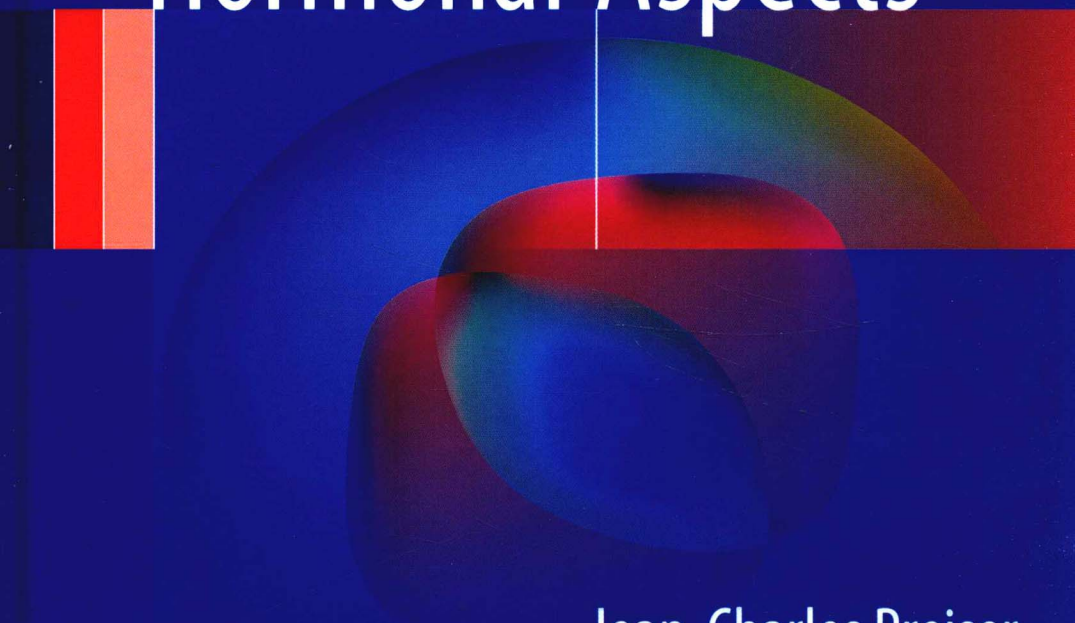
The Stress Response of Critical Illness: Metabolic and Hormonal Aspects



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Foreword

Life is like riding a bicycle. To keep your balance, you must keep moving.

Albert Einstein

All living organisms share common biological characteristics, developed over hundreds of millions of years, which have allowed them to adapt and survive since the beginning of life on earth. This is particularly true for human beings, so weak and frail before the occurrence of organized civilizations. The importance of effective adaptation abilities was recognized very long ago by the Chinese and Greek physicians, although it was not before the nineteenth and twentieth centuries that the real importance of the stress response with its complex multisystem mechanisms was discovered. Claude Bernard recognized the importance of a constant *milieu intérieur*, insuring the function of body cells in a changing environment via adaptive mechanisms in the vital organs. Later, Walther Cannon developed further the concept of *homeostasis*, leading in case of failure of the homeostatic mechanisms to disequilibrium and illness.

In 1936, Hans Selye published the historical Letter to the Editor of Nature, "A syndrome produced by diverse nocuous agents," describing stress as the consequence of an inadequate response to harmful physical and psychological agents. The stress response was originally believed to be mainly related to the neuroendocrine system activation, but Selye later realized that nearly all systems were involved and the concept of a multisystem general response was developed.

Although the clinical relevance of such adaptive mechanisms in trauma and acute conditions was long recognized, their long-term effects on the mood and behavior were not acknowledged before the second part of the twentieth century: the post-traumatic stress disorder was only included in 1980 in the third edition of the DSM of the American Psychiatric Association. This underlines the central role of the brain in the response to stress, as a regulation but also as a target organ, when its vulnerability to emotional and psychological challenges, exceeds its resilience capacity and induces undesirable emotional and behavioral symptoms.

In the field of stress response, the critical care environment is unique, since it gathers individuals with different kinds of stress: patients with life-threatening conditions, health-care professionals, mainly physicians and nurses, as well as family members. In the early phase of critical illness, the patients are submitted to acute challenges such as hemorrhage, ischemia, hypoxia, sepsis and pain, as well as psychological or emotional threats. The initial adaptation to the critical illness is mainly related to the multiple autonomic, endocrine, tissue, and immune mediators; it promotes survival and recovery. However, when the critical illness is prolonged, inadequate regulation of this response may occur, inducing damaging effects, such as depressed immunity, metabolic dysfunctions, and malnutrition. At longer term, patients with prolonged or complicated stay are at risk to develop post-traumatic stress disorder, mainly characterized by psychological, emotional, and behavioral symptoms.

The family is submitted to intense psycho-emotional stress, leading to adverse psychological responses, the so-called post-intensive care syndrome-family. The latter is mainly characterized by insomnia, anxiety, depressive symptoms, inability to perform the grief, and difficulty or inability to work. Surprisingly, the clinical importance of post-intensive care syndrome-family was only discovered about 20 year ago, despite quite a high prevalence: about a third of family members are affected by PTSD symptoms in both pediatric and adult ICUs. The process of decision making involving families and proxies plays a critical role, particularly the methods of communication and inclusion. Various strategies of communication with family members have shown to be associated with decreased anxiety, improved resilience, and coping.

In addition to emotional, psychological stress, the health-care givers are submitted to work-related stress, promoting burnout symptoms, as emotional and physical exhaustion, inability to work, depersonalization, and depression. The prevalence of PTSD in ICU nurses is particularly high, due to the daily contact with suffering, uncertainty of therapy, and death. This is also the case of health-care professionals working in emergency and mental health care, which in addition are often submitted to violence and physical assaults. The occurrence and severity of work-related stress is affected by several factors, the type, nature, and severity of the stressor, the presence of a team support, and the quality of professional training, as well as by individual factors, such as the individual personality, mental health, and social-family support.

The publication of *The Stress Response of Critical Illness: Metabolic and Hormonal Aspects* by Jean-Charles Preiser and more than 20 top-level scientists must be highlighted, since it constitutes a remarkable high level and original contribution. This book comes at a right stage, as a large body of recent information has brought new insights on the metabolic and endocrine aspects of the stress response during the last decade, such as the corticoadrenal response in sepsis, the regulation of blood glucose, and substrate metabolism in the settings of critical care.

Lausanne, Switzerland René Chioléro

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Chapter 1
Introduction

Jean-Charles Preiser

> The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them. William Henry Bragg

One of the most challenging tasks on earth is to bring people together and to build bridges to promote the cross-fertilization of knowledge!

In the field of care of the critically ill, this statement can be translated into the integration of new discoveries or major advances in the understanding of physiology into unbiased evaluations of new therapeutic strategies adapted from novel experimental findings. Conversely, basic science should be open to clinical data and able to understand and to integrate clinical concerns into research questions. This book aims to bridge the new knowledge gathered in experimental research with new clinical results.

Historically, the *"stress response"* was quoted by the Canadian physiologist Hans Selye, who discovered the mechanisms of the "fly or fight response" designed to restore the homeostasis needed for an independent life, as described by Claude Bernard. Some of the basic and adaptive mechanisms were preserved over the evolution, in keeping with the Darwinian theory of evolution.

Now, the changes and improvements in the practice of medicine allow patients to survive critical illness, allow surgeons to perform risky interventions, allow anesthesiologists to sedate very weak patients, etc. The support of the vital functions prolongs the lifespan of a critically ill thanks to improvements in pharmacological agents, in the technology of ventilators, renal replacement therapies, and extracorporeal membrane oxygenators. However, the metabolic and functional consequences of the critical illness can last weeks or months, representing a major burden for the society and cannot be supported by any dedicated device. Only a few drugs

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and nutritional formulas can slightly influence metabolism. Therefore, a detailed knowledge of the intimate mechanisms of the stress response is warranted to help clinicians to support the adaptive and desirable metabolic responses while trying to minimize the maladaptive ones.

In this book, several world-leading experts accepted to share their knowledge and to summarize the current understanding of the metabolic response to stress, including the cellular and subcellular mechanisms, the use of macro- and micronutrient as energy substrates during catabolism or anabolic resistance typically associated with critical illness. The roles and patterns of endocrine mediators will be discussed in detail. The final section will address difficult clinical situations, as examples of how the new findings can be translated into daily practice.

Specifically, in the first section, the bioenergetics of the stress response has been revisited in detail by C Faisy, using the concept of stress as a challenge to the equilibrium at each level of the body. The successive phases of the metabolic response to stress were being reviewed in a temporal and clinically relevant sequence. Novel insights as hibernation and mitochondrial mechanisms of adaptation have been updated by J Grip, N Tardif, and O Rooyackers, while the development of anabolic resistance has been reviewed by JP Thissen. The ensuing alterations in the use of lipids, carbohydrates, and protein metabolism were updated by Ph Calder, P Singer, L Tappy, A Norberg, F Liebau, and J Wernerman, whereas the current roles of micronutrients have been reviewed by MM Berger. A Thooft, R Machado, and myself summarized the related issue of stress hyperglycemia.

In Part 2, the current understanding of the functional changes of hormonal systems has been described by L Langouche and G Van den Berghe for the thyroid axis and P Marik for the adrenal system. The roles and relevance of new important endocrine mediators, the enterohormones released from the gastrointestinal tract, and the adipokines released from fat tissue have been reviewed by M Plummer, A Reintam, A Deane, K Robinson, J Prins, and B Venkatesh.

In Part 3, the clinical views and attitudes in situations accompanied by challenging metabolic alterations have been addressed. The issue of severe undernutrition was revisited by P Singer and J Cohen; the specificities of traumatic brain injury by H Quintard, C Ichai, and JF Payen; the particular aspects of sepsis and organ failures by V Fraipont and myself; morbid obesity by M Coeffier and F Tamion; and the issues related to burn injury by A Abdullahi, D Patsouris, SR. Costford, and MG Jeschke.

I would like to thank wholeheartedly each one of the authors who brought his own contribution and his personal stone to the huge enterprise of understanding the metabolic response to stress, an indispensable step to improve the quality of care and the quality of the lives of the survivors of critical illness.

Part I
Metabolic Changes

Chapter 2
Successive Phases of the Metabolic Response to Stress

Jean-Charles Preiser, Carole Ichai, and A.B. Johan Groeneveld

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

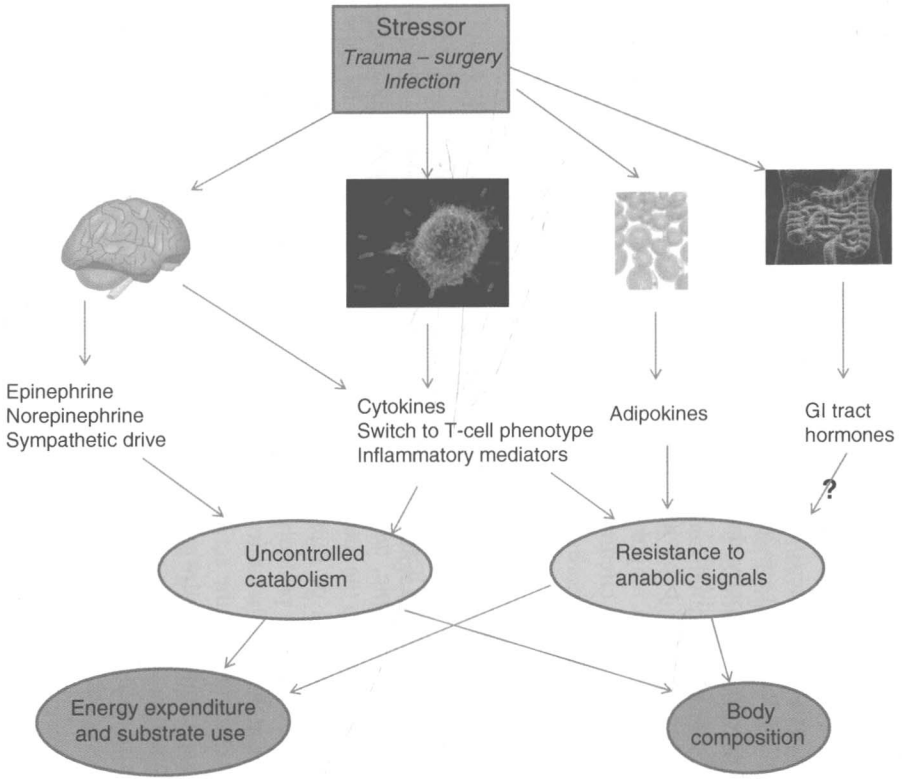

Fig. 2.1 Different levels of the metabolic response to stress. Once a stressor has been sensed, systems/organs are activated (first level). Mediators are released upon activation (second level). Physiological and phenotypical changes are triggered (third level)

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

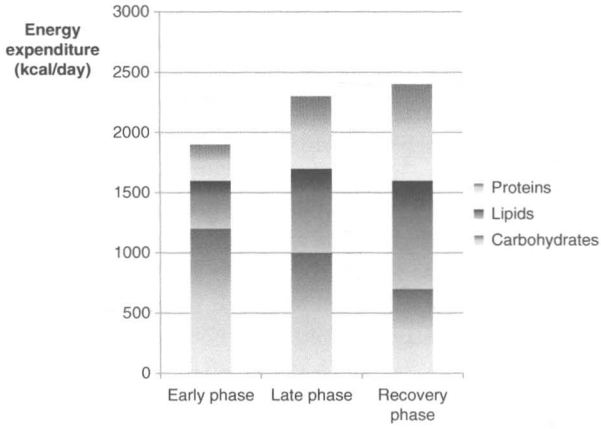

Fig. 2.2 Schematic representation of the three successive phases of the metabolic response to stress, depicting the changes in energy expenditure, and use of energy substrates occurring during the early, late, and recovery phases

[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