Chapter 3
Bioenergetics of the Stress Response

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Abstract Energy is a property of matter which obeys the two principles of thermodynamics: energy conservation within a given system and the general trend toward a higher degree of disorder, i.e., the concept of entropy (diminution of the amount of energy available within a given system). Chemical reactions in biological and biomolecular systems are based on a succession of energy transmission provided by redox reactions involving the exchange of electrons between the oxidized and the reduced organic substrates. The major energy source of all cells in aerobic organisms is adenosine triphosphate (ATP). Oxidation reactions in nutrients allow ATP synthesis by oxidative phosphorylation. The most common chemical reaction to produce energy in cells is the hydrolysis of ATP to ADP and inorganic phosphate. Before the formalization of the principles of thermodynamics, Antoine-Laurent de Lavoisier (1743–1794) has already anticipated the key principle of bioenergetics among living organisms: "Life is a slow combustion sustained by respiration. Animals are composed of fuel elements. The food replaces loss of substances arising from the combustion of matters present in the body." Indeed, living systems are open systems drawing their energy from substrates like nutrients. This is why living organisms are fundamentally different from inert material: biochemical reactions lead to an increase in energy availability, i.e., negative entropy. What has perhaps best characterizes a living system is the negative entropy to allow a dynamic and unstable balance between this open system and its environment. See from this thermodynamic perspective, homeostasis (degree of organization of the organism) is only the consequence of the accumulation of negative entropy. It should be therefore possible to consider the frontier between life and dying processes by estimating negative entropy. This opens up new prospects in fields like critical care medicine.

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3.1 Introduction

Energy is a property of matter which obeys the two principles of thermodynamics: energy conservation within a given system and the general trend toward a higher degree of disorder, i.e., the concept of entropy (diminution of the amount of energy available within a given system). Chemical reactions in biological and biomolecular systems are based on a succession of energy transmission provided by redox reactions involving the exchange of electrons between the oxidized and the reduced organic substrates. The major energy source of all cells in aerobic organisms is adenosine triphosphate (ATP). Oxidation reactions in nutrients allow ATP synthesis by oxidative phosphorylation. The most common chemical reaction to produce energy in cells is the hydrolysis of ATP to ADP and inorganic phosphate. Before the formalization of the principles of thermodynamics, Antoine-Laurent de Lavoisier (1743–1794) has already anticipated the key principle of bioenergetics among living organisms: "Life is a slow combustion sustained by respiration. Animals are composed of fuel elements. The food replaces loss of substances arising from the combustion of matters present in the body." Indeed, living systems are open systems drawing their energy from substrates like nutrients. This is why living organisms are fundamentally different from inert material: biochemical reactions lead to an increase in energy availability, i.e., negative entropy [26]. What has perhaps best characterizes a living system is the negative entropy to allow a dynamic and unstable balance between this open system and its environment. See from this thermodynamic perspective, homeostasis (degree of organization of the organism) is only the consequence of the accumulation of negative entropy. It should be therefore possible to consider the frontier between life and dying processes by estimating negative entropy. This opens up new prospects in fields like critical care medicine.

3.2 Cellular and Molecular Aspects: Toward New Paradigms

The survival of living organisms depends on the interactions with their environment to which they must adapt. As an open system, living organisms must maintain three functions or functional complexes: Physical composition (homeostasis), form or size (heterostasis), and permanence or temporal evolution (teleostasis) [18, 19, 21]. Homeostasis refers to the maintenance of the physicochemical characteristics like ion concentration, temperature, or pH. It is therefore the functions of the metabolism. According to the duality of energy–matter, anabolism refers to the assimilation and transformation of nutrients in own structures, whereas catabolism is the degradation of such structures to produce the energy required for the physiological functioning. The most important elements of metabolism are carbon, hydrogen, and oxygen, which represent the physical aspect of metabolism (Fig. 3.1). Indeed, these elements constitute carbohydrates and fats which are the major energy reserves (close to 100,000 kcal in healthy human). At the cell level, the metabolism ensuring homeostasis took place in the cytoplasm and is carried

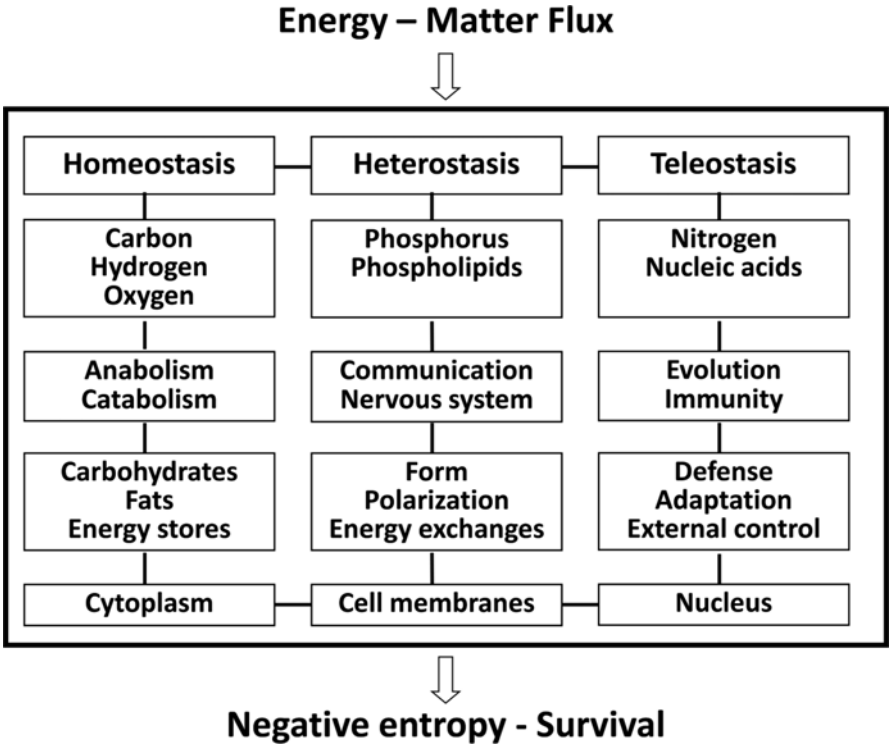

Fig. 3.1 Systemic model of functional integration: the three main biological functions. The black rectangle in bold represents a dissipative structure, i.e., a system open to its environment and traversed by a flux of energy or matter, increasing information and negative entropy into the system. Living organisms are dissipative structures

out by redox reactions (Fig. 3.1). Pertinently, indirect calorimetry, the "gold standard" for the assessment of resting energy expenditure in critically ill patients, merely measures energy produced by metabolism (first column in Fig. 3.1), but does not give direct information on the energy flows required to support the functions of heterostasis and teleostasis. This point may explain why the balance between energy expenditure and energy intakes is very difficult to estimate; thereby the aim of reducing energy deficit in critically ill patients cannot be achieved with the current methodology. All functions related to heterostasis (cross talk and environment delimitation) are provided at the cell level by the membrane, especially its polarization. The element phosphorus from membrane phospholipids plays a crucial role in the energy exchanges during polarization–depolarization processes. A typical example is the information transmission by nervous system. Teleostasis is the adaptation functions devoted to the evolution of living organisms, i.e., genetic and immunologic properties. At the cell level, this corresponds to the nuclear functions (nucleic acids). At the organ level, this corresponds to the reticuloendothelial system (Fig. 3.1). According to Ilya Prigogine (1917–2003), the conditions of

evolution by self-organization of matter depend on the three fundamental properties of the model of "functional integration": a complex structure, an environment providing energy, and an information integrating the system [21]. A dissipative system is a thermodynamically open system which is traversed by energy and matter flows. A portion of this energy is turned into information, i.e., it creates negative entropy [2, 26]. The dissipative systems self-organize in order to dissipate energy. From the thermodynamic perspective, determining the energy balance of critically ill patients would estimate the variation of a physical parameter corresponding to a dissipative system.

3.3 Energy Needs in the Critically Ill

Despite limitations related to the determination of energy expenditure by the exclusive estimation of energy from metabolism (see above), the current model used for establishing the global energy expenditure is the sum of the following components: Basal metabolism, thermic power of nutrients (digestion, absorption, and storage of carbohydrates, lipids, and proteins), thermoregulation, and physical activity [29]. Since the work of David Paton Cuthbertson (1900–1989) published in 1942, it is accepted that the metabolic response to stress in critically ill patients corresponds firstly to a hypometabolic "ebb" phase during the first 24–48 h, followed by a hypermetabolic "flow" phase [5]. Nevertheless, it is likely that many patients were already in the "flow" phase by the time they were admitted to ICU, and the modern fluid resuscitation would shorten the period of hypotension resulting in a short "ebb" phase [9, 30]. The magnitude and the duration of energy expenditure fluctuations are highly variable and influenced by the underlying disease, body composition, medications, or therapeutic procedures (sedatives, analgesics, curare, catecholamines, cooling, physiotherapy, and nursing), dietary carbohydrate-to-lipid ratio, and genetic factors [1, 6, 15, 23, 28, 29, 32, 33]. Similarly, substantial adjustments occur during denutrition, leading to a reduction of energy expenditure. To that must be added the effect of mechanical ventilation on oxygen consumption [16]. All these factors make estimating resting energy expenditure very complex in the critically ill. Another critical point is the estimation of the energy cost of metabolic interconversion of substrates, such as gluconeogenesis, ketogenesis, lipogenesis, or lactate production (any situation where the respiratory quotient is outside the range 0.7–1) [27]. For example, indirect calorimetry can only measure the total (or apparent) but not the real oxidation rate of glucose (Q_{ox}): Q_{ox} (total) = Q_{ox} (real) + Q_{ox} (lipogenesis) − Q_{ox} (gluconeogenesis). Interestingly, body cell mass, a component of the fat-free mass, is associated with oxygen consumption and resting energy expenditure [12, 13]. Body cell mass is altered by changes of nutritional status and the catabolic effects of disease. Therefore, development of clinical tools for evaluating body composition, especially body cell mass/weight ratio, could help demonstrate the relevance of the concept of energy balance by patients hospitalized in intensive care units (ICU) [8, 14, 25].

3.4 Energy Balance in the Critically Ill

Perturbations of the normal metabolic response to starvation with hyperglycemia, high lactate level, hypertriglyceridemia, and high level of nonesterified fatty acids due to insulin resistance characterize the hypermetabolic state of the critically injured patients [20, 22]. Energy deficit results from a combination of hypermetabolism and reduced intake due to frequent interruptions in feedings because of gastrointestinal intolerance and diagnostic and therapeutic procedures. In intubated and mechanically ventilated patients, the great variability of resting energy expenditure and nutrient delivery compared to prescription, partly due to frequent use of sedatives, analgesics, or vasoconstrictors, increases the risk of mismatch between energy requirements and intakes [9]. According to the current model used, energy balance corresponds to energy (calorie) really delivered minus resting energy expenditure. Total energy delivered must also take account of glucose infusions and propofol used for continuous sedation [29]. However, stored energy (adipose tissue, intramuscular triglycerides, and blood fatty acids or triglycerides) is ignored for the calculation of energy balance by using this method. From a thermodynamic point of view, it would be more appropriate to have a measurement tool integrating the overall energy dissipated by an individual patient.

3.5 Energy Deficit in the Critically Ill

Protein–energy malnutrition is commonly associated with impaired immune responses and affects the clinical course of some infections, such as pneumonia or bacteremia [3, 4, 24]. ICU patients are prone to develop early protein–energy deficit. The latter is associated with a higher rate of nosocomial infections, longer ICU stays, and higher healthcare costs. Energy deficit in ICU patients is mainly caused by reduced intake due to underprescribed calories and frequent feeding interruptions because of gastrointestinal intolerance or diagnostic and/or therapeutic procedures. Energy deficit results in an early energy gap during the first week of ICU stay, which is never overcome thereafter [31]. Cumulated energy deficit buildup during the first days of ICU stay appears to be an independent factor contributing to nosocomial infections [7, 10]. In addition, a large negative energy balance was observed during prolonged acute mechanical ventilation in the most critically ill patients and might affect their ICU outcomes. However, randomized intervention studies limiting energy deficit by combining parenteral nutrition with insufficient enteral nutrition have yielded conflicting results among ICU-acquired nosocomial infections [17]. Indeed, limiting early energy deficit in ICU patients might be reserved for those that are in a situation of chronic critical illness, i.e., patients with prolonged acute mechanical ventilation and severe energy deficits are likely to benefit most from preventive measures [7, 10].

3.6 A Dissipative System: Body Cell Mass

A dissipative system is a physical (inert or living) structure open to its environment and traversed by a flux of energy or matter. During its passage through the system, a fraction of this energy is transformed into information, creating negative entropy. The most obvious example is food consumption by living organisms. The energy flux through a dissipative structure is an increasing function of its information content [2, 21]. Therefore, per unit of mass, the energy expanded by the human brain is 5000 higher than the sun (Fig. 3.2). Body cell mass is the metabolically active compartment of fat-free mass that reflects the body's cellular components involved in oxygen consumption, carbon dioxide production, and resting metabolism. Body cell mass also interacts with energy stores (Fig. 3.3) and is altered by denutrition [11]. To

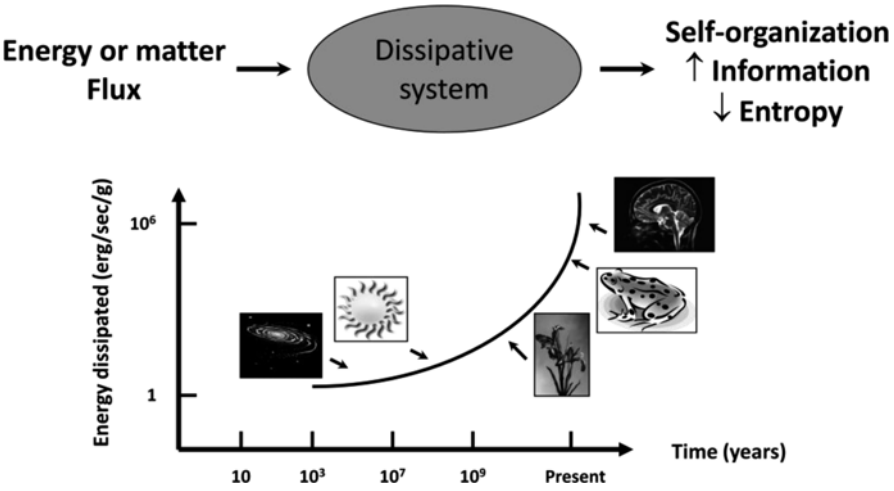

Fig. 3.2 Evolution of dissipative structures in the history from the universe (Adapted from [2, 21])

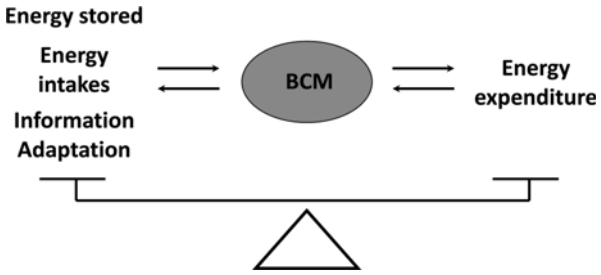

Fig. 3.3 Body cell mass (*BCM*) can be regarded as the reserve of negative entropy in living organisms. Estimating body cell mass would make it possible a thermodynamic approach of the nutritional assistance in critically ill patients

put in a simplified way, body cell mass corresponds to a dissipative system, i.e., a negative entropy reserve. Body cell mass could be a relevant tool for estimating nutritional status and prognosis in the critically ill patient, making it possible to override the uncertain estimate of energy balance by current models (Fig. 3.3).

Conflict of Interest The author has not disclosed any potential conflicts of interest.

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