

Shivering Thermogenesis in Birds and Mammals

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Abstract. Shivering is the only universal facultative thermogenic mechanism in endothermic vertebrates. Skeletal muscle constitutes a large proportion of body mass and a high scope of metabolic rate, and thus heat production, between resting level and active contraction. Its contractile activity is under rapid and accurate neural control. Together with the inherently low metabolic efficiency of muscle, these “preadaptive” factors have led to an independent evolution of shivering as the main facultative thermogenic effector in birds and mammals as well as other modes of contraction-related muscle thermogenesis in some heterothermic animals. Shivering fulfils the requirements of a facultative mechanism, since it accurately and rapidly tracks variations in thermal conditions and obligatory thermogenesis and is adjusted accordingly to maintain thermal balance. In contrast to the other facultative thermogenic tissue, mammalian brown fat, aerobic muscle has a high inherent capacity for ATP-splitting, which drives the combustion of cellular fuels. Thus, any uncoupling of mitochondrial respiration for thermogenic purposes would incur little selective advantage.

Introduction

Endothermy in birds and mammals, including humans, is based on high basal metabolism and facultative thermogenesis. By definition, facultative thermogenesis is specifically activated in response to cooling during cold exposure (IUPS Thermal Commission, 2003). All biochemical reactions in the cell produce heat as their byproduct (Hochachka, 1974; Block, 1994), and in the resting state at thermoneutrality, these reactions comprise the obligatory basal metabolic rate (BMR). The much higher rate of this basal metabolism forms the basis of

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homeothermy in endotherms (Hulbert and Else, 2000; Ruben, 1995). Its origin is itself an intriguing question, but outside the scope of this overview. When the organism is in a steady state and no external work is done, anabolic and catabolic reactions balance each other, and the amount of heat liberated equals total oxidative metabolism (oxygen consumption). Thus, any reaction has the potential to become a thermogenic effector.

Despite this, only certain reactions were recruited for the specific function of cold-induced thermogenesis during the evolution of endothermy in birds and mammals. This is because there are at least three prerequisites for a reaction to function as a thermogenic effector: (1) It must occur in a sufficiently large tissue mass or be very intense in order to have enough capacity for defending the body against cooling. (2) It must be under instantaneous nervous control so that the level of thermogenesis is accurately set according to the needs imposed by swiftly varying thermal conditions. (3) It must be capable of long-term activation in order to be adaptive during seasonal changes in ambient temperature.

Perhaps not surprisingly, heat production by cold-induced involuntary muscle contraction, known as shivering, was “selected” as the main thermogenic mechanism in both endothermic vertebrate groups, birds and mammals (Hohtola, 2002). Muscle tissue comprises a significant part of their body mass, and the same motoneurons that control normal muscle contraction also form the final commanding pathway for shivering (Hemingway, 1963; Kleinebeckel and Klussmann, 1990). Muscle tissue also has a very large metabolic scope. Its factorial increase from resting to active surpasses that of most other tissues (Clark et al., 2000).

Another indication of the suitability of muscle for thermoregulatory heat production can be found in some heterothermic species. These include brooding python (Hutchison et al., 1966), moths, and honeybees warming up for flight (e.g., Esch et al., 1991), and swimming tunas (Altringham and Block, 1997), all of which use muscular heat production analogous to shivering (i.e. driven by alpha-motoneurons and including muscle contraction) for warming up, or defending against heat loss and thus attain partial endothermy. The other well established thermogenic effector, mammalian brown adipose tissue, fulfils these criteria despite its small mass because it can sustain an intense metabolism and is under sympathetic nervous control (Cannon and Nedergaard, 2004). It is interesting to note that evolution has produced fewer effectors for facultative heat production than for heat dissipation. This probably attests to the higher acute lethality of overheating compared with cooling.

In the following overview, examples and evidence of shivering as a true facultative mechanism that fulfills the criteria listed above are given. Furthermore, evidence for an independent evolution of shivering in mammals and birds is discussed.

Mechanism of Thermogenesis: Simple Principles and Some Misconceptions

The term shivering (cf. *Kältezittern*, *frisson thermique* etc.) is actually rather misleading, since the mechanical consequences of thermoregulatory muscle tone, tremor and microvibrations, which arise from the motor unit contraction cycle, are not prerequisites for thermogenesis and do not add to it in any way. Similar mechanical events accompany all types of static muscle activation, e.g., postural tone. Tremor can actually increase heat loss by increasing convection. The amplitude of tremor and surface vibrations depends very much on the gross anatomy and motor unit function of the species, being invisible in birds but very prominent in some mammals (Kleinebeckel and Klusmann, 1990). Cold acclimation decreases shivering-related tremor in quails (Hohtola and Stevens, 1986). Tremor and microvibrations can be reliable indicators of shivering intensity (May, 2003; Hohtola, unpubl.), but since tremor amplitude depends heavily on motor unit synchronization, it does not always accurately reflect the amount of active motor units (thermogenesis). Although electromyograms (EMGs) also have several limitations in estimating total shivering activity, it is the preferred and most common method to measure shivering (West, 1965; Hohtola, 1982; Tøien, 1992; Hohtola et al., 1998).

Another misleading term, “chemical thermogenesis,” for modes of heat production other than shivering (as if shivering thermogenesis was nonchemical) has been a source of much confusion regarding the simple principles of all cellular thermogenesis. Fortunately, not many textbooks perpetuate this confusing definition any more. All heat emanates, of course, from the chemical combustion of cellular fuels driven by the ATP-consuming cycle at the myofilaments. In a shivering muscle these reactions are exactly the same as during normal isometric muscle contraction. Some of the chemical energy is temporarily transformed into elastic and other types of mechanical potential energy within a muscle cell even when it is contracting isometrically, only to be released as heat when the contraction cycle proceeds. Since no external work is done in shivering, all the chemical energy liberated by cellular combustion is released as heat within the muscle tissue from where it is transported by the convective effect of circulation.

The efficiency of the chemical reactions resulting in muscle contraction is inherently low: only about one fifth of the input energy (in cellular fuels) is converted to external work, even in exercising muscles.

There is also a long-lasting standpoint that shivering is somehow “uncomfortable” and disturbs normal muscle functions (Hochachka and Somero, 2002) and “must” be replaced by some other mechanism during cold acclimation. Although this happens in a number of small mammals, most endothermic vertebrates use shivering thermogenesis even when they are cold-acclimated. It has been repeatedly shown, for example, that winter-acclimatized birds always increase shivering below their lower critical temperature (e.g. Aulie, 1976; Saarela and Hohtola, 2003). Winter-acclimatized arctic fox shiver to increase heat production (Korhonen et al., 1985). Shivering resembles postural activity and interacts with actual muscle contraction with equal flexibility. Firstly, of course, the need for shivering is decreased during activity because of the heat production from the concomitant normal muscle contraction. Secondly, it has been shown both in birds (Nomoto and Nomoto, 1985a; Hohtola et al., 1998) and mammals (Meigal et al., 1998) that shivering can persist during voluntary muscle activity. This is seen as an increased muscle tone in EMGs during a motor task. Furthermore, the increased muscle tone in cold does not affect the accuracy of muscle force control in a biofeedback situation (Meigal et al., 1998).

Interaction of Shivering with Obligatory Thermogenesis

A crucial point for a facultative thermogenic mechanism is that it tracks the rate of heat loss and internal nonthermoregulatory heat production. A vast body of data exists showing that shivering is accurately adjusted to counteract changes in ambient and body temperature (see e.g., Kleinebeckel and Klussmann, 1990). Less data exist, however, on the interaction of shivering with obligatory heat production.

The major components of obligatory thermogenesis besides BMR are motor activity and feeding-related processes (digestion-related thermogenesis, DRT). Facultative heat production should be accurately adjusted according to the changes in these modes of obligatory heat production. Several reports show that the obligatory DRT-related postprandial increase in metabolic rate is absent or lower in cold environments. This suggests that shivering (or NST, in some species) is the facultative component of thermogenesis that is adjusted to a lower level, but this is not usually verified by direct measurements. In pigeons, it was shown that the increase in body temperature from nocturnal to diurnal

levels towards the end of the dark phase incurs an increase in thermogenesis. Electromyographic recordings of shivering show that in fasted or food-restricted pigeons, a higher shivering intensity is needed for this as DRT is less or absent (Rashotte et al., 1999). Furthermore, in a thermoneutral environment, pigeons retain food in the crop and preferably digest it at this time (Laurila et al., 2003). Thus, the heat that would otherwise would have to be dissipated, can be used adaptively.

Although vigorous activity can suppress shivering to some extent via direct neural inhibition (Arnold et al 1986; Nomoto et al., 1985b) the thermal consequences of activity have been shown to modulate the intensity of shivering, and shivering can continue during voluntary muscle activity (Nomoto and Nomoto-Kozawa, 1985b; Hohtola et al., 1998; Meigal et al.; 1998).

Capacity and Endurance

Not all muscle types are suitable for shivering, however. Since the need for thermogenesis can last for hours or even days, only the most aerobic, fatigue-resistant muscles and motor units can be recruited for shivering. In man, it has been shown that the contraction level of a shivering muscle reaches maximally 16–20% of the maximal voluntary contraction (Bell et al., 1992; Haman et al., 2004). This indicates that only a very limited population of muscle fibers are recruited for shivering, these being obviously of the most fatigue-resistant type. Thus shivering can increase the rate of oxygen consumption maximally 4–5-fold, while bouts of running or flying can incur a 20-fold increase. The duration of such bouts is limited to hours, while shivering goes on for days or weeks. In that sense, shivering resembles very much the activity of postural muscles.

The metabolic fuel for shivering is either carbohydrate or lipid (fatty acids), as in normal muscle contraction. Many species differ in the pattern of shivering, showing either a bursting or continuous electrical activity (Hohtola and Stevens, 1986). In man, it has been shown that the pattern of shivering has an influence on the partition of fuels for shivering, the bursting and continuous pattern favoring carbohydrates and lipids, respectively. Cold exposure often causes changes in muscle metabolism that increase aerobic capacity and fatty acid oxidation (see Dawson et al., 1992). In addition, changes in fiber composition (Ballantyne and George, 1978) and mitochondrial biogenesis (Wu et al., 1999) have been observed.

Phylogeny of Shivering

A survey of literature reveals that all mammals and birds that have been appropriately tested show electromyographic signs of shivering when exposed to cold (Kleinebeckel and Klussmann, 1990). By contrast, no such response is seen in reptiles, although the evidence is mostly indirect, i.e., based on measurements of metabolic rate in cold-exposed animals. At least one experiment, however, shows a complete lack of muscle tone during cooling in a lizard (*Tubinambis* sp., Hohtola and Johansen, unpublished).

Phylogenetic evidence shows that mammals and birds evolved from separate reptilian ancestors. Although the possible endothermy of theropod dinosaurs (the ancestor of birds) has been widely discussed, there is no evidence of a common endothermic ancestor for both birds and mammals. Therefore, shivering thermogenesis probably evolved in both groups independently.

Shivering is basically an increase in muscle tone and thus resembles postural activity of skeletal muscles. The differences in the postural system of reptiles and endothermic vertebrates have prompted the suggestion that postural activity formed the neuromuscular substrate that was transformed to shivering (Heath, 1968). Subsequent studies have provided indirect theoretical and experimental evidence for this (Hohtola, 1981; see also Muir, 2000).

Can we find any differences in shivering between birds and mammals, which would support the notion that they originated independently? Since the biochemical reactions producing the heat are certainly identical, eventual differences must be sought in the function of motor units, the basic contractile units of skeletal muscle, and the central nervous system pathways that drive shivering. Motor unit function can be studied by recording the electrical events coupled to muscle contraction. Using such electromyographic methods, the size and synchronization of contracting motor units can be analyzed.

Both in birds and mammals, small motor units are first recruited for shivering. In birds, there is a gradual recruitment of larger units with increasing level of shivering in a smooth “crescendo” pattern (Hohtola, 1982, Tøien, 1992). In mammals, however, the initial recruitment of small units produce a “thermoregulatory muscle tone” that is followed by grouped discharges of motor units (“true shivering”) at higher contraction intensities (Klussmann et al., 1969; Lupandin, 1980). Thus, there seems to be a clear difference of motor unit control during shivering between birds and mammals, which could be used to shed more light on the notion of an independent evolutionary origin.

Another interesting difference in the motor control of shivering exists between birds and mammals: in both groups the intensity of shivering is modulated by the respiratory cycle but in opposite directions. In mammals, shivering is facilitated during inspiration (Kleinebeckel and Klusmann, 1990), but in birds during expiration (Hohtola and Johansen, 1987; Tøien, 1993).

Because of the differential control of motor units and body shape differences, shivering in mammals usually incurs clear visible tremors, while in birds with smooth muscle contraction and compact body form, shivering-related tremors are rarely observed. Birds probably benefit from this as the convective heat loss is smaller with low tremor intensities. Small birds are known to be more cold-resistant than small mammals. In humans, tremors and the basic recruitment of motor units for shivering can influence muscle function in cold. However, by adaptive use of distal and proximal muscles for work and shivering, such problems can be minimized (Meigal et al., 1998).

Muscle NST?

Muscle NST, by definition, would mean thermally driven heat production without contractile activity. There are several studies that report an increase in thermogenesis (oxygen consumption) either without an associated increase in muscle electromyograms (EMGs) or a disparity between the two, even in species that do not have brown adipose tissue (El Halawani et al., 1970; Hohtola et al., 1989; Saarela and Heldmaier, 1987). Although electromyography is the most reliable method for measuring muscle activity related to shivering, the correlation between EMG and thermogenesis is influenced by a host of confounding factors (Tøien, 1992; Hohtola et al., 1998, Marjoniemi and Hohtola, 1999). Different muscles may have different thermal thresholds for shivering (Carey et al., 1989), shivering may be highly localized if a species has only a few very aerobic muscles (Aulie and Tøien, 1988). Thus such disparities should not be taken as evidence of (muscle) NST without careful analysis. To date, the strongest evidence for nonshivering thermogenesis in muscle in true endotherms comes from cold-acclimated juvenile ducks (Duchamp et al., 1999).

The recent discovery of various uncoupling proteins (UCPs) both in mammals and birds has of course precipitated hypotheses on their role in facultative heat production. It now seems clear, however, that they have a role in the regulation of muscle metabolism rather than actual cold-induced thermogenesis (for examples, see Brand, 2000; Talbot et al., 2003). Interestingly, UCP1-ablated

mice acclimate to cold by shivering thermogenesis despite an increase in other types of UCPs (Golozoubova et al., 2001).

That muscle has a very high capacity of heat production without any uncoupling of oxidative phosphorylation is shown by malignant hyperthermia, a pathological condition, where abnormal Ca^{2+} -cycling can induce a lethal hyperthermia. At least one example exists where the contractile activity of muscle has been sacrificed for increased heat production. In swordfish, an anatomically circumscribed endothermy in the eye region is maintained by a specially transformed muscle (Block, 1994) that produces heat by the sarcoplasmic calcium-cycling without contraction but obviously under the control of alpha-motoneurons. It is noteworthy that the modifications that serve heat production in swordfish have resulted in gross anatomical changes, which cannot be seen in true endotherms.

Resting muscle metabolism is known to vary significantly with changes in blood flow. By diverting arterial blood to intramuscular arteries or to connective tissues of the muscle, blood flow can be nutritive or non-nutritive (Clark et al., 2000). This brings about a significant change in muscle metabolism. Whether this could be thermally driven and be rapidly controlled to enable it to act as a facultative thermogenic mechanism is not known (Eldershaw et al., 1997).

It should be once more emphasized that because muscle has an high inherent capacity for ATP-splitting, there is no need for any uncoupling mechanism for heat production (see Hochachka, 1974). Although it could be argued that such a mechanism without muscle contraction would be more adaptive since the tremor and "uncomfortable" muscle tension would be absent, the basic function of muscle, contraction, would be severely compromised. It is difficult to envision such a selective force. Theoretically, this could work if uncoupling could be turned on and off rapidly by some neuronal system, but neither the motor or autonomic system are known to influence the function of muscle UCPs.

From a viewpoint of the history of science, it seems that the search for thermoregulatory thermogenic mechanisms has recently become reductionistic as physiologists want to find specific molecule or reaction that would explain the facultative thermogenesis in muscle (Lowell and Spiegelman, 2000). This may be because of the renowned success in the discovery of the reactions involved in non-shivering thermogenesis in brown adipose tissue (Cannon and Nedergaard, 2004). However, it is well known that temperature regulation and endothermy are largely based on existing physiological functions (Satinoff, 1978). Shivering thermogenesis is an excellent example of this: normal muscle tone has been modified such that it is driven by thermal stimuli.

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