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Commentary

Responses to temperature variation: integration of thermoregulation and metabolism in vertebrates

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Summary

Many vertebrates regulate their body temperature in response to thermal variability of the environment. Endotherms maintain relatively stable body temperatures by adjusting metabolic heat production in response to varying environmental heat loads. Although most ectotherms do not display adaptive thermogenesis, they do acclimate cellular metabolism to compensate for environmental temperature variation. The components of the thermoregulatory systems in endotherms and ectotherms are evolutionarily conserved, and I suggest that metabolic acclimation in ectotherms relies on the same regulatory pathways as adaptive thermogenesis in endotherms. Both groups rely on transient receptor potential ion channels to sense environmental temperatures. Thermosensory (afferent) information is relayed to the hypothalamus, which initiates a sympathetic efferent response. Cardiovascular responses to heat are similar in ectothermic crocodiles and in mammals, and are mediated by the autonomic nervous system in both cases. The sympathetic nervous system also modulates cellular metabolism by inducing expression of the transcriptional regulator peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α), which interacts with a range of transcription factors that control glycolysis, fatty acid oxidation, gluconeogenesis, mitochondrial biogenesis and bioenergetics, and metabolic rate. PGC-1α is best known from mammalian model species but there is increasing evidence that it is also instrumental in non-mammalian vertebrates. Hence, endothermic adaptive thermogenesis may result from the same regulatory pathways as ectothermic metabolic acclimation, and both could be considered as adaptive metabolic responses to temperature variation.

Key words: body temperature, transient receptor potential ion channels, hypothalamus, sympathetic nervous system, cutaneous blood flow, PGC-1α.

Introduction

The response of animals to thermal variation in their environment can be broadly partitioned into thermoregulation and regulation of cellular rate functions. In endotherms, these two aspects are closely connected because cellular metabolism also generates the heat that determines body temperature [adaptive thermogenesis (Morrison et al., 2008)]. In ectotherms, the interaction between body temperature and metabolism is reversed. Thermal variation in the environment can determine body temperature and thereby affect metabolism thermodynamically. Like endotherms, however, most ectotherms regulate the metabolic capacity of their tissues in response to longer-term (days to weeks) thermal variation (Guderley, 2004; Seebacher, 2005). Variation in body temperature of ectotherms may result either from environmental variation when body temperature passively follows environmental temperatures or from regulation to different set-points in those animals that do thermoregulate. In both cases, and particularly during thermoregulation, there must be a connection between sensing the environment and regulatory responses, because the latter are in the direction opposing thermodynamics.

Ectotherms regulate body temperature behaviourally and by cardiovascular modulation of heating and cooling rates (Seebacher, 2000; Seebacher and Grigg, 2001). At the same time, metabolism and other essential rate functions can be regulated so that reaction rates remain relatively constant even when body temperatures vary [a process referred to as temperature compensation, acclimation or acclimatisation (Fry, 1958)]. For example, many fish adjust metabolic capacities to compensate for seasonal variation in water temperature with the result that metabolic performance remains relatively stable throughout the year (St Pierre et al., 1998; Wakeling et al., 2000) (Fig. 1A). Reptiles often regulate their body temperature to different levels in different seasons to minimise the behavioural cost of thermoregulation (Seebacher et al., 2003a) (Fig. 1B). At the same time, tissue metabolic capacities are adjusted to counteract thermodynamically-induced changes in rate functions (Seebacher et al., 2003b) (Fig. 1C). Hence, similar to endotherms, thermal information and metabolic responses must be coordinated. I suggest that the pathways that link thermal signals from the periphery to metabolic acclimation in ectotherms are similar to those mediating endothermic thermoregulation. That is, thermosensory proteins [transient receptor potential ion channels (TRPs)] send afferent signals *via* the dorsal horn to the hypothalamus, resulting in efferent sympathetic outflow to stimulate transcriptional regulators of metabolism.

Thermoregulation

Thermoregulation is a neural process that matches information about the external environment with the appropriate animal response to maintain a more or less stable internal environment relative to external variation (Nakamura and Morrison, 2008). The several stages of this process can be divided into: sensation of environmental conditions and the internal thermal state of the

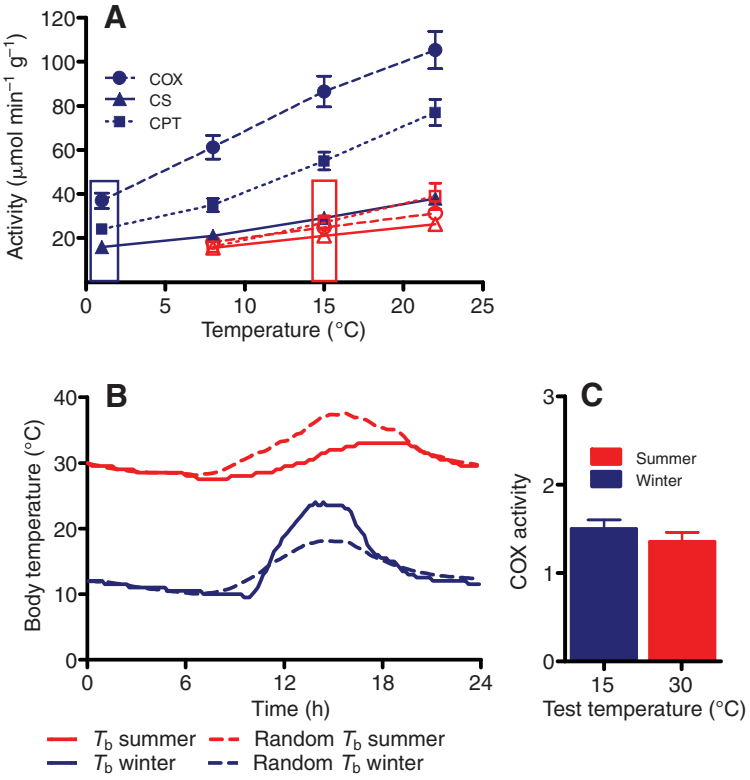

Fig. 1. Compensation of mitochondrial capacities for temperature change in ectotherms. The activities of the mitochondrial enzymes cytochrome *c* oxidase (COX), citrate synthase (CS) and carnitine palmitoyl transferase (CPT, ×100) are lower in warm acclimatised (body temperature T_b=16°C; red lines and symbols) than in cold acclimatised (T_b=1°C; blue lines and symbols) trout (A) so that activities in winter are not depressed at winter compared with summer body temperatures (indicated by the blue and red boxes) despite the 15°C difference in seasonal body temperatures [data from St Pierre et al. (St Pierre et al., 1998)]. American alligators thermoregulate to significantly different body temperatures in winter and summer (B). This example shows measured body temperatures of alligators in winter and summer (solid blue and red lines, respectively) and the predicted body temperature of randomly moving animals under identical thermal conditions (broken blues and red lines). Alligators are significantly warmer than random in winter and significantly cooler than random in summer; however, despite thermoregulating, mean body temperatures differ by around 15°C between seasons [data from Seebacher et al. (Seebacher et al., 2003a)]. Similar to trout, however, cytochrome *c* oxidase activity (in μmol min^{-1} g^{-1} wet tissue) is regulated so that there is no difference in activity between seasons at the respective seasonal body temperatures [C; data from Seebacher et al. (Seebacher et al., 2003b)].

animal, the transmission of this information to the brain *via* afferent neural pathways, and the initiation of the response by efferent signals from the brain. Among vertebrates, thermoregulatory processes are best understood in mammals because of their clinical significance. Adaptive thermogenesis in mammals is defined as heat production in response to environmental temperature variation that protects the organism against cold exposure (Lowell and Spiegelman, 2000). However, even though metabolic heat production in ectotherms is negligible, the components of the thermoregulatory system are conserved at least between mammals and reptiles.

Afferent pathways: TRPs

TRPs are a group of proteins that are associated with free nerve endings of somatosensory neurons with cell bodies in the dorsal root and trigeminal ganglia. A number of TRPs are gated by temperature, and different members of the group have different thresholds of temperature activation (Patapoutian et al., 2003). For example, TRPM8 (Bautista et al., 2007) and maybe TRPA1 (Kwan et al., 2006) act as low temperature sensors (<20°C) whereas TRPV1 is a high temperature sensor (>40°C) (Caterina, 2007). In addition to mammals, TRPV1 also occurs in birds, crocodiles, lizards, amphibians and fish (Caron et al., 2008; Seebacher and Murray, 2007), and TRPM8 occurs at least in birds, crocodiles and amphibians (Seebacher and Murray, 2007). Blocking TRPV1 pharmacologically causes hyperthermia in rats, because in the absence of the high temperature sensor the environment is perceived to be cooler than it actually is, and a regulatory response is initiated (Gavva et al., 2007) (Fig. 2A). Blocking TRPV1 and TRPM8 in crocodiles abolishes the characteristic thermoregulatory shuttling behaviour (Seebacher and Murray, 2007) (Fig. 2B). Rats and crocodiles are similar therefore and thermoregulation in both relies on the sensation of the immediate thermal environment by TRPs.

In mammals, afferent signals from the periphery are relayed to the preoptic area of the hypothalamus and act as feed-forward mechanisms that elicit a thermoregulatory response before core body temperature changes (Boulant, 2000; DiMicco and Zaretsky, 2007). Core body thermoreceptors do not contribute to the response to environmental signals in mammals except in extreme environments where they can enhance the feed-forward mechanism from the periphery when the latter could not prevent changes in core temperature. Internal sensors are important, however, in responses to non-environmental changes in heat load, for example resulting from exercise (Morrison et al., 2008). TRP proteins transmit information through primary somatosensory fibres to the dorsal horn (Patapoutian et al., 2003) where the ascending sensory pathway is *via* lamina I neurons that synapse directly on neurons in the hypothalamus (Craig et al., 1994). The lateral parabrachial nucleus also receives projections from the dorsal horn, including from lamina I neurons, and it mediates the thermosensory pathway to the preoptic area, which constitutes the main feed-forward reflex by which body temperature is regulated in mammals (Nakamura and Morrison, 2008).

Compared with mammals, little is known about the thermoregulatory pathways in ectothermic vertebrates or in birds. Nonetheless, based on experiments using local brain lesioning or heating and cooling it is evident that the hypothalamus and particularly the preoptic area are involved in thermoregulation of all vertebrates (Bicego et al., 2007). Neurons in the preoptic hypothalamus of lizards and fish function as a feedback reflex that direct thermoregulatory behaviour (Cabanac et al., 1967; Nelson and Prosser, 1981). The presence and function of TRPs in crocodiles shows that the afferent thermoregulatory pathways are similar at least in mammals and in crocodiles. The fact that most other groups of vertebrates express TRP genes points toward a evolutionary conserved

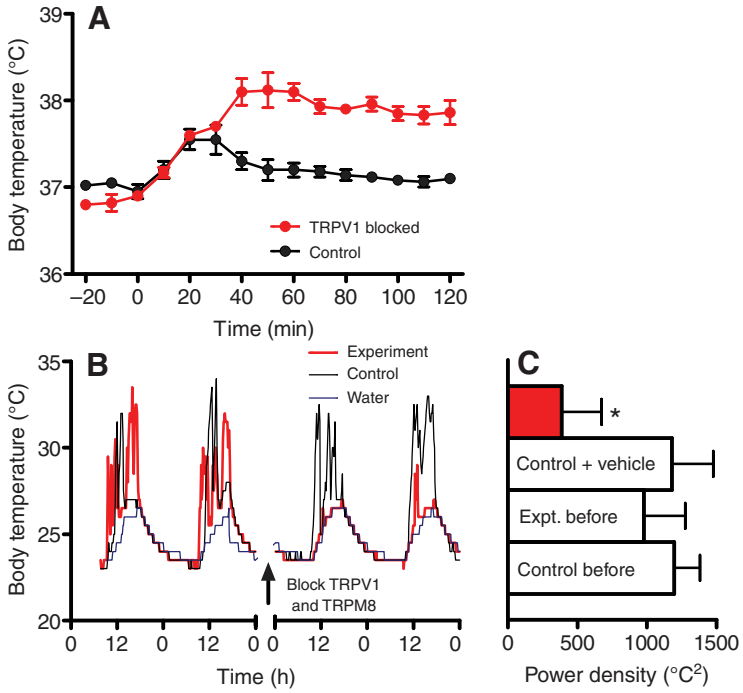

Fig. 2. Transient receptor potential ion channels (TRPs) provide afferent thermosensory information in endotherms and ectotherms. Blocking the heat sensor TRPV1 in rats causes hyperthermia [A; redrawn from fig. 2a in Gavva et al. (Gavva et al., 2007)]. The typical thermoregulatory shuttling behaviour between heating and cooling environments ceases in crocodiles when TRPV1 and the cool sensor TRPM8 are blocked (B). A control animal continues to thermoregulate after administration of the vehicle dimethylsulphoxide (DMSO) (black line; right section in B) whereas the body temperature of the experimental animal (red line) follows water temperature (blue line) except for occasional excursions. Thermoregulation in crocodiles is best analysed by the frequency of body temperature oscillations, the regularity (power density) of which decreases significantly when TRPV1 and TRPM8 are blocked [C; crocodile data from Seebacher and Murray (Seebacher and Murray, 2007)].

afferent thermosensory pathway. However, the importance of TRPs in thermoregulation needs to be confirmed experimentally for vertebrates other than mammals and crocodiles.

Efferent pathways

The efferent thermoregulatory response in mammals is mediated by the dorsomedial hypothalamus *via* sympathetic premotor neurons in the medulla oblongata (Nakamura et al., 2004; DiMicco and Zaretsky, 2007). The nucleus raphe pallidus of the medulla oblongata activates sympathetic preganglionic neurons controlling thermoregulatory responses such as skin vasoconstriction, cardiovascular responses and metabolic changes (Cano et al., 2003; Nakamura et al., 2004). Sympathetic outflow from the dorsomedial hypothalamus is inhibited by warm sensitive neurons in the medial preoptic area. The inhibitory input from the preoptic area is reduced by decreases in brain temperature and by inputs from cool-sensitive peripheral thermoreceptors. A decrease in inhibitory input causes an increase in endothermic heat production (Nakamura et al., 2005; Morrison et al., 2008).

In all vertebrates there are homologous brain regions (Ghysen, 2003) but whether or not the mammalian pattern of transmission is representative of most vertebrates remains to be demonstrated experimentally. Nonetheless, there is considerable similarity in the cardiovascular response to peripheral heating and cooling in mammals and crocodiles (Fig. 3), and many vertebrates regulate their body temperature by modulating blood flow between the surface and the core of the body (Seebacher and Franklin, 2005). For example, moderate skin cooling elicits sympathetically mediated vasoconstriction in the skin of humans as a thermoregulatory response to minimise convective heat loss to the environment (Thompson et al., 2005). Conversely, skin perfusion increases with heat exposure to facilitate heat loss from the body, which may be partially mediated by sympathetic cholinergic stimulation and by nitric oxide (Green et al., 2006; Kellogg, 2006) (Fig. 3A). Similarly, ectothermic vertebrates modify transient heat transfer between their body and the environment to facilitate thermoregulation. Heart rates vary in response to heating or cooling, and slower heart rates during cooling decrease heat exchange between the body core and the periphery thereby retarding rates of cooling, and increased heart rates during heating facilitate heat uptake (Seebacher, 2000; Franklin and Seebacher, 2003) (Fig. 3C). Cutaneous blood flow in the crocodile (*Crocoylus porosus*) is significantly greater during heating than during cooling, reflecting vasodilation and constriction, respectively (Seebacher and Franklin, 2007) (Fig. 3B). Cardiovascular responses in reptiles and birds are principally mediated by autonomic mechanisms (Altimiras and Crossley, 2000; Galli et al., 2007; Seebacher and Franklin, 2007) (Fig. 3B), and may also be stimulated locally by nitric oxide and prostaglandins (Seebacher and Franklin, 2003; Seebacher and Franklin, 2004). The common pattern of autonomic regulation of cardiovascular responses in mammals and reptiles hint at a broader similarity of efferent thermoregulatory responses that may also encompass control of tissue metabolic capacities.

Regulation of cellular metabolism

The sympathetic nervous system regulates cellular metabolism by inducing expression of transcriptional regulators of metabolic genes. Efferent autonomic pathways therefore provide the link between external temperatures and cellular metabolism (Morrison et al., 2008). Oxidative metabolism is controlled to a large extent by transcription factors and their co-activators. These act in concert to induce mitochondrial biogenesis and the expression of genes coding for proteins that function in metabolic pathways, such as the electron transport chain and oxidative phosphorylation (Scarpulla, 2008). One of the most important regulatory proteins in mammals is the peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α), which modulates metabolism in response to multiple stimuli such as exercise, diet and temperature (Puigserver et al., 1998; Lin et al., 2005). PGC-1α is one of several proteins in the PGC family, which also includes PGC1β (Kressler et al., 2002; Lin et al., 2002; St Pierre et al., 2003). The expression of mitochondrial proteins – both those encoded by the nuclear and mitochondrial

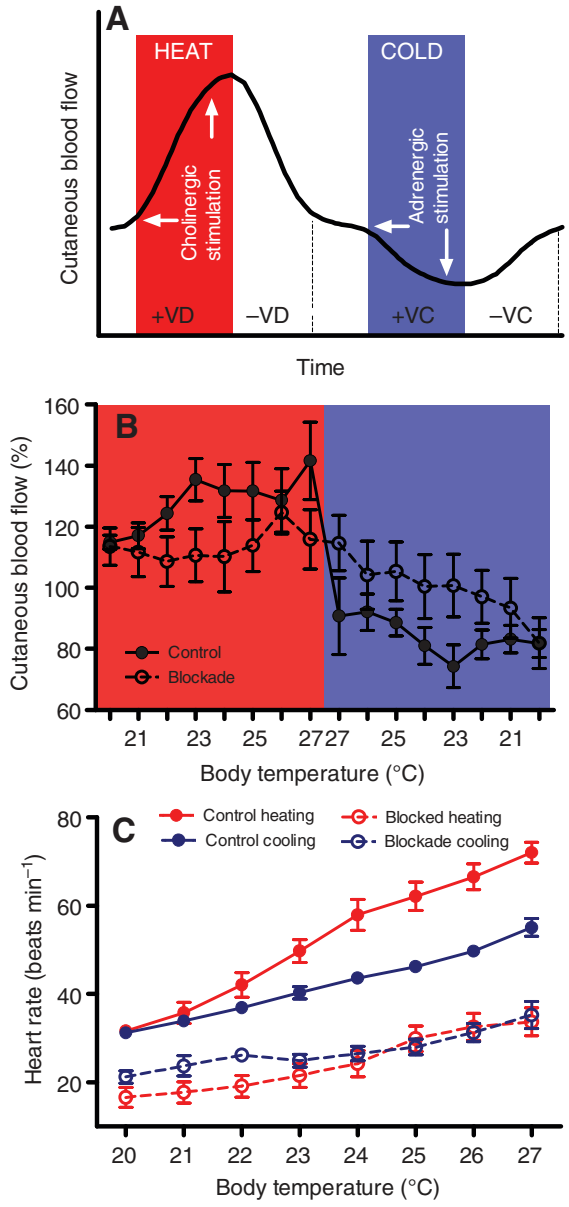

Fig. 3. Efferent cardiovascular responses to heat. (A) Schematic representation of changes in cutaneous blood flow in response to heat and cold stress in humans [redrawn from Kellogg (Kellogg, 2006)]. When surface heat load passes a temperature threshold (red shading), sympathetic cholinergic stimulation increases and peripheral blood vessels dilate (+VD) thereby increasing cutaneous blood flow to facilitate heat loss to the environment. Cholinergic tone and vasodilation decrease when the heat stress is removed (–VD). Peripheral cooling (blue shading) causes sympathetic adrenergic stimulation and vasoconstriction (+VC) thereby decreasing blood flow and heat exchange. Removal of cold stress will decrease adrenergic tone and vasoconstriction (–VC). Broken lines indicate the periods of decrease in vasodilation and vasoconstriction following hot and cold, respectively. Crocodiles show similar patterns (B), and cutaneous flow increases during heating (red shading, control, closed circles) but decreases abruptly when the heat source is removed (blue shading). Pharmacological blockade of β-adrenergic and cholinergic receptors (blockade, open circles) attenuates blood flow responses to heat, indicating that these responses to heat are partly regulated by the sympathetic nervous system [data from Seebacher and Franklin (Seebacher and Franklin, 2007)]. Similarly, the difference in heart rates during heating and cooling that is characteristic of many reptiles disappears when autonomic receptors are blocked [C, data from Seebacher and Franklin (Seebacher and Franklin, 2007)].

genomes – is under the control of a relatively small number of transcription factors that interact with PGC-1α and β (Scarpulla, 2008). PGC-1α coordinates mitochondrial biogenesis and the expression of proteins that function in fatty acid oxidation and mitochondrial respiration of skeletal muscle and brown adipose tissue (Gerhart-Hines et al., 2007; Lin, 2009). The principal targets of PGC-1α include transcription factors of the peroxisome proliferator activated receptor (PPAR) family (α, δ, γ) and nuclear respiratory factors (NRF-1 and 2). NRF-1 controls expression of the mitochondrial transcription factor Tfam, which is responsible for regulating gene expression in the mitochondrial genome (Scarpulla, 2008). Both NRF-1 and NRF-2 also coordinate expression of nuclear encoded mitochondrial proteins, such as nuclear subunits of cytochrome *c* oxidase (Ongwijitwat and Wong-Riley, 2005). In liver, PGC-1α regulates fatty acid oxidation and gluconeogenesis (Herzig et al., 2001).

Gene expression of PGC-1α and, hence, downstream metabolic responses are under autonomic control in mammals, and sympathetic neurons provide the communication between the hypothalamus and target tissues such as skeletal muscle and liver. Stimulation of β_2 and β_3 adrenergic receptors at the cell surface initiate transcription of PGC-1α *via* the intracellular messenger molecules cAMP and cAMP response element binding protein (CREB) (Puigserver et al., 1998; Pearen et al., 2008).

The sympathetic nervous system can also have an indirect effect on cellular metabolism by modulating circulating thyroid hormone concentrations (Arancibia et al., 1996). The paraventricular nucleus of the hypothalamus regulates thyroid hormone release by secretion of thyroid-releasing hormone. Thyroid-releasing hormone stimulates the pituitary gland to secrete thyroid-stimulating hormone, which induces thyroid hormone secretion by the thyroid gland (Chiamolera and Wondisford, 2009). Exposure to cold in rats can increase adrenergic input from the medulla oblongata to the paraventricular nucleus, which increases circulating levels of thyroid hormone and thereby increases metabolic thermogenesis (Arancibia et al., 1996). One mechanism by which thyroid hormone affects metabolism is by binding to thyroid hormone receptors on the cell nucleus. When bound by thyroid hormone, thyroid hormone receptors dislodge from the nuclear envelope to bind to thyroid hormone response elements on DNA to induce transcription of various genes, including PGC-1α (Wulf et al., 2008). In addition to mammals (Wulf et al., 2008), induction of PGC-1α mRNA expression by thryoid hormone also occurs in muscle of bird embryos (Walter and Seebacher, 2009). Additionally, feeding and nutrition can have a pronounced influence on muscle and liver metabolic capacities, and this effect is also mediated by the sympathetic nervous system *via* its effect on PGC-1α gene expression (Cha et al., 2007).

The sympathetic nervous system is the mechanism that links environmental temperatures to metabolic responses (Thomas and Palmiter, 1997). Whether or not the sympathetic nervous system is a universal efferent regulatory system of metabolism in vertebrates is as yet unknown. However, beyond the common mammalian model species, there is some evidence that PGC-1α and β and their associated transcription factors also mediate metabolic responses to temperature in other vertebrate classes.

In goldfish, cold acclimation causes an increase in PGC1β mRNA concentration in liver where it regulates mitochondrial gene expression by its interaction with NRF-1 (LeMoine et al., 2008). The induction of PGC-1β following cold exposure is interesting because its mRNA concentration does not increase with cold exposure in mice (Lin et al., 2002). PGC-1α mRNA concentration

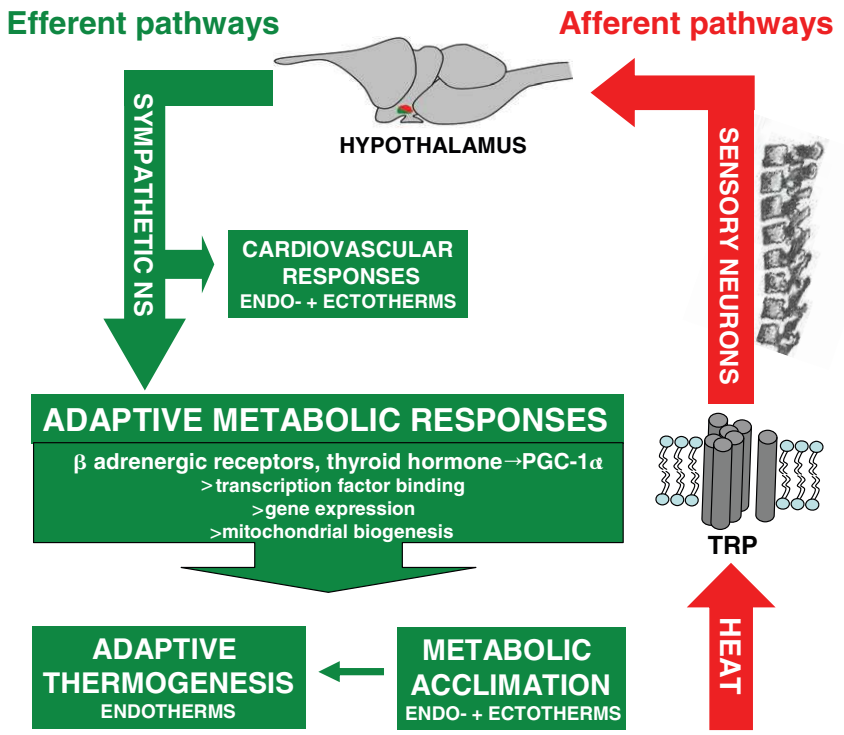

Fig. 4. Hypothetical scheme linking cellular metabolism to environmental thermal conditions in endotherms and ectotherms. Afferent pathways (red) comprise transient receptor potential ion channels (TRP) that sense environmental conditions (heat) and relay thermosensory information to the hypothalamus (red and green colouring in crocodile brain shown here) *via* sensory neurons. The hypothalamus initiates an efferent response (green) mediated by the sympathetic nervous system (NS). Efferent responses include cardiovascular adjustments as well as modulation of cellular metabolism. Adaptive thermogenesis and metabolic acclimation can be mediated by transcriptional controllers such as peroxisome proliferator activated receptor γ coactivator 1α (PGC-1α). Resting metabolic rate of endotherms can also acclimate to changing thermal conditions thereby affecting thermogenesis. The evolutionary conservatism of each component of this scheme suggests that the regulatory pathways are the same in endotherms and ectotherms.

by contrast decreases with cold acclimation in skeletal muscle of goldfish. The role of PGC-1α in goldfish muscle seems to be regulation of fatty acid oxidation in concert with PPARα (LeMoine et al., 2008), and its decrease in response to cold exposure could indicate nutrient switching at different temperatures. In crocodile liver, both PGC1α and PPARγ mRNA concentrations increase with cold acclimation and could play a role in regulating gluconeogenesis and fatty acid oxidation. Additionally, PGC-1α mRNA is positively correlated with mitochondrial ribosomal 16S RNA concentrations in muscle, which suggests that it induces mitochondrial biogenesis (Seebacher et al., 2009). In developing chicken embryos, low incubation temperatures induce PGC-1α and PPARγ gene expression in liver but not in skeletal muscle (Walter and Seebacher, 2007). In juvenile (28-days-old) chickens, cold exposure does induce PGC-1α gene expression in skeletal muscle (Ueda et al., 2005). Increased expression of PGC-1α is associated with greater tissue metabolic capacities in chicken embryos and, hence, PGC-1α may be important in facilitating endothermic heat production in birds (Ueda et al., 2005; Walter and Seebacher, 2007).

Conclusions

The recent developments in understanding thermal sensation by TRPs and transcriptional regulation of metabolism suggest that there is a universal regulatory system that integrates body temperature and metabolism among vertebrates. Endothermic adaptive thermogenesis may result from the same regulatory pathways as ectothermic metabolic acclimation, and both could be considered as adaptive metabolic responses to temperature variation (Fig. 4). The functional similarity is that in both groups metabolism is adjusted to compensate for potentially negative thermodynamic effects resulting from environmental temperature variation. In mammals, the result is that body temperature remains stable because of increased heat production resulting from greater tissue metabolic rates and uncoupling of mitochondrial electron transport from oxidative phosphorylation. In ectotherms, the result is that thermodynamic effects on cellular reaction rates are counteracted by quantity adjustments of mitochondria and proteins.

Most knowledge of thermoregulation and metabolism stems from few mammalian model species. Nonetheless, pathways of energy metabolism, and the nervous system are highly conserved among vertebrates (Ghysen, 2003; Smith and Morowitz, 2004). It is unlikely, therefore, that different groups of vertebrates have evolved fundamentally different regulatory systems. The implication is that metabolic acclimation and thermogenesis are the result of the same evolutionary process, except that endotherms have also evolved high resting metabolic rates, higher metabolic capacities and regulated uncoupling of mitochondrial electron transport from oxidative phosphorylation (Lowell and Spiegelman, 2000). As dramatic as these differences may seem, they are quantitative and not qualitative evolutionary differences. Hence, endothermy does not require the evolution of *de novo* structures or pathways, and all of the components necessary for endothermy are also present in ectotherms. The challenge now lies in determining how vertebrates differ in their capacity to respond to thermal variability.

Glossary

Adaptive thermogenesis
: Heat production by metabolic processes in response to environmental temperature with the purpose of protecting the organism from cold exposure and buffering body temperature from environmental temperature fluctuations.

Adrenergic receptors
: Receptors (α and β) that serve as targets for the sympathetic nervous system. Stimulation of beta adrenergic receptors can entrain a signalling cascade that leads to modulation of cellular metabolism. Beta adrenergic receptors also determine heart rate, and both α- and β receptors can cause vasoconstriction and -dilation.

Afferent neural pathways
: Sensory fibres that carry information to the brain.

Autonomic nervous system
: The part of the peripheral nervous system that functions below the level of consciousness to control involuntary processes such as heart rate, respiration, digestion and metabolism. There are two antagonistic parts, the sympathetic and the parasympathetic nervous systems.

CREB
: cAMP response element binding protein is a transcription factor that, in association with cAMP, regulates transcription of PGC-1α among other genes.

Cytochrome *c* oxidase
: One of the mitochondrial electron carrier molecules that transfers electrons to oxygen thereby producing water. The activity of this enzyme is a widely used measure of tissue metabolic capacity.

Dorsal root
: The afferent sensory root of a spinal nerve. The dorsal root ganglion, which contains the cell bodies of the nerve fibres of the root, is situated at the distal end of the dorsal root.

Ectotherm
: An animal with metabolic rates and consequent heat production that are too low to affect body temperature.

Efferent neural pathways
: Motor fibres that carry information from the brain to the periphery.

Endotherm
: An organism that at rest produces sufficient metabolic heat to affect its body temperature, so that body temperatures are often higher than environmental temperatures. The metabolic rates at rest (standard metabolic rates) of endotherms are 5–10 times higher than those of ectotherms.

Fatty acid oxidation
: The breakdown of fatty acids to be used as substrates in energy metabolism of mitochondria. Fats are important energy storage molecules and are often used in mammalian metabolism for heat production.

Gluconeogenesis
: Metabolic pathway in liver that synthesises glucose from non-carbohydrate molecules such as lactate and some amino acids. It is important in maintaining appropriate blood sugar levels during periods of fasting.

Hypothalamus
: Part of the vertebrate forebrain that is involved in the regulation of body temperature, water balance and emotion, among other functions.

Mitochondrial electron transport
: The energy contained in food is converted into high energy molecules, adenosine triphosphate (ATP), which drive most cellular processes. Mitochondria produce most of the ATP in the cell by transporting electrons along a series of carrier proteins situated in their inner membrane. The energy released by electron transport is used to pump protons (H^+) across the membrane to establish a gradient. The release of this proton gradient fuels ATP production by a mitochondrial enzyme called ATP synthase. However, a relatively large proportion of the proton gradient is lost as heat without ATP production. Hence, mitochondria play an integral part in metabolic heat production of endotherms.

Nitric oxide
: A gas that acts as an important signalling molecule. Among other places, nitric oxide is produced by the endothelium of blood vessels where it causes dilation of blood vessels and thereby an increase in blood flow. Increased blood flow facilitates heat exchange at the periphery.

NRF
: Nuclear respiratory factors (1 and 2) are transcription factors that control metabolic processes and particularly the gene expression of mitochondrial proteins.

Transcription factors
: A protein that binds to DNA to regulate the transcription (expression) of genes.

Transient receptor potential ion channels (TRPs)
: A family of ion channel proteins that are permeable to positively charged ions such as Ca^{2+}. In response to environmental factors such as temperature TRPs can release a large amount of ions thereby stimulating a neural response.

PGC-1α
: The peroxisome proliferator activated receptor gamma coactivator 1 α (PGC-1α) is a protein that acts as coactivator of transcription factors. It is an important molecular control mechanism of metabolism.

PPAR
: Peroxisome proliferator activated receptors (α, δ and γ) are nuclear receptors that act as transcription factors to control metabolic processes.

Prostaglandins
: Molecules derived from fatty acids that have multiple functions, primarily in reproduction and inflammation. Some prostaglandins can cause dilation or constriction of blood vessels and can thereby alter blood flow rates and heat exchange.

Somatosensory neurons
: Afferent nerve fibres that carry sensory information to the brain.

Sympathetic cholinergic stimulation
: Sympathetic nerve fibres mostly stimulate adrenergic receptors at their target organs. However, some sympathetic nerves involved in thermoregulation (e.g. sudomotor nerves that control sweating) stimulate cholinergic receptors, which are usually part of the parasympathetic nervous system.

Sympathetic preganglionic neurons
: Nerve fibres of the sympathetic autonomic nervous system that exit the central nervous system and synapse at ganglia, which are often close to the spinal cord.

Thermoregulatory shuttling behaviour
: Regular movements between heating (e.g. basking) and cooling (e.g. water or shade) environments that result in a relatively narrow range of body temperatures.

Trigeminal nerve
: The fifth cranial nerve conveying sensation from the head.

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