The dependence of body temperature on ambient temperature in a poikilotherm (ectotherm) reptile and a homeotherm (endotherm) mammal.
The concept of homeothermy and poikilothermy

- Birds and mammals have high, relatively constant core temperatures (warm-blooded animals), temperature regulation depends heavily on their high metabolic rate and heat production.
- Rest of the animals do have temperature regulation, but their body temperature is affected more by the environment (cold-blooded, poikilotherm animals).

Hibernation: switching to poikilothermy

- Hummingbirds survive the nights without possibility to feed by becoming poikilotherm (torpor).
Homeostasis + behavior: winter furcoat + fat stores + hibernation + nest building + food stores + body posture + social bonds = key to survival

Body temperature: How much is it? Where to measure?

- ♦ = ear (tympanic)
- ♠ = sublingual (oral)
- ♥ = rectal
- ♠ = axillary

The concept of body “core” and “shell”

Only “core” temperatures are relatively constant!
Body temperature: The facts

- Daily minimum: 36.2 °C (97.3 °F)
- Daily maximum: 37.1 °C (98.8 °F)
- Average: 36.6 °C (98.0 °F)
- Physiologic maximum (heavy exercise): 40.0 °C (104.0 °F)
- Physiologic minimum (swimming in cold water) 34 °C (93.2 °F)
- Postovulatory rise: 0.3-0.5 °C (0.5-0.9 °F)
Constant body temperature requires heat balance

Heat storage = 0

- Metabolic heat production
- Radiation*
- Conduction*
- Convection*

- Radiation*
- Conduction*
- Convection*
- Evaporation

Heat gain
Heat loss

*These mechanisms are bidirectional and can be called collectively as heat exchange mechanisms

Bidirectional heat exchange mechanisms are taking place between the body surface and the environment and they are dependent on the difference between the skin (lung) temperature and the environmental temperature. Skin temperature because of the WAT insulation is primarily dependent on cutaneous blood flow!
Heat exchange mechanisms: Radiation

- Described by the Stefan-Boltzman equation
- \( \text{HR (W)} = \delta e_1 x e_2 x (T_1^4 - T_2^4) x A \)
- where \( \delta \) is the Stefan Boltzmann constant (5.67x10^{-8} W/m^2 K^4), \( T \) is temperature (K), \( e \) is surface emissivity and \( A \) is the radiant surface
- we can gain or lose significant heat by radiation: (sunbathing \textit{versus} staying in a room with cold walls)
- anti-hypothermia blankets can reflect heat waves (containing thin gold foil)

Heat exchange mechanisms: Conduction

- Conduction takes place when there is a direct contact between the body surface and a medium (air or solid medium) \( C = (T_1 - T_2) x R \) (\( R \) is thermal resistance)
- sitting on a cold surface can result in significant heat loss
- water is much better heat conductor than air, so heat transfer is much faster to water than to air
**Heat exchange mechanisms: Convection**

- Convection is caused by medium (air) currents induced by conductive heat transfer $C = (T_1 - T_2) \times h_c$ ($h_c$ is convection heat transfer coefficient).
- Wind can cause forced convection resulting in rapid heat loss.
- Piloerection in furbearing animals and traditional clothing traps air, and prevents heat loss by conduction/convection. Wet cloths are malfunctioning!

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**Unidirectional heat loss: Evaporation**

Sweat is produced from plasma water thus evaporative heat loss is also dependent on cutaneous blood flow!
**Unidirectional heat loss: Evaporation**

- Evaporation of every ml water removes 2.41 kJ from the evaporative surface (skin and lung).
- Only heat loss mechanism operating if the environment is hotter than the skin (not in water).
- Insensible perspiration: through the skin and the lung, uncontrollable, can be high if the air is dry (airplanes), hyperventilation also increases it.
- Evaporation from upper airways can be significant regulated heat loss mechanism (panting in dogs).
- Sensible perspiration: sweating from eccrine sweat glands.

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**Constant body temperature requires heat balance**

Heat storage = 0

- Metabolic heat production
- Radiation*
- Conduction*
- Convection*

*These mechanisms are bidirectional and can be called collectively as heat exchange mechanisms.*
Thermoneutral comfort zone

- The ambient temperature range where neither homeostatic heat production/heat conserving nor heat dissipating mechanisms are activated.
- In humans (no clothing) the TNZ is around 25-27 °C.
- Basal metabolic rate is determined at TNZ temperature.

Thermoregulation at equilibrium

\[ M \pm R \pm C \pm C - E = 0 \]

<table>
<thead>
<tr>
<th>Thermoneutral zone</th>
<th>25-27 °C</th>
</tr>
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<tbody>
<tr>
<td>M↑</td>
<td>R+C+C↑</td>
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<table>
<thead>
<tr>
<th>Metabolic zone</th>
<th>Vasomotor zone</th>
<th>Sudomotor zone</th>
</tr>
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<tbody>
<tr>
<td>Metabolic thermogenesis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Shivering thermogenesis (skeletal muscle)</td>
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<tr>
<td>2. Non-shivering thermogenesis (BAT)</td>
<td></td>
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</tr>
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Behavioral thermoregulation

<table>
<thead>
<tr>
<th>SKIN Vasoconstriction-vasodilation</th>
<th>Vasodilation+ Sweating</th>
</tr>
</thead>
</table>
Social interactions for thermoregulation

Emperor penguin

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![Heat production graph](image)

- Intact thermoregulation
- Regulatory heat-production
- Van’t Hoff’s rule!
- Thermoregulation switched off (narcosis)

Rectal temperature [°C]

Heat production [W/m²]
Metabolic heat production I.

- Most chemical energy released in the cells eventually becomes heat (except external work)
- since heat production is the result of chemical reactions, temperature itself has an effect on heat production:
  
  The rule of van't Hoff says that the speed of a reaction doubles at a temperature increase of 10K

Jacobus Henricus van 't Hoff
1859-1911, Nobel prize 1901

The van't Hoff rule works against thermoregulatory needs.

Metabolic heat production II.

- heat production in the different cells (organs) is in direct proportion with their O₂ consumption (at rest mainly the brain, heart, liver)
- Systemic circulation has an important role in heat transport: hotter organs are cooled, cooler organs are warmed by the arterial blood.
Metabolic heat production III.

- heat production at BMR=7000kJ/day (~ 80W (J/s))
- “diet-induced thermogenesis” +1000kJ/day (~ 12W)
- skeletal muscle activity can produce a lot of heat, therefore daily heat production may vary greatly according to physical activity (and involuntary shivering)
- non-shivering thermogenesis: special brown adipose tissue! (in humans: newborns only!)
Regulatory heat-production

Intact thermoregulation

Thermoregulation switched off (narcosis)

Rectal temperature [°C]

Heat production [W/m²]

White Adipose Tissue (WAT)
- large lipid droplets
- few mitochondria
- sparse blood supply
  lipid storage and insulation!

Brown Adipose Tissue (BAT)
- small lipid droplets
- abundant mitochondria
  (brown color)
- rich blood supply
- rich sympathetic innervation
  (NA, β1-receptors, cAMP↑)
  heat production!
Brown adipose tissue (BAT)

- In BAT, terminal oxidation and ATP synthesis are dissociated.
- BAT mitochondria contain special uncoupling proteins (UCP-1) that break down the H⁺ gradient without synthesizing ATP.
- All chemical energy released may be dissipated as heat.
- Vital importance in mammals that truly hibernate.

Thermogenesis via UCPs

Collins Figure 1

COUPLING (oxidative phosphorylation)  UNCOUPLING (proton leak)

Intermembrane space  Matrix

Mitochondrial inner membrane

ATP synthase  Electron transport chain

UCP

ATP synthesis  Heat

H⁺  H⁺  H⁺  H⁺  H⁺  H⁺  H⁺  H⁺
Thermoregulation at equilibrium

\[ M \pm R \pm C \pm C - E = 0 \]

Thermoneutral zone

\[
\begin{array}{c|c|c}
M \uparrow & \downarrow & E \uparrow \\
\hline
\text{Metabolic zone} & \text{Vasomotor zone} & \text{Sudomotor zone}
\end{array}
\]

Metabolic thermogenesis:
1. Shivering thermogenesis (skeletal muscle)
2. Non-shivering thermogenesis (BAT)

Maximal vasoconstriction

SKIN
Vasoconstriction-
Vasodilation+
Sweating

Behavioral thermoregulation

Behavioural thermoregulation against heat: midday nap (searching for shadow, wind), posture, decreasing muscle activity - sleeping)
The Cutaneous Circulation

- The skin comprises 4-5% of body weight, and has considerable metabolic activity
- transient ischemia results in reactive hyperemia
- and irritation produces local vasodilation via axon-reflex mechanism
- CuBF can vary between 5-60% of cardiac output depending on thermoregulatory needs NOT metabolic ones
- blood flow in subcutaneous WAT is similarly regulated to skin, vasoconstriction results in better insulation
- skin venous plexuses are the biggest “blood store” of the human body

Cutaneous blood flow

- **Acral areas** (large surface/weight ratio)
  - Ear
  - Nose
  - Lips
  - Distal limbs, fingers

- **Non-acral areas** (small surface/weight ratio)
  - Neck
  - Trunk
  - Proximal portion of limbs
Microcirculation in acral areas

Heat dissipation with a radiator regulated by acral circulation
Acral circulation in birds...

Toco toucan

Heat conductance through skin (times the vasoconstricted rate)

Environmental temperature (°C)

Vasodilated

Vasoconstricted
Cutaneous blood flow

- **Acral areas**
  - AVA
  - No myogenic tone
  - Sympathetic vasoconstrictor tone
  - Only passive vasodilation
  - 0.2-50 ml/100g/min

- **Non acral areas**
  - No AVA
  - Myogenic tone
  - Sympathetic vasoconstrictor tone
  - Active vasodilation associated with sweating
  - 1-8 ml/100g/min

Regulation of cutaneous blood flow

**Acral regions**
- Sympathetic innervation
  - neurotransmitter: noradrenaline
  - receptor: α1 adrenergic receptor
  - effect: vasoconstriction
  - vasodilation: decreased constrictor tone

**Non-Acral regions**
- Sweat glands
  - Ach
- Bradykinin
- “NANC”
- VIP, NO

Arterioles, AVA
Thermoregulation at equilibrium
$M \pm R \pm C \pm C - E = 0$

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Metabolic thermogenesis:
1. Shivering thermogenesis (skeletal muscle)
2. Non-shivering thermogenesis (BAT)

Maximal vasoconstriction

Vasoconstriction-vasodilation

Vasodilation+
Sweating

Behavioral thermoregulation

Heat dissipation with evaporation: taking a bath (no loss of body water!)
Heat dissipation with evaporation: panting

Rapid, shallow (dead space) ventilation results in cooling of blood in the upper airways, not changing alveolar gas.

Heat dissipation with evaporation: licking
Heat dissipation with evaporation: sweating
- 2 million eccrine sweat glands (versus apocrine glands)
- Sympathetic innervation
- Neurotransmitter: Ach
- Receptors: atropine-sensitive muscarinic receptors (small portion receives NA innervation)
- 1-2 L/h!, in acclimatized person can be 2-4 L/h!

**Histology of the secretory coil**
Histology of the duct

The mechanism of hypotonic sweat production: isotonic secretion, salt reabsorption

NKCC1: Na⁺-K⁺-2Cl⁻ symporter (different from Henle’s loop TAL: NKCC2)
ENaC: Epithelial Na⁺ channel (under aldosterone regulation)
CLCA: Ca²⁺-dependent chloride channel
CFTR: cystic fibrosis conductance transmembrane regulator (chloride channel)

Patients with cystic fibrosis can sweat, and they lose a lot of salt – basis of diagnostic test: high sweat osmolarity
The (in)famous CFTR

• belongs to the superfamily of ABC transporters (ABCC7) but works as an ion channel
• Involved in fluid secretion in the small intestine, colon, airways, pancreas, etc., also in reabsorption of salt (sweat glands, colon)
• It is regulated (gated) by cAMP levels: the more Ser residues are phosphorylated by PKA – the more time the channel spends in the ATP-binding (open state - see figure)
Its mutation is causing cystic fibrosis (CF) – hence the name of the channel.

Summary of acute thermoregulatory responses

Against COLD:
- Behavioural response
- Motor response: shivering
- Skin vasoconstriction (sympathetic vasoconstrictor tone increases)
- BAT activation (sympathetic activation)
- Piloerection (sympathetic activation)

Against HEAT:
- Behavioural response
- Skin vasodilation (sympathetic vasoconstrictor tone DECREASES)
- Sweating (sympathetic activation)
- Panting (respiratory motor pattern)
The central mechanisms of thermoregulation

- The temperature of the body “core” and the “shell” are monitored by central and peripheral THERMORECEPTORS, respectively.
- Thermoreceptor activity affects various neuronal groups in the brainstem and especially in the HYPOTHALAMUS to activate/inhibit the different thermoregulatory effector mechanisms. These regulatory loops can function independently, their sensitivity can also be independently regulated.
- The hypothesis of a single integrated temperature controller „center” producing a so-called set point temperature is no longer valid.

Central thermoreceptors

- Most of them are WARM-sensitive neurons in the anterior preoptic area (POA). They constantly monitor core temperature.
- They have pacemaker activity, warming increases, cooling decreases their AP frequency.
- The POA neurons play fundamental roles in the regulation of autonomic effector mechanisms (see rat in the following slide)
Peripheral Thermoreceptors

- Free nerve endings of primary sensory neurons in the skin
- Cold (Aδ-fibres) >> OR warm receptors (C-fibres)
- The nerve endings contain temperature-sensitive (gated) non-selective cation channels of the TRP (transient receptor potential) family, their activation leads to receptor potential translated into action potential trains
- Rapid adaptation.
- Distinct neuronal pathways are responsible for the conscious (discriminative) temperature sensation and the homeostatic regulation.
- Their activity is often the first to initiate BEHAVIOURAL responses BEFORE the core temperature would change (feed-forward regulation).
Temperature sensitive TRP channels

Central connections of peripheral thermoreceptors

Central nervous system

<table>
<thead>
<tr>
<th>Discriminative sensation</th>
<th>Homeostatic control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>Cortex</td>
</tr>
<tr>
<td>Thalamus</td>
<td>VMpo</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>VMb</td>
</tr>
<tr>
<td>Brainstem</td>
<td>POA</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Lamina I</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>DRG</td>
</tr>
</tbody>
</table>

VMpo, VMb: posterior and basal ventromedial thalamus, POA: preoptic area, PBN: parabrachial ne. ?: reticular formation in the medulla, pons and midbrain (not precisely identified) DRG: dorsal root ganglion

Changes in regulated temperature: Physical work

- Depending on the environmental temperature, sustained physical work elicits hyperthermia, heat production exceeds heat loss in a regulated way
- Rectal temperature can reach 39-40°C (NOT FEVER)
- Moderate hyperthermia promotes performance "warm-up"

Effect of sustained exercise on body temperature

Temperature rise depends on the percent of maximal aerobic power rather than absolute heat production!
Changes in regulated temperature: Fever

- Cytokines (endogenous pyrogens) induce fever (IL-1, IL-6, TNF)
- actions on the OVLT neurons? (no BBB), PGE$_2$ (aspirin blockade) also plays mediator role to affect the preoptic area (according to the old terminology: a new set-point is created)
- febrile response: shivering, vasoconstriction
- defervescence: vasodilation, sweating
- endogenous antipyretics: AVP, αMSH
Acclimation

- Heat acclimation: increased sweat rate (15 L/day!), diminished NaCl loss with sweat, lower sweat threshold, higher cutaneous blood flow
- Cold acclimation: sustained exposure to cold (months) elicits activation of the thyroid axis, T3/T4 increase, BMR increases

Evolutionary acclimation

- Bergmann’s rule (1847): Within a polytypic warm-blooded species, the body size of the sub-species usually increases with decreasing mean temperature of its habitat.
- Allen’s rule (1877): In warm-blooded species, the relative size of exposed portions of the body decreases with decrease of mean temperature
- Eskimos have much fewer sweat glands than other people!

Bergmann’s rule in humans

• There is an overall decrease in the surface area to mass ratio, meaning that heat loss is reduced

Allen’s rule in hares
Allen’s rule in humans

Keeping mass constant, surface area is increased by assuming a more linear form—taller, with long, slender arms and legs; shorter trunk.