Organ	Organ mass kg		% of body mass		Heat production at rest kcal h^{-1} (W)		% of total	
Kidneys	0.29		0.45		6.0	(7.0)	7.7	
Heart	0.29		0.45		8.4	(9.8)	10.7	
Lungs	0.60	5.03	0.9	7.7	3.4	(3.9)	4.4	72.4
Brain	1.35		2.1		12.5	(14.5)	16.0	
Splanchnic organs[a]	2.50		3.8		26.2	(30.5)	33.6	
Skin	5.00		7.8		1.5	(1.7)	1.9	
Muscle	27.00	59.97	41.5	92.3	12.2	(14.2)	15.7	27.6
Other	27.97		43.0		7.8	(9.1)	10.0	
Total	65.00		100.0		78.0	(90.7)	100.0	

[a] Abdominal organs, not including kidneys.

Table 7.1 Heat production in the major organs of a man at rest (body mass, 65 kg; heat production, 1872 kcal per day = 78 kcal per hour = 90.65 W). The main internal organs weigh about 5 kg but account for 72% of the total heat production. [Aschoff et al. 1971]

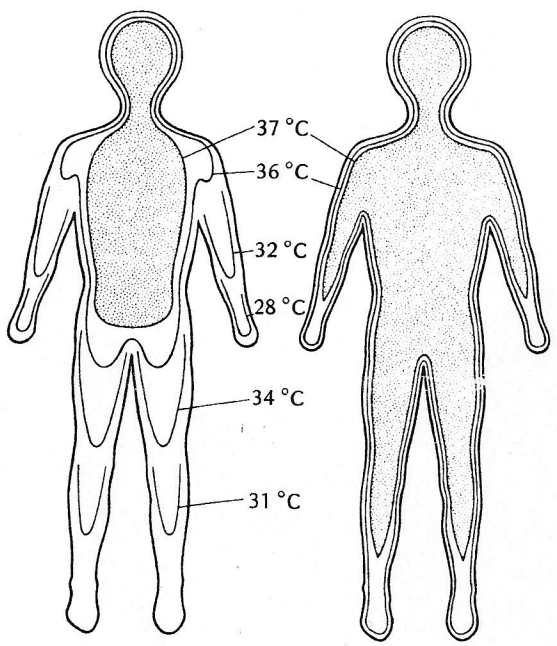
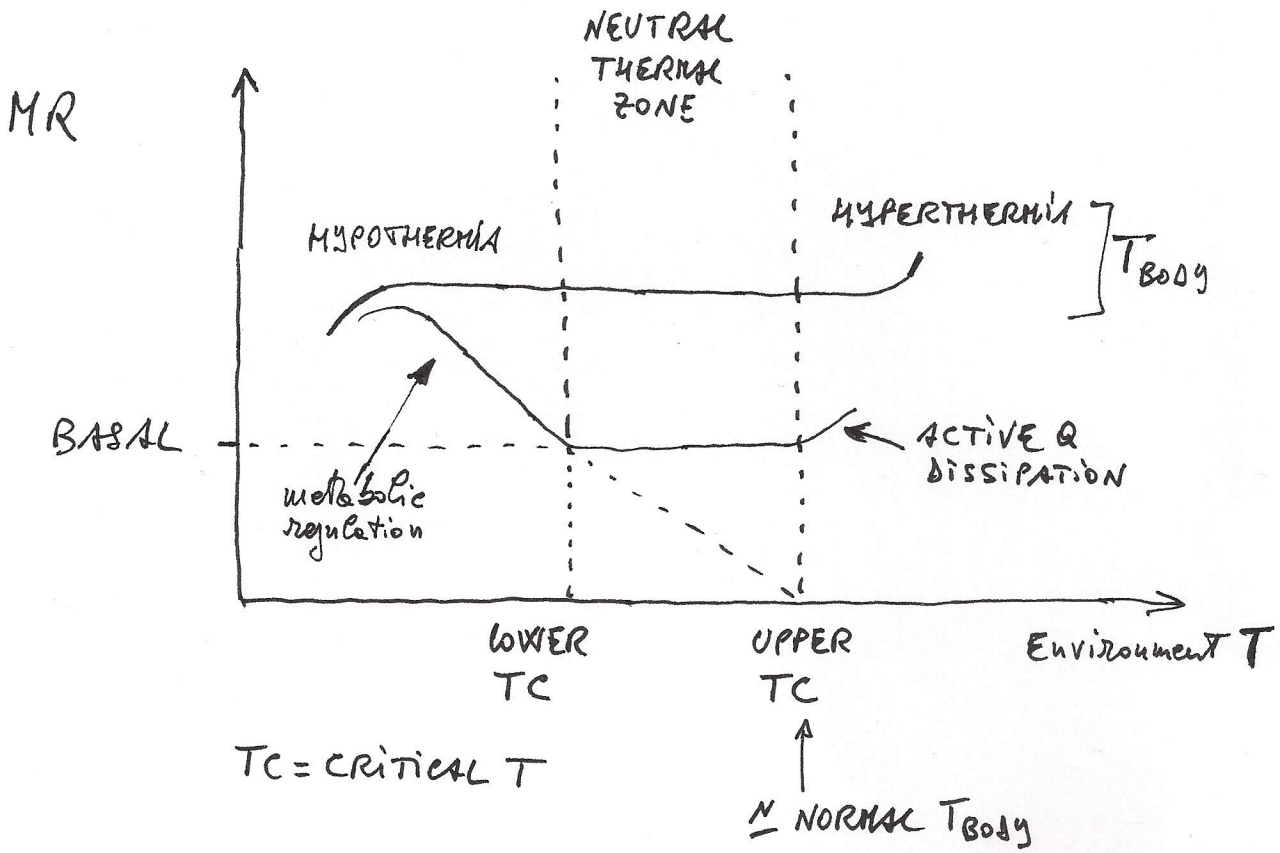


Figure 7.1 Temperature distribution in the body of a person at room temperatures of 20 °C (left) and at 35 °C (right). The isotherms, which indicate sites of equal temperature, show that, at 35 °C room temperature, a core temperature of 37 °C (shaded area) extends into the legs and arms. At 20 °C room temperature, the temperature gradients in the shell extend throughout the legs and arms, and the core temperature is restricted to the trunk and head. [Aschoff and Wever 1958]

Da: SCHMIDT-NIELSEN. ANIMAL PHYSIOLOGY. VERL. CAMBRIDGE UNIV. PRESS.

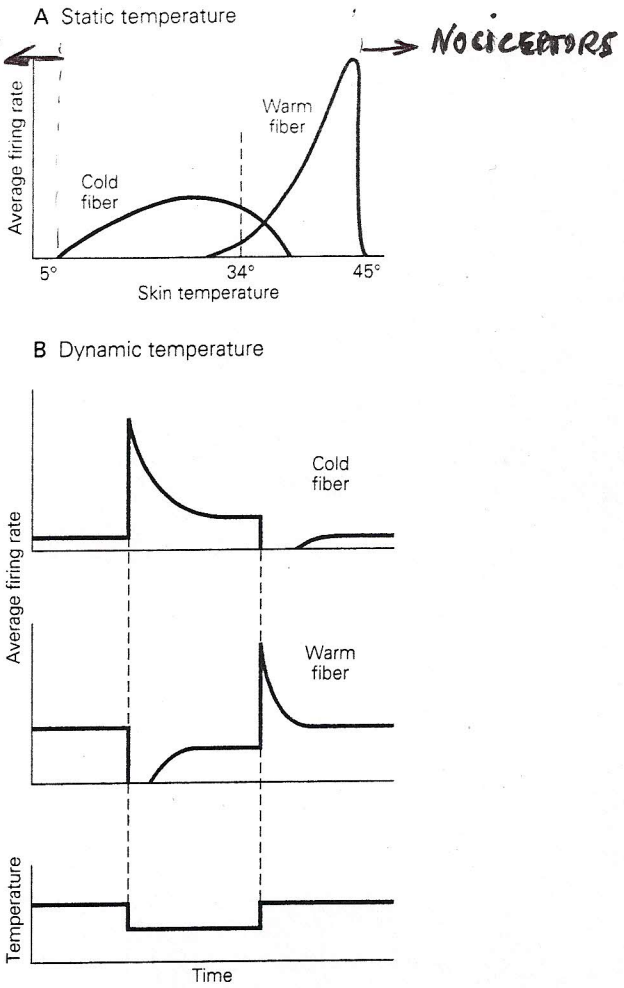


$$\text{HEAT LOSS} = Q = C\left(T_B - T_A\right)$$

(e.g. cal/min)

$$T_B = T_{BODY}$$

$$T_A = T_{AMBIENCE}$$



NOCICEPTORS ← → NOCICEPTORS

NON HYPOTHALAMIC T RECEPTORS

mammals
birds

skin
spinal cord
abdomen

Figure 22-9 Skin temperature is coded by warmth receptors and cold receptors.

(TONIC and PHASIC

A. Static temperatures. Cold receptors and warmth receptors differ in the range of steady-state temperatures to which they respond and in their peak temperature sensitivities. Cold receptors respond to steady-state temperatures of 5–40°C. Warmth receptors are tonically active at steady temperatures of 29–45°C. Cold receptors fire at highest rates at a skin temperature of 25°C, while warmth receptors are most active at 45°C. At the normal skin temperature of 34°C, cold receptors are more active than warmth receptors. (Adapted from Darian-Smith 1973.)

B. Dynamic temperatures. Both receptors are more sensitive to changes in skin temperature than to constant temperatures. Cooling the skin below the resting level evokes a sharp rise in the firing rate of cold receptors and silences warmth receptors. If the cold temperature is maintained, the firing rates of the cold receptors adapt. When the skin temperature is rewarmed to the resting level, cold receptors are briefly silenced, whereas warmth receptors fire a burst of impulses. Warming the skin produces the opposite firing patterns in warmth and cold receptors. (Adapted from Hensel 1973.)

Kandel et al. PRINCIPLES OF NEVRL SCIENCE - IV ED. McGRAW-HILL 2000.

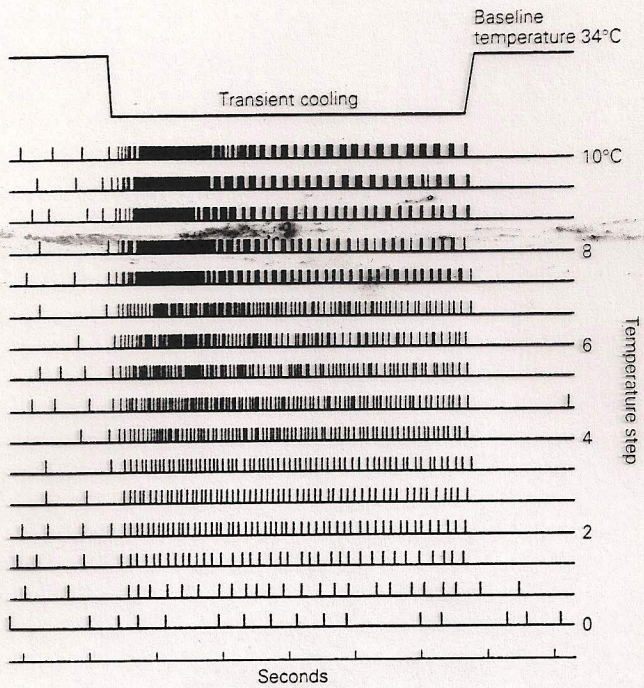


Figure 22-10 The rate and amplitude of cooling the skin is coded by the firing rates of cold receptors. Action potentials were recorded from a cold fiber when the skin was cooled rapidly. Each successive trace shows a smaller cooling pulse. The cold fiber shows a sharp rise in firing rate when the skin is cooled by 10° from 34°C to 24°C. Smaller cooling steps (eg, from 34°C to 30°C) evoke a smaller rise in the firing rate of the cold fiber. The frequency of discharge of cold fibers is linearly related to the size of the cooling step. Warming the skin at the end of the stimulus silences the cold fiber. (Reproduced from Darian-Smith et al. 1973.)

SENSIT.: 0.01 °C

TONIC and PHASIC RECEPTORS

THE EMBO JOURNAL

Have you seen ...?

The EMBO Journal (2009) 28, 1195–1196 | © 2009 European Molecular Biology Organization | Some Rights Reserved 0261-4189/09
www.embojournal.org

TREKing noxious thermosensation

Olaf Pongs*

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The EMBO Journal (2009) **28,** 1195–1196. doi:10.1038/emboj.2009.107

The ability to sense environmental temperature as pleasant or unpleasant is associated with the activity of thermo-sensitive neurons in the peripheral nervous system. Differential sensation of pleasant environmental temperatures (warm and cool) versus unpleasant and noxious (cold and hot) temperatures requires the definition of thresholds and temperature ranges for activating thermonociceptors. In this issue of *The EMBO Journal*, a study by Noël *et al* (2009) entitled 'The mechano-activated K^+ channels TRAAK and TREK-1 control both warm and cold perception' shows that the potassium leak channels TREK-1 and TRAAK have an important regulatory role in noxious thermonociceptors to ensure a high-enough activation threshold that does not interfere with the sensing of innocuous (warm and cool) temperature, but low enough in order to avoid tissue damage.

Of the five senses—sight, hearing, smell, taste, and touch—touch is perhaps the most varied. Touch describes the ability to sense chemical stimuli, mechanical forces, and temperature. Temperature sensing comes essentially in two flavours: pleasant (innocuous) and unpleasant (noxious). In the peripheral nervous systems, at the level of the skin two basic classes of innocuous- and noxious-temperature-sensing neurons have been recognized: myelinated Aδ-fibres responsible for the first sharp pain, and C-fibres responsible for the slow, longer-lasting nociception of noxious temperature (Kandel *et al*, 2000).

A major breakthrough in the identification of molecules involved in temperature sensing was the discovery of temperature-activated transient receptor potential (TRP) ion channels that were directly gated by a change in temperature. Four heat-activated TRP ion channels (TRPV1–4) and two cold-sensitive TRP ion channels (TRPM8 and TRPA1) were identified. Recently, two studies (Brauchi *et al*, 2004; Voets *et al*, 2004) convincingly have argued that the temperature-sensing properties of TRPM8 and TRPV1 channels arise directly from intrinsic thermodynamic channel properties. Whether this also applies to the other TRP channels is still a matter of debate (Dhaka *et al*, 2006). Importantly, TRPM8 and TRPV1 are voltage activated and temperature shifts the voltage-dependent activation of the channels to more physiological ranges. The implication of this observation is that membrane potential plays an important role in the temperature-sensing activity of the TRP channels. Given the sophistication of thermo-sensitivity, it most likely involves complex interactions of ion channels, receptors, and proteins

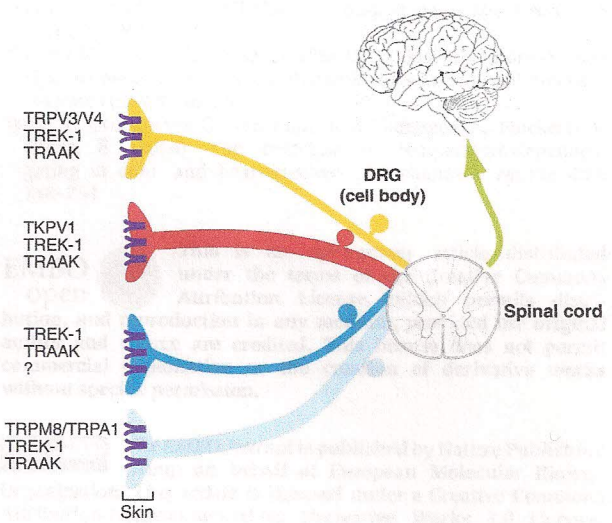


Figure 1 Temperature sensing at peripheral terminals of unmyelinated C-fibres (thin axons) and myelinated Aδ-fibres (thick axons) is transmitted to the spinal cord, and from there onwards to the cortex via central pathways. The diagram illustrates schematically ion channel populations in four subgroups of sensory neurons investigated in the study of Noël *et al* (2009). One group represented capsaicin-insensitive, heat-sensitive C-fibres, probably expressing TRPV3 and TRPPV4 channels, which responded to temperature increases between 30 and ~48°C (coloured in yellow). The population of these neurons was markedly increased in the TREK−/−, TRAAK−/− double knockout mice. A second group corresponded to heat-sensitive, capsaicin-sensitive, TRPV1-expressing Aδ neurons (coloured in red), which are normally in charge of signalling high temperature (⩾50°C)-induced pain, but were activated within a significantly lower temperature range. On the cold side, a small population of neurons (lightly blue coloured, Aδ fibres?) sensitive to menthol, allyl-isothiocyanate (AI) and cold is increased. However, the major effect concerns the population of menthol- and AI-insensitive and cold-sensitive C-fibre neurons (coloured in blue) that are normally active only at temperatures below 12°C. The question mark indicates that the nature of the cold-sensing excitatory ion channel is unclear. In the double knockout mice the population of these sensory neurons is significantly increased and their response activity is shifted to temperatures between 30 and 12°C.

TREK-1 < K+ SELECT. MECH + T 2P-Ch NOCIC. T-DEP

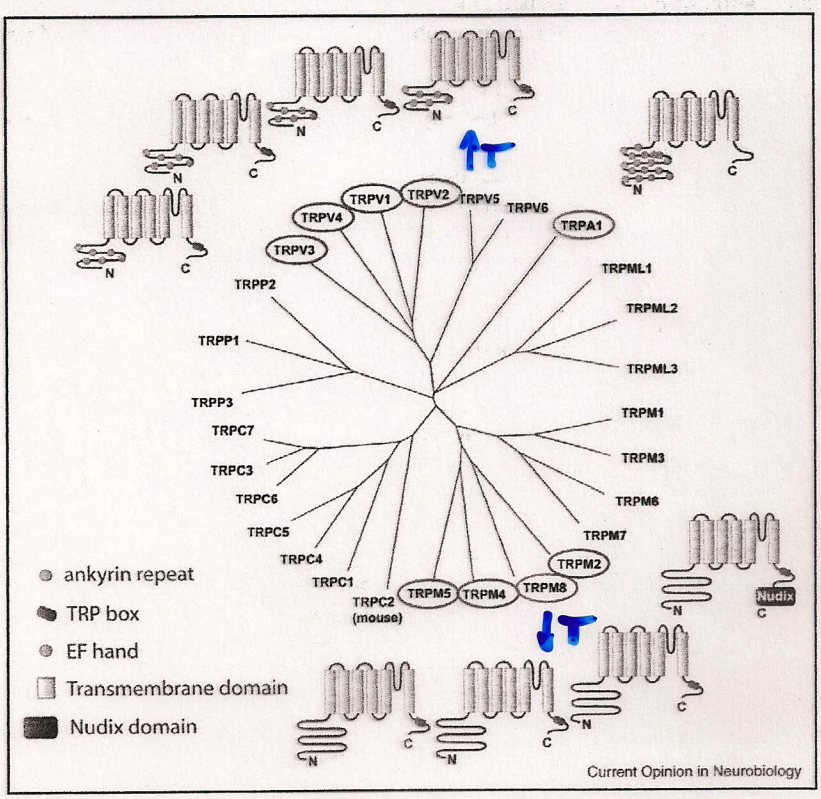
Table 1

ThermoTRP	Thermal activation	Chemical agonist	Sensory neuron/skin expression	Temperature phenotype of null mutant
TRPV1	>42 °C	Capsaicin, acidic pH, camphor, ethanol, resiniferatoxin, 2-APB, piperine, eugenol, gingerol, VaTx1–3 (spider toxin)	Sensory neuron	Impaired thermal avoidance and hyperalgesia
TRPV2[c]	>52 °C	2-APB, Δ^9-tetrahydrocannabinol	Sensory neuron	Not reported
TRPV3	>33 °C	Camphor, menthol, thymol, carvacrol, eugenol, 2-APB	Keratinocytes/ sensory neuron?	Impaired thermotaxis and thermal avoidance
TRPV4	>25–34 °C	4αPDD, bisandrographolide	Keratinocytes/ sensory neuron	Impaired thermotaxis, thermal avoidance, and hyperalgesia
TRPM2[a]	>35 °C	H_2O_2, ADP-ribose, βNAD	Not reported	Not reported
TRPM4[a]	Heat[b]	Cytosolic Ca^{2+}	Not reported	Not reported
TRPM5[a]	Heat[b]	Cytosolic Ca^{2+}	Not reported	Not reported
TRPM8	<25 °C	Menthol, icilin, l-carvone, eucalyptol, isopulegol, geraniol, linalool	Sensory neuron	Impaired cold sensation
TRPA1	<17 °C	Cinnamaldehyde, mustard oil, eugenol, icilin, allicin, acrolein, methyl salicylate, gingerol, GsMTx-4 (spider toxin), Δ^9-tetrahydrocannabinol, etc.	Sensory neuron	Impaired cold sensation [5] No thermal deficits observed [35]

HEAT COLD

[a] Properties of temperature sensitive TRP channels TRPM2, TRPM4, and TRPM5 are temperature-sensitive; however, evidence for their expression in DRG or skin is lacking [28,72]. The expression of TRPM5 in taste cells however suggests a potential explanation for the intriguing observation that temperature can affect taste perception [72].
[b] Activity of TRPM4 and TRPM5 is increased by heating but thermal activation thresholds have not been determined.
[c] Properties for rodent TRPV2 are shown, which are different from human TRPV2 (see [78]).

Figure 1



Q10 FIND A 20 (UP TO 20)

Phylogenetic analysis of TRP channels. ThermoTRPs are indicated by blue (cold-activated) and red (heat-activated) circles. Human TRP amino acid sequences were used for the analysis with the exception of TRPC2 for which the mouse channel was used. Topology models are shown including several characteristic domains (predicted using http://www.ebi.ac.uk/InterProScan and/or indicated in [17,19,24,55]). TRPM2, TRPM4, and TRPM5 are temperature-sensitive; however, evidence for their expression in DRG or skin is lacking [28,72].

- Dhaka et al. Annu. Rev. Neurosci. 29: 135-161, 2006

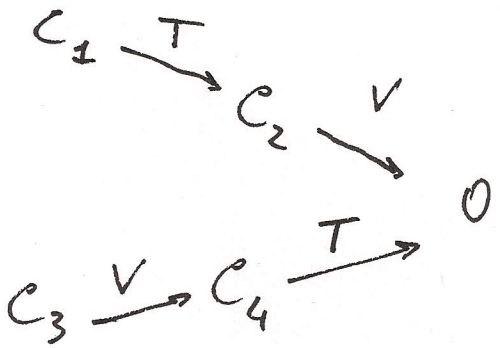
- Bandell et al. Curr. Opin. Neurobiol. 17: 490-497, 2007

POSSIBLE MECHANISMS OF T SENSITIVITY:

a) $C \overset{V,T}{\rightleftharpoons} O$ (C closed, O open) MUTATIONS ON S4 DOMAIN

(but TRPM2 is not Voltage-dependent, thus T and V may act independently)

b) T and V activate the channel independently, but they interact allosterically.



ROLE OF C-TERMINAL DOMAIN:

C-term. of TRPV1 → TRPM8 (COLD SENSATION) → TRPM8 (WARMTH SENSATION)

C-term. of TRPM8 → TRPV1 (warmth sens.) → TRPV1 (cold sens.)

ANNUAL REVIEWS

Annual Review of Physiology

Temperature Sensation: From Molecular Thermosensors to Neural Circuits and Coding Principles

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Keywords

heat, cold, somatosensation, pain, TRP, thermoregulation

Abstract

Temperature is a universal cue and regulates many essential processes ranging from enzymatic reactions to species migration. Due to the profound impact of temperature on physiology and behavior, animals and humans have evolved sophisticated mechanisms to detect temperature changes. Studies from animal models, such as mouse, *Drosophila*, and *C. elegans*, have revealed many exciting principles of thermosensation. For example, conserved molecular thermosensors, including thermosensitive channels and receptors, act as the initial detectors of temperature changes across taxa. Additionally, thermosensory neurons and circuits in different species appear to adopt similar logic to transduce and process temperature information. Here, we present the current understanding of thermosensation at the molecular and cellular levels. We also discuss the fundamental coding strategies of thermosensation at the circuit level. A thorough understanding of thermosensation not only provides key insights into sensory biology but also builds a foundation for developing better treatments for various sensory disorders.

Da: MORUZZI - FISIOLOGIA - UTET 1986

Magoun, Harrison, Brobeck e Ranson (1938) hanno studiato l'effetto del riscaldamento localizzato di varie parti dell'ipotalamo con corrente alternata ad alta frequenza. La fig. 273 dimostra che solo in un breve tratto posto al di sopra del chiasma ottico si ottiene la tipica risposta al riscaldamento del cane e del gatto: la polipnea termica. Vi sono dunque in questa regione neuroni o recettori che rispondono in modo adeguato ad un riscaldamento locale, quale si può avere in natura solo per un aumento della temperatura del sangue carotideo.

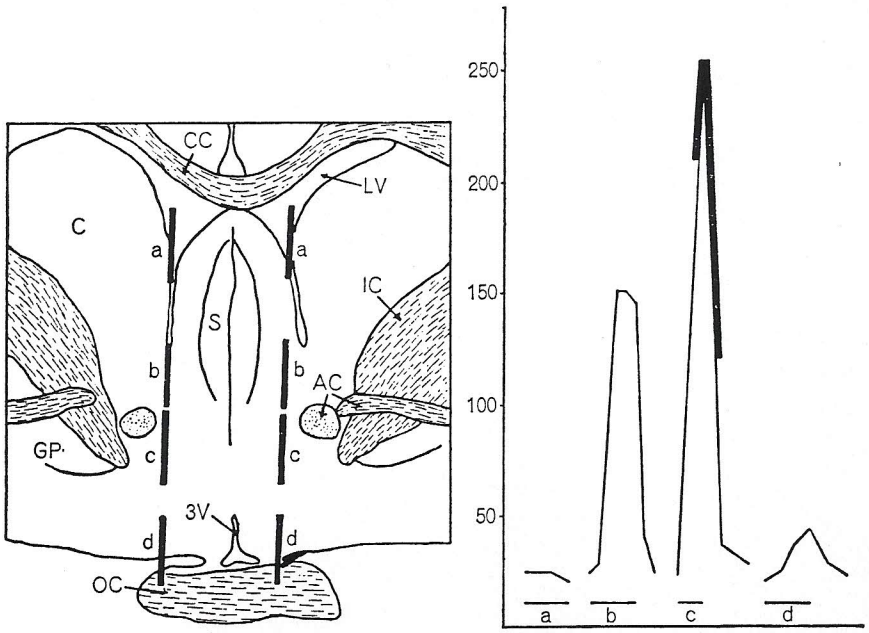


Fig. 273. Effetti del riscaldamento localizzato dell'ipotalamo.

Gatto in narcosi di uretano. La figura *a sinistra* indica le diverse posizioni (aa,bb,cc,dd) della coppia di elettrodi riscaldanti, a livello della parte dell'ipotalamo che sovrasta il chiasma ottico. *A destra* si vede che la ventilazione polmonare aumenta per il riscaldamento a livello di b, tuttavia la tipica polipnea termica (linea nera spessa) compare solo quando il riscaldamento si ha a livello di c.

CC, corpo calloso; C, nucleo caudato; LV, ventricolo laterale; IC, capsula interna; S, septum; AC, commissura anteriore; GP, globus pallidus; 3V, terzo ventricolo; OC, chiasma ottico.

(Da H. W. MAGOUN, F. HARRISON, J. R. BROBECK e S. W. RANSON, in *J. Neurophysiol.*, *1*: 101-114, 1938, fig. 2A e 2B).

Regulatory response up to 20 times as effective as the one elicited by peripheral receptors, for the same ΔT.

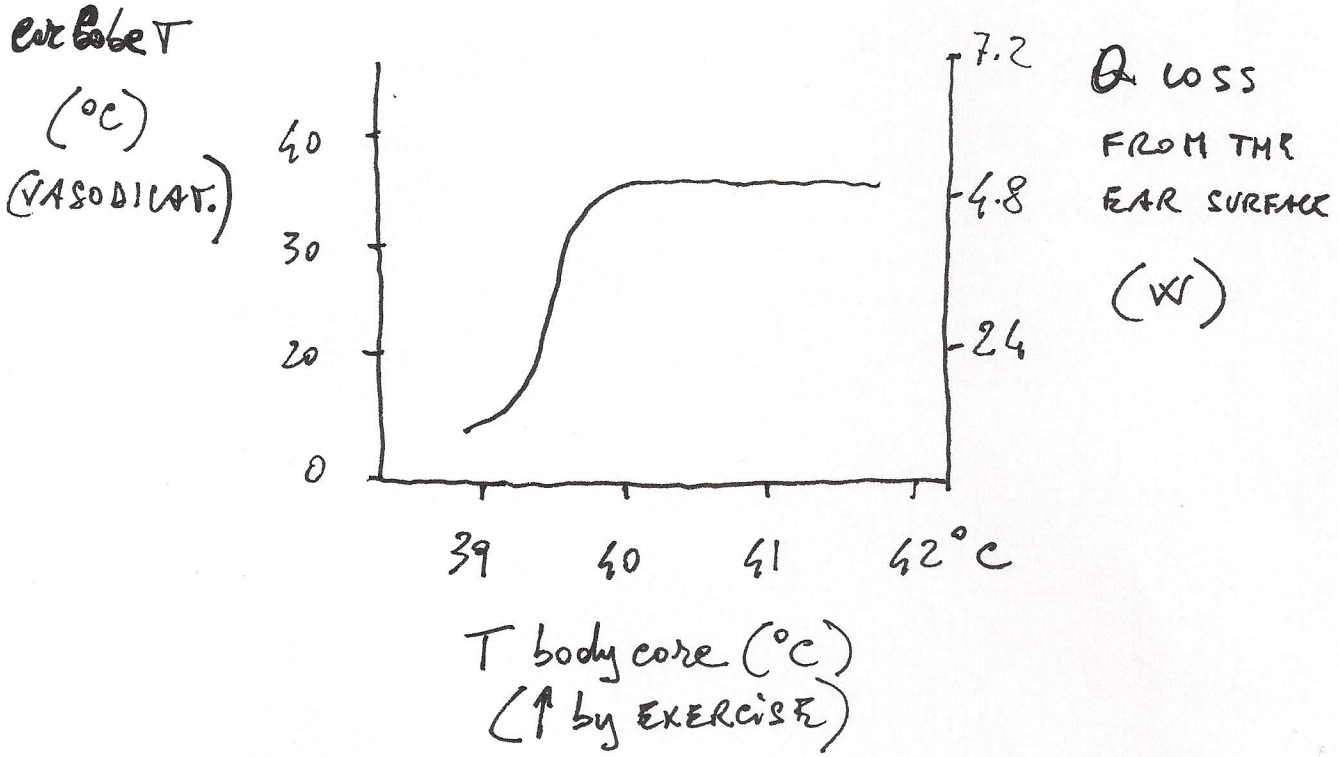
Hypothalamic control also in the other Vertebrates, but the responses are different, e.g. behavioral.

Sensors in birds appear to be extra-hypothalamic.

SENSITIVITY OF T RESPONSE

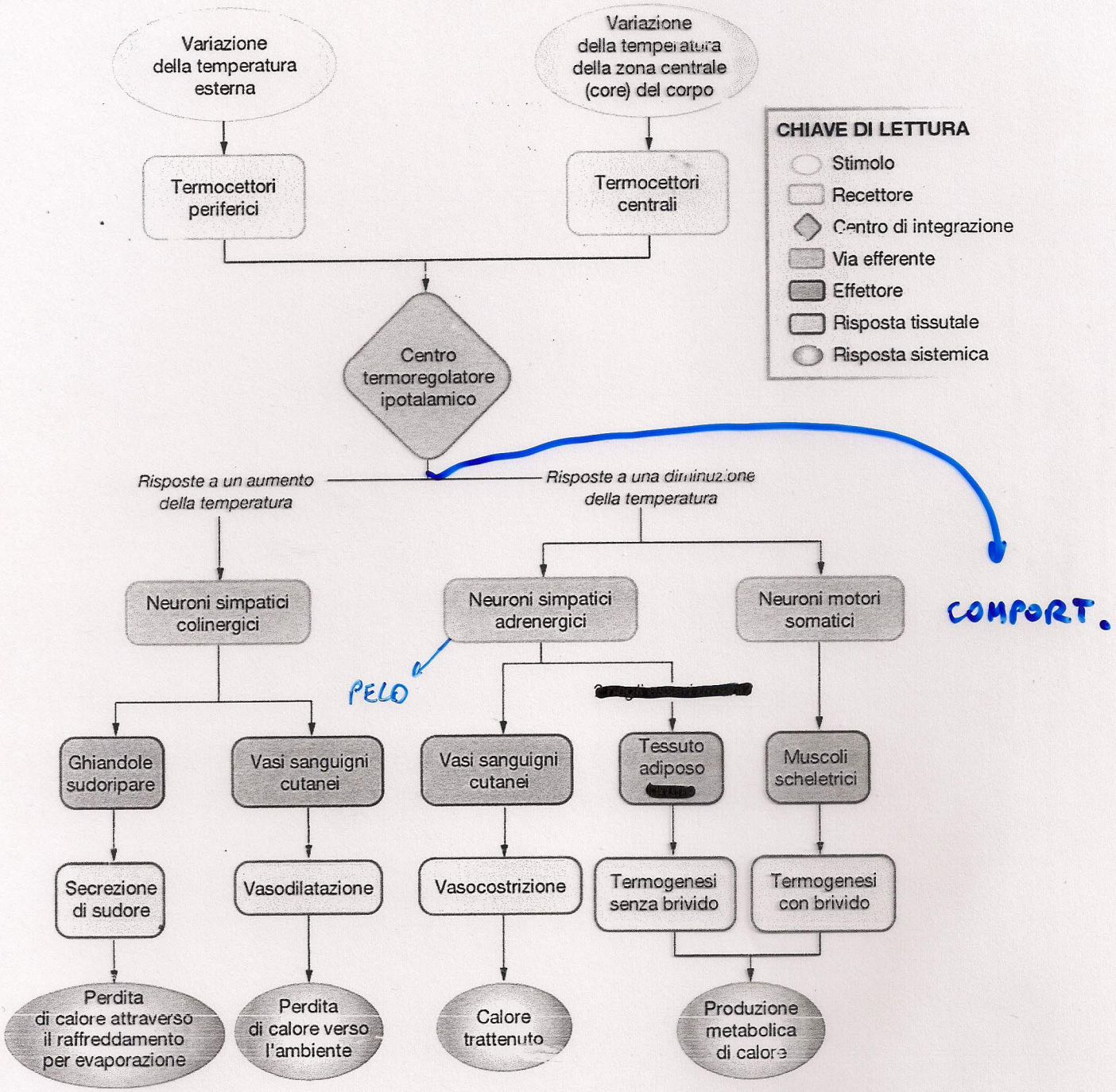
EXAMPLE: THERMAL RESPONSE IN RABBITS

A)



B) ↓ HYPOTHALAMIC T ⟶ ↑ T BODY

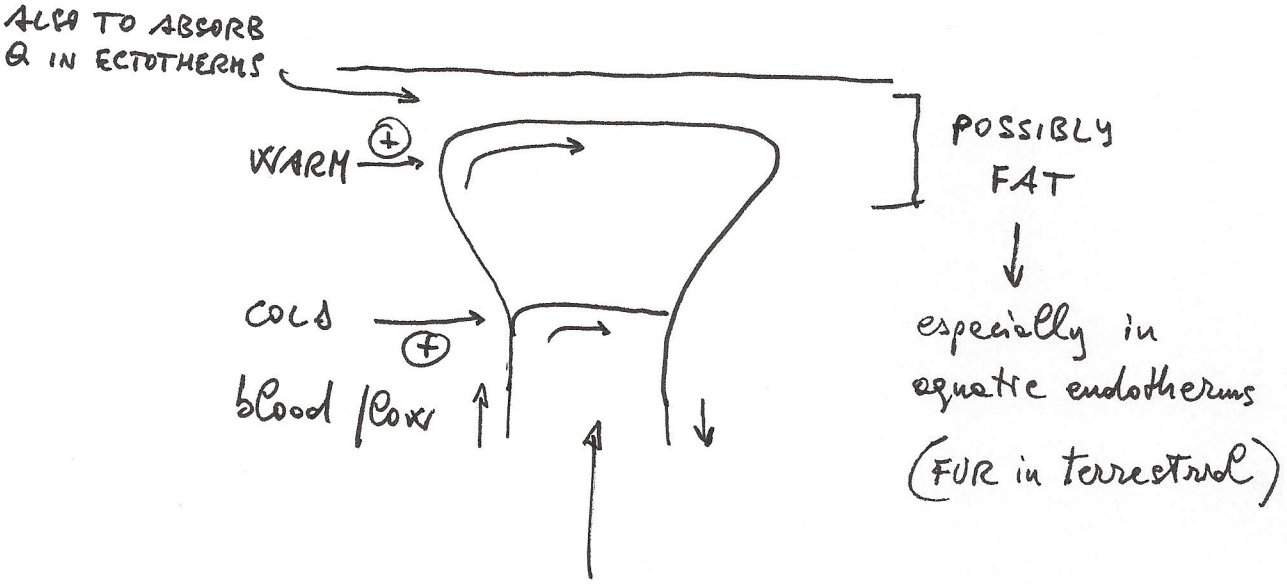
↑ MR



Fisiologia

D.U. Silverthorn

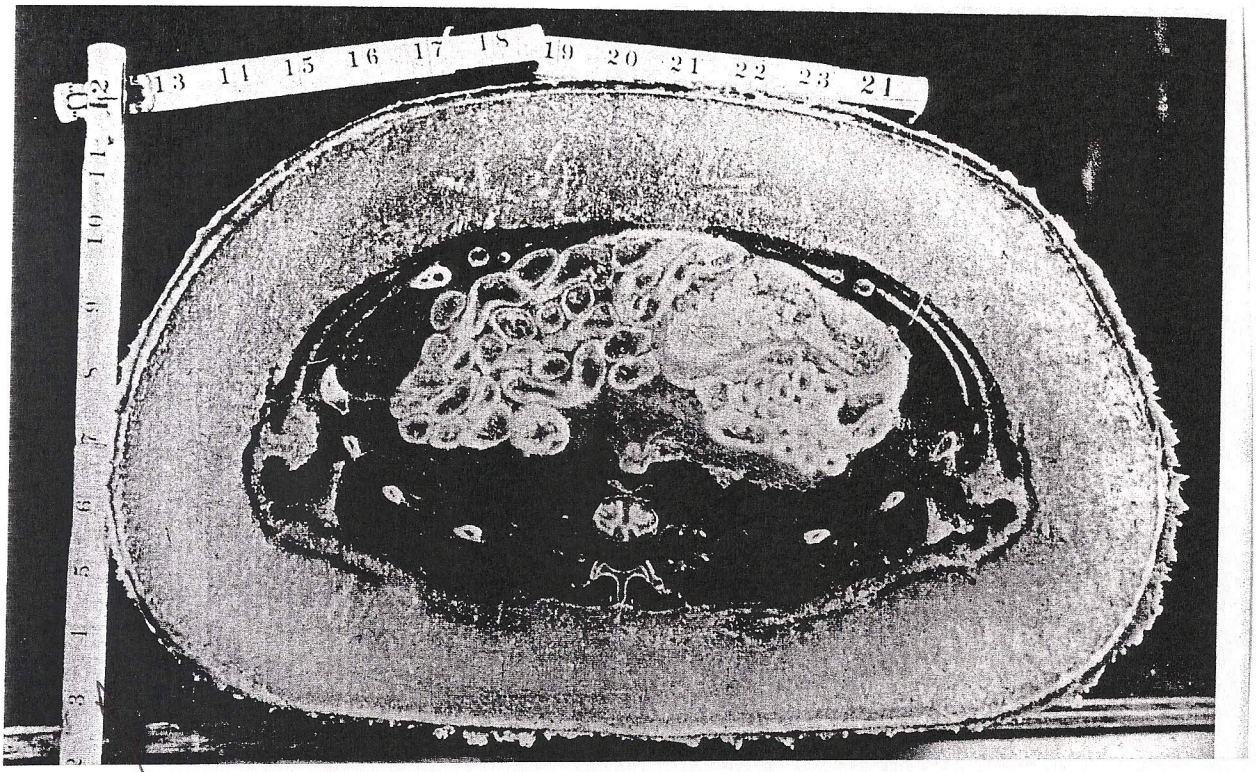
VASOCONSTRICTION / VASODILATION



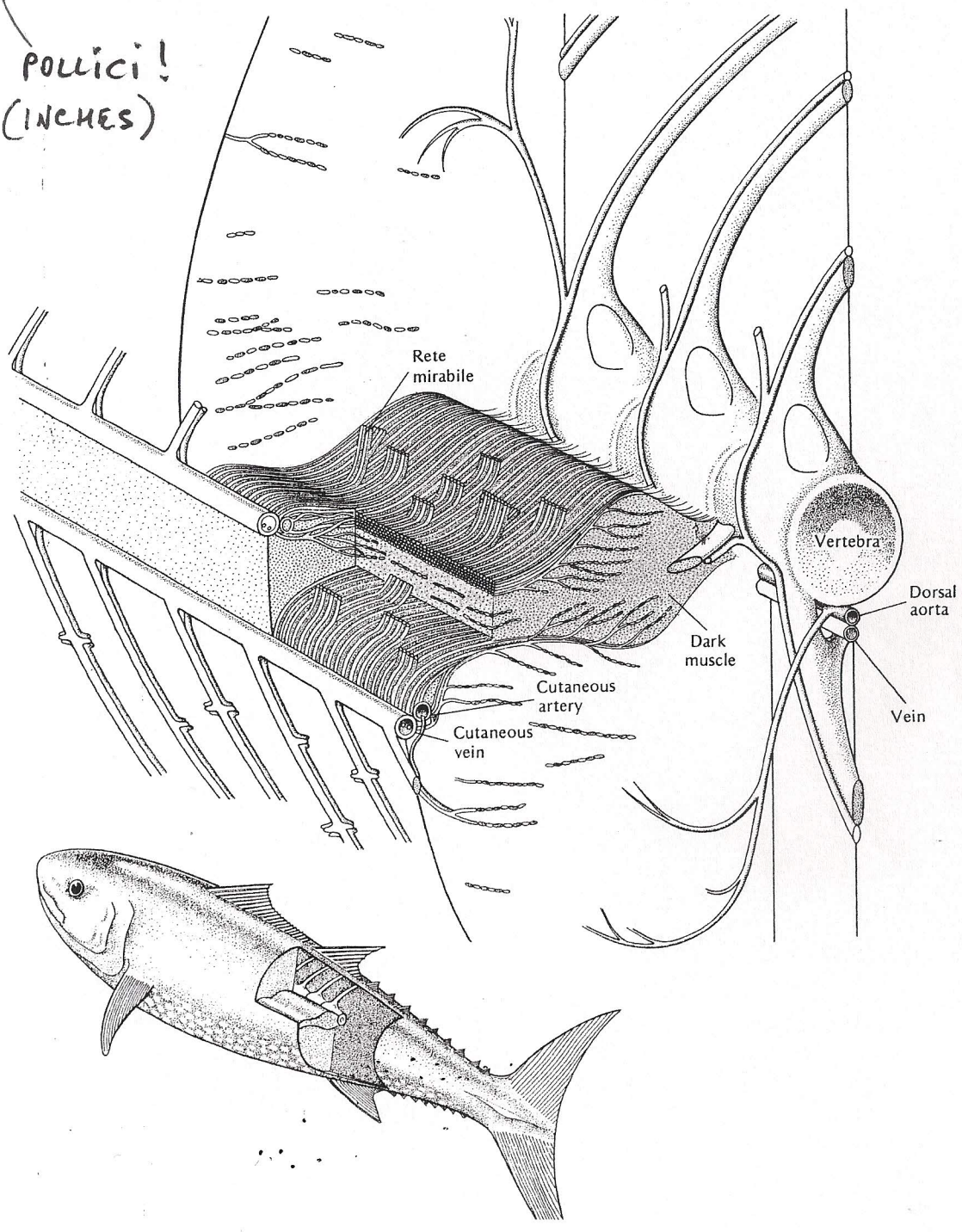
- A/V ANASTOMOSIS (CAPILLARY SHUNTING)
  especially effective with subcutaneous fat.

- COUNTERCURRENT FLOW AND REGIONAL HETEROTHERMIA

- " " CAN BE ALSO USED FOR REGIONAL ENDOTHERMIA (e.g. TUNA)



POLLICI!
(INCHES)



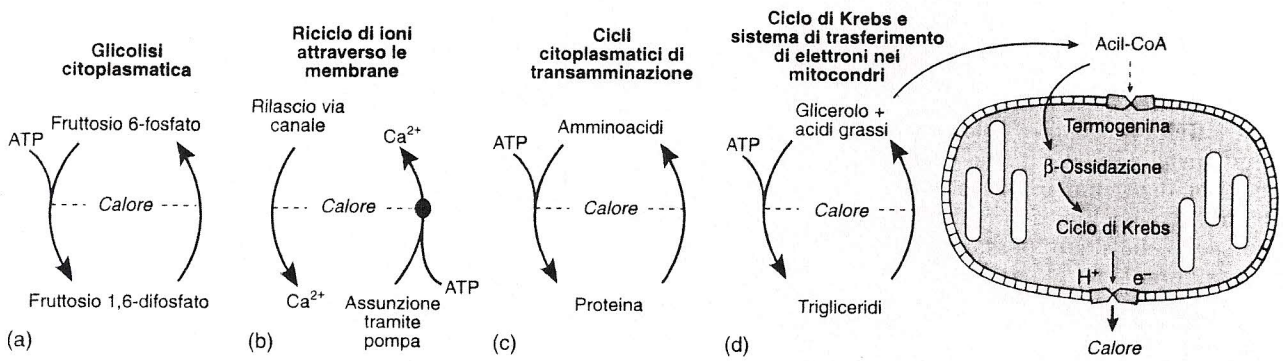


Figura 8.35. Possibili cicli biochimici futili in grado di generare calore: (a) usato da alcuni insetti endotermi, (b) in alcune cellule calorigene di pesce, (d) è probabilmente la via seguita nel tessuto adiposo bruno (BAT) dei tetrapodi.

Da WILLMER ET AL. FISIOLOGIA AMBIENTALE DEGLI ANIMALI ZANICHELLI 2003.

FROM BAT: UP TO 500 W per Kg.

THERMOGENESIS

1) SHORT-TERM

- WITH SHIVERING (block by neuromuscular blockers like curare)

- WITHOUT SHIVERING

NOR-ADRENALINE → ADIPOCYTES (mainly)

↑ LIPOLYSIS

↑ E usage to generate heat (futile cycles)

→ BROWN ADIPOSE TISSUE

(some mammals also hibernating human newborn)

THERMOGENIN

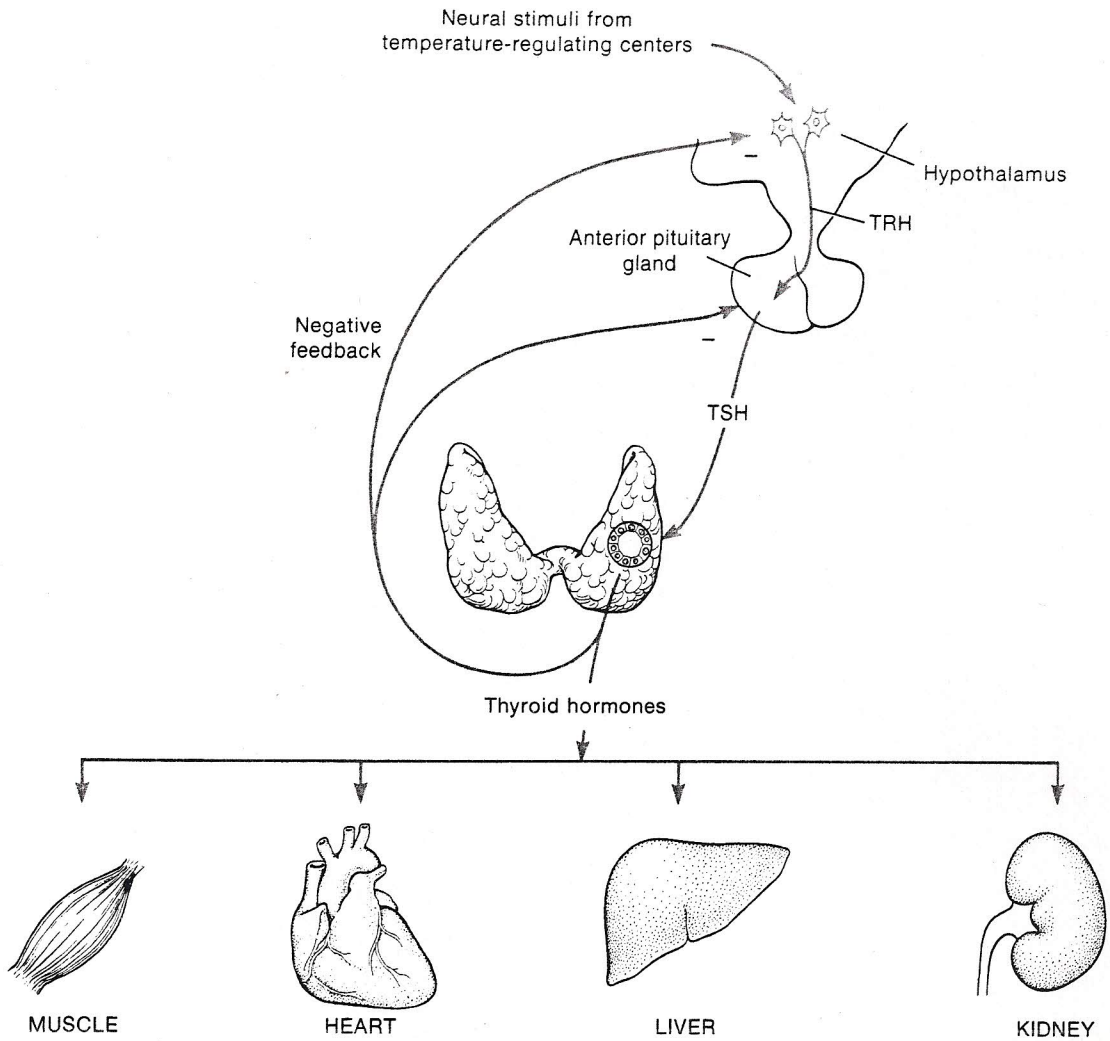
(uncouples oxid. phosph. similar to ADP/ATP translocase)

2) LONG-TERM

(- BEHAVIOR
- MOLT (fur, etc.) } NOT THERMOGENESIS)

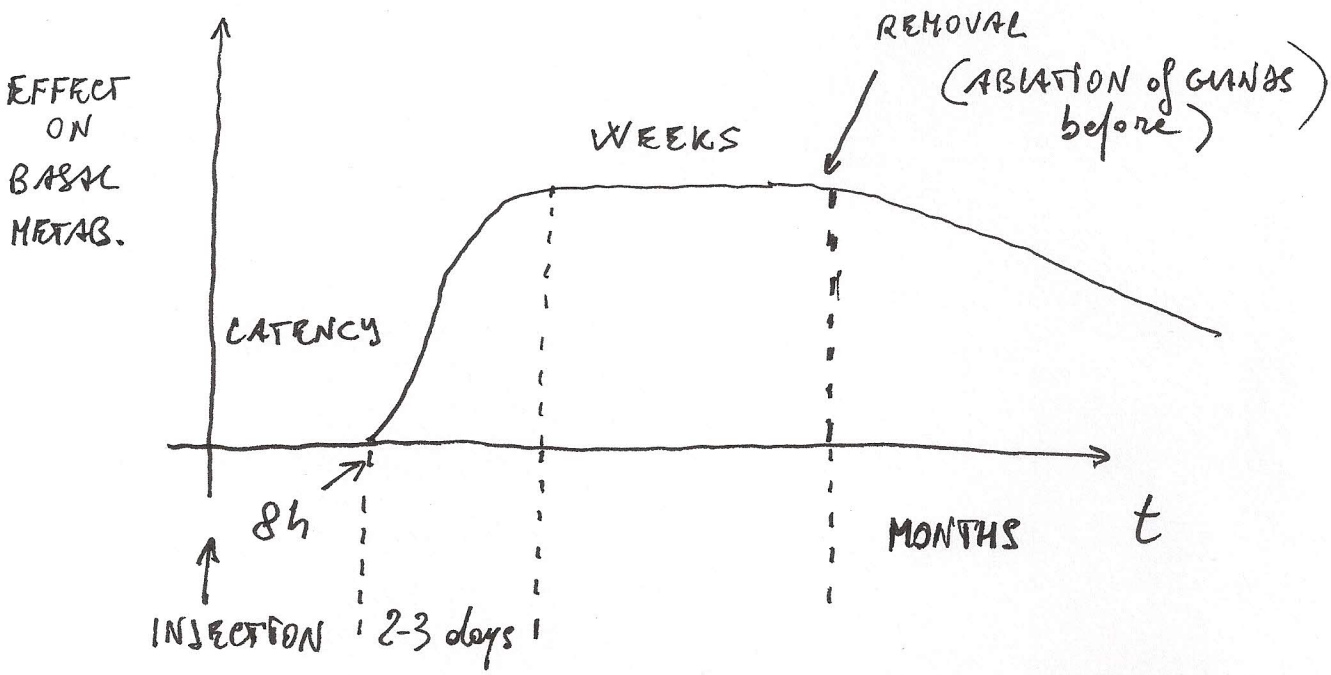
- ↑ ALIMENTATION

- THYROID EFFECTS ON METABOLISM



Increased oxygen consumption and heat production

KINETICS OF THE EFFECT OF THYROID HORMONES



THE ACTION OF NOR-ADRENALIN IS INSTEAD VERY RAPID.

The two effects cooperate.

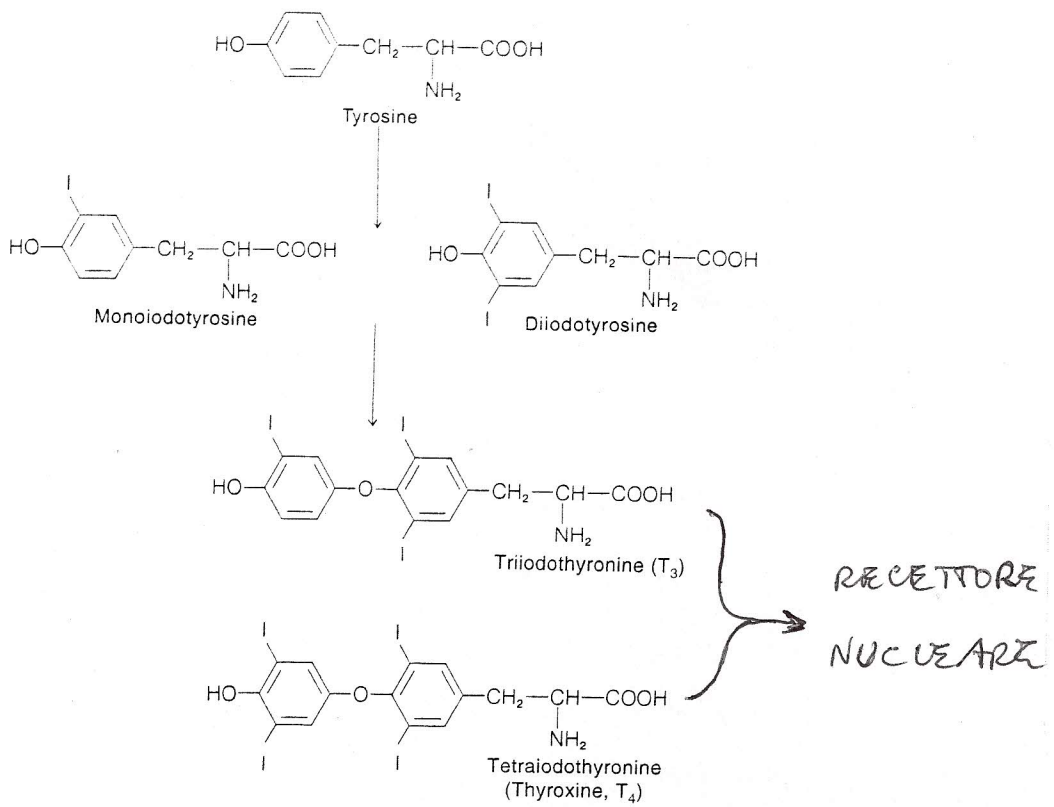
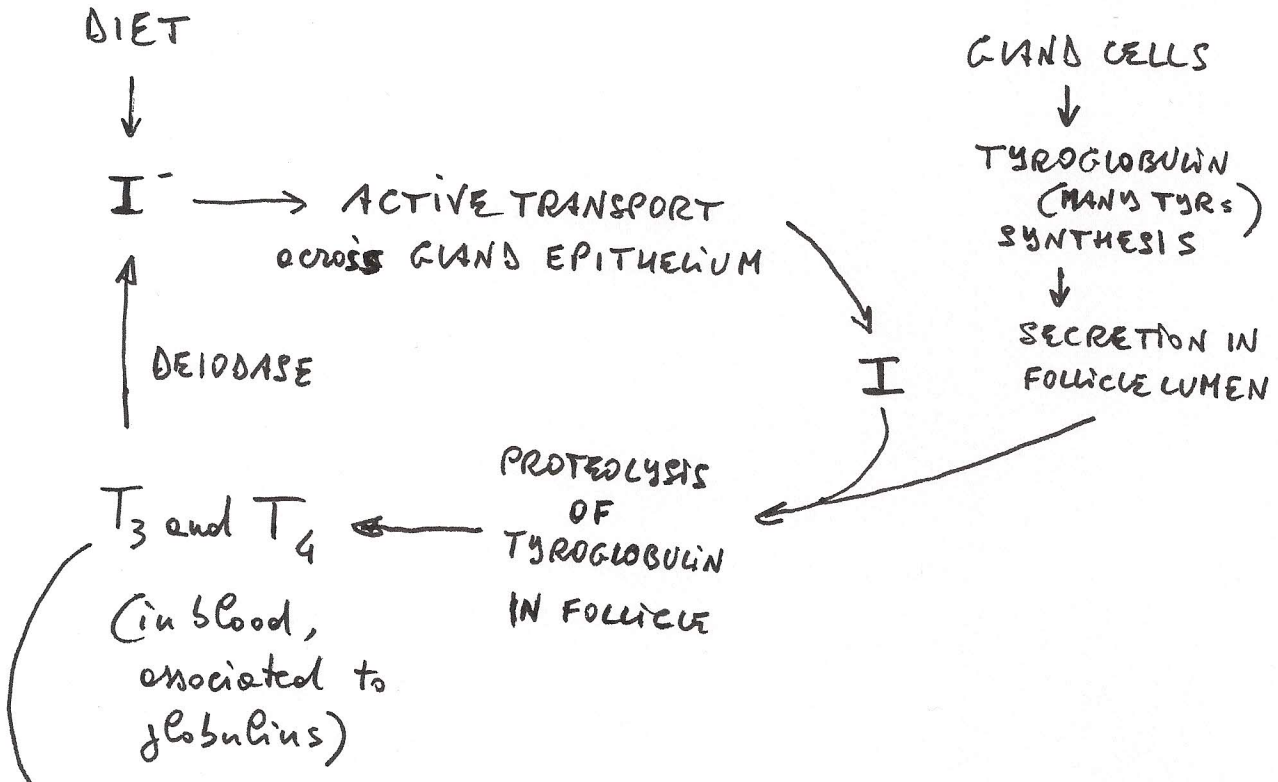


Figure 9-25 The thyroid hormones are produced from iodinated derivatives of the amino acid tyrosine. Condensation of the tyrosine derivatives yields 3,5,3′-triiodothyronine (T_3) and thyroxine (T_4); the two rings in each hormone are linked by an ether bond. T_3 is also produced by removal of one iodide from thyroxine.



1) ↑ BASAL METABOLISM (liver, muscle, kidney)

a) TONIC ACTION

b) PHASIC ACTION IN RESPONSE TO COLD

(nuclear receptor)

2) DEVELOPMENTAL EFFECTS IN PRESENCE OF GH

(if GH is lacking: tyroid dwarfism
with severe mental retardation)

METAMORPHOSIS IN AMPHYBIA and POIKILOTHERMS
in general,
(no effect on metabolism).

FEVER (also in POIKILOTHERMS

↳ PISCES
AMPHYBIA
REPTILIA
INSECTA (roach)
(behav. response)

GRAM- BACTERIA
other pathogens → TOXINS (endogenous pyrogens)
high MW polysacc.

↓ IMMUNOCYTES

↓ PYROGENS (IL1, IL6, some interferons, TNF...)

? ↓

↑ SETPOINT T of the HYPOTHALAMIC THERMOSTAT

↓

↑ BODY T (also thermogenesis ? without shivery)

↓

BACTERIOSTATIC EFFECT

↑ IF EFFICACY (interferons)
↑ Leukocyte function

VARIOUS TISSUES ↓

(PROT. → MEMB. → ↑ ANTIVIR. ENZ.)

Example: DESERT IGUANA
(Dipsosaurus dorsalis,
USA and MEXICO)

↓

a) BACTERIAL INFECTION

↓

the animal cooks for sun exposure
to reach a $T_{Body} \approx 40-42°C$
(usually 38°C preferred)

b) BACTERIAL INFECTION (experimental)

→ 34°-36° → DEATH in NG days

→ 38°

→ 40° → higher survival rate

→ 41°

→ 42° → maximal survival

THERMOSENSITIVE PITS

INSECTS[†]: e.g. Melanophila (fire beetle)
(maybe really IR)

BLOOD-SUCKERS (e.g. ticks)

SNAKES

Thermoceptors that work with different mechanisms:

- ELECTRORECEPTORS OF SOME SHARKS

  small $\Delta T \rightarrow \Delta V$

  extracellular glycoprotein gel works as a semiconductor

  Brown B.R. Nature 421: 495, 2003
  (SEEBECK EFFECT)

† Evans W.G.

ANN. ENTOMOL. SOC. AM.

103: 823-826, 2010.

hν ≃ 57 Kcal/m
½ Uv (λ ≃ 500 nm)

hν ≃ 1-3 Kcal/m
IR (λ ≃ 10000)

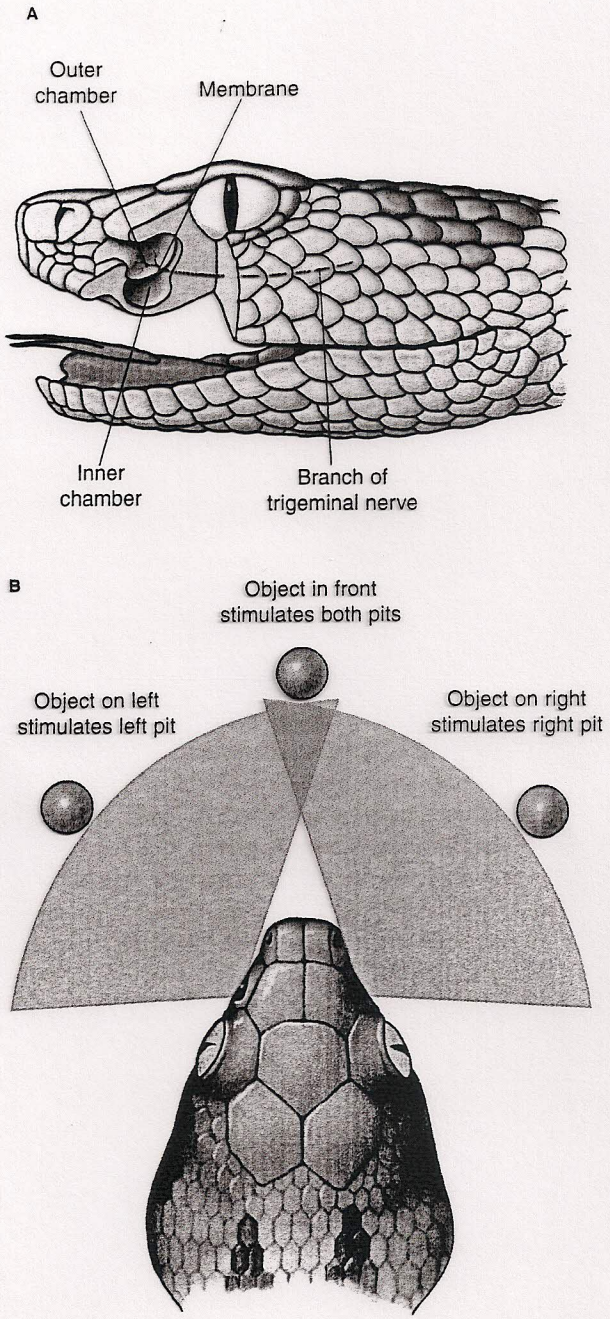
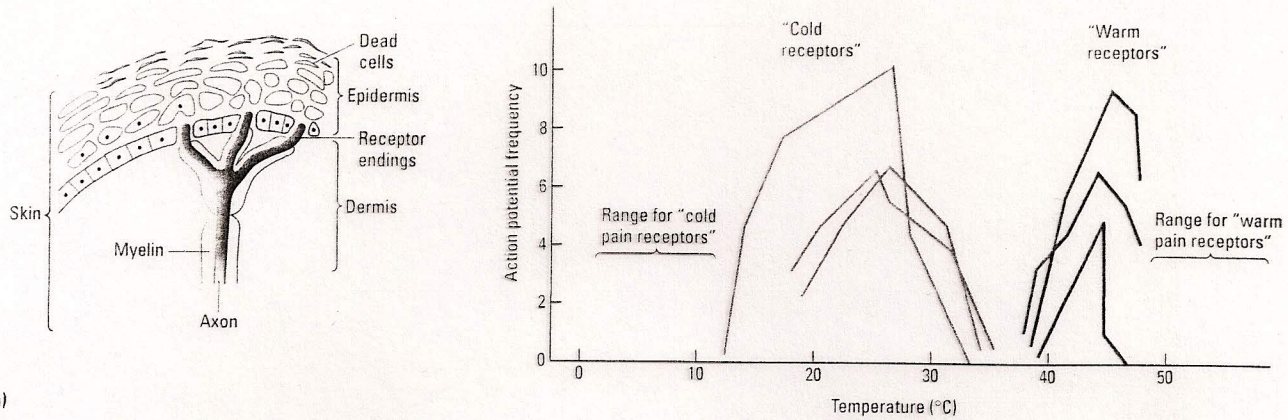
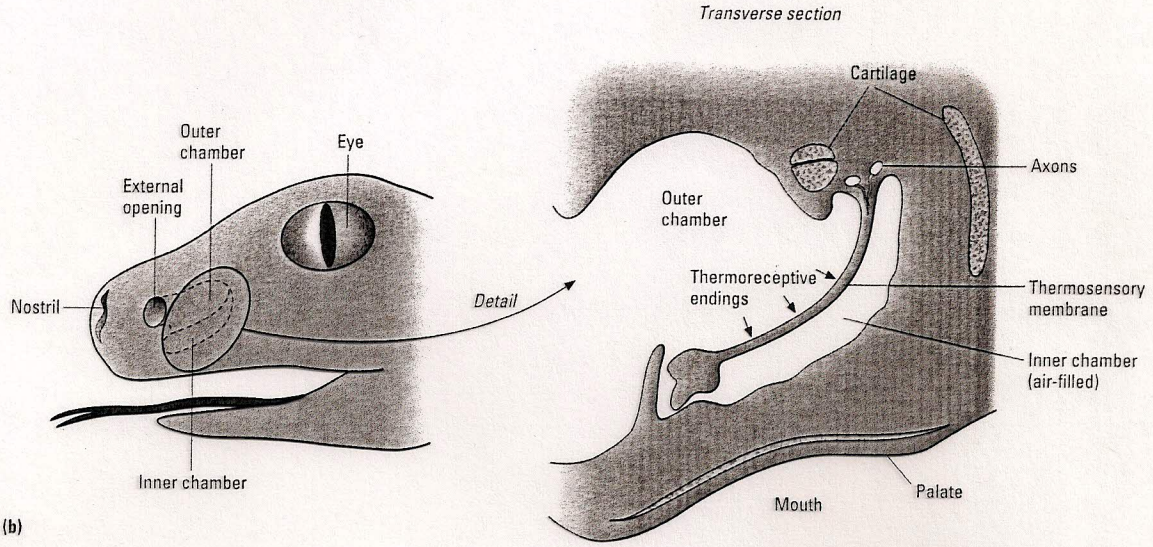


Figure 7-39 The facial pits of rattlesnakes contain extremely sensitive thermoreceptors. **(A)** Structure of a facial pit in the rattlesnake *Crotalus viridis*. **(B)** The position of the facial pits makes thermoreception by the pit organs directionally sensitive. [Adapted from Bullock and Diecke, 1956.]


Dead cells
Epidermis
Receptor endings
Dermis
Skin
Myelin
Axon
"Cold receptors"
"Warm receptors"
Action potential frequency
Range for "cold pain receptors"
Range for "warm pain receptors"
Temperature (°C)
0
2
4
6
8
10
0
10
20
30
40
50

(a)


Transverse section
Outer chamber
Eye
External opening
Nostril
Inner chamber
Detail
Cartilage
Axons
Outer chamber
Thermoreceptive endings
Thermosensory membrane
Inner chamber (air-filled)
Mouth
Palate

(b)

HYGROCEPTORS (moisture, humidity)

Terrestrial animals

ANTENNAS, PALPS OF MANY ARTHROPODS

- Myriapods
- Insects
- Spiders
- Ticks

VERTEBRATES : - TOADS

DUBIOUS IN OTHER ANIMALS

TWO TYPES :

↑ DISCHARGE FREQUENCY
- DRIER AIR
- more humid AIR

Δ relative humidity of even 1-2%

TRASDUCTION : UNCERTAIN

- STRUCTURAL CHANGE ← probably
- Δ OSMOTIC P
- ΔT from evaporation