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Evolutionary adaptation to thermosensation

Elena O Gracheva[1,2] and Sviatoslav N Bagriantsev[1]

Organisms continuously evolve to adapt to changing environmental conditions. Chief among these are daily and seasonal temperature fluctuations. Relatively small in terms of real physical values, temperature fluctuations of just a few degrees can profoundly affect organismal functions. In vertebrates, temperature is detected by primary afferents of somatosensory neurons, which express thermo-gated ion channels. Most of our knowledge about temperature receptors comes from seminal studies in mice and rats. Recent work uncovered thermosensory mechanisms in other vertebrates, shedding light onto the diversity of thermosensory adaptations. Here, we summarize molecular mechanisms of thermosensation in different species and discuss the need to use the standard laboratory rodents and non-standard species side-by-side in order to understand fundamental principles of somatosensation.

Addresses
[1] Department of Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, CT 06520, USA
[2] Program in Cellular Neuroscience, Neurodegeneration and Repair, Yale University School of Medicine, New Haven, CT 06520, USA

Corresponding authors: Gracheva, Elena O (elena.gracheva@yale.edu) and Bagriantsev, Sviatoslav N (sviatoslav.bagriantsev@yale.edu)

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Introduction

Environmental and internal body temperatures affect virtually all aspects of animal physiology, including feeding and mating behavior, circannual and seasonal rhythms. Temperature fluctuations influence functionality of the entire organism at multiple levels, leading to the emergence of complex evolutionary adaptations to sudden and prolonged environmental temperature changes. Whether it is a short exposure to extreme cold or heat or a prolonged subjection to cooling or warmth, the organism responds by rapid adjustments of cellular metabolism, ultimately affecting all organs and systems. Physiologically, temperature adaptation responses are manifested through changes in blood circulation, oxygen consumption, shivering and non-shivering thermogenesis, piloerection and sweating. While some of these features are universal and pertain to all vertebrates, others are clade-specific, the one property these features have in common is that they represent organismal *reaction* to temperature changes detected through cutaneous thermoreceptors. Thermoreceptors are somatosensory neurons which send their afferent projections to the superficial layer of the skin [1]. Temperature changes in the skin cause neuronal depolarization through activation of excitatory receptor channels (temperature receptors), leading to generation of action potential. While the molecular identity of the receptor channels remains debatable for some of the physiologically relevant temperatures, for others — such as painful heat or mild cooling — they are commonly recognized [2].

The known receptors are nonselective ion channels of the TRP family: TRPV1, TRPM8 and TRPA1 [3–11]. These molecules are expressed in the cutaneous endings of primary afferents and are responsible for depolarization of the somatosensory neuron membrane potential in response to changes in temperature. Most of our knowledge in the field of thermosensation originates from experiments on mice and rats, while other vertebrates are significantly less well researched. Recent studies showed that species from different vertebrate orders use various molecular platforms to adapt to their physiological and behavioral needs. This finding is somewhat unexpected given the relatively high level of conservation among the orthologues of the known temperature receptors. Comparisons of molecular strategies adapted by various vertebrates to cope with environmental temperature fluctuations (or lack thereof) are essential for understanding of the molecular evolution of the somatosensory system. Here, we discuss molecular specialization to thermosensitivity in fish, amphibians, retiles, birds and mammals.

Fish

Fish occupy various ecological niches with a wide range of temperature variations, including extreme geographical and climate zones such as Artic, Antarctic and Africa. Interestingly, many fish species can flourish in a broad range of temperatures. For example, the common carp (*Cyprinus carpio*) can tolerate from 3°C to 35°C [12,13], zebrafish (*Danio rerio*) — from 14°C to 35°C [14], threespine stickleback (*Gasterosteus aculeatus*) can survive at 2°C and 30°C [15], whereas Atlantic salmon's (*Salmo salar*) comfort zone ranges anywhere from 2°C to ~22°C [16,17]. Even though these fish species are only

distantly related to each other, they appear to have the same kind of molecular adaptation which underlies the strikingly similar physiological phenotype: these animals do not seem to have the TRPM8 gene in their genome [18,19]. TRPM8, a cation-selective cold-activated ion channel, is the receptor for menthol — the chemical that produces cooling sensation — and also is the principal molecular receptor of cold temperatures *in vivo* in mammals, within a temperature range from 10°C to 26°C [3,6,7]. As discussed below, the channel has been cloned and functionally characterized in a number of animals, including amphibians, birds and mammals [6,20]. However, sequencing of the genomes of twelve fish species from ten different orders, including cod (*Gadus morhua*), salmon, stickleback, fugu (*Takifugu rubripes*) and medaka (*Oryzias latipes*) failed to reveal the presence of the TRPM8 gene cluster. Possibly, the absence of TRPM8 in fish genome facilitated their colonization of a remarkably wide range of climate zones.

Interestingly, even though fish tolerate cold, they maintain very high sensitivity to warm and hot temperatures. Moreover, they are much less tolerant to warm temperature range than other vertebrates. Temperatures above 32°C are beyond the comfort zone of many fish species. A molecular foundation for this behavior could lie within the biophysical properties of TRPV1, a cation-selective ion channel activated by hot temperatures and capsaicin [5,21••]. Mouse somatosensory neurons expressing TRPV1 are activated at above 42°C. Accordingly, in heterologous systems, mouse and rat TRPV1 is activated at the same temperature range. In contrast, a zebrafish TRPV1 orthologue, which is essential for noxious heat avoidance in this species, is activated at 32°C in the same conditions [22,23].

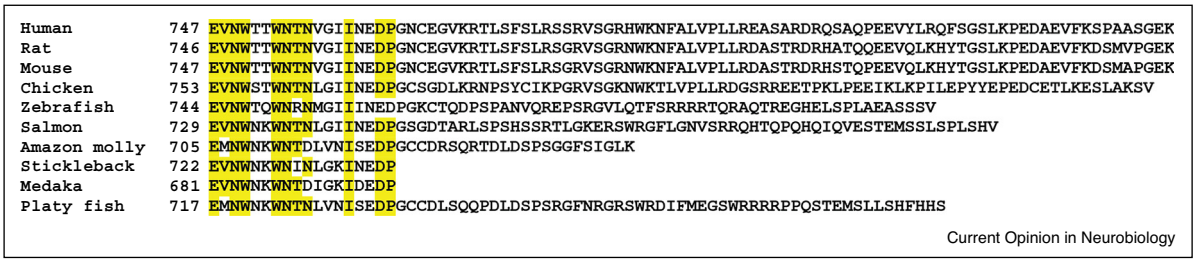
Compared to mammals and birds, zebrafish TRPV1 has a truncation in exon 15, leading to the production of a shortened intracellular C-terminal domain. This structural alteration could be a cause for the shift in the apparent temperature activation threshold of zebrafish TRPV1 [23]. Indeed, a similar truncation of a mammalian TRPV1 shifts detectable channel activation from 42°C to ~30°C [24]. Analysis of predicted TRPV1 protein sequences from stickleback, salmon, platyfish (*Xiphophorus maculatus*), amazon molly (*Poecilia formosa*), tilapia (*Oreochromis niloticus*) and medaka reveal a similar truncation of the C-terminus compared to mammalian and bird orthologues, suggesting the distantly related fish species have utilized a seemingly identical molecular strategy to modify TRPV1 function (Figures 1 and 2).

Amphibians

Amphibians evolved from fish over 400 million years ago. Since that time, amphibians colonized diverse ecological niches, some of them habituating severe cold and hot geographical zones. Amphibians can survive in extreme cold due to their ability to hibernate, whereas in hot desert they succumb to estivation [25–27]. To protect tissues from damage by cold, amphibians have developed significant biochemical and metabolic adaptations such as the production of cryoprotectants and osmolytes, and the ability to perform reversible organ dehydration [26]. Recent studies revealed that evolution also shaped somatosensory responses of the amphibians at the level of primary afferents. Somatosensory neurons isolated from dorsal root ganglia (DRG) of the South African clawed frog *Xenopus laevis* exhibit robust excitatory responses to cold stimuli only at 10°C. This finding stands in a striking contrast to mammalian DRG neurons, which have a detectable temperature activation threshold at approximately 26°C. In accordance with these data, biophysical characterization of the TRPM8 channels cloned from DRG neurons of the South African clawed frog and Western clawed frog (*Xenopus tropicalis*) demonstrated a significant left-shifted temperature response with a half-maximal activation value at 15°C. This again strikingly contrasts detectable activation temperature of rat TRPM8, which exhibits robust current in heterologous systems at 26°C. The relatively low apparent activation threshold of TRPM8-expressing frog neurons provides an explanation to the ability of amphibians to withstand prolonged periods of hypothermia [20].

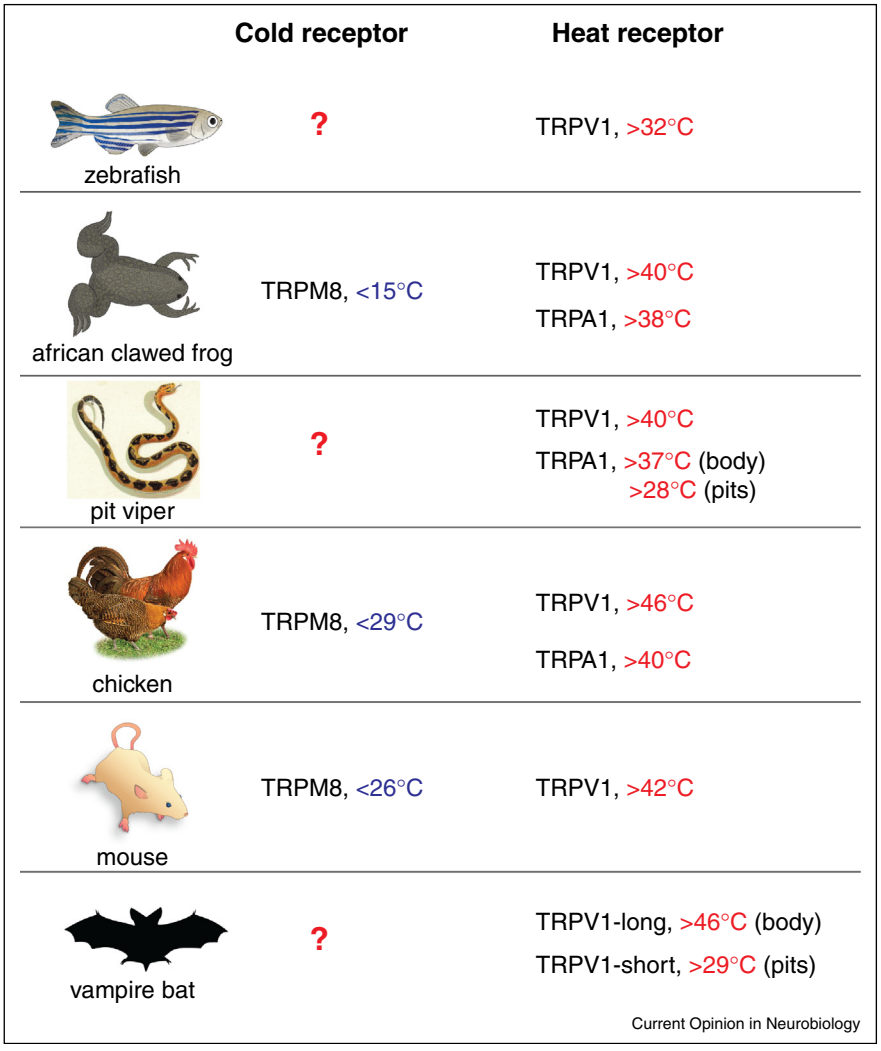
Interestingly, unlike TRPM8, molecular adaptations in the amphibian somatosensory system did not significantly affect the heat receptor TRPV1 and the polymodal receptor TRPA1 [28,29]. Like its mammalian orthologue,

Figure 1



Alignment of distal C-terminal region of TRPV1 orthologues from mammals, birds and fish. Conserved amino acids are highlighted in yellow.

Figure 2



Heat and cold receptors of vertebrates. Temperature denotes apparent activation threshold for the indicated channels in heterologous systems.

which exhibits detectable activity in heterologous systems at 42°C, frog TRPV1 is activated in the same conditions at 40°C. Frog TRPA1 is activated at 38°C, which contrasts the behavior of its heat-insensitive mammalian orthologues, but comes near the properties of the heat-sensitive TRPA1 from reptiles and birds (see below). In agreement with the biophysical data, *X. tropicalis* demonstrates nocifensive behavior when exposed to temperatures above 38°C, suggesting both TRPV1 and TRPA1 channels could contribute to noxious heat avoidance *in vivo* [28]. Notably, the painful temperature threshold of the frog is similar to that reported for mammals, suggesting that amphibians primarily modified pathways within the somatosensory system that are involved in cold, but not in noxious heat temperature detection [4].

Reptiles

Unlike the heat-insensitive mammalian orthologue, TRPA1 from reptiles and birds is activated by increasing temperature. At the physiological level, TRPA1 is proposed to act synergistically with TRPV1 to mediate thermosensation in lizards, snakes and birds [29]. Species from three different clades of evolutionary distant snake families: vipers (*Viperidae*), pythons (*Pythonidae*) and boas (*Boidae*) express TRPA1 in trigeminal neurons. Primary afferents from the trigeminal neurons highly innervate the pit organ — the principal detector of the infrared radiation emitted by the snake's warm blooded prey. Biophysical analyses in heterologous cells showed that TRPA1 orthologues cloned from trigeminal neurons of the infrared sensing snakes are activated at 28–30°C. Accordingly, functional analysis of cultured trigeminal neurons from the ball python (*Python regius*) revealed robust excitatory responses in the same temperature range [9]. Recent phylogenetic studies on 24 snakes, including different species of pythons, boas and rattlesnakes, revealed that the TRPA1 gene is under a strong

positive selection in infrared sensing snakes, but not in non-pit snakes or other vertebrates [30]. This is consistent with the hypothesis that TRPA1 together with the specialized anatomical features of the pit membrane contribute to cellular and molecular mechanism which mediates the detection of infrared radiation by the pit organ.

Birds

Birds are homeothermic animals with a high basal metabolic activity and much higher basal core body temperature (40–44°C) when compared to mammals (36–38°C) [31]. The ability to maintain high constant body temperature and to fly long distances allowed birds to inhabit various climate zones, including tropical and polar regions. Biophysical studies showed that temperature receptors in birds have adapted to the higher core body temperature. For example, TRPV1 from the chicken is detectably activated by heat in heterologous systems at 46–48°C, whereas mammalian TRPV1 is activated at 42°C [5,32]. Interestingly, the cold receptor TRPM8 is also modified in birds. The half-maximal temperature activation for chicken TRPM8 is shifted to warmer temperatures by 5°C [20]. These observations together with previously described molecular adaptations support the notion that somatosensory system actively communicates with the environment and the rest of the body and has the flexibility to adjust molecular receptors according to physiological phenotype and behavioral needs.

Mammals

The body temperature of most mammals is set within a narrow range from 36°C to 38°C. However, despite being homeothermic animals, some mammals have the ability to adjust their core body temperature as well as temperature sensitivity of primary afferents according to environmental changes and behavioral and feeding needs. Desert species are the great example of such adaptability. The round-tailed ground squirrel (*Spremophilus tereticaudus*) lives in an extremely hot desert climate and can tolerate heat up to 46°C. In the desert, when ambient temperature reaches 32°C, round-tailed ground squirrels can increase their core body temperature to as high as 43°C [33]. Similarly, a close relative of the squirrels, the least chipmunk (*Eutamias minimus*), can tolerate extreme hyperthermia (43°C) and hot climate conditions for a long period of time [34]. Despite such a remarkable physiological phenotype, there is no information about molecular components of these adaptations in either the somatosensory system, which senses environmental temperature, or the thermoregulatory unit of the preoptic area of hypothalamus, which detects temperature of the body.

Some mammals have developed extreme temperature sensitivity to support their feeding behavior. Vampire bats are obligate blood feeders. Like pit vipers, they can find 'hot spots' (superficial blood vessels) on the surface of their warm-blooded prey (cows, pigs, etc.), using highly specialized anatomical structures, which in the case of blood feeders are located on the tip of their nose and are referred to as leaf pits. The pits are innervated by primary afferents of the trigeminal nerve. A study showed that the trigeminal neurons express a splicing isoform of the TRPV1 channel with a truncated C-terminus, TRPV1 'short' (TRPV1-S). In heterologous systems, TRPV1-S exhibits detectable activity at a significantly lower temperature (29°C) compared to the standard 'long' isoform (TRPV1-L) activated at 42°C. Notably, TRPV1-S is specific to trigeminal neurons, which innervate the head, including the three leaf pits. The long TRPV1-L isoform, on the other hand, is expressed in dorsal root ganglia, which innervate different parts of the body [23]. These observations suggest that the TRPV1-S isoform is part of a molecular mechanism that mediates low-intensity heat detection by the leaf pit organ. Accordingly, since TRPV1-S is activated at a temperature well below core body temperature, trigeminal afferents of vampire bats are sheathed in a thick layer of connective tissue, which probably serves as a thermal insulator from blood vessels and protects them from activation by core body temperature. As a result, the insulation keeps the leaf pits cooler than the rest of the body, which helps to increase sensitivity and makes blood source detection more efficient.

Some mammals that cannot migrate for long distances have evolved the ability to hibernate — a unique form of adaptation to harsh temperatures and the lack of food. Almost all orders of mammals have hibernating species. For example, in primates, it is the fat-tailed dwarf lemur (*Cheirogaleus medius*). Rodents from two suborders, *Myomorpha* (rats, mice, hamsters) and *Sciuromorpha* (squirrels, woodchucks, chipmunks), represent the most prominent examples of hibernating mammals. Despite such a diverse species distribution, all hibernating mammals have a similar physiological phenotype, which includes dramatic reduction in metabolic rate, precipitous drop of core body temperature to ambient, and exceptional cold tolerance [35]. The 13-lined ground squirrel (*Spermophilus tridecemlineatus*) colonized a wide range of latitudes, from southern Canada to the Gulf of Mexico. When the ambient temperature drops, the squirrels hibernate in underground burrows for up to six month and can reduce their body temperature to as low as 2–4°C. They can survive this whole period without food and water [36]. Some extreme hibernators, such as the arctic ground squirrel (*Spermophilus undulatus*) can hibernate at −20°C and can reduce internal temperature to as low as −2.9°C [37]. Despite the robustness of the hibernation phenotype, the molecular basis remains unknown.

Perspectives

Mouse-centric research has proven useful at uncovering the molecular basis of a number of physiological processes. The versatility of modern genetic and bioinformatics

tools have taken mouse research to a whole new level and made this rodent an even better model with which to tackle fundamental biological problems. Significant discoveries of mouse biology are made with an incredible pace, and we know more and more about how the mouse works. At the same time, as mouse physiology is understood at a much deeper level, the scope of research sharpens, and the perspective narrows down with it. It is most certainly not possible to understand evolution if most of our efforts are applied to the study of a single rodent species. Furthermore, some specific physiological problems, such as the molecular basis of somatosensitivity appear particularly refractory even to the most advanced and sophisticated approaches when applied to the mouse model alone. The relatively modest, as compared to other physiological problems, progress in sensory physiology in identification of molecular thermoreceptors and mechanoreceptors testifies to this point. For example, the cold receptor TRPM8 provides a strong molecular foundation for the detection of mildly cooling temperatures in mice (10–20°C) [3,38,39], whereas the identity of noxious cold receptor(s) remains elusive [40••,41••], even though a number of contributing molecules have been suggested over the years [10,42,43••,44–46]. TRPV1 well explains sensitivity of mice to noxious heat, whereas warm temperature receptors are yet to be identified [41••]. The molecular mechanism of somatosensory mechanoreception, a sister field to thermoreception, is even less well understood. A long quest for molecular receptors of mechanical force has been largely frustrating until the cloning of the mechano-gated channel Piezo2 from a neuroblastoma cell line [47,48••,49], while other mechanotransducers remain unidentified. Perhaps it is a good idea to start exploiting the magnificent diversity of living organisms which have been continuously shaped and changed in evolution for over hundreds millions of years. Indeed, studies from non-standard species such as snakes and bats have yielded much unexpected insights into physiology of thermal reception [9,23]. The unique physiological attributes of hibernating mammals, such as their ability to drop core body temperature and remain comfortably cold for a long period of time at temperatures that are unbearable for most other mammals, warrant immediate attention from researchers interested in studying thermosensation, thermoregulation and thermogenesis [50•]. Species with organ-specific acuity of mechanoreception, such as star-nosed moles [51•] or tactile foraging ducks [52•] can provide unexpected insights into the molecular basis of force detection. One can come up with other such examples, thanks to the incredible diversity of species that surrounds us. The advent of affordable techniques for genome and transcriptome sequencing, even at the single cell level [53•], genetic engineering and more, is bound to facilitate the development of methods to perform genetic modifications of non-standard models. Then there will be even fewer reasons to stick to the good old mouse as the workhorse of laboratory research. We know the mouse biology fairly well now compared to other species. This is a great time to start actively looking outside the mouse box.

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Conflict of interest statement

Nothing declared.

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50. • Laursen WJ, Mastrotto M, Pesta D, Funk OH, Goodman JB, Merriman DK, Ingolia NT, Shulman GI, Bagriantsev SN, Gracheva EO: **Neuronal UCP1 expression suggests a mechanism for local thermogenesis during hibernation**. *Proc Natl Acad Sci U S A* 2015, **112**:1607-1612.
Thirteen-lined ground squirrels are champions among vertebrates in their ability to survive deep cold for a long period of time. This study reveals robust expression of the thermogenic protein UCP1 in the neurons of hibernating squirrels, suggesting a mechanism for local thermogenesis during prolonged hypothermia.

51. • Gerhold KA, Pellegrino M, Tsunozaki M, Morita T, Leitch DB, Tsuruda PR, Brem RB, Catania KC, Bautista DM: **The star-nosed mole reveals clues to the molecular basis of mammalian touch**. *PLoS ONE* 2013, **8**:e55001.
In this paper the authors perform molecular profiling of trigmenial ganglia, which innervate the acutely mechanosensitive Eimer's organ of the star-nosed mole. The paper reveals changes in the expression of somatosensory neuronal markers associated with potentiation of light touch perception.

52. • Schneider ER, Mastrotto M, Laursen WJ, Schulz VP, Goodman JB, Funk OH, Gallagher PG, Gracheva EO, Bagriantsev SN: **Neuronal mechanism for acute mechanosensitivity in tactile-foraging waterfowl**. *Proc Natl Acad Sci U S A* 2014, **111**:14941-14946.
Like the star-nosed moles in Gerhold *et al*., ducks have taken the sense of light touch to the extreme in an organ-specific manner. This study reveals robust intrinsic mechanosensory ability of low-threshold mechanoreceptors innervating duck bill, and points to a key role of the mechanoreceptors in fine-tuning the acuity of light touch perception through the glabrous skin.

53. • Usoskin D, Furlan A, Islam S, Abdo H, Lonnerberg P, Lou D, Hjerling-Leffler J, Haeggstrom J, Kharchenko O, Kharchenko PV *et al.*: **Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing**. *Nat Neurosci* 2015, **18**:145-153.
The authors perform comprehensive transcriptome analysis of 622 mouse somatosensory neurons, using the single-cell RNA-sequencing strategy. The study reveals 11 principal types of sensory neurons and identifies novel somatosensory markers.