

Commentary

The physiology of long-distance migration: extending the limits of endurance metabolism

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Summary

Long-distance migrants have evolved specific adaptations that make their athletic records possible. Unique mechanisms explaining their amazing capacity for endurance exercise have now been uncovered, particularly with respect to energy storage, mobilization, transport and utilization. Birds are champions of migration because flying offers a key compromise: it allows more rapid movement than swimming, but has a lower cost of transport than running. High efficiency for muscle contraction, pointed wings, low wingloading, travelling in V-formations, storing fuel as energy-dense lipids and atrophy of non-essential organs are some of their strategies to decrease the cost of transport. The ability to process lipids rapidly also emerges as a crucial component of the migrant phenotype. High lipid fluxes are made possible by lipoprotein shuttles and fatty acid binding proteins (FABPs) that accelerate lipid transport and by upgrading the metabolic machinery for lipolysis and lipid oxidation. Preparation for long flights can include natural doping on n-3 polyunsaturated fatty acids (n-3 PUFAs) from unique invertebrate diets. Muscle performance is improved by restructuring membrane phospholipids and by activating key genes of lipid metabolism through peroxisome proliferator-activated receptors (PPARs). The physiological secret to long migrations does not depend on a single 'magic' adaptation but on the integration of multiple adjustments in morphology, biomechanics, behavior, nutrition and metabolism. Research on the physiology of migrants improves the fundamental knowledge of exercise biology, but it also has important implications for wildlife conservation, treating obesity and improving the performance of human athletes.

Key words: natural doping, lipid metabolism, lipoprotein, membrane phospholipid, endurance exercise, cost of transport, animal energetics.

Introduction

The endurance capacity of long-distance migrants has fascinated biologists for centuries, but recent work probing the physiological mechanisms that underlie their athletic performance has further strengthened this interest. Electronic tracking can now document animal migrations by exact monitoring of global position, travel speed and distance. Using satellite technology, scientists have characterized the migration patterns of aquatic species such as the white shark (*Carcharodon carcharias*, L.) and bluefin tuna (*Thunnus thynnus*, L.) that criss-cross major oceans annually (Block et al., 2005; Bonfil et al., 2005). Modern tracking has allowed the shattering of former migration records by demonstrating yearly roundtrips of more than 64,000 km in some marine birds (Shaffer et al., 2006). Amazingly, these outstanding physical achievements are overshadowed by the discovery of single non-stop flights exceeding 11,000 km, authenticated in the bar-tailed godwit (*Limosa lapponica*, L.), a wading bird that migrates between Alaska and New Zealand without refueling (Gill et al., 2005; Griggs, 2007). Physiologists are left with the exciting task to unravel the mechanisms that make these exploits possible. Are traditional concepts of exercise physiology simply stretched to suit the extreme needs of migrants, or do these athletes rely on original adaptations? Here, I focus on the fuel metabolism of endurance exercise because exceptional capacities for energy storage, mobilization, transport and utilization are absolutely essential for migration. Specialized neuro-sensory systems involved in orientation and navigation also play important roles in energy economy, but they have been

extensively reviewed elsewhere and will not be addressed here (Alerstam, 2006; Lohmann et al., 2008).

Energetics of long migrations

The complex compromises migrants must make to use seasonally available food resources and breeding sites are strongly influenced by the cost of transport, or the energy spent to move a unit body mass by a unit distance. If the evolution of migratory behaviour had been orchestrated exclusively by locomotion energetics, large swimming animals would beat all records because the mass-specific cost of transport decreases with body size and it is much lower for swimming than for other modes of locomotion (~3- and 10-fold lower than for flying and running, respectively) (see Table 1). This simple argument explains why the longest migrations of land mammals barely reach a few thousand kilometers and can only be performed by large species such as wildebeest (*Connochaetes taurinus*, Liechtenstein) and caribou (*Rangifer tarandus*, L.). However, it fails to clarify why the most extreme migrations are achieved by birds rather than fish, a somewhat perplexing observation, unlikely to be challenged even when the monitoring of aquatic environments becomes more accessible. Soaring, rather than flapping flight, can significantly reduce the energy gap between flying and swimming, but this strategy is restricted to large birds and cannot explain the high incidence of long migrations among small avian species. Theoretical analyses suggest that birds outcompete fish because flying is a useful compromise between running (with prohibitive cost of transport) and swimming (with low maximal speed) (Alexander, 1998).

Table 1. Allometric equations for mass-specific cost of transport in animals using different modes of locomotion

Locomotory mode	Cost of transport
Swimming	$1.1(\text{body mass})^{-0.38}$
Flying	$3.6(\text{body mass})^{-0.31}$
Running	$10.7(\text{body mass})^{-0.32}$

Cost of transport is the energy needed to move 1 unit body mass by 1 unit distance. The equations provided are from Alexander (Alexander, 2003) for cost of transport expressed in $\text{J kg}^{-1} \text{m}^{-1}$ and body mass in kg. For same-size animals, note that the difference in cost of transport between modes of locomotion is almost entirely accounted for by large differences in the constants (1.1 vs 3.6 vs 10.7) because the exponents are very similar.

Successful migrations depend on the economic management of time as well as energy, and high speed is one of the main advantages that flying provides. Travelling long distances slowly offers no benefit if it does not leave enough time for essential activities such as feeding and reproduction.

Minimizing the cost of transport

Migrants have evolved multiple strategies to decrease their cost of transport. The locomotory muscles of some species appear to generate force with unusually high efficiency, and this physiological trait might be unique to long-distance migrants (Klaassen et al., 2000; Kvist et al., 2001). However, this observation stems from the lower than expected whole-organism metabolic rate during flight, and the exact nature of this hypothetical muscle adaptation has never been characterized. To save energy, migrant birds also rely on morphological features such as pointed wings and low wingloading (Bowlin and Wikelski, 2008), as well as biomechanically advantageous behaviors such as travelling in V-formations (Weimerskirch et al., 2001). Animal migrants further decrease the cost of transport by minimizing body mass. They do so by selecting lipids to store energy for muscle work and temporarily atrophy non-essential organs. Pre-migration lipid reserves can reach 50% of total body mass (Blem, 1990). The existence of extremely rapid and ample fluctuations in lipid stores makes migratory birds a fascinating model for obesity research. Understanding the regulation of such drastic and reversible changes in fat reserves is bound to bring important insights to this field of human medicine. These lipids provide the highest ATP yield per gram of fuel because they are stored with virtually no free water and are more chemically reduced than other substrates (Weber and Haman, 2004). For land migrants risking dehydration, lipids offer the additional advantage of generating more metabolic water upon oxidation than proteins or carbohydrates. It has also been established that 5–15% of the energy used by migrating birds comes from the oxidation of proteins. The reasons why they increase the cost of transport by making significant use of this heavier fuel are unclear. Among the proposed hypotheses (see McWilliams et al., 2004), the most convincing are: first, the use of amino acids in anaplerotic pathways, where amino acid metabolites generated by protein breakdown replenish stocks of citric acid cycle intermediates to ensure that lipid catabolism can proceed and, second, downsizing of the flight muscle ‘engine’ when heavy fuel loads are progressively reduced throughout the migration (Jenni and Jenni-Eiermann, 1998). Finally, birds are known to atrophy their digestive organs before take-off to decrease the maintenance and transport costs of tissues that are not essential for locomotion (McWilliams and Karasov, 2004).

A record capacity to process lipids: a requirement for long migrations

The metabolic rate that birds maintain during migration is 10 to 15 times higher than in the resting state, or about twice the maximal oxygen consumption (mass-specific $\dot{V}_{\text{O}_2, \text{max}}$) of similarly sized mammals (Butler and Woakes, 1990). Most of the energy is provided to working muscles from extra-muscular adipose reserves, and it is estimated that migrant birds can mobilize, transport and oxidize lipids at more than 10 times the maximal rates ever recorded in mammals (McWilliams et al., 2004). Even though this amazing ability to process lipids is a clear functional requirement of migration, no direct measurement of fat metabolism has been performed in a flying bird, and little information is available on the actual adaptations that support these high fluxes.

Lipid mobilization

Lipid oxidation provides more than two-thirds of the energy migrant birds consume during shivering or running (Vaillancourt et al., 2005). Even at rest and under normothermic conditions, the ruff (*Philomachus pugnax*, L.), a wading bird, reveals its extraordinary capacity to mobilize lipids by maintaining a higher lipolytic rate than any other animal measured to date. These first *in vivo* measurements of lipid kinetics in migratory birds demonstrate that, in the resting state, they hydrolyse triacylglycerol at the astonishing rate of 55–60 $\mu\text{moles of glycerol kg}^{-1} \text{min}^{-1}$ (Vaillancourt and Weber, 2007). These baseline values are 2–3 times higher than in similarly sized mammals (resting or after prolonged submaximal exercise), and it is also quite clear that ruff and other sandpipers have to stimulate lipolysis even further to be able to support flight. Yet, quantifying the effects of flying on avian lipid fluxes remains a challenge for the future. Valuable *in vitro* information has been obtained on preferential selection of particular fatty acids from adipocytes (Price et al., 2008). Birds mobilize shorter and unsaturated fatty acids more rapidly, whereas long-chain and more saturated ones take longer to become available for oxidation. This selection pattern has also been observed in mammals and appears to apply generally among animals.

The capacity for lipolysis has not been determined in long-distance migratory fish such as salmon. However, these endurance swimmers are probably also able to mobilize fatty acids rapidly if the high lipolytic rates measured in their sedentary trout relatives are taken as an indication (Bernard et al., 1999; Magnoni et al., 2008b). We have proposed that all ectotherms could have this high capacity to provide fatty acids of different chain length and saturation level, thereby allowing them rapid homeoviscous adaptation when body temperature fluctuates. However, more research is needed to determine whether the need to fuel endurance swimming or to restructure membrane phospholipids is the main determinant of lipolytic capacity in migrant fish.

Lipid transport

The classic mammalian strategy of providing lipids to muscles as albumin-bound nonesterified fatty acids does not suit the needs of long-distance migrants. Instead, they rely on circulating lipoproteins to reach the high rates of energy supply necessary for migration because the energy carrying capacity is much higher for lipoproteins than for fatty acids. This alternative way to fuel working muscles appears to have evolved in animals as phylogenetically distant as fish, birds and insects. In fish, evidence for the use of lipoproteins as an energy shuttle is strongest for salmonids because they show particularly high plasma lipoprotein levels that account for over 90% of total circulating lipids. More

importantly, the lipoproteins of sockeye salmon (*Oncorhynchus nerka*, Walbaum) vary dramatically over the course of migration and in a manner consistent with their utilization as a fuel (Magnoni et al., 2006). The use of this important energy source has also been confirmed by the recent demonstration that endurance swimming activates lipoprotein lipase in red muscle (Magnoni and Weber, 2007) and that lipoprotein turnover rate is higher in trout (*Oncorhynchus mykiss*, Walbaum) than in any endotherm (Magnoni et al., 2008a). The presence of a lipoprotein shuttle to supply muscles had also been proposed several years ago for migrant birds (Jenni-Eiermann and Jenni, 1992), and this idea is supported by more recent work on the western sandpiper (*Calidris mauri*, Cabanis). The lipoproteins of this species undergo major fluctuations during migration along the Pacific coast of North and Central America (Guglielmo et al., 2002b). As in migrating salmon, the observed changes in concentration and composition strongly support the idea that lipoproteins are used as the main oxidative fuel for prolonged exercise.

Ironically, the molecular machinery for lipoprotein supply to working muscles has been better characterized in insects than in any vertebrate. With some of the highest mass-specific metabolic rates of any organism, migrant lepidopteran and orthopteran insects have to support phenomenal lipid fluxes. They achieve them by using a lipophorin shuttle for rapid transport of diacylglycerol (DAG) between fuel reserves and flight muscles (Van der Horst, 2003). In the fat body, high-density lipophorin (HDLp) is loaded with DAG and converted to low-density lipophorin (LDLp) that, in turn, supplies DAG to the muscles. The unloading of DAG in flight muscles regenerates HDLp, which returns to the fat body to repeat the cycle.

In the absence of an adequate transporter, the hydrophobic nature of fatty acids would preclude their efficient transfer across the cytosol. Therefore, animals rely on a family of fatty acid binding proteins (FABPs) that solubilize intracellular fatty acids and accelerate their movements. The supply of fatty acids to muscle mitochondria depends on the presence of a specific muscle FABP (M-FABP) that has been characterized in fish (Londrville and Sidell, 1995), birds (Guglielmo et al., 1998) and insects (Haunerland and Spener, 2004). The expression of M-FABP in the muscles of migrants is seasonally modulated from wintering values to much higher levels during migration (Guglielmo et al., 2002a).

'Natural doping' to stimulate oxidative capacity

The activities of marker enzymes for flux capacity through the citric acid cycle and β -oxidation have been measured in several species of migrant birds. As expected, the oxidative capacity of their flight muscles is higher than in sedentary species (Bishop et al., 1995; Driedzic et al., 1993; Suarez et al., 1990) and it is further upregulated seasonally at the time of migration (Guglielmo et al., 2002a; Maillet and Weber, 2007). Recent research reveals that some migrant birds use components of their diet as performance-enhancing substances to achieve a large increase in aerobic capacity just before departure. This form of 'natural doping' was discovered in semipalmated sandpipers (*Calidris pusilla*, L.) preparing for the longest non-stop flight of their annual cycle: a ~4500 km transatlantic trip from eastern Canada to South America, requiring a 3 day flight at ~60 km/h (Maillet and Weber, 2006; Maillet and Weber, 2007). While refueling in the Bay of Fundy (New Brunswick, Canada), these sandpipers double their body mass (from ~20 to 40 g) by feeding on small burrowing amphipods (*Corophium volutator*, Pallas) that contain very high levels of n-3 polyunsaturated fatty acids (n-3 PUFAs) (Fig. 1). This behaviour is

Migration cycle of the semipalmated sandpiper (*Calidris pusilla*)

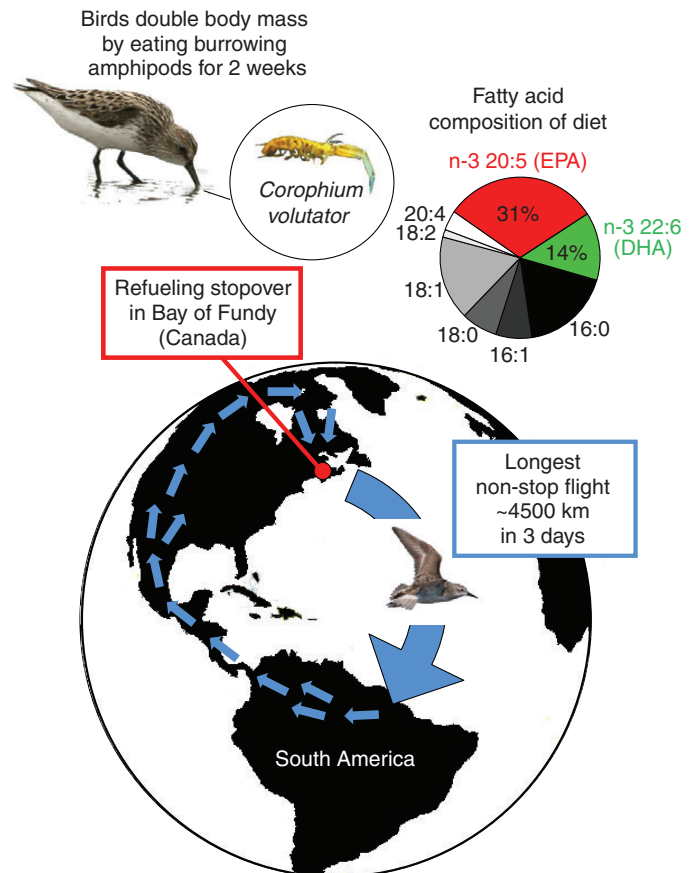


Fig. 1. The semipalmated sandpiper (*Calidris pusilla*) stops in the Bay of Fundy (New Brunswick, Canada) during its fall migration from breeding areas in the Arctic. This crucial stopover allows the migrant to store large lipid reserves by eating seasonally abundant amphipods (*Corophium volutator*) buried in the mudflats. It is currently estimated that 75% (~1 million individuals) of the world population of semipalmated sandpipers stops at this location. The *Corophium* mudshrimp contains unusually large amounts of n-3 polyunsaturated fatty acids (45% of total lipids) and is found only in the Bay of Fundy and along the coast of Maine. Dietary n-3 fatty acids are not only used as an energy source but they also act as performance-enhancing substances to increase the capacity for endurance exercise, just before the sandpiper crosses the Atlantic ocean to South America (Maillet and Weber, 2006; Maillet and Weber, 2007). The remainder of the annual migration cycle appears to be achieved through multiple short flights over land and along coastal areas. Pollution and rising sea levels caused by global warming are major threats to strategic stopover sites such as the Bay of Fundy and to the future of this migrant bird. [Photographs adapted from: Ferrin 2004 (*Calidris*) and S. Mautner (*Corophium*).]

worthy of attention because the fatty acid composition of artificial diets has been shown to influence the capacity for endurance exercise in a variety of animals, including rats (Ayre and Hulbert, 1997), Atlantic salmon (*Salmo salar*, L.) (McKenzie et al., 1998), and the red-eyed vireo (*Vireo olivaceus*, L.), a migrant songbird (Pierce et al., 2005).

In the diet naturally consumed by the semipalmated sandpiper, eicosapentaenoic acid (EPA, n-3 20:5) and docosahexaenoic acid (DHA, n-3 22:6) account for 45% of total lipids. Therefore, these birds boost the aerobic capacity of their flight muscle by eating large amounts of n-3 PUFA that are known to cause

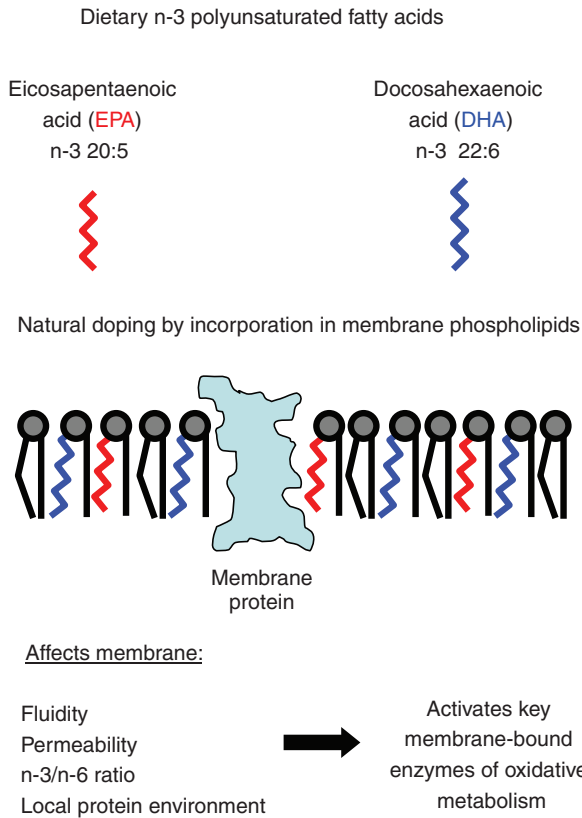
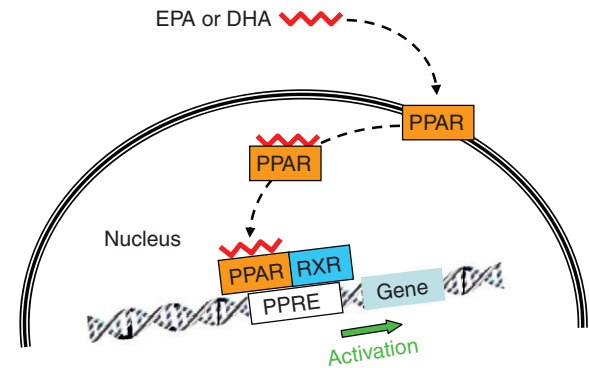


Fig. 2. Figure showing the first mechanism of natural doping whereby dietary n-3 fatty acids are incorporated into membrane phospholipids. Before crossing the ocean, the semipalmated sandpiper (*Calidris pusilla*) doubles its body mass by eating n-3 eicosapentaenoic acid (EPA 20:5) and n-3 docosahexaenoic acid (DHA 22:6). These lipids are from the n-3 family of fatty acids because their first double bond is located after the third carbon from the terminal methyl group (n). The X:Y nomenclature indicates that these fatty acids have X carbon atoms and Y double bonds. EPA and DHA have multiple double bonds, imposing many angles upon their carbon chains. Therefore, their addition to phospholipids increases membrane fluidity and alters the properties of membrane-bound proteins. Carnitine palmitoyl transferase (CPT) is one of the enzymes activated by the presence of EPA in mitochondrial membrane phospholipids.

pharmacological-like effects in mammalian cells *in vitro*. The exact molecular mechanisms are unknown, but natural doping appears to be mediated by two processes: the incorporation of dietary n-3 PUFAs in membrane phospholipids and their binding to nuclear receptors. The incorporation of PUFAs causes changes in membrane fluidity, permeability, n-3/n-6 ratio and the local molecular environment that affect key membrane proteins (Gerson et al., 2008; Guderley et al., 2008). Among others, these proteins include carnitine palmitoyl transferase (Guo et al., 2005), Na^+/K^+ -ATPase (Turner et al., 2005), $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase (Swanson et al., 1989), ion channels (Leaf et al., 2005) and the insulin receptor (Corcoran et al., 2007) (Fig. 2). In addition to their membrane effects, EPA and DHA are natural ligands for peroxisome proliferator-activated receptors (PPARs) that regulate the expression of genes controlling fundamental aspects of lipid metabolism (Fig. 3). Individual members of the PPAR family regulate different genes, and their distribution varies among tissues. Genes regulated by PPAR α and β are mostly concerned with fatty acid oxidation and transport, whereas those regulated by PPAR γ deal with lipid storage and adipocyte differentiation (Feige et al.,

Natural doping by binding of n-3 fatty acids to PPAR α and β



Binding to PPAR causes:

Mitochondrial and peroxisomal proliferation

Stimulation of gene expression for key proteins of lipid metabolism:

CPT, HOAD, FABP, CD36, FAT and others

Fig. 3. Figure showing a second mechanism of natural doping whereby the binding of dietary n-3 fatty acids to the transcription factors peroxisome proliferator-activated receptors α and β (PPAR α and β) activates genes regulating lipid metabolism. n-3 eicosapentaenoic acid (EPA) and n-3 docosahexaenoic acid (DHA) are natural ligands for PPARs. Ligand binding causes the dimerization of PPAR with the retinoid-X-receptor (RXR). The PPAR-RXR complex activates target genes by recognizing promoter regions called peroxisome proliferator response elements (PPREs). Target genes include the β -oxidation enzymes carnitine palmitoyl transferase (CPT) and hydroxyacyl dehydrogenase (HOAD), fatty acid binding proteins (FABPs) and the transmembrane fatty acid transporters CD36 and FAT.

2006). The semipalmated sandpiper is the first documented case of a long-distance migrant using natural doping to prime its locomotory muscles for endurance exercise. It provides a useful starting point to improve the understanding of exclusive metabolic innovations in migrants. Some promising avenues for future work will be to determine: first, the relative roles of changes in membrane composition, PPAR-mediated effects or other unknown pathways in this doping response; second, whether dietary n-3 fatty acids are used by different animals for the same purpose; and finally whether alternative strategies have evolved in other long-distance migrants.

No marine invertebrate other than *Corophium volutator* contains such large amounts of long-chain n-3 PUFAs, and, in North America, this amphipod is only found in the Bay of Fundy and in the Gulf of Maine. Pollution and rising sea levels caused by global warming are thought to be responsible for the recent decline in *Corophium* abundance that could threaten the migration cycle of the semipalmated sandpiper. This example illustrates the need to protect crucial stopover areas when attempting to provide a healthy future for migrant birds.

Conclusions

The physiological secret to long migrations does not depend on a single 'magic' adaptation but on the integration of multiple adjustments in morphology, biomechanics, behavior, nutrition and metabolism. Only as a coordinated unit does this collection of

distinctive attributes provide long-distance migrants with the capacity for extreme endurance. The ability to rapidly process lipids emerges as a crucial component of the migrant phenotype, but remarkably few data are available on fuel metabolism in these athletes. High lipid fluxes are made possible by lipoprotein shuttles, by high concentrations of FABP that accelerate lipid transport and by boosting the metabolic machinery for lipolysis in adipocytes and lipid oxidation in muscle mitochondria. In one bird species, the final preparation for long flights is performed by natural doping on n-3 PUFA from its unique invertebrate diet. Muscle performance is improved by restructuring membrane phospholipids and by activating essential genes of lipid metabolism through PPARs. The bag of physiological tricks currently known for migrants provides numerous intriguing questions for future work and promises startling discoveries. Research on the physiology of long-distance migrants not only improves fundamental knowledge of comparative exercise biology but has important implications for wildlife conservation, for the treatment of obesity and for improving the performance of human athletes.

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