face on one side (unilateral deficit)

1 Drooping eyelid (Ptosis)
2 Constricted pupil
3 Reduced sweating on the affected facial side



Horner' syndrome due to grenade wound of right side of neck (Bing's p. 102)

Organophosphates block degradation of ACh



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Organophosphate pesticides (Malathion) and "nerve gas" (Sarin) are AchE inhibitors. Poisoning will present with symptoms of cholinergic activation.

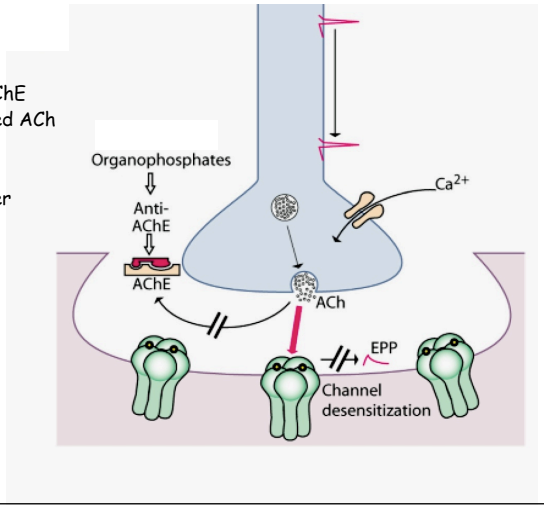
Activation of nicotinic ACh receptors on ganglionic synapses and neuromuscular junction.

Activation of muscarinic ACh receptors at parasympathetic target synapse

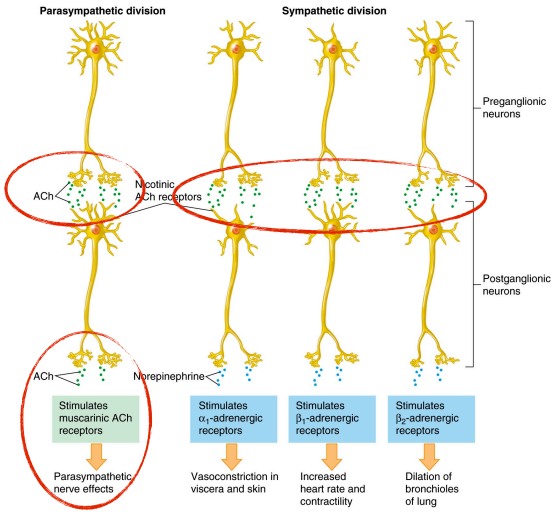
(and activation of sweat glands at cholinergic sympathetic synapse).

Organophosphates are powerful (long-lasting) AChE inhibitors used as pesticides

inhibition of AChE causes increased ACh in cholinergic synapses, so bigger, longer response



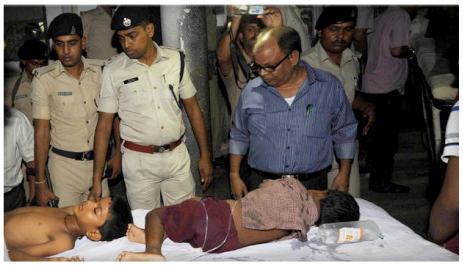
AChE inhibitors boost ACh everywhere



By RYAN JASLOW / CBS NEWS / July 24, 2013, 5:05 PM

Organophosphate pesticides eyed as cause of India poisonings: How toxic?

July 2013



Some states require employers to enroll their employees who handle such pesticides in a cholinesterase-monitoring program. Although Florida law does not require employers of pesticide handlers to monitor these employee's cholinesterase levels, some employers in Florida — including the University of Florida — voluntarily enroll their employees who handle pesticides in a cholinesterase-monitoring program.

The BBC quoted a police official last week who said, "It was the high quantity of monocrotophos insecticide found in the food which proved fatal for the schoolchildren." The incident has been blamed on a bottle of pesticide being used instead of cooking oil to cook the free school lunches of rice, lentils, soybeans and potatoes.

The affected children, who were between the ages of 5 and 12, got sick shortly after eating lunch Tuesday July 16 at the school in Gandamal village. School authorities stopped serving the meal once the children began vomiting. The school's principal, who went into hiding after the incident, was arrested Tuesday.

Treatment of organophosphate (OP) poisoning involves assisted ventilation, blocking muscarinic activation with atropine and attempting to reactivate AchE

1. Organophosphorus (OP) insecticide poisoning is a major global clinical problem, killing an estimated 200,000 people each year.
2. Restricting agricultural use of highly toxic OP insecticides will reduce regional suicide rates. However, current agricultural policies make it unlikely that they will soon be banned. Effective clinical therapies are required.
3. OP compounds inhibit acetylcholinesterase (AchE), resulting in overstimulation of cholinergic synapses. Patients die mostly from respiratory failure and lung injury, although there is variability in the clinical syndrome.
4. Treatment involves resuscitation, administration of the muscarinic antagonist **atropine** and an oxime **acetylcholinesterase reactivator** , such as pralidoxime, and assisted ventilation as necessary.

(Eddleston et al. PLoS Med 6(6): e1000104, 2009)

Be able to compare and contrast sympathetic and parasympathetic nervous system

Location of preganglion neurons

Location of ganglia

Neurotransmitters used by pre- and post ganglionic neurons

Role of sympathetic vs. parasympathetic system

Some examples of target organs:

airways, pupil, sweating

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Application	Effect of Vial 1	Effect of Vial 2
onto eye	no effect	Dilation of pupil
onto adrenal gland	epinephrine secretion	no effect
onto heart	no effect	speeds up heart
onto sweat gland	no effect	decreases sweating
into sympathetic chain ganglion	increased sympathetic response	no effect
into parasympathetic ganglion	increased parasympathetic response	no effect

You conclude that vial 1 or 2 contains:

a. acetylcholine
b. atropine
c. cocaine
d. epinephrine
e. nicotine

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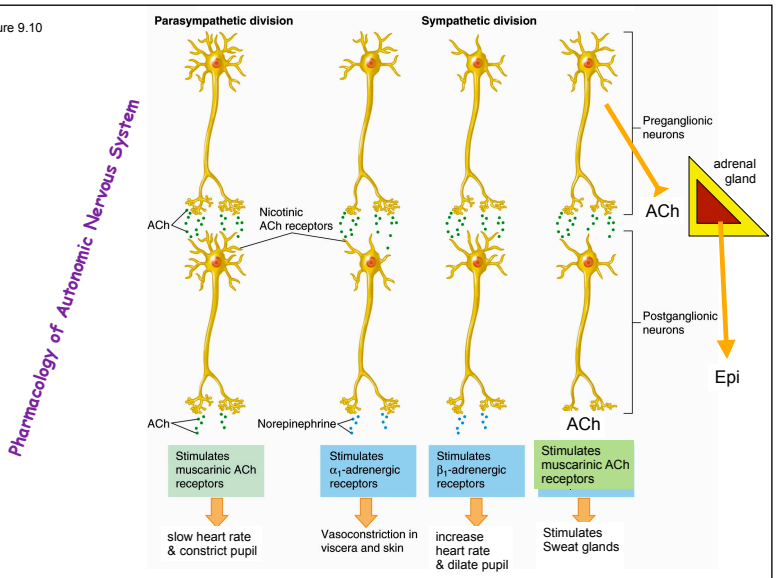
Figure 9.10



Application	Effect of Vial 1
onto eye muscarinic ACh (constriction) vs. beta-adrenergic receptors (dilation)	no effect
onto adrenal gland nicotinic ACh receptors	epinephrine secretion
onto heart muscarinic ACh (slow) vs. beta-adrenergic receptors (speed up)	no effect
onto sweat gland muscarinic ACh receptors	no effect
into sympathetic chain ganglion nicotinic ACh receptors	increased sympathetic response
into parasympathetic ganglion nicotinic ACh receptors	increased parasympathetic response

1. You conclude that vial 1 contains:

a. acetylcholine → muscarinic & nicotinic ACh receptors
b. atropine → block muscarinic ACh receptors
c. cocaine → enhance adrenergic receptors
d. epinephrine → adrenergic receptors
e. nicotine → nicotinic ACh receptors

Application	Effect of Vial 2
onto eye muscarinic ACh (constriction) vs. beta-adrenergic receptors (dilation)	Dilation of pupil
onto adrenal gland nicotinic ACh receptors	no effect
onto heart muscarinic ACh (slow) vs. beta-adrenergic receptors (speed up)	speeds up heart
onto sweat gland muscarinic ACh receptors	decreases sweating
into sympathetic chain ganglion nicotinic ACh receptors	no effect
into parasympathetic ganglion nicotinic ACh receptors	no effect

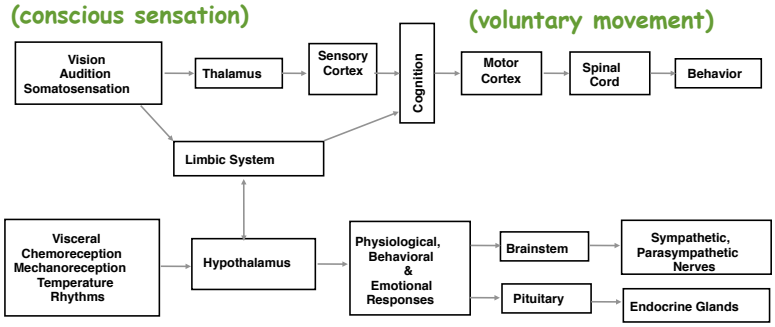
2. You conclude that vial 2 contains:

a. acetylcholine → muscarinic & nicotinic ACh receptors
b. atropine → block muscarinic ACh receptors
c. cocaine → ~~enhance adrenergic receptors~~
d. epinephrine → adrenergic receptors
e. nicotine → nicotinic ACh receptors

Autonomic vs. Somatic Axes

(conscious sensation)

(voluntary movement)



(unconscious sensation)

(homeostatic & autonomic responses)

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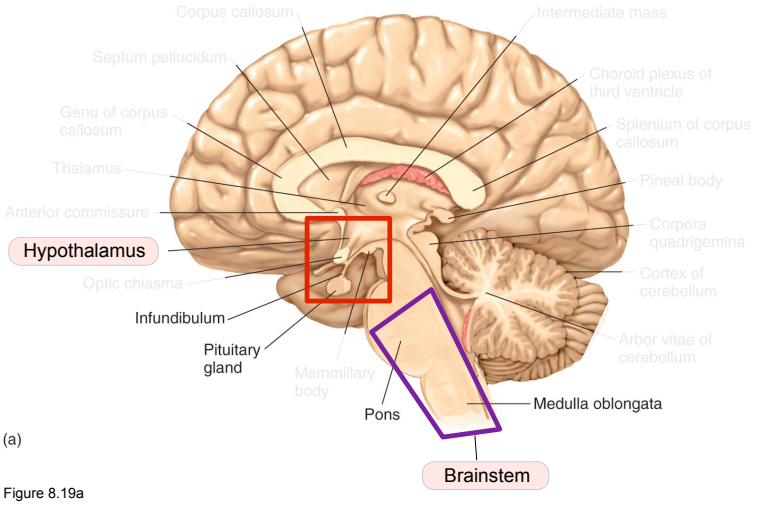
Central control of autonomic nervous system: hypothalamus and brainstem



(a)

Figure 8.19a

Hypothalamus as Integrator

To maintain homeostasis, hypothalamus uses two control mechanisms:

1. Setpoint
areas of hypothalamus integrate information about a physiological variable, and attempt to maintain that variable at a particular setpoint.

2. Feedback loops
High levels of regulated variable cause hypothalamus to downregulate behavior & physiology that drive the variable up. negative feedback loop balances positive input; no setpoint

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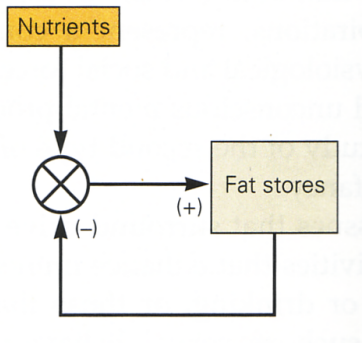
Feedback Regulation

High levels of regulated variable cause hypothalamus to downregulate behavior & physiology that drive the variable up.



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negative feedback loop balances positive input; no setpoint

Setpoint Regulation

areas of hypothalamus integrate temperature information, and attempt to maintain temperature at a particular setpoint.

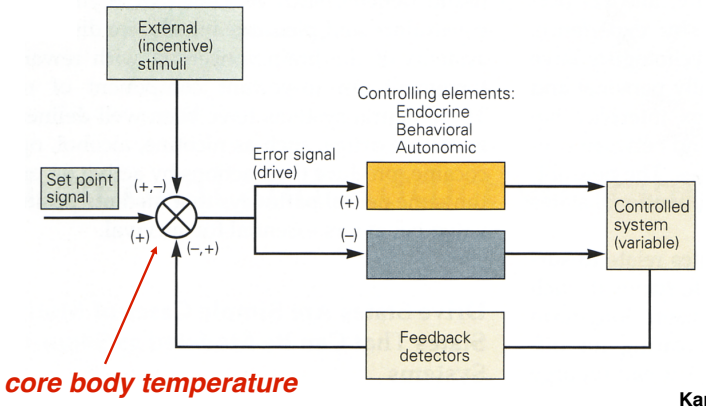

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Figure 1.1

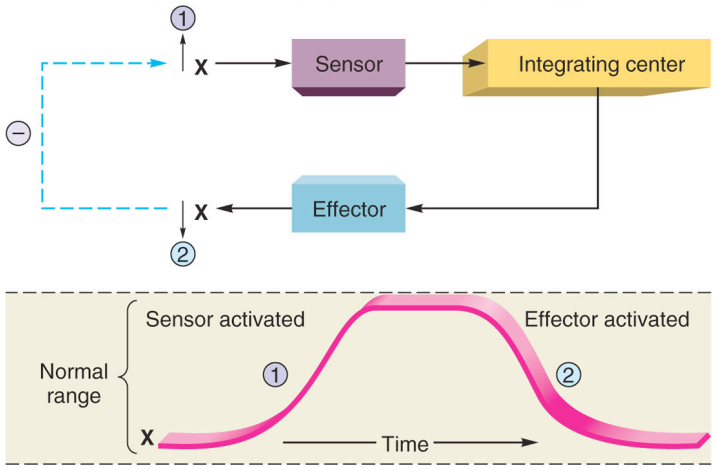

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Figure 1.2

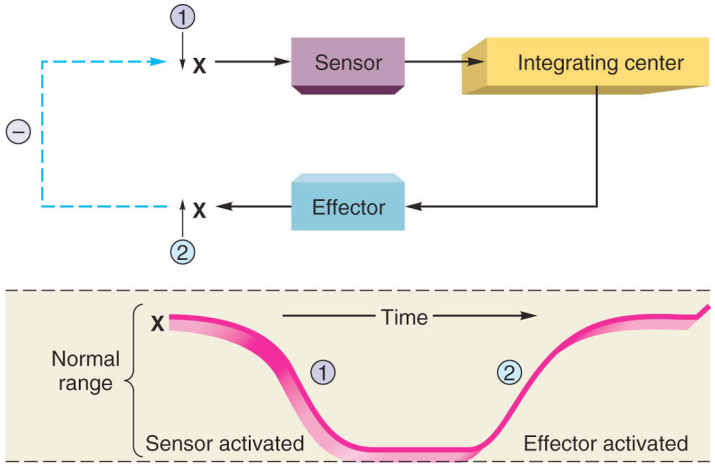

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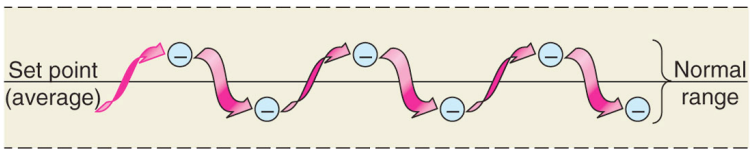
Figure 1.3



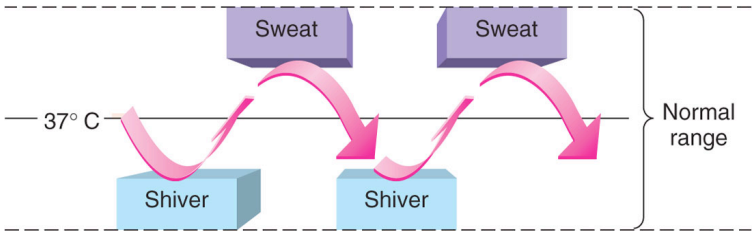


Figure 1.4

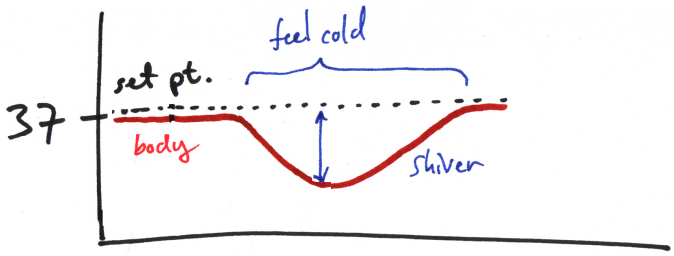
Thermoregulatory responses

engaged if:

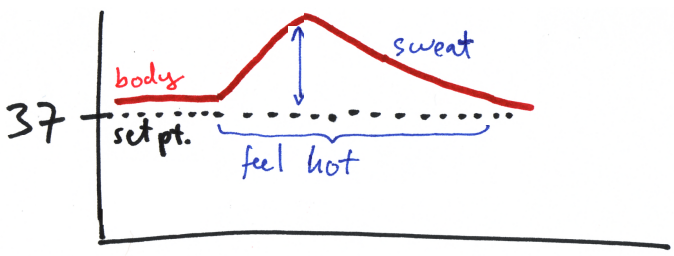
1) body temp. moves away from setpoint
–> responds to restore body temp
or
2) the central setpoint changes
–> bring body temp to new set point
lowering setpoint –> body responds as if too hot.
raising setpoint –> body responds as if too cold.

if temperature > setpoint
too hot, so sweat & vasodilate skin
if temperature < setpoint
too cold, so shiver & conserve heat
If temperature = setpoint
feel fine (even if elevated)

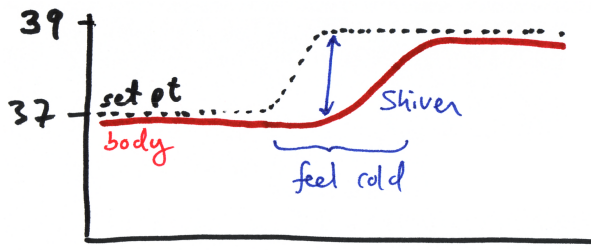
Drop in body temperature



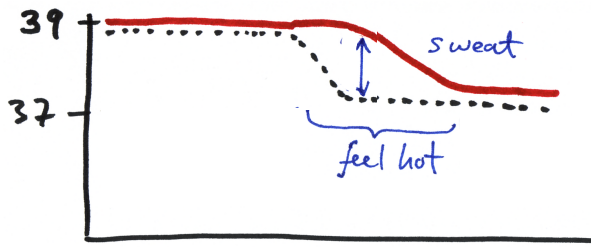
Rise in body temperature



Rise in set point = fever



Drop in set point = fever breaking



Compare temperature to set point:

if temperature > setpoint

too hot, so sweat & vasodilate skin

if temperature < setpoint

too cold, so shiver & conserve heat

If temperature = setpoint

feel fine (even if elevated)

Thermoregulatory Inputs

peripheral temperature sensors (e.g. skin)

central temperature sensors (warm and cold responsive neurons in hypothalamus)

hypothalamus integrates both peripheral and central inputs

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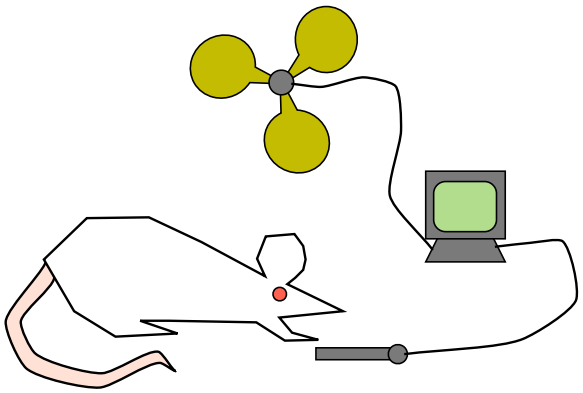
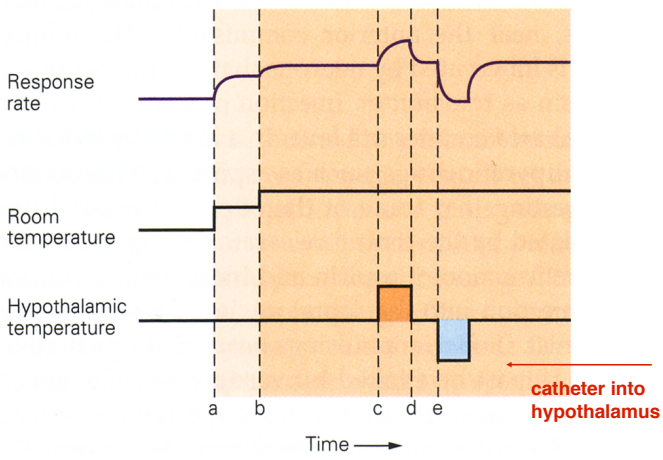
Rat pressing bar for cold air



Rat bar-pressing for cold air



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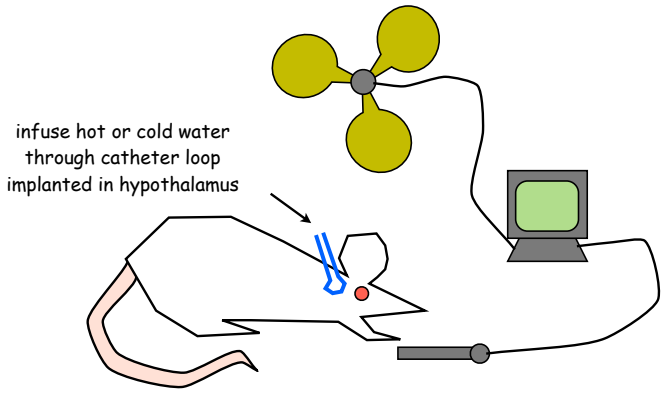
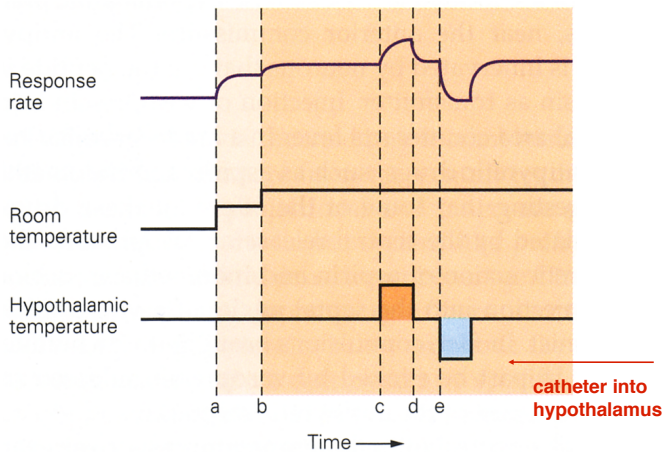
Rat pressing bar for cold air



Rat bar-pressing for cold air



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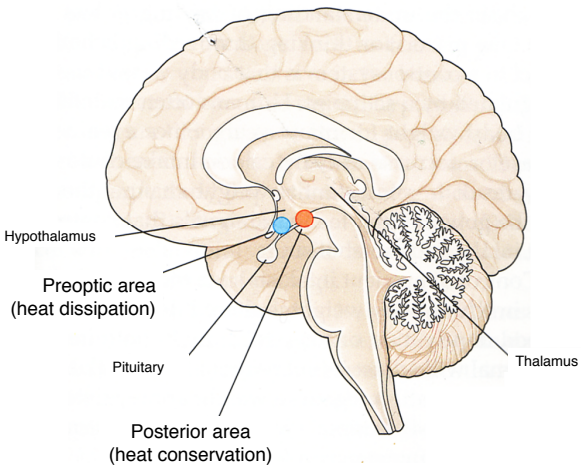
Thermoregulatory Sites of integration



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Thermoregulatory Sites of integration:
two opposing centers

	stimulate	lesion
Preoptic Area	panting, sweating	hyperthermia
Posterior Area	shivering	hypothermia (when in cold)

Thermoregulatory Outputs

controlled by mixed but independent circuits localized in hypothalamus.

Short-term neural outputs:

sweating, panting, salivation: evaporative cooling

vasodilation: conduction of heat from core by blood and radiation from skin

shivering: generation of metabolic heat

non-shivering thermogenesis: burn off adipose stores

Behavior! – conscious perception drives voluntary behaviors to restore temp to set point.

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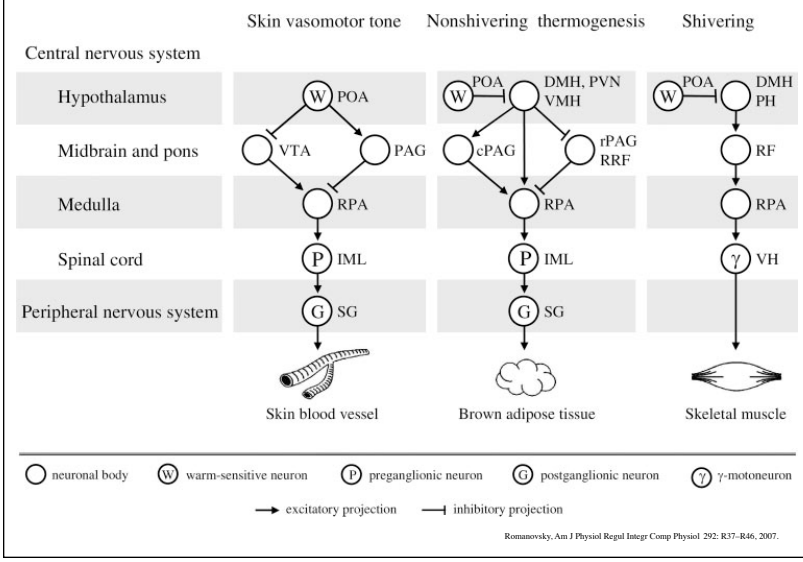
Thermoregulatory Outputs



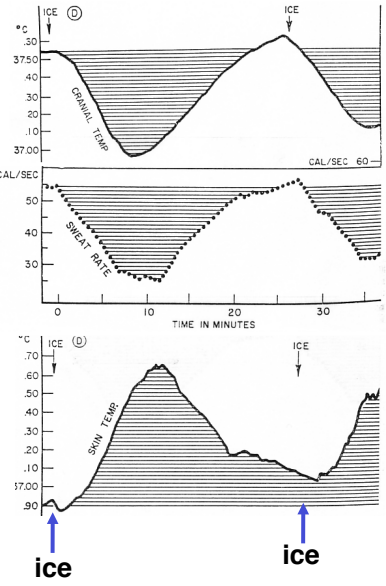
Romanovsky, Am J Physiol Regul Integr Comp Physiol 292: R37–R46, 2007.

Decrease Core Temp (eat ice)

cranial °C

sweat

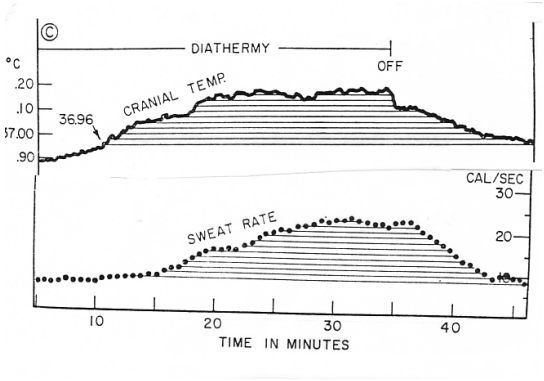
skin °C



Increase cranial temp (microwave neck)

cranial °C

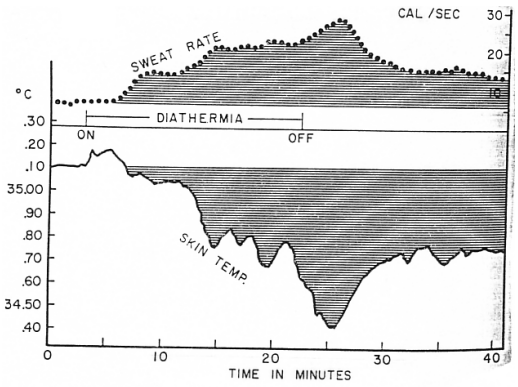
sweat



Increase cranial temp (microwave neck)

sweat

skin °C



Long-Term Thermoregulatory Outputs

secretion of thyroid releasing hormone (TRH) to increase thyroid hormone (TH) to increase metabolism

increased feeding to match metabolic heat generation

(autonomic system can only change metabolic rate by 4x, so need behavior to compensate for big environmental shifts).

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Disregulation of Body Temperature

Postsurgical shivering:
anesthesia depresses normal thermoregulatory response, body starts to cool to RT; as anesthesia wears off, hypothalamus regains function and induces shivering.

Hot flashes:
lack of estrogen causes occasional lowering of setpoint (i.e. hypothalamus decides its too hot, so tries to lower body temperature) -> sweating, perception of heat.

Fever induced by infection and pyrogens
Chemical components of bacteria activate immune system to produce prostaglandins (PGs). PGs stimulate brain to change set-point (induced fever) and "sickness syndrome".

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Cytokines, Fever, and Sickness Syndrome

increased sleep, anorexia, adipsia, stress response, fever

the behavioral & physiological alterations that develop during infection are NOT the consequence of reduced bodily functions,

but are a set of coordinated responses to infection and inflammation mediated by the hypothalamus

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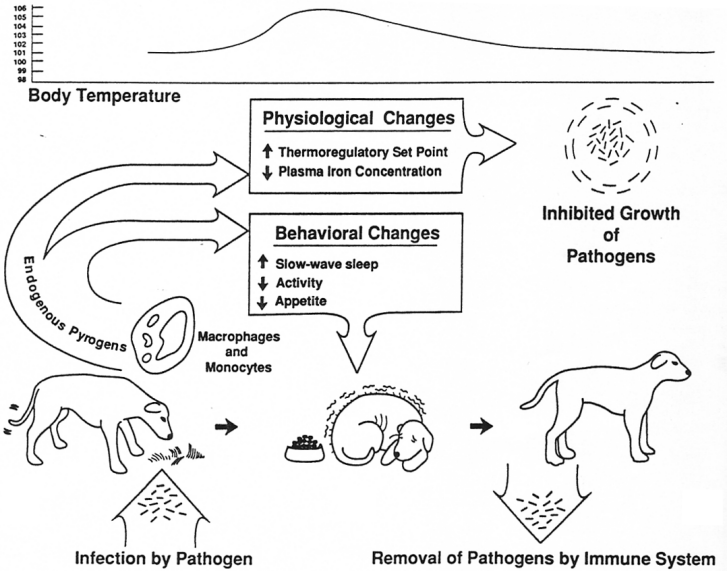

Lipopolysaccharide (LPS) & Cytokines

active fragment of endotoxin from gram-negative bacteria

LPS induces synthesis and release of proinflammatory cytokines from activated immune system cells (monocytes and macrophages):

cytokines:

interleukin 1a (IL-1a)

interleukin 1b (IL-1b)

tumor necrosis factor-alpha (TNFa)

two pathways of activation

visceral infection
peritoneum, lung
–> cytokine receptors on vagus nerve
–> brainstem and hypothalamus

blood borne infection
LPS, cytokines
–> endothelium of brain capillaries
–> activation of cyclooxygenase (COX2)
–> synthesis of prostaglandin E2 (PGE2)
–> diffuse to glial cells
–> activation of EP3 receptors
–> release of cAMP -> hypothalamic areas

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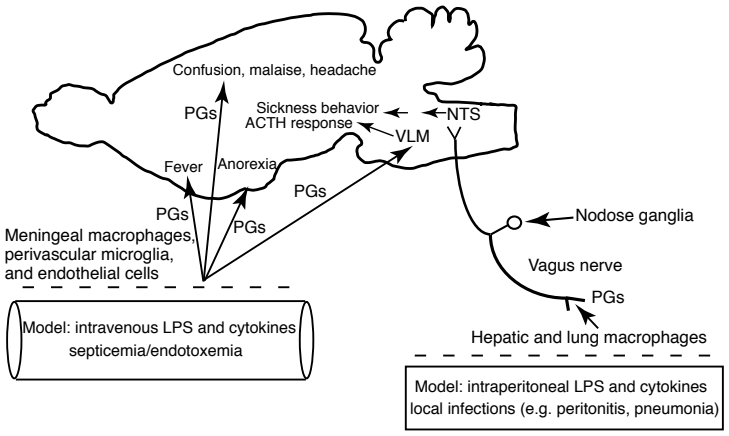
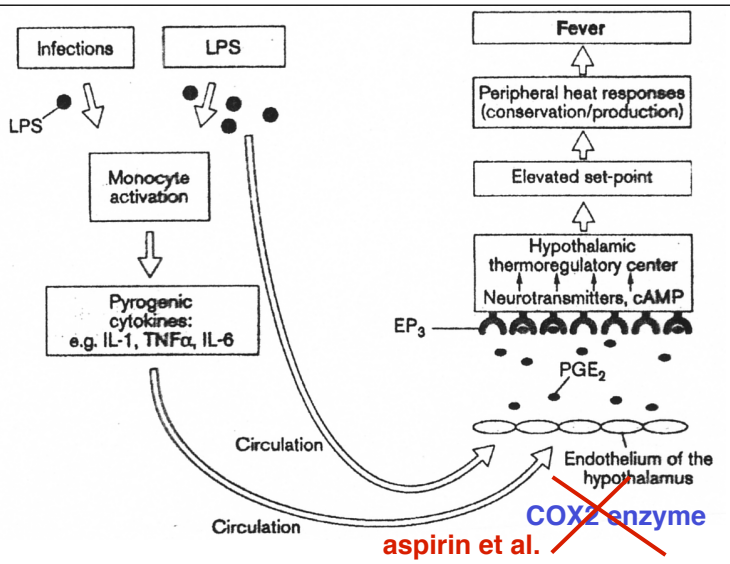
infection induces COX2 enzymes to produce prostaglandins (PGs)

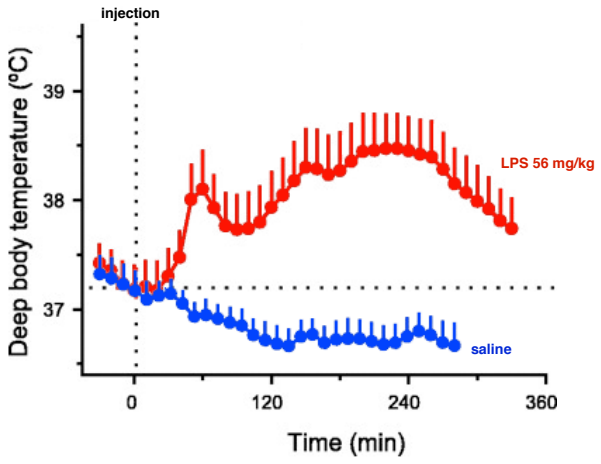
PGs act as signal to brain to respond to infection



Elmquist 1997, PMID 9416669

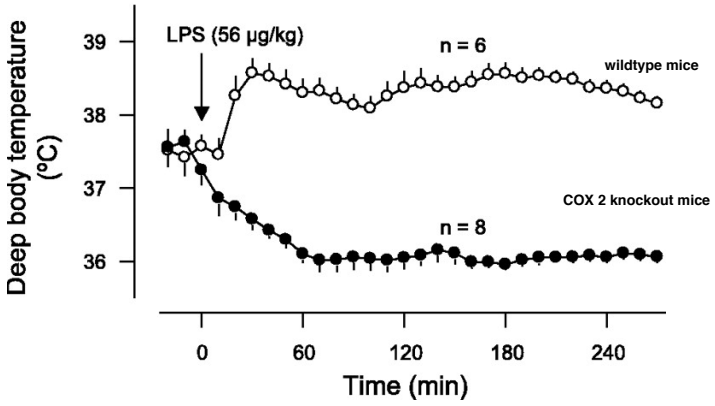


LPS injection induces polyphasic fever in mice



Rudaya et al, 2005, PMID: 16081879

LPS injection does not induce fever in mice without the COX 2 enzyme



Steiner et al, 2005, PMID: 16081878

Thermoregulation Conclusions

Temperature is regulated around a setpoint

Thermoregulation uses both peripheral and central sensors

Fever is a pathological change in setpoint

Infection causes "sickness" by indirectly affecting the hypothalamus through humoral and nervous signaling.

cytokines and prostaglandins signal the presence of infection

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