Chapter 2
Successive Phases of the Metabolic Response to Stress

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Abstract The metabolic response to stress have been selected as an adaptive response to survive critical illness. Several mechanisms well preserved over the evolution, including the stimulation of the sympathetic nervous system, the release of pituitary hormones, a peripheral resistance to the effects of these and other anabolic factors are triggered to increase the provision of energy substrates to the vital tissues. After an acute insult, alternative substrates are used as a result of the loss of control of energy substrate utilization. The clinical consequences of the metabolic response to stress include sequential changes in energy expenditure, stress hyperglycemia, changes in body composition, psychological and behavioral problems. The loss of muscle proteins and function is a major long-term consequence of stress metabolism. Specific therapeutic interventions, including hormone supplementation, enhanced protein intake and early mobilization are investigated.

2.1 Introduction

The understanding and knowledge of metabolic response to critical illness has dramatically changed during the last decade, following several important discoveries in line with the findings of pioneering scientists of the nineteenth and twentieth

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century. In his theory of the evolution, Charles Darwin reported that "It is not the strongest or the most intelligent that survives. It is the most adaptable to change." This statement is particularly relevant after any life-threatening injury triggering a "critical illness," when survival in a hostile environment strongly relies on the ability to mount an appropriate adaptive response. In terms of the metabolic response to stress, the principle of homeostasis of Claude Bernard ("The constancy of the internal environment is the condition for a free and independent life") is highly relevant to the critically ill whose homeostasis must be restored as rapidly as possible to survive the injury. The mechanisms allowing the maintenance of homeostasis, vital functions, and ultimately survival in a hostile environment have been unraveled by Hans Selye, who described the "fight or flight" response, "a nonspecific response to a wide variety of stimuli." Sir David Cuthbertson described several phases of the metabolic response over time, including the ebb phase and the flow phase. A third sequence, the chronic phase, preceding recovery, was more recently suggested and is probably relevant to the post-injury phase frequently encountered in modern intensive care [1, 2]. The mechanisms of these successive adaptive changes mounted to survive a stress are increasingly understood and are now gathered into a general theory.

2.2 Pathophysiological Mechanisms

The metabolic response to stress involves a neuroendocrine and an inflammatory/immune component. Recent data suggest that hormones released from the adipose tissue and from the gastrointestinal tract can play an important role as well (Fig. 2.1).

The neuroendocrine component is triggered in a region located near the hypothalamus, paraventricular nucleus/locus coeruleus. When a stressor is detected and signaled to the central nervous system, a prototypical response will be triggered, resulting in the activation of the sympathetic nervous system (SNS), the hypothalamic-pituitary axis, and later by behavioral changes. Many different stressors can be sensed and transmitted; for instance, a peripheral tissular injury induced by a trauma will activate afferent nerves, hypoxemia or hypercapnia will trigger chemoreceptors, hypovolemia will activate baroreceptors, and inflammatory mediators will change the phenotype of microglial cells.

The SNS is involved in the fast control of most of the body's internal organs, via the activation of adrenergic receptors. After any stress, an immediate release of norepinephrine occurs from the postganglionic neuron in response to the stimulation of its nicotinic receptors by acetylcholine released from the preganglionic neurons [3]. The adrenal medulla is a functional sympathetic ganglion, where chromaffin cells release norepinephrine and epinephrine into the bloodstream upon stimulation by the preganglionic neuron.

The activation of the hypothalamus-pituitary axis results in the release of adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, and follicle-stimulating and follicle-luteinizing hormones by the anterior pituitary gland. The circulating levels of hormones released from peripheral glands in response to these

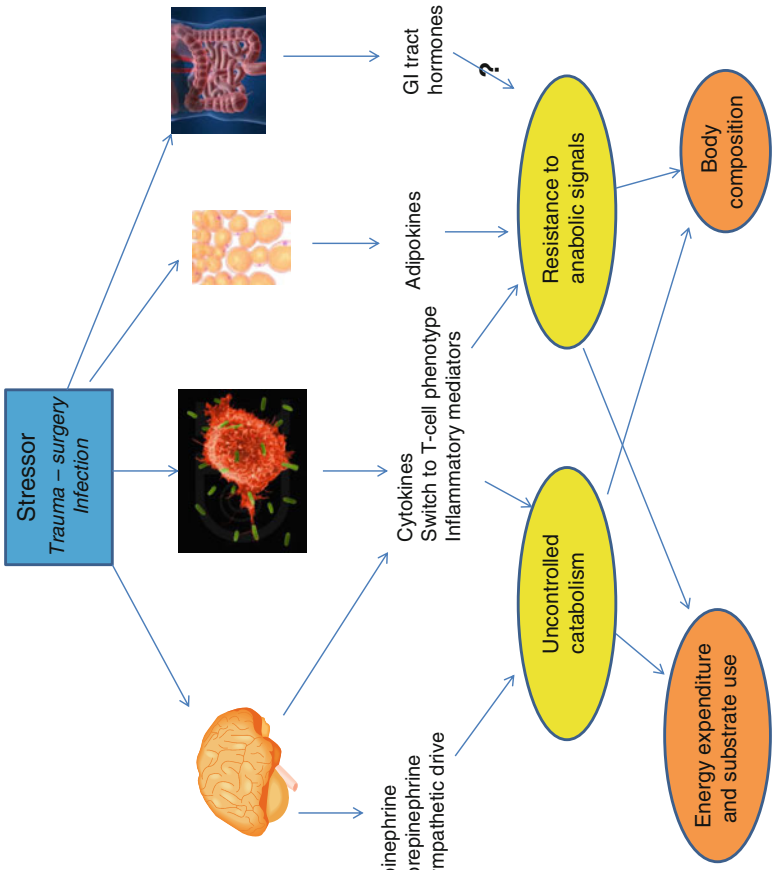

Fig. 2.1 Different levels of the metabolic response to stress. Once a stressor has been sensed, systems/organs are activated (first level). Mediators are released upon activation (second level). Physiological and phenotypical changes are triggered (third level)

pituitary factors are decreased, with the notable exception of cortisol. Peripheral inactivation of the active hormones is the likely mechanism [2], while recently reported alterations in the cortisol breakdown [4] could account for its increased concentration. During the chronic phase, the plasma levels of both pituitary factors and peripheral hormones are lowered, while a peripheral resistance to the effects of growth hormone, insulin, thyroid hormone, and cortisol persists. These hormonal alterations profoundly and sequentially affect the energy, protein, and fat metabolism. The metabolic response to stress thus depends on the time lag after the initial insult.

In addition to these well-characterized pathways, adipokines released from the different cell types of the fat tissue, including leptin, resistin, and adiponectin, are currently being investigated as potential contributors to the metabolic changes related to sepsis [5–8]. The role played by hormones released from the gut is also under scrutiny. Recent data reviewed by Deane et al. [9] indicate that the circulating levels of ghrelin are mostly decreased, while the levels of cholecystokinin and peptide YY are increased [10, 11]. These changes have been related to anorexia, a common feature of the behavioral adaptation to stress. Of note, the metabolic changes associated with adipokines and with the gastrointestinal hormones vary according to the clinical circumstances. The elucidation of the metabolic roles of these hormones requires more clinical research.

The inflammatory component is partially regulated at the level of the central nervous system, via cytokines and inflammatory mediators. The immune response of the host to an infection comprises an innate and a specific immune response. This latter response is subdivided into cell-mediated and humoral components, including antibodies and cytokines. These cytokines can impair some of the body's physiological functions. For example, tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 play pivotal roles in the metabolic changes associated with sepsis. In addition to typical clinical signs of sepsis (fever, lethargy), these cytokines also induce weight loss and increase proteolysis and lipolysis. In addition, these cytokines trigger anorexia at the hypothalamic level. Several other metabolic effects are indirectly exerted by cytokines via the activation of other cells [12, 13].

The final common pathway of the metabolic response to stress implies the development of a resistance to anabolic signals, including insulin, in order to reset the hierarchy of the delivery of energy substrates to prioritize vital tissues over the insulin-dependent organs, mainly fat and muscle [14, 15]. Therefore, insulin resistance is considered as an adaptive mechanism designed to provide enough glucose to the vital organs, unable to use other energy substrates in stress conditions [16, 17], which results in the inability to suppress central hepatic glucose production [14, 18] and to a decrease of insulin-mediated glucose uptake in the periphery. Insulin resistance is mediated through the reduction of post-receptor insulin signaling defects and downregulation of glucose transporter (GLUT)-4, especially in skeletal muscle. Moreover, impaired nonoxidative glucose disposal results from a reduction in skeletal muscle glycogen synthesis. Despite decreased insulin-mediated glucose uptake, there is an early increase in whole-body glucose uptake, primarily a result of cytokine-mediated upregulation of GLUT-1 [18].

The complexity of the metabolic response is further enhanced by the currently increasing prevalence of obesity and the (type of) metabolic and nutritional support

that is given and may either attenuate or aggravate some of the metabolic responses to stress. The latter depends, among others, on the level of feeding – under- and overnutrition – as well as, indirectly, the level of inflammation that is either evoked or attenuated by nutrition. Also preoperative fasting is a metabolic stress, and losses of energy and proteins following bleeding, hemofiltration, gastrointestinal dysfunction, and others may further compound the metabolic response to stress [19]. Some of the hormones released early from endocrine glands such as (nor)epinephrine, cortisol, thyroid hormone, and glucagon are clearly associated with hypermetabolism aimed at survival, whereas the later changes, with impaired production and/or increased resistance, are more likely adaptive and aimed at a long-term protection of the organism. The latter may, theoretically, be associated with mitochondrial changes, some type of hibernation, and a shutdown of excessive organ function and may thereby, together with an inflammatory response, herald development of multiple organ dysfunction syndrome [19]. Some of these chronic hormonal changes may, however, be regarded as maladaptive when contributing to ultimate mortality by increasing organ dysfunction, immunodepression, and wasting [20–25].

2.3 Clinical Consequences

The clinical consequences of the metabolic response to stress include several different aspects, from changes in resting energy expenditure, use of macronutrients as sources of energy, stress hyperglycemia, and changes in body composition to behavioral changes (Table 2.1 and Fig. 2.2).

2.3.1 Energy Expenditure (EE)

Traditionally, the EE is thought to be lower during the first ebb phase described by Cuthbertson. During the later flow phase, EE is considered to be higher than the EE predicted for a matched healthy subject [26–28]. During the third chronic phase of critical illness, EE decreases slightly. Kreymann et al. serially measured EE in patients with sepsis and septic shock and found lower values during severe sepsis

Table 2.1 Typical patterns of metabolic changes

	Usual patterns of change
Energy expenditure	Decrease (ebb phase or early phase) followed by increase (flow phase or late and recovery phases)
Use of energy substrates	Increased oxidation of carbohydrates, more than lipids/proteins Use of alternative substrates (lactate)
Stress hyperglycemia	Systematic
Changes in body composition	Decreased active cell mass Decreased fat-free mass, increased or unchanged fat mass
Behavior	Lethargy, anorexia

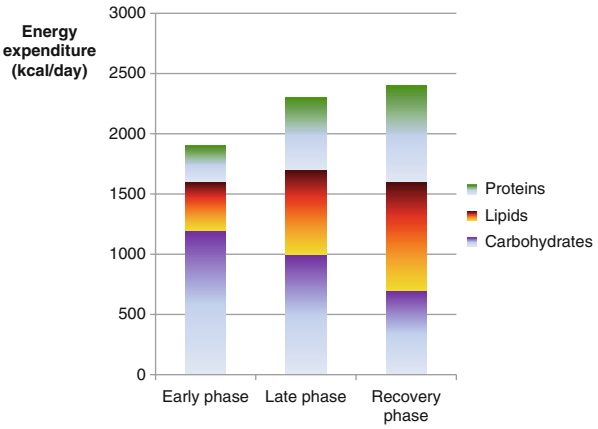

Fig. 2.2 Schematic representation of the three successive phases of the metabolic response to stress, depicting the changes in energy expenditure, and use of energy substrates occurring during the early, late, and recovery phases

[29]. Due to these temporal changes, the actual EE is extremely difficult to predict during critical illness [30]. Indeed, EE is influenced of several physiological derangements, such as fever of hypothermia, changes in heart rate, shivering, agitation, as well as by therapeutic interventions such as sedative agents, nonselective beta-blockers, and active cooling. The use of indirect calorimetry is the best way to assess EE, even though its use to guide the caloric prescription is debatable [31–34].

2.3.2 Use of Energy Substrates

The metabolism of macronutrients is altered at several levels, including the digestive absorption, the intracellular intermediate metabolism, and the oxidation of substrates.

Facing the increased requirements, the oxidation of macronutrients is largely increased during critical illness, and the relative contribution and metabolism of each type of macronutrient is regulated by the circulating hormones (Table 2.2). Overall, the oxidation of carbohydrates is globally more increased than the oxidation of lipids and proteins [35]. Later on, decreased glucose utilization, increased fat turnover, and loss of muscle and visceral (organ) protein mass with wasting occur. A negative nitrogen balance – pointing to increased protein breakdown over protein synthesis – is the ultimate result, even when reprioritization leads to an increased overall hepatic protein synthesis. Indeed, muscle may lose amino acids at the benefit of the liver. These changes are hardly amenable to any fruitful intervention to improve protein synthesis, attenuate lipogenesis, and thereby conserve lean body mass needed for rehabilitation.

Carbohydrates Glucose is the preferential energy substrate during critical illness and will be able to yield 2 ATP after anaerobic glycolysis and 36 additional molecules of ATP by the Krebs cycle when the mitochondrion is functional. At the whole-body level, changes in the metabolism of carbohydrates include the rapid

Table 2.2 Use of substrates during the successive phases

Macronutrient	Anabolic	Catabolic
Carbohydrates	Insulin	Cortisol Glucagon Growth hormone Catecholamines
Lipids	Insulin	Catecholamines
Proteins	Insulin Growth hormone – IGF-1 Testosterone Catecholamines	Cortisol Glucagon Catecholamines

utilization of the glycogen stores, followed by a high level of endogenous glucose production from lactate, glycerol, and alanine in the liver, the kidney, and the intestine [36, 37]. As the turnover of glucose is increased, plasma concentrations of glucose will rise, resulting in the typical stress hyperglycemia [18]. While nonoxidative metabolism (e.g., glycogen synthesis) is impaired, oxidative glucose metabolism is upregulated early [38]. Alterations in the digestion of dietary carbohydrates occur as well: once ingested, the long molecules of polysaccharides are cleaved into oligosaccharides (3–10 sugars) by the amylase enzymes. The resulting oligosaccharides will be cleaved by enzymes of the intestinal brush border. The activity of one of these enzymes, lactase, can be inhibited in the critically ill, thereby reducing the absorption of enteral carbohydrates [39].

Use of lactate as an alternative substrate Alteration of lactate metabolism is one of the prominent component of the metabolic stress response. Lactate is a physiological substrate (carbohydrate) issued from pyruvate reduction during glycolysis. In stable conditions, lactate production and elimination are equivalent, i.e., 1200–1500 mmol per day, leading to a stable blood lactate concentration of 0.8–1.2 mmol/L [40]. Most organs, except those without mitochondria, simultaneously release and take up lactate. As a result, the net flux of lactate depends on the difference between release and uptake and varies upon organs and their energetic condition [41]. In stable conditions, the brain, muscles, and digestive tract are producing lactate organs, whereas the liver is responsible for more than 70 % of lactate clearance. Lactatemia and lactate metabolism (turnover) are often confused. Lactatemia indicates an instantaneous equilibrium between total body lactate production and clearance. Accordingly, lactatemia can be in a normal value, while lactate turnover can be normal, high, or low, just indicating that there is an equilibrium between production and elimination.

Lactate, is a physiological intermediate energetic substrate. The Cori cycle (conversion of lactate into glucose) confirms the ability of lactate to serve as a very efficient interorgan shuttle, allowing to provide fuel useable by organs in various stress conditions [42]. For instance, red blood cells not equipped with mitochondria produce ATP only *via* an anaerobic glycolysis leading to lactate production, the latter being further metabolized in glucose in the liver in the presence of oxygen. Growing data support that these exchanges are favored during stress condition and that lactate "per se" is at least a useful if not an obligatory substrate used by organs

and tissues during energetic crisis conditions and has been particularly demonstrated to fuel the heart and brain.

At rest, the heart consumes energy issued for 60–90 % from fatty acids ß-oxidation. But in case of hypoxia such as during myocardial ischemia, increased O_2 consumption, or decreased O_2 delivery, metabolic pathways shift toward a preferential use of carbohydrate oxidation for ATP production [43]. The role of lactate as a myocardial fuel has been confirmed experimentally during septic and hemorrhagic shocks [44, 45].

Stress hyperglycemia The etiology of hyperglycemia in type 2 diabetes is a combination of insulin resistance and beta cell secretory defects [14, 18]. The development of stress hyperglycemia involves a much more dramatic, complex interplay of counterregulatory hormones such as catecholamines, growth hormone, and cortisol, and cytokine resulting in excessive hepatic glucose production (from gluconeogenesis and glycogenolysis) and insulin resistance. Increased hepatic output of glucose, particularly through gluconeogenesis, appears to be the most important contributor to stress hyperglycemia (see Chap. 8 for further discussion).

Numerous association studies [46, 47] confirm the presence of a U-shaped relationship between admission BG value and outcome, i.e., low and high BG are associated with poor outcome. An admission BG value of 5.5–6.1 mmol/L is associated with the lowest mortality rate. Similarly, high GV and low BG complexity are also associated with a worsened outcome.

Lipids The use of lipids as energy substrate is relatively less increased than carbohydrates, during critical illness [35]. Indeed, the conversion of lipids into ATP requires large amounts oxygen and functional mitochondria. During critical illness, endogenous triglycerides stored in the adipose tissue and exogenous triglycerides released from chylomicrons and other lipoproteins are avidly hydrolysed to release FFAs and glycerol into the bloodstream. In contrast to physiological conditions, this increased lipolysis cannot be efficiently inhibited by infusion of carbohydrates. The oxidation of FFAs is increased in peripheral tissues, while in the liver they are converted to ketone bodies or re-esterified to triglycerides and released into the bloodstream as very-low-density lipoprotein (VLDL), which is subject to impaired clearance. However, the production of FFAs from exogenous and endogenous triglycerides still exceeds the utilization of FFAs, and plasma FFA levels are typically increased in critically ill patients. Overall, the metabolism of lipids is increased, although complete oxidation can only be achieved in tissues where mitochondria are functional.

Proteins Under normal conditions, proteins are constantly broken down and replaced in a highly selective and closely balanced process. The majority of intracellular proteins are degraded via activation of the ubiquitin-proteasome pathway. In a series of enzymatic reactions, ubiquitin forms a chain on a protein to be degraded. Once tagged, the protein is recognized by a proteasome. The protein unravels and is injected into the central core of the proteasome where it is broken down into peptides.

Stress metabolism is characterized by over-activation of the ubiquitin-proteasome pathway that causes excessive protein degradation and muscle wasting.

Overall, the large increases in protein breakdown are partially balanced by increased protein synthesis (of inflammatory mediators). The amino acids released during the degradation of proteins will be either reused (cf. alanine, glutamine) or oxidized and will provide waste products: urea and ammonium. The nitrogen balance will be negative, with a rate of breakdown largely exceeding the rate of synthesis. Consequently, the stores of proteins, i.e., the skeletal muscles, will be rapidly depleted. These losses are related to the large wastage of muscles, which is involved in ICU-acquired weakness [48–52]. This is one of the most devastating consequences of the metabolic response to stress. A major complaint of patients who had a prolonged stay in an ICU is weakness, even a considerable time after discharge. In a study by Herridge et al., survivors of an acute respiratory distress syndrome had persistent muscle wasting and weakness 5 years after discharge from the ICU [48]. Thus, it is essential to take muscle function into consideration when assessing and monitoring the nutritional status of ICU patients.

2.3.3 Changes in Body Composition

The changes in body composition systematically found during critical illness include a loss of lean body mass and a relative preservation of the fat tissue [6]. As a result, body cell mass is typically decreased, while extracellular fluid is increased. Recently, functional and morphological changes of the fat tissue have been identified. These changes can be summarized as a preservation of the fat mass, with increased number of small adipocytes and increased infiltration of the fat tissue by macrophages [53]. Functionally, these changes result in increased lipid storage.

2.3.4 Psychosocial and Behavioral Problems

Long-term psychosocial and behavioral issues have been consistently reported in different cohorts of critically ill patients [54]. Some of these changes, such as prolonged catabolism, are clearly related to the metabolic response to critical illness. Behavioral changes, including anorexia, might be related to changes in the release of gastrointestinal hormones [10].

2.4 Therapeutic Implications

Generally speaking, hormone repletion in the chronic phase by exogenous administration, even though attempted in the past on numerous occasions, has not been successful in attenuation morbidity and mortality of the critically ill, even though successful from a metabolic point of view [55]. For instance, growth or

thyroid hormone suppletion may have anabolic effects by increasing protein synthesis and ameliorating protein breakdown in the critically ill but may even increase morbidity and mortality because of other unwanted effects [56–59]. Although insulin may have some albeit controversial anabolic effects and may help, by overcoming resistance and glucose control, the patient-centered outcome effects are highly controversial. Recently, expert guidelines recommend to avoid severe hyperglycemia, although an universally acceptable high limit to titrate insulin therapy cannot be defined [60–62]. Sex steroid hormones are still explored to increase anabolism [63]. Intervening with intermediary metabolism by administering (pharmacologic quantities of) substrates, often together with other nutritional supplements seemed promising in the last decades, but recent evidence suggests that this may be less helpful. For instance, glutamine supplementation of nutrition improved immunologic, gut function and protein metabolism, and even patient-centered outcomes in prior studies, but recent, large studies demonstrate that this may be associated with worse rather than better vital outcomes [64]. This is not to say that adequate nutrition lacks sufficient evidence in improving patient outcomes. Whatever route, quantities, or composition is chosen – these issues remain highly controversial – there is no doubt that prolonged starvation and resultant malnutrition in the critically ill substantially contribute to morbidity and mortality. The question, however, remains whether altered composition – branched chain amino acids, immunonutrition with L-arginine and glutamine, antioxidants, and others – is meaningfully contributing to altered utilization and metabolic processes, particularly in sepsis and trauma patients where metabolism is driven by underlying inflammatory and host defense mechanisms rather than by exogenous supply. Then, metabolic or nutritional support may have some cosmetic effects, including normalization of altered plasma and tissue amino acid and protein levels, but without large effects on gluconeogenesis from protein breakdown, protein synthesis and lean body mass, and even in the presence of hyperinsulinemia. Early mobilization and the avoidance of prolonged sedation are other daily therapeutic measures that are likely to attenuate catabolism.

Hence, other interventions include raising ambient temperature (to decrease energy-consuming heat production) and administering beta-blockers to attenuate sympathetic overstimulation, inflammation, and protein breakdown and to improve organ and muscle function, particularly in burns and sepsis [65, 66]. The latter is still under investigation and certainly not uniformly and routinely accepted. Animal studies suggest that gut-derived ghrelin has anabolic properties, and studying its administration in critically ill patients has been proposed, since circulating levels have been found to be increased or lowered depending on the phase of disease.

2.5 Conclusion

The metabolic response to stress is a complex combination of neurological, endocrine, immune, and inflammatory mechanisms which lead to multiple functional changes in each tissue of the body. A better understanding of the physiology of this

response is needed when the progresses of intensive care medicine allow the survival of patients whose adaptive metabolic mechanisms are developing. Therapeutic interventions need to account for the complexity and sequential pattern of the metabolic response to critical illness.

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