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Inside JEB

THE BIOLOGY OF ENERGY EXPENDITURE


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Energy is the currency of life. Eat more than you use and you store fat; use more than you eat and you won't last long. But understanding bioenergetics is more than just a matter of our waistlines; it is fundamental to life and the interactions of all living things with the environment. Understanding how organisms use energy is also key to the survival of many species during this time of dramatic change. How will altering wind patterns impinge on migrating birds? What sets the upper limits on the amount of energy that animals can produce? How can we combat metabolic syndrome and the obesity epidemic? These are fundamental biological questions that go well beyond the protein structures and reaction mechanisms that underpin bioenergetics. Fascinated by biological energy use, Raul Suarez at the University of California, Santa Barbara, USA, has drawn together a collection of review articles addressing the issue of bioenergetics from a wide range of perspectives, from the ecological to biomedical. 'I wanted to come up with an issue that demonstrates the range of research activity that goes on and shows that this is a vibrant and exciting area of science,' says Suarez. Teaming up with JEB Editor-in-Chief Hans Hoppeler to invite contributors from various backgrounds with an interest in bioenergetics, Suarez has drawn together a unique collection of review articles addressing 'The Biology of Energy Expenditure'.

METABOLISM IN AN EVOLUTIONARY CONTEXT

The metabolisms of many creatures have to adapt in the face of changing energetic challenges, and *Drosophila melanogaster* is no exception. Having originated in the tropics of Africa, the insect has colonised a wide range of temperate environments as human populations moved across the globe. Focusing on natural selection in the insect's energy-producing glycolytic pathway, Walter Eanes from Stony Brook University, USA looked for genetic polymorphisms in populations that could indicate adaptation to new environments. Analysing gene polymorphisms in the context of geographical location (p. 165), Eanes found that enzyme genes at the top of the pathway, around glucose-6-phosphate, may be adapting to the insect's altered circumstances. He suggests that these genes may control flux through the pathway to enable survival in the temperate environments that the insects have occupied recently.

Switching from insects to mammals, Raul Suarez explains that few vertebrates have modified their exercise energy metabolism to the extent of hovering nectarivorous bats and hummingbirds. Suarez and his colleagues Gerardo Herrera and Kenneth Welch explain that, instead of relying primarily on stored carbohydrates or fats to fuel exercise, hovering bats and hummingbirds essentially refuel on the wing, rapidly transporting oxygen and nectar sugars to directly fuel the fast twitch muscles that power flight (p. 172). Outlining elements of the sugar transport and oxidation cascades that consume sugar and oxygen to produce ATP, Suarez and his colleagues describe how hummingbirds sustain the highest vertebrate metabolic rates ever measured. Pointing out that fuelling exercise with sugar yields 15% more ATP per oxygen atom than fuelling exercise with fat, the team suggests that 'ingested sugar serves as a premium fuel for hummingbird flight'.

While Suarez and his colleagues have detailed the uniquely adapted metabolism of hovering flight in vertebrates, Anthony Zera, from the University of Nebraska, USA, discusses the evolutionary lessons that can be learned from analysing metabolic pathways (p. 179). Describing various metabolic pathways in organisms ranging from *Escherichia coli* to *D. melanogaster* and the cricket *Gryllus firmus*, Zera discusses how changes in an organism's resource allocation lead to trade-offs, where an increase in resource allocation to one life history trait leads to a decrease in the resources available to another. Reviewing Ronald Burton's work on the mitochondrial electron transport chain in copepods, Zera explains how this has shed light on fundamental evolutionary processes such as the mechanisms of reproductive isolation. Zera also describes how analysing the kinetics of allozymes (enzymes encoded by different alleles of a gene) such as alcohol dehydrogenase in *D. melanogaster* and looking at their effect on lipid metabolism has shown how different metabolic allozymes can confer fitness advantages on the insects carrying them.

A group of animals that routinely experiences metabolic challenge is fish exposed to hypoxia. Starved of oxygen, they either have to improve oxygen uptake from the environment or reduce energy expenditure to survive. A group of fish that routinely experience hypoxia are the tide-pool-dwelling sculpins. Intrigued by the evolution of hypoxia tolerance, Jeffrey Richards from the University of British Columbia, Canada outlines his work on the behavioural and metabolic adaptations of sculpin species exposed to different levels of hypoxia across the tidal range (p. 191). Richards describes variations in mass-specific gill surface area, red blood cell haemoglobin oxygen-binding affinity and oxygen consumption rates that allow hypoxia-tolerant species to survive conditions that could prove lethal for less tolerant species further down the tidal range. He also outlines the metabolic reorganisation that is required to reduce ATP consumption rates as oxygen levels decline. Speculating that hypoxia tolerance will have selected for higher levels of metabolic rate suppression and fuel storage, Richards adds '[but] we are still far from a unified concept of the important adaptations underlying hypoxia tolerance'.

ENERGY DEMANDS

Having discussed metabolism in an evolutionary context, the collection moves on to address metabolic demands in a variety of circumstances. Considering the energetic costs of communication, Philip Stoddard from Florida International University, USA and Vielka Salazar from Cape Breton University, Canada describe how some animals invest little in signalling while others expend more of their energy budget on signalling than on the rest of their energy demands. Focusing on gymnotiform electric fish (p. 200), the duo explain that the fish can rapidly modulate signal power in response to social conditions and say that 'territorial or sexually selected species may be under selective pressure to boost signal power'. Males expend more energy than females on both signal production and cellular metabolism, but the more a male spends on signals, the less he spends on cellular metabolism. This apparent trade-off suggests that males are up against an intrinsic limit on total metabolic output.

Moving on to consider human energy budgets, Ted Garland and colleagues from various US institutes and The Netherlands discuss potential ways of increasing our activity to combat the modern obesity epidemic (p. 206). Recommending that we spend less time in sedentary activities, such as watching television, Garland considers the lessons that we can learn about the physiological effects of activity from mice that have been selectively bred for voluntary exercise. Explaining that the brain's endocannabinoid system may play an important role in the control of voluntary activity in mice, Garland and his colleagues warn that, in addition to adjusting our activity levels, we may have to alter our eating habits too, as 'energy expenditure is not necessarily tightly coupled to energy intake during relatively short-term exposure'.

While the energy budgets of obese humans are tipped so that they expend significantly less energy than they ingest, many other creatures' metabolic outputs are routinely stretched to the limit. But what imposes this limit? This is the question that has intrigued John Speakman at the University of Aberdeen, UK for much of the past decade. Working on mice, Speakman explains that the period when a lactating mother feeds her young is one of the most intense and sustained periods of metabolic output that any creature can endure. With Elzbieta Król, he tested whether the mothers were peripherally limited (by the sum of the maximum energetic outputs of all tissues) or limited by the amount of heat that they can dissipate (p. 230). Shaving the lactating mice, the duo found that the limit that had prevented the mothers from increasing their metabolic output beyond a certain level had risen, suggesting that the mother's ability to dissipate heat limited the amount of energy that she could expend. Speakman and Król say, 'the heat dissipation limit and peripheral limitations are likely to be important to all animals, but to different extents'.

Another factor that contributes to energy budgets is the production of metabolic heat through nonshivering thermogenesis. During World War II, mice were found to adapt to life in cold rooms. Brown fat was later identified as the source of nonshivering thermogenesis, which allowed the rodents to survive in the cold without shivering. Barbara Cannon and Jan Nedergaard from Stockholm University, Sweden explain that a mitochondrial protein, uncoupling protein 1 (UCP1), is the thermogenic protein (p. 242) that produces heat by discharging the mitochondrial proton gradient. Also, high fat diets trigger nonshivering thermogenesis, leading to the suggestion that the rodents could use brown fat to 'combust excess energy in the diet and thus not become obese'. More recently, the discovery that adult humans have brown fat has led to an increased interest in the role of nonshiverng thermogenesis in human metabolism and obesity. However, the duo raise concerns about the conclusions drawn from animal studies that are routinely conducted at temperatures below the animal's thermoneutral zone; i.e. at temperatures where diet-induced thermogenesis would not be revealed due to thermoregulatory thermogenesis. They recommend that future studies be conducted at the animals' thermoneutral temperatures (29–30°C) in order to 'identify agents and genes important for human energy balance'.

ASPECTS OF METABOLIC REGULATION

Metabolism is tightly regulated at many levels and, if disrupted, can lead to severe metabolic disorders such as insulin-resistant diabetes and cardiovascular disease. So, building an understanding of metabolic regulation is essential if we are to begin to combat many of the disorders that characterise metabolic syndrome and the obesity crisis. David Wasserman and colleagues at Vanderbilt University School of Medicine, USA discuss the control of glucose flux in muscle (p. 254). Describing the delivery of glucose to muscle tissue, transport in and glucose phosphorylation – which traps glucose in the muscle and completes the uptake process – Wasserman explains that glucose uptake is under distributed control by all three of these processes. Ultimately, the team hopes that 'one or more of these steps should be effective targets for treatment of glucose intolerance and insulin resistance'.

Considering the role of diffusion in metabolic processes, Stephen Kinsey and colleagues from the University of North Carolina, Wilmington and Florida State University, USA explain that 'metabolic processes are often represented as a group of metabolites that interact through enzymatic reactions'. However, they go on to add that diffusion may exert greater control over reaction rates as distances increase and reaction rates rise or diffusion coefficients decrease. Focusing on muscle fibres, which vary enormously in size, Kinsey and his colleagues discuss the effects of muscle fibre organisation and the intracellular environment on metabolic diffusion (p. 263) and conclude that 'metabolic processes in muscles… are not greatly limited by diffusion,' but add, 'the influence of diffusion is apparent in patterns of fibre growth and metabolic organization'.

Life in the cold has profound effects on metabolism for ectotherms. Kristin O'Brien from the University of Alaska Fairbanks, USA says, 'As temperature declines, one of the greatest challenges is maintaining the production of ATP'. One strategy for survival in frigid conditions is to increase the levels of enzymes involved in aerobic metabolism by increasing the volume of mitochondria in cells. O'Brien reviews the current understanding of the molecular pathways that govern mitochondrial molecular remodelling (p. 275). She also outlines the consequences of increased mitochondrial density, such as increased lipid densities, raised oxygen solubility and reduced diffusion distances. As well as increasing protein synthesis levels, O'Brien explains that cold-adapted fish also increase membrane synthesis rates, and she speculates about the signalling molecules that regulate the process of mitochondrial biosynthesis.

Animals also have to select which metabolic fuels they use in response to different energetic demands. Jean-Michel Weber from the University of Ottawa, Canada explains that each fuel type has different strengths and weaknesses. Lipids are light to transport and abundant but are insoluble in water and slow to produce ATP. Alternatively, carbohydrates can synthesise ATP rapidly but are heavy and scarce, so a particular fuel is only selected for use when its advantages outweigh its disadvantages. Weber explains that animals use a variety of strategies to optimise fuel use (p. 286), including AMPK regulation of fuel selection and the recruitment of specific muscle fibre types that metabolise the most appropriate fuel for a particular activity. Migrating animals that maintain intense exercise for days at a time must also be able to sustain record fluxes of fuel to their locomotory muscles. They do so by boosting lipid mobilisation, transport and oxidation to maximise aerobic ATP production during their marathon odysseys.

METABOLIC RESPONSES AND UNIQUE ENVIRONMENTAL ADAPTATIONS

After discussing the evolutionary implications of bioenergetics, energy budget management and regulation, the collection of reviews now turns to consider metabolic strategies employed by organisms in a wide range of environments.

Discussing the upper metabolic limits that animals can maintain for extended periods, Theunis Piersma from the University of Groningen, The Netherlands describes the extreme metabolic outputs maintained by polar explorers, athletes and long-distance migrants (p. 295). Explaining that trained human athletes can only maintain metabolic rates that are tens of times their basal metabolic rates (BMR) for a few seconds or minutes, Piersma points out that even polar explorers and Tour de France cyclists can only maintain metabolic rates that are 4–5 times their BMR over sustained periods. However, migrating shorebirds routinely exceed this apparent limit, expending 8–10 times their BMR as they cover thousands of kilometres to reach their breeding grounds. Explaining that the birds fuel these extreme endurance feats by breaking down their fat stores and even their own organs, Piersma suggests that shorebirds may be able to sustain these high-performance levels because they do not have to guard against predators and infection as these threats are minimal in the birds' native environments. He suggests that animals may have evolved 'laziness' to protect from potentially fatal metabolic and tissue damage incurred by extreme performance and says, 'there is scope for experimental studies in which relationships between energy expenditure levels, wear and tear and survival in well-described ecological contexts are investigated'.

So far, the collection has focused on metabolic energy expenditure by organisms, but energy must be taken in to balance the energy budget, and this must be acquired either by eating food or adopting a photosynthetic lodger; i.e. symbiosis. Mary Rumpho and colleagues from the University of Maine and Rutgers University, USA describe a 'solar-powered' sea slug, *Elysia chlorotica*, which consumes *Vaucheria litorea* and incorporates chloroplasts from the alga into cells lining the sea slug's digestive tract (p. 303). Living as a plant, the sea slug is provided with carbon and energy by the chloroplasts. However, Rumpho explains that chloroplast genomes 'encode a small percent of the predicted 1000–5000 proteins required to sustain the full metabolic capacity of the plastid,' and she suggests that long-term chloroplast function is sustained by a combination of unusual plastid stability, very limited horizontal gene transfer and, possibly, long-term maintenance of algal DNA, RNA and proteins in the sea slug.

Although most life forms on the planet's surface ultimately depend on the sun for energy, chemoautotrophs exploit alternative energy sources. Without access to the sun, some deep-sea hydrothermal vent species have struck up symbiotic relationships with chemoautotrophs. However, the hosts may pay a high metabolic price for this convenient relationship. 'Chemoautotrophy is very demanding of oxygen, and a previous study suggests that up to 80% of oxygen uptake is driven by symbiont metabolism,' say Jim Childress from the University of California, Santa Barbara and Peter Girgius from Harvard University, USA (p. 312). Measuring the oxygen consumption rates of the tube worm, *Riftia pachyptila*, and its symbionts, Childress and Girgius report that the symbiont consumes 13.5 times more oxygen than its host. Explaining that, 'the ability of the animal hosts to support these high oxygen demands is a critical determinant of the rates of carbon fixation that can be achieved,' the duo describe how *Riftia* delivers oxygen and hydrogen sulphide to the symbiont by high-affinity haemoglobin. They suggest that the high oxygen demands of chemoautotrophic symbionts have prevented cnidarians from striking up symbiotic relationships with chemoautotrophs.

Remaining on the theme of bioenergetics in the ocean, Brad Seibel from the University of Rhode Island, USA discusses the effects of oceanic oxygen minimum zones on the species that inhabit them (p. 326). Defining two critical oxygen thresholds – one threshold where all animals have to make specific adaptations in oxygen uptake to sustain metabolism and a second threshold that is the oxygen partial pressure below which animals cannot adapt to utilise oxygen – Seibel outlines the adaptations that permit organisms to inhabit oxygen minimum zones. Explaining that many creatures migrate daily to depth and pass though oxygen minimum zones, Seibel points out that climate change could drop oxygen levels below the level where midwater species can extract oxygen, resulting in a drastic ecosystem shift from ‘an ecosystem dominated by diverse midwater fauna to one dominated by diel migrant biota that must return to surface waters at night’.

Concluding the section on metabolic responses, Bente Pedersen from the University of Copenhagen, Denmark discusses the role of muscles in metabolic regulation (p. 337). Muscle is one of the major metabolic organs and it has long been appreciated that exercise protects against diseases of inactivity. Pedersen’s discovery of a cytokine produced by contracting muscle in 2000 was the first identification of the elusive ‘exercise factor’ that could regulate metabolic change in other organs in response to exercise. IL-6, the first of these so-called ‘myokines’, stimulates glucose uptake and fat oxidation in response to exercise, while IL-15 reduces visceral fat, which is a potential source of inflammation and is implicated in metabolic diseases such as type-2 diabetes, cardiovascular disease and several cancers. Pedersen concludes that ‘skeletal muscle is an endocrine organ producing and releasing myokines, which work in a hormone-like fashion, exerting specific endocrine effects on other organs,’ and adds that, ‘myokines may contribute to mediate exercise-induced protection against several chronic diseases’.

IN CONCLUSION

Having discussed bioenergetics from the impact of evolution on metabolism through to the regulation of energetics in response to multiple environmental factors, Suarez concludes that this collection of reviews will ‘demonstrate that the study of energy metabolism in animals continues to be relevant, exciting and fundamentally important’. Pointing out that energy metabolism responds to climate change and has to adapt in many organisms if they are to survive, Suarez adds that bioenergetics is also relevant to human health and welfare, affecting every aspect of our ecosystem at this time of rapid environmental change.

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