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Metabolic response to the stress of critical illness

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Editor's key points

- The metabolic response to stress is complex and involves multiple organ systems.
- In this review, the authors summarize the physiological changes, the clinical implications, and potential interventions to ameliorate the response.

The metabolic response to stress is part of the adaptive response to survive critical illness. Several mechanisms are well preserved during 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, triggered to increase the provision of energy substrates to the vital tissues. The pathways of energy production are altered and alternative substrates are used as a result of the loss of control of energy substrate utilization by their availability. The clinical consequences of the metabolic response to stress include sequential changes in energy expenditure, stress hyperglycaemia, changes in body composition, and psychological and behavioural 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. This review aims to summarize the pathophysiological mechanisms, the clinical consequences, and therapeutic implications of the metabolic response to stress.

Keywords: body composition; critically ill; energy expenditure; energy substrate; hormone supplementation; macronutrient; neuroendocrine response

The understanding and knowledge of metabolic response to critical illness has dramatically changed during the last decade, after several important discoveries in line with the findings of pioneering scientists of the 19th and 20th centuries. In his theory of evolution, Darwin postulated 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 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 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 unravelled by Hans Selye, who described the 'fight or flight' response, 'a non-specific 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 intensive care.[1] [2] The mechanisms of these successive adaptive changes are increasingly understood and are now gathered into a general theory of the metabolic response to stress. The
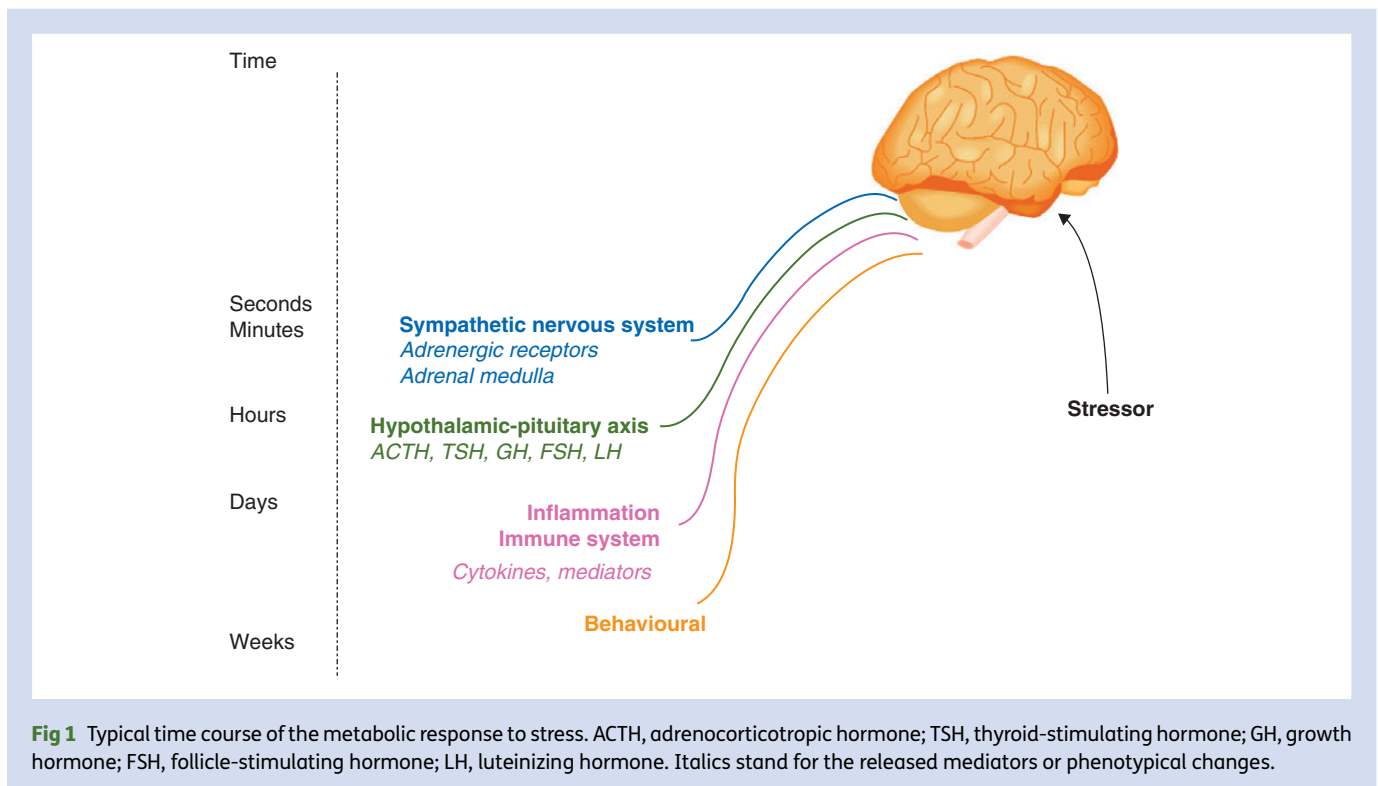
aim of this narrative review written for educational purposes is to summarize current insights into the pathophysiology, clinical consequences, and therapeutic implications of the metabolic response to stress.

Pathophysiology

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.

The neuroendocrine component is triggered in a region located near the hypothalamus, the paraventricular nucleus, and the locus coeruleus. When a stressor is detected and signalled to the central nervous system (Fig. 1), a prototypical response will be triggered, resulting in the activation of the sympathetic nervous system (SNS), the hypothalamic–pituitary axis, and later by inflammatory, immune, and behavioural changes. Many different stressors can be sensed and transmitted; for instance, a peripheral tissue injury induced by a trauma will activate afferent nerves, hypoxaemia or hypercapnia will trigger chemoreceptors, hypovolaemia will activate baroreceptors, and inflammatory mediators will trigger microglial cells in the brain.

The SNS is involved in the fast control of most of the body's internal organs, via the activation of adrenergic receptors (Fig. 1, blue line). After any stress, an immediate release of

Fig 1 Typical time course of the metabolic response to stress. ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; GH, growth hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone. Italics stand for the released mediators or phenotypical changes.

norepinephrine from the post-ganglionic neurone in response to the stimulation of its nicotinic receptors by acetylcholine released from the preganglionic neurones.[3] The adrenal medulla is a functional sympathetic ganglion, where chromaffin cells release norepinephrine and epinephrine into the bloodstream upon stimulation by the preganglionic neurone.

The activation of the hypothalamus–pituitary axis (Fig. 1, green line) results in the release of adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, follicle-stimulating hormone, and luteinizing hormone by the anterior pituitary gland. The circulating levels of hormones released from peripheral glands in response to these 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.

In addition to these well-characterized neuroendocrine 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 by the gut is also under scrutiny. Recent data[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 behavioural adaptation to stress. The metabolic changes associated with adipokines and with the gastrointestinal hormones vary according to the clinical circumstances. Clearly, 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 (Fig. 1, pink line). The immune response comprises an innate and a specific immune response. This latter response is subdivided into cell-mediated and humoral components, including the release of antibodies and cytokines. These cytokines can impair some of the body's physiological functions. For example, tumour necrosis factor, 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, 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] A new paradigm for the human immunological response to severe injury based on the pattern of gene expression by leucocytes after injury postulates that the early leucocyte genomic response is consistent with simultaneously increased expression of genes involved in the systemic inflammatory innate immune, and compensatory anti-inflammatory responses, and also simultaneous suppression of genes involved in adaptive immunity.[14]

Uncontrolled oxidative stress, defined by an imbalance between reactive oxygen species (ROS) generation and antioxidant levels, is likely to play an important role as well.[15] Acute inflammation, ischaemia–reperfusion, hypoxia, and hyperoxia

are involved in the abnormal enhancement of this phenomenon by increasing the production of ROS, by consuming the stores of antioxidants, or both. In turn, oxidative stress will increase the inflammatory response, which further increases the production of ROS like a vicious circle. The resulting imbalance between ROS and antioxidant defence mechanisms induces severe damage on essential structures such as protein, membrane lipids, carbohydrate, and DNA, which need subsequent repair.[16] Numerous studies have already shown the presence of an oxidative stress during shock, after cardiac arrest, or during acute respiratory distress with a proportional relationship between the magnitude of the oxidative stress and the severity of the condition.[17] [18]

Metabolic consequences

The final common pathway of the metabolic response to stress (Fig. 2) implies an uncontrolled catabolism and 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.[19] [20] Therefore, insulin resistance is considered as an adaptive mechanism designed to provide a

sufficient amount of glucose to the vital organs, unable to use other energy substrates in stress conditions,[21] [22] which results in the inability to suppress central hepatic glucose production[19] [23] and to a decrease in insulin-mediated glucose uptake in the periphery. The magnitude of insulin resistance has been correlated with the severity of condition.[24] Insulin resistance results from defects in the post-receptor insulin signalling pathways and from the down-regulation of glucose transporter (GLUT)-4, in skeletal muscle and fat tissue (Fig. 3). Impaired non-oxidative 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 up-regulation of GLUT-1.[23]

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 alter some of the metabolic responses to stress. The latter depends, among others, on the level of feeding—under- and overnutrition—and also, indirectly, the level of inflammation that is either evoked or attenuated by nutrition. Also, preoperative fasting is a metabolic stress[25] and losses of energy and proteins after bleeding, haemofiltration,
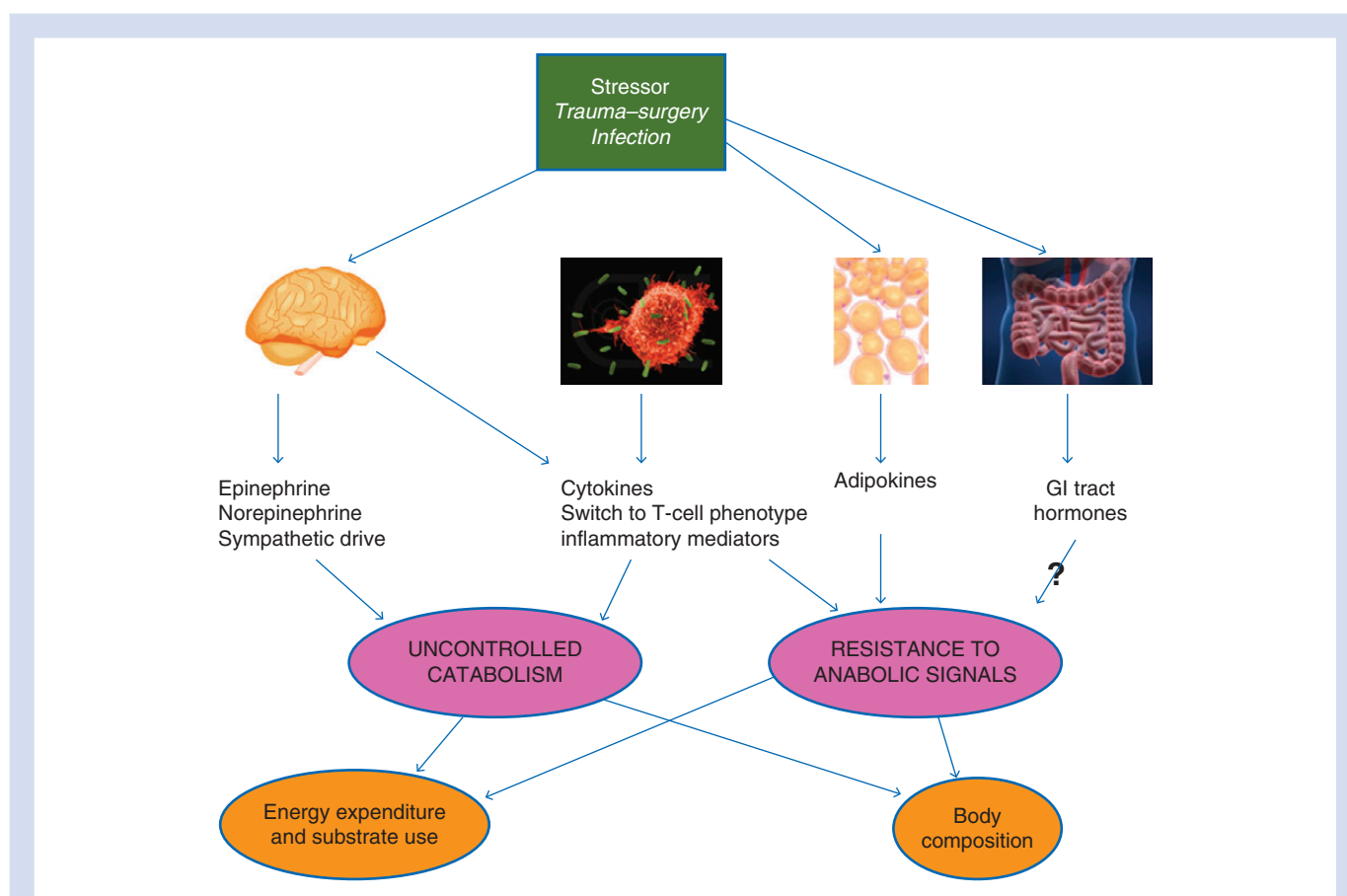

Fig 2 Different levels of the metabolic response to stress. Once a stressor has been sensed (green rectangle), systems/organs are activated. Mediators are released upon this activation and will increase catabolism and induce a resistance to anabolic factors (pink ovals), resulting in changes in EE, in the type of substrates used and in the body composition (orange ovals).
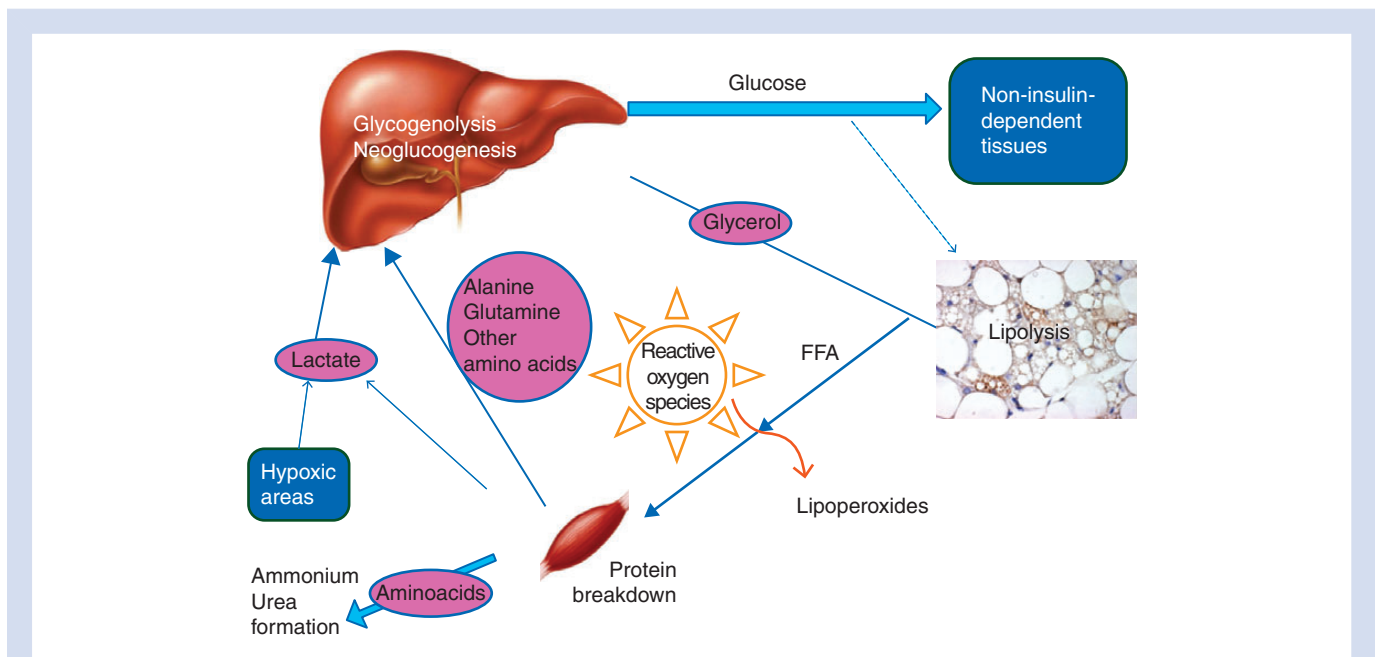
Fig 3 Metabolic changes during stress. The liver produces large amounts of glucose, from glycogenesis and neoglucogenesis. Glucose will be mainly used by non-insulin-dependent organs, while lipolysis will occur in fat tissue and proteolysis in muscles. FFA released by lipolysis are highly susceptible to peroxidation by the ROS massively released after stress-induced mitochondrial dysfunction. Glycerol released from lipolysis will be regenerated by the liver into glucose. Muscular proteolysis will release amino acids that will be recycled into glucose (mainly alanine and glutamine) or degraded into urea or ammonium. Lactate generated in hypoxic areas will be used by the liver to generate glucose by the Cori cycle.

gastrointestinal dysfunction, and others may further compound the metabolic response to stress.[26] Some of the hormones released early from endocrine glands such as (nor)epinephrine, cortisol, thyroid hormone, and glucagon are associated with hypermetabolism aimed at survival, whereas the later changes, with impaired production, increased resistance, or both, 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 a multiple organ dysfunction syndrome.[26] Some of these chronic hormonal changes may, however, be regarded as maladaptive when contributing to ultimate mortality by increasing organ dysfunction, immunodepression, and wasting.[27–31]

Mitochondria have strong links with oxidative stress as they handle oxygen. They have several essential functions including energy production.[32] During physiological oxidative phosphorylation, it is assumed that 1% of oxygen leads to ROS generation. During severe stress such as septic shock or cardiac arrest, mitochondria are injured due to nitrosative and oxidative stress resulting in damage to the mitochondrial DNA. This mitochondrial damage will result in decreased energy production, and ultimately multiple cellular functions, similarly to hibernation. The magnitude of mitochondrial dysfunction is correlated to prognosis in sepsis.[33] Interestingly, the ability to regenerate mitochondria via early biogenesis is associated with a better outcome,[34] suggesting a critical role for mitochondria to overcome cellular injury.

Clinical consequences

The clinical consequences of the metabolic response to stress include a wide array of aspects, from changes in metabolic rate, use of macronutrients as sources of energy, stress hyperglycaemia, muscle wasting, changes in body composition, and behavioural changes.

Energy expenditure

During the early post-injury phase, energy expenditure (EE) is usually lower than before the injury. During the later phases, EE increases to values higher than before the injury.[35 36] During the chronic phase of critical illness, the changes of EE are less typical. Owing to these temporal changes, the actual EE is extremely difficult to predict during critical illness.[37] Indeed, EE is not only influenced by several physiological derangements (fever, hypothermia, changes in heart rate, shivering, agitation), but also by therapeutic interventions such as sedative agents, non-selective β-blockers, and active cooling. Hence, a direct measurement of the EE by indirect calorimetry cannot be replaced by equations; however, the importance of an accurate knowledge of EE to guide the caloric prescription at the bedside is hotly debated.[38–41]

Use of energy substrates

A general feature of stress is the loss of control of the use of substrates by substrate availability (Fig. 4). In other words, the use of substrates in healthy subjects is largely determined by the composition of diet, and the time elapsed from the last
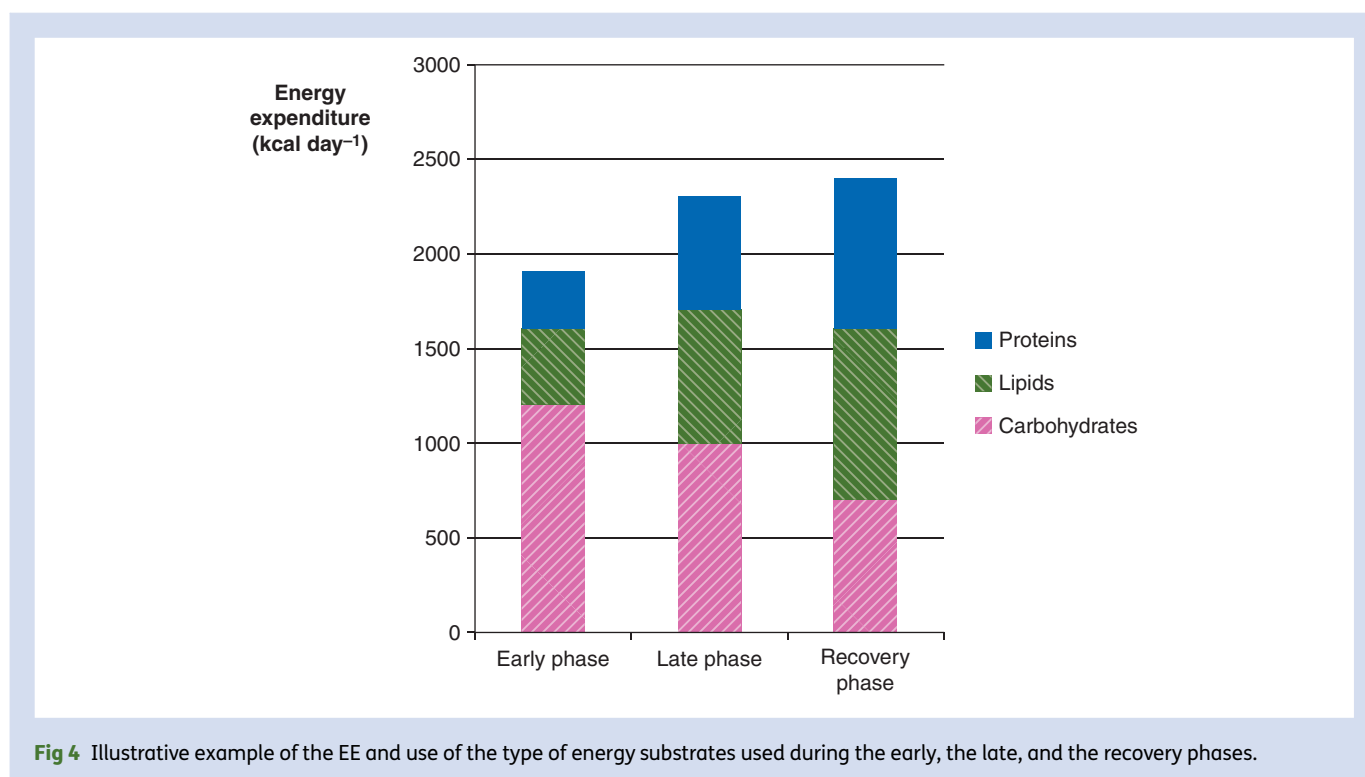
Fig 4 Illustrative example of the EE and use of the type of energy substrates used during the early, the late, and the recovery phases.

intake. In contrast, during critical illness, the use of energy substrates is mostly dictated by the use of endogenous stores controlled under the regulation of the various mechanisms described above. Indeed, the metabolism of macronutrients is altered at several levels during critical illness, including the digestive absorption, the intracellular intermediate metabolism, and the oxidation of substrates. Overall, the oxidation of carbohydrates is globally more increased during the early phase than the oxidation of lipids and proteins.[42] 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. When increasing nitrogen intake while maintaining calorie load unchanged, or changing only the composition of nitrogen carriers, the supply of essential amino acids could became inadequate. In both cases, the net protein utilization decreases and urea production increases.

Carbohydrates

Glucose is the preferential energy substrate during critical illness, and will be able to yield two ATP after anaerobic glycolysis and 36 additional molecules of ATP by the Krebs cycle when the mitochondrion is fully functional. At the whole-body level, changes in the metabolism of carbohydrates include the rapid 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.[43 44] As the turnover of glucose is increased, plasma concentrations of glucose will increase, resulting in the typical stress hyperglycaemia.[18] While non-oxidative metabolism (e.g. glycogen synthesis) is impaired, oxidative glucose metabolism is up-regulated early.[45] 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.[46]

Stress hyperglycaemia

The aetiology of hyperglycaemia in type 2 diabetes is a combination of insulin resistance and β-cell secretory defects.[15 19] The development of stress hyperglycaemia involves a much more complex interplay of counter-regulatory 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 hyperglycaemia. Numerous association studies[47 48] confirm the presence of an U-shaped relationship between admission blood glucose value and outcome, that is, low and high blood glucose values are associated with poor outcome. An admission blood glucose value

of 5.5–6.1 mmol litre^{-1} is associated with the lowest mortality rate. Similarly, high glucose variability and low blood glucose complexity are also associated with a worse outcome.

Use of lactate as an alternative substrate

Alteration of lactate metabolism is one of the prominent components of the metabolic stress response. Lactate is a physiological substrate issued from pyruvate reduction during glycolysis. In stable conditions, lactate production and elimination are equivalent, that is, 1200–1500 mmol day^{-1}, leading to a stable blood lactate concentration of 0.8–1.2 mmol litre^{-1}.[49] 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.[50] In stable conditions, the brain, muscles, and digestive tract are producing lactate, whereas the liver is responsible for more than 70% of lactate clearance. Plasma lactate concentration and lactate metabolism (turnover) are often confused. Plasma lactate concentration indicates an instantaneous equilibrium between total body lactate production and clearance. Accordingly, lactate concentration can be within a normal range, while lactate turnover can be normal, high, or low, 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.[49] 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 favoured 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 by β-oxidation. However, in the case of hypoxia such as during myocardial ischaemia, increased O$_2$ consumption, or decreased O$_2$ delivery, metabolic pathways shift towards a preferential use of carbohydrates oxidation for ATP production.[51] The role of lactate as a myocardial fuel has been confirmed experimentally during septic and haemorrhagic shock.[52 53]

Lipids

The use of lipids as energy substrate is relatively less increased than carbohydrates, during the early phase of critical illness[42] (Fig. 4). Indeed, the conversion of lipids into ATP requires large amounts oxygen and fully functional mitochondria. These conditions are hardly met early after injury as tissue hypoxia and mitochondrial dysfunction are common. These alterations explain why an increase in the proportion of lipids will not result in higher lipid oxidation rate.[42] In addition, endogenous triglycerides stored in the adipose tissue and exogenous

triglycerides released from chylomicrons and other lipoproteins are avidly hydrolysed to release free fatty acids (FFA) and glycerol into the bloodstream during critical illness, regardless of the amount of exogenous lipids provided.[54–56] This increase in lipolysis cannot be efficiently inhibited by infusion of carbohydrates or exogenous lipids. During the acute phase, the production of lipid peroxides is increased as well and likely contributes to the perpetuation of organ damage,[28–31] as a result of the imbalance between the increased lipolysis and the maximal rate of use of FFAs. Later on, the oxidation of FFAs can be increased in peripheral tissues, while in the liver, these are converted to ketone bodies or re-esterified to triglycerides and released into the bloodstream as very-low-density lipoprotein, which is subject to impaired clearance. Plasma FFA levels are typically increased in critically ill patients over the first few days. Overall, the metabolism of lipids is increased, although complete oxidation can only be achieved in tissues where mitochondria are functional. Finally, cholesterol synthesis and turnover are impaired.

Proteins

Under normal conditions, proteins are constantly broken down and replaced in a highly selective and closely balanced process. In contrast, after stress, the protein breakdown is largely increased and largely exceeds the rate of protein synthesis, under the influence of hormones and inflammatory mediators. The majority of intracellular proteins are degraded via activation of the ubiquitin–proteasome pathway.[57 58] 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 overactivation of the ubiquitin–proteasome pathway, which causes excessive protein degradation and muscle wasting. Overall, the large increases in protein breakdown are partially balanced by increased synthesis of inflammatory mediators. The amino acids released during the degradation of proteins will be either re-used by the neoglucogenic organs (mainly alanine, glutamine, Fig. 3) or oxidized and will provide urea and ammonium as waste products (Fig. 3). The nitrogen balance will be negative, reflecting the difference between the rate of breakdown and the rate of synthesis. Body composition studies have shown that up to 5% of lean body mass can be lost every day.[59 60] Consequently, the skeletal muscles will be rapidly depleted. These losses are related to the large wastage of muscles, which is involved in intensive care unit (ICU)-acquired weakness.[61–63] 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.[64] In a study by Herridge and colleagues,[61] survivors of an acute respiratory distress syndrome had persistent muscle wasting and weakness 5 yr after discharge from the ICU. The loss of muscle function and bulk, proximal weakness, and fatigue

are the most frequent long-term complaints of patients who have received prolonged mechanical ventilation. Even after 5 yr, significant functional disability was present in survivors of the acute respiratory distress syndrome, as assessed by the 6 min walking distance and the physical functioning section of the Short Form 36 Health Survey (SF-36) questionnaire.[3]

Changes in body composition

As a result of the various mechanisms triggered by stress, some changes of body composition are systematically found during critical illness, including a loss of lean body mass and a relative preservation of the fat tissue.[6 59 60] 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.[65] Functionally, these changes result in increased lipid storage.

Psychosocial and behavioural problems

Long-term psychosocial and behavioural issues have been consistently reported in different cohorts of critically ill patients.[66] Some of these changes, such as prolonged catabolism, are clearly related to the metabolic response to critical illness. Behavioural changes, including anorexia, might be related to changes in the release of gastrointestinal hormones.[10 67]

Therapeutic implications

In addition to appropriate nutrition, two types of therapeutic interventions can be suggested to modulate the metabolic response to stress: (i) hormone repletion (including insulin) and (ii) strict limitation of the use of treatments whose adverse effects are likely to aggravate the metabolic derangements induced by the stress response.

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 of morbidity and mortality of the critically ill, even though successful from a metabolic point of view.[68] For instance, growth or thyroid hormone supplementation 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.[69 70] Although insulin may have some albeit controversial anabolic effects and may help, by overcoming resistance, glucose control, the patient-centred outcome effects are highly controversial. After consistent stress (major surgery, injury, and in severe burn), insulin-mediated euglycaemia was found useful, as it improved insulin sensitivity, stimulated protein synthesis in skeletal muscle, and inhibited proteolysis in extramuscular tissues, presumably within the splanchnic region. Moreover, as in healthy subjects, euglycaemia increases muscle *de novo* glutamine synthesis leading to

greater glutamine systemic availability.[71–73] Recently, expert guidelines recommend to avoid severe hyperglycaemia, although an universally acceptable high limit cannot be defined.[74 75] Sex steroid hormones are still explored to increase anabolism.[76] Intervening with intermediary metabolism by administering (pharmacological quantities of) substrates seemed promising in the last decades, but recent evidence suggests that this may be less helpful. For instance, glutamine supplementation of nutrition improved immunological, gut function and protein metabolism and even patient-centred outcomes in prior studies, but recent, large studies demonstrate that this may be associated with worse rather than better vital outcomes.[77] 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 under-nutrition in the critically ill contributes to morbidity and mortality. The question, however remains, whether altered composition—branched chain amino acids, immune-nutrition with L-arginine and glutamine, antioxidants—is contributing to altered utilization and metabolic processes. In addition, each change for a single nutrient may result in an imbalance of the overall diet. 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, even in the presence of hyperinsulinaemia. Early mobilization and the avoidance of prolonged sedation are other daily therapeutic measures that are likely to attenuate catabolism.

Hence, other intervention includes increasing ambient temperature (to decrease energy-consuming heat production) and administering β-blockers to attenuate sympathetic overstimulation, inflammation, and protein breakdown, and to improve organ and muscle function, particularly in burns and sepsis.[78 79] The latter is still under investigation and certainly not uniformly and routinely accepted. Animal studies suggest that ghrelin has anabolic properties and could hence be studied during critical illness.

As oxidative stress is associated with a poor prognosis, different interventions were initiated to mitigate it. Most potential effective therapies prescribed in patients rely on enteral or parenteral antioxidant administration. The heterogeneity of patients and protocols led to conflicting results of individual trials and meta-analyses. The REDOXs study[77] evaluated the effects of an antioxidant cocktail on severely ill patients. This antioxidant association had no effect on mortality and secondary endpoints. However, the appropriate dose, combination, and clinical settings for which antioxidants could improve outcome are largely unknown.[28] New mitochondria-targeted antioxidant molecules could be more effective and seem promising modern therapies.

The failures of recent therapeutic trials using modulators of the metabolic response could be related to the complexity of the metabolic response, but also to the diversities of the pathophysiology of various diseases. The metabolic responses of

critically ill patients to stresses would be different according to the type of diseases, and thus, the specific pathophysiology of various diseases and the subsequent metabolic responses to therapeutic interventions during specific conditions should be separately evaluated in future studies. Hence, to prevent the failure of clinical trials, the mechanism, feasibility, and safety of candidate materials should be fully evaluated by well-conducted preclinical studies using clinically relevant models.

Conclusion

The metabolic response to stress is the result of a complex combination of mechanisms leading to multiple functional changes in each type of tissue. A better understanding of the physiology of this response is needed if continuing intensive care will allow the survival of patients whose adaptive metabolic mechanisms are developing. Therapeutic interventions need to account for the complexity and sequential patterns of the metabolic response to critical illness.

Declaration of interest

None declared.

References

1 Jeevanandam M, Shamos RF, Petersen SR. Substrate efficacy in early nutrition support of critically ill multiple trauma victims. *J Parenter Enteral Nutr* 1992; **16**: 511–20

2 Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab* 1998; **83**: 1827–34

3 Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. *Ann Neurol* 1987; **21**: 438–43

4 Boonen E, Vervenne H, Meersseman P, *et al.* Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013; **368**: 1477–88

5 Koch A, Gressner OA, Sanson E, Tacke F, Trautwein C. Serum resistin levels in critically ill patients are associated with inflammation, organ dysfunction and metabolism and may predict survival of non-septic patients. *Crit Care* 2009; **13**: R95

6 Marques MB, Langouche L. Endocrine, metabolic, and morphologic alterations of adipose tissue during critical illness. *Crit Care Med* 2013; **41**: 317–25

7 Hillenbrand A, Weiss M, Knippschild U, Wolf AM, Huber-Lang M. Sepsis-induced adipokine change with regard to insulin resistance. *Int J Inflam* 2012; **2012**: 972368

8 Fantuzzi G. Adiponectin and inflammation. *Am J Physiol Endocrinol Metab* 2009; **296**: E397.

9 Deane A, Chapman MJ, Fraser RJL, Horowitz M. Bench-to-bedside review: the gut as an endocrine organ in the critically ill. *Crit Care* 2010; **14**: 228

10 Nematy M, O'Flynn JE, Wandrag L, *et al.* Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study. *Crit Care* 2006; **10**: R10

11 Nematy M, Brynes AE, Hornick PI, *et al.* Postprandial ghrelin suppression is exaggerated following major surgery; implications for nutritional recovery. *Nutr Metab (Lond)* 2007; **4**: 20

12 Losser MR, Damoisel C, Payen D. Bench-to-bedside review: glucose and stress conditions in the intensive care unit. *Crit Care* 2010; **14**: 231

13 Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. *World J Surg* 2000; **24**: 630–8

14 Xiao W, Mindrinos MN, Seok J, *et al.* A genomic storm in critically injured humans. *J Exp Med* 2011; **208**: 2581–90

15 Preiser JC. Oxidative stress. *J Parenter Enteral Nutr* 2012; **36**: 147–54

16 Huet O, Dupic L, Batteux F, *et al.* Postresuscitation syndrome: potential role of hydroxyl radical-induced endothelial cell damage. *Crit Care Med* 2011; **39**: 1712–20

17 Motoyama T, Okamoto K, Kukita I, Hamaguchi M, Kinoshita Y, Ogawa H. Possible role of increased oxidant stress in multiple organ failure after systemic inflammatory response syndrome. *Crit Care Med* 2003; **31**: 1048–52

18 Alonso de Vega JM, Díaz J, Serrano E, Carbonell LF. Oxidative stress in critically ill patients with systemic inflammatory response syndrome. *Crit Care Med* 2002; **30**: 1782–6

19 Lena D, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. *Anesthesiology* 2011; **114**: 438–44

20 Biolo G, Grimble G, Preiser JC, *et al.* European Society of Intensive Care Medicine Working Group on Nutrition and Metabolism. Position paper of the ESICM Working Group on Nutrition and Metabolism. Metabolic basis of nutrition in intensive care unit patients: ten critical questions. *Intensive Care Med* 2002; **28**: 1512–20

21 Soeters MR, Soeters PB. The evolutionary benefit of insulin resistance. *Clin Nutr* 2012; **31**: 1002–7

22 Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care* 2013; **17**: 305

23 Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798–80

24 Mowery NT, Dortch MJ, Dossett LA, *et al.* Insulin resistance despite tight glucose control is associated with mortality in critically ill surgical patients. *J Intensive Care Med* 2009; **24**: 242–51

25 Ljungqvist O, Jonathan E. Rhoads lecture 2011: insulin resistance and enhanced recovery after surgery. *J Parenter Enteral Nutr* 2012; **36**: 389–98

26 Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated metabolic response to overwhelming systemic inflammation. *Lancet* 2004; **364**: 545–8

27 Siegel JH, Cerra FB, Coleman B, *et al.* Physiological and metabolic correlations in human sepsis. *Surgery* 1979; **86**: 163–93

28 Wilmore DW. Metabolic response to severe surgical stress: overview. *World J Surg* 2000; **24**: 705–11

29 Kyle UG, Jolliet P, Genton L, *et al.* Clinical evaluation of hormonal stress state in medical ICU patients: a prospective blinded observational study. *Intensive Care Med* 2005; **31**: 1669–75

30 Donatelli F, Corbella D, Di Nicola M, *et al.* Preoperative insulin resistance and the impact of feeding on postoperative protein balance: a stable isotope study. *J Clin Endocrinol Metab* 2011; **896**: E1789–97

31 Hoffer LJ, Bistrian BR. Why critically ill patients are protein deprived. *J Parenter Enteral Nutr* 2013; **37**: 300–9

32 Cuesta JM, Singer M. The stress response and critical illness: a review. *Crit Care Med* 2012; **40**: 3283–9

33 Brealey D, Brand M, Hargreaves I, *et al.* Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet* 2002; **360**: 219–23

34 Carré JE, Orban JC, Re L, *et al.* Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med* 2010; **182**: 745–51

35 Kreymann G, Grosser S, Buggisch P, Gottschall C, Matthaei S, Greten H. Oxygen consumption and resting metabolic rate in sepsis, sepsis syndrome, and septic shock. *Crit Care Med* 1993; **21**: 1012–9

36 Uehara M, Plank LD, Hill GL. Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. *Crit Care Med* 1999; **27**: 1295–302

37 Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. *J Parenter Enteral Nutr* 2013; **37**: 705–13

38 Vincent JL, Preiser JC. When should we add parenteral to enteral nutrition? *Lancet* 2013; **381**: 354–5

39 Heidegger CP, Berger MM, Graf S, *et al.* Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* 2013; **381**: 385–93

40 Casaer MP, Mesotten D, Hermans G, *et al.* Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; **365**: 506–17

41 Schetz M, Casaer MP, Van den Berghe G. Does artificial nutrition improve outcome of critical illness? *Crit Care* 2013; **17**: 302

42 Tappy L, Schwarz JM, Schneiter P, *et al.* Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. *Crit Care Med* 1998; **26**: 860–7

43 Watford M. Is the small intestine a gluconeogenic organ. *Nutr Rev* 2005; **63**: 356–60

44 Battezzati A, Caumo A, Martino F, *et al.* Nonhepatic glucose production in humans. *Am J Physiol Endocrinol Metab* 2004; **286**: E129–35

45 Shangraw RE, Jahoor F, Wolfe RR, Lang CH. Pyruvate dehydrogenase inactivity is not responsible for sepsis-induced insulin resistance. *Crit Care Med* 1996; **24**: 566–74

46 Burgstad CM, Besanko LK, Deane AM, *et al.* Sucrose malabsorption and impaired mucosal integrity in enterally fed critically ill patients: a prospective cohort observational study. *Crit Care Med* 2013; **41**: 1221–8

47 Krinsley JS, Egi M, Kiss A, *et al.* Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; **17**: R37

48 Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; **37**: 3001–9

49 Van Hall G, Stromstadt M, Rasmussen P, *et al.* Blood lactate is an important source of energy for the human brain. *J Cereb Blood Flow* 2004; **29**: 1121–9

50 Leverve XM. Energy metabolism in critically ill patients: lactate is a major oxidizable substrate. *Curr Opin Clin Nutr Metab Care* 1999; **2**: 165–69

51 Ichai C, Armando G, Orban JC, *et al.* Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med* 2009; **35**: 471–9

52 Stanley WC, Recchia FA, Lopasschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005; **85**: 1093–129

53 Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet* 2005; **365**: 871–5

54 Iapichino G, Radrizzani D, Armani S, Noto A, Spanu P, Mistraletti G. Metabolic treatment of critically ill patients: energy balance and substrate disposal. *Minerva Anestesiol* 2006; **72**: 533–41

55 Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL. Insulin resistance and substrate utilization in human endotoxemia. *J Clin Endocrinol Metab* 2000; **85**: 3770–8

56 Krogh-Madsen R, Plomgaard P, Akerstrom T, Møller K, Schmitz O, Pedersen BK. Effect of short-term intralipid infusion on the immune response during low-dose endotoxemia in humans. *Am J Physiol Endocrinol Metab* 2008; **294**: E371–9

57 Klaude M, Fredriksson K, Tjäder I, *et al.* Proteasome proteolytic activity in skeletal muscle is increased in patients with sepsis. *Clin Sci (Lond)* 2007; **112**: 499–506

58 Hasselgren PO. Catabolic response to stress and injury: implications for regulation. *World J Surg* 2000; **24**: 1452–9

59 Hill GL, Jonathan E. Rhoads lecture. Body composition research: implications for the practice of clinical nutrition. *J Parenter Enteral Nutr* 1992; **16**: 197–218

60 Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr* 2004; **79**: 613–8

61 Herridge MS, Tansey CM, Matte A, *et al.* Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293–304

62 Lecker SH. Protein degradation by the ubiquitin–proteasome pathway in normal and disease states. *J Am Soc Nephrol* 2006; **17**: 1807–19

63 Friedrich O. Critical illness myopathy: what is happening? *Curr Opin Clin Nutr Metab Care* 2006; **9**: 403–9

64 Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med* 2007; **33**: 1876–91

65 Langouche L, Perre SV, Thiessen S, *et al.* Alterations in adipose tissue during critical illness: an adaptive and protective response? *Am J Respir Crit Care Med* 2010; **182**: 507–16

66 Broomhead LR, Brett SJ. Clinical review: intensive care follow-up—what has it told us? *Crit Care* 2002; **6**: 411–7

67 Hill NE, Murphy KG, Singer M. Ghrelin, appetite and critical illness. *Curr Opin Crit Care* 2012; **18**: 199–205

68 Ligtenberg JJ, Girbes AR, Beentjes JA, Tulleken JE, Van der Werf TS, Zijlstra JG. Hormones in the critically ill patients: to intervene or not to intervene? *Intensive Care Med* 2001; **27**: 1567–77

69 Takala J, Ruokonen E, Webster NR, *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341**: 785–92

70 Voerman HJ, Strack van Schijndel RJM, Groeneveld ABJ, *et al.* Effects of recombinant human growth hormone in patients with severe sepsis. *Ann Surg* 1992; **216**: 648–55

71 Gore DC, Chinkes DL, Hart DW, Wolf SE, Herndon DN, Sanford AP. Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. *Crit Care Med* 2002; **30**: 2438–42

72 Meyer C, Woerle HJ, Gerich J. Paradoxical changes of muscle glutamine release during hyperinsulinemia euglycemia and hypoglycemia in humans: further evidence for the glucose-glutamine cycle. *Metabolism* 2004; **53**: 1208–14

73 Biolo G, De Cicco M, Lorenzon S, *et al.* Treating hyperglycemia improves skeletal muscle protein metabolism in cancer patients after major surgery. *Crit Care Med* 2008; **36**: 1768–75

74 Ichai C, Preiser JC; Société Française d'Anesthésie-Réanimation; Société de Réanimation de langue Française; Experts group. International recommendations for glucose control in adult non diabetic critically ill patients. *Crit Care* 2010; **14**: R166

75 Groeneveld ABJ, Beishuizen A, Visser FC. Insulin: a wonder drug in the critically ill? *Crit Care* 2002; **6**: 102–5

76 Maggio M, Nicolini F, Cattabiani C, *et al.* Effects of testosterone supplementation on clinical and rehabilitative outcomes in older men undergoing on-pump CABG. *Contemp Clin Trials* 2012; **33**: 730–8

77 Heyland D, Muscedere J, Wischmeyer PE, *et al.* A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; **368**: 1489–97

78 Kelemen JJ, Cioffie WG, Mason AD, Mozingo DW, McManus WF, Pruitt BA. Effects of ambient temperature on metabolic rate after thermal injury. *Ann Surg* 1996; **223**: 406–12

79 De Montmolin E, Aboab J, Mansart A, Annane D. Bench-to-bedside review: β-adrenergic modulation in sepsis. *Crit Care* 2009; **13**: 230

Handling editor: J. G. Hardman