

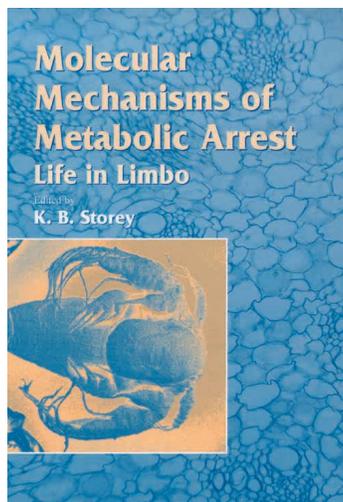
## Life in limbo

### Molecular mechanisms of metabolic arrest: life in limbo

Edited by K. B. Storey

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A wide variety of organisms possess the capacity to reversibly reduce metabolism, either in response to adverse environmental conditions or as a programmed part of their life cycle. A hallmark feature of metabolic arrest in these organisms is that there is little or no decrease in the structural or functional integrity of cells and tissues. The mechanisms used by these organisms to decrease metabolic rates and to

survive at these lower rates is a fascinating biological question. The book *Molecular mechanisms of metabolic arrest: life in limbo*, edited by K. B. Storey, attempts to tackle this question.

The book begins with several chapters that examine metabolic rate reduction during seasonal dormancy: hibernation in mammals; over-wintering in frogs and turtles; and summer dormancy (or estivation) in toads and snails. In the lead-off chapter, Storey reviews enzymatic correlates of metabolic depression during hibernation in ground squirrels and during estivation in the spadefoot toad. The activities of key metabolic enzymes are modulated by multiple regulatory mechanisms, including both post-translational modification (e.g. phosphorylation) and transcriptional control. In their chapter on mammalian hibernation, McCarron, Sieckmann, Yu, Frerichs, and Hallenbeck summarize evidence for plasma borne 'hibernation factors' and describe changes occurring in brain tissue that improve the tolerance of this tissue to low oxygen, low blood glucose, and low temperatures. This chapter also reviews a small number of genes whose expression changes during hibernation, focussing on an increase in the expression of the melatonin receptor measured in a variety of tissues. Perhaps, the authors contend, an increased sensitivity to melatonin is linked to either the induction or maintenance of hibernation. Both of these chapters cite identified genes whose levels are altered during hibernation or estivation. For some of these, the link between gene expression and metabolic reorganization during dormancy has been established; for others, this relationship has yet to be elucidated.

An excellent chapter by Brand, Boutilier, Wass, St-Pierre, and Bishop evaluates the contribution of mitochondrial proton leakage to the metabolism of dormant animals. Over the past decade, Brand and his colleagues have found that as much as 20–25% of the standard metabolic rate of a variety of animals can be accounted for by the futile cycling of proton pumping and leakage across the inner mitochondrial membrane. If the absolute energy expenditure due to proton cycling were to remain constant during dormancy, then this process could potentially account for all of the metabolic rate of animals whose metabolism is reduced by 80% or more. Concurrently, the efficiency of mitochondrial oxidative phosphorylation would approach zero, a situation that would seem to defeat the purpose of metabolic dormancy, i.e. preservation of energy reserves. Alternatively, this energetically costly process may be curtailed during dormancy, due to a lower proton conductance of the inner mitochondrial membrane, lower maximum rates of substrate oxidation, or a combination of both. Brand et al. examine these questions in over-wintering frogs and estivating snails. The rates of proton cycling in frog and snail tissues drop during metabolic dormancy, and experiments with isolated mitochondria suggest that the lower cycling is a result of lower rates of substrate oxidation rather than changes in proton conductance. These results are intriguing and provide insight into the general processes involved in metabolic suppression during dormancy.

Another remarkable example of metabolic suppression occurs in certain species of freshwater turtles during long-term winter submergence. Jackson addresses the contributions of low temperature and low oxygen to the profound reduction of metabolic rate during dormancy. This chapter also includes a brief consideration of aquatic respiration by turtles. In addition to a dramatic reduction in metabolism, these animals display an impressive tolerance of anoxia. Because the "typical" vertebrate nervous system is exquisitely sensitive to hypoxic injury, much attention has focused on the specializations of turtle neurons that confer such marked anoxia tolerance. In their contribution, Bickler, Donohoe, and Buck describe a decrease in the excitability and an increase in membrane resistance of turtle neurons under anoxia. Both processes serve to limit ion fluxes during anoxia, thereby reducing the energetic costs of ion homeostasis and prolonging cell survival. Bickler and colleagues present evidence that ion channel inactivation depends upon a modest elevation in intracellular  $\text{Ca}^{2+}$  during anoxia. These observations have led to the idea that specific levels of  $\text{Ca}^{2+}$  are associated with dramatically different consequences: large elevations of  $\text{Ca}^{2+}$ , as a result of uncontrollable calcium influx typical of anoxia-sensitive neurons, are ultimately toxic; small elevations of intracellular  $\text{Ca}^{2+}$ , as seen in turtle neurons, may be necessary to promote full protection and neuronal survival. This concept of 'Ca<sup>2+</sup> windows' may prove to be a fundamental insight into the ability of certain tissues to survive anoxia. A chapter by Ashcroft and Trapp on ATP-sensitive potassium channels also addresses ion homeostasis during metabolic transitions. This chapter presents

a detailed description of the structure and function of the channel from mammalian tissues. The mechanistic link between changes in metabolism and channel activity, however, remains elusive.

There are two chapters on how low oxygen affects thermostasis in organisms, i.e. the selection and maintenance of body temperature. Wood explores the ability of animals to lower body temperature, either through physiological or behavioral means, as a mechanism of metabolic rate reduction. Regulated hypothermia during hypoxia is widespread among animals, occurring in a variety of ectothermic and endothermic vertebrates, and several molecules have been examined as potential signaling agents for this response. In addition to a decrease in oxygen demand at lower temperatures, other advantages that may accrue from a lower body temperature are an increase in hemoglobin's ability to bind oxygen at the respiratory surfaces and a decrease in the hypoxic ventilatory response. Malvin extends the consideration of behavioral hypothermia as a strategy to cope with hypoxia to the protozoan *Paramecium caudatum*. In a thermal gradient, this unicellular organism selects a 'preferred' temperature and the temperature selected varies with environmental oxygen: lower temperatures are selected at lower oxygen tensions. This response has a marked effect on survival time during hypoxia. The widespread nature of regulated hypothermia, coupled with the dramatic survival benefits, should stimulate further inquiry into the molecular events responsible for this process.

There are also a pair of chapters on diapause, an endogenously programmed, metabolically dormant period that occurs at specific stages in the life cycle of several animals. Denlinger reviews diapause in insects and MacRae examines diapause in the brine shrimp *Artemia franciscana*. While in diapause, these organisms display incredible resistance to harsh environments (e.g. extreme temperatures, desiccation, anoxia). Surveys of gene expression have identified a handful of mRNA transcripts and protein products that are upregulated during diapause. These include the heat shock genes *hsp23* and *hsp70* in insects and *p26* in *Artemia*. These stress proteins presumably help prevent protein denaturation or stabilize partially denatured proteins during diapause. In certain insects, the proliferating cell nuclear antigen is up-regulated immediately following the termination of diapause, leading to the suggestion that this gene may be involved in resumption of cell division after diapause. In several insect examples, as well as in *Artemia*, whether an individual enters diapause is determined by the environmental conditions experienced by the mother. The molecular bases of these maternal effects is an exciting and fertile area for future research.

Rounding out the book are chapters on metabolic dormancy in yeast and plants. As described by Ruis, the molecular details of switching between various metabolic states in response to environmental changes are probably best described in the budding yeast, *Saccharomyces cerevisiae*. A wide array of stresses will induce a generalized stress response, mediated, in part, by the binding of transcription factors to stress-responsive elements in various genes. Protein kinase A (PKA) plays a pivotal role in determining the sensitivity of yeast to stress by negatively regulating these transcription factors. Interestingly, PKA also regulates cell growth and division, filamentous invasion, meiosis and sporulation, thereby coupling the stress response to changes in growth and reproductive mode. This fascinating chapter demonstrates the utility of a genetically tractable organism and illustrates the complexity of the molecular circuitry involved in changes in metabolic status of this organism. The final chapter by Bartels examines desiccation-induced dormancy in resurrection plants, a small and diverse group of plants that can withstand near complete dehydration (removal of >95% of tissue water). Measures of gene expression in dehydrated tissues have revealed a broad spectrum of genes whose expressions are altered relative to hydrated controls. Some of these confer desiccation resistance by stabilizing membranes and proteins, whereas others are involved in carbohydrate metabolism, water balance, signal transduction, and gene regulation.

The territory covered by this book is vast, due, in part, to the fact that metabolic dormancy is a widespread biological phenomenon. Furthermore, it is apparent from these pages that the bases of metabolic arrest are diverse, and range from changes in gene expression to behavioral temperature selection. A chapter summarizing this diversity would have been nice. The omission of such a chapter represents a missed opportunity to identify processes that unify the many examples of metabolic depression covered in this book. Although the scope of the book is a bit unwieldy, the individual chapters are engaging, enlightening, and point the direction for future research. It is clear that substantial progress has been made in understanding the mechanisms of metabolic arrest, but to quote closing words of the first chapter, 'much more remains to be learned about how nature turns down the fires of life'.

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