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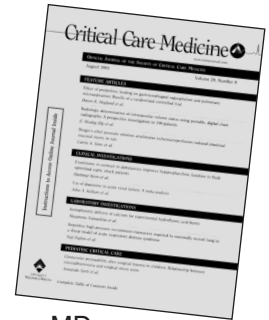
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Repair of metabolic processes

Jason Shipman, MD; Jeffrey Guy, MD; Najj N. Abumrad, MD, FACS

Inflammation is primarily an immune response aimed at protecting the organism from the devastating effects of pathogens, chemicals, and tissue injury. It is well established that once the body sustains an insult, local inflammatory mediators like prostaglandins and interleukins begin to circulate in the blood stream. These act both locally to direct inflammation and globally to indicate to the central nervous system the need for both added nutritional substrate directed toward vital organ systems and for blunted systemic inflammation. The hypothalamic-pituitary axis responds with cortisol and similar hormones that in the short term increase circulating carbohydrates, lipids, and proteins while simultaneously governing the immunologic response so that its potency will be precise and effective. In the acute phase of injury, these responses seem well founded and a natural answer to insult. Yet when the initial inflammatory phase wanes, the critically ill continue to show effects of protein catabolism, resulting in muscle wasting and dependence on ventilator support and immunosuppression, leaving them susceptible to severely debilitating infection, despite adequate nutritional support. Herein lies the principle paradox: despite alleviation of the initial insult, the critically ill continue to react to stress that is not there.

Without fail, critical care physicians have at some time in their career dealt with patients who survive their initial insult only to succumb to inevitable complications of protracted critical care. Their prognosis depended solely on the

duration of intervention; the initial injury seemed not to matter. This was rationalized, without foundation, by transitively applying immunologic and endocrinologic principles of the initial or acute phase of injury to the heretofore unknown protracted or chronic phase of injury.

Irrespective of the nature of the insult, bacterial, viral, chemical, or physical, the initial response usually consists of damage to the immune cells with potential compromise to the blood supply of tissues. These events would then set into motion a cascade of feed-forward inflammatory responses, mediated by cytokines and hormones that aim at protecting the organism. Carl Nathan has defined these responses as a "system of information flow in response to injury and infection," whereby various cells are recruited, with each committed to release proinflammatory signals. Mast cells are recruited and release histamine, eicosanoids, tryptases, preformed tumor necrosis serum, proteases, and chemokines. Neurons release bioactive peptides in response to pain (1). Cell death ensues, and several intracellular proteins (e.g., heat shock proteins (2), high mobility group 1—HMGB1 (3)—and mitochondrial peptides bearing the N-formyl group (4)) enter into the extracellular space, which in turn triggers the production of cytokines, eicosanoids, nitric oxide, and reactive oxygen species (5, 6). Progression of the inflammatory responses requires continuous activation of macrophages and further recruitment of neutrophils. The net result is further release of cytokines, breakdown of hyaluronic acid in the extracellular matrix to low molecular weight hyaluronan that, in turn, further release chemokines and perhaps matrix metalloproteinases. Neutrophils release elastases, which with RO1 will activate matrix metalloproteinases, which in turn activate macrophage-derived latent transforming growth factor- β , the most potent known chemoattractant for neutrophils.

Interruption of the feed-forward cascade should theoretically result in transformation of the inflammatory responses to that of a healing response. Recent observations have pointed to several areas of effective interruption. A recent review (7) has identified several "checkpoints" at which early interruptions could lead to anti-inflammatory responses. Examples include a) shifting of arachidonate metabolism toward lipoxin formation in neutrophils, which in turn bind cellular receptors and block neutrophil influx; b) induction of COX2 in macrophages by microbial products and cytokines, and these in turn induce prostaglandin E₂, which at a later stage shift arachidonate metabolism to lipoxin formation; c) elevated levels of interleukin (IL)-10 and transforming growth factor- β inhibit the release of tumor necrosis factor (TNF) α and other proinflammatory mediators (8); d) presence of an intact hypothalamic-pituitary-adrenal axis is also necessary for appropriate anti-inflammatory response. Selective deficiencies of corticotropin-releasing factor, adrenocorticotrophic hormone, and cortisol are all known to enhance the endotoxemic responses (9–11).

Kevin Tracey has also recently reviewed the evidence for the involvement of the autonomic nervous system as a check point at which cholinergic discharge blocks the release of TNF α from macrophages in the viscera. He termed this response as the "cholinergic anti-inflammatory pathway" that is mediated by the vagus nerve (12). Several studies have shown that vagal stimulation results in inhibition of proinflammatory cytokine synthesis, particularly TNF α , in macrophages and in liver and cardiac tissue (13). The primary effect on macrophages seems to be mediated by nicotinic, α -bungarotoxin-sensitive macrophage acetylcholine receptor (14), which is distinct from the muscarinic receptor activities identified on lymphocytes, peripheral blood mononuclear cells, and alveolar macrophages (15, 16).

Key Words: metabolism; inflammation; growth hormones

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DOI: 10.1097/01.CCM.0000081547.31084.23

In brief, it seems that many of the agents that are essential to induce and sustain inflammation, such as TNF α , prostaglandin E₂, interferon- γ , transforming growth factor- β , ROIs, and RNIs are also agents that are important in sustaining the healing responses. Hence, the timing of intervention becomes important in promoting the healing processes. Thus far, most of the interventions have been nonspecific. Many of these relate to inherent advances in critical care, such as advances in ventilator support, utilization of better and more specific antimicrobial therapy, and the widespread use of enteral and parenteral nutrition. These advances have enabled physicians to improve the outcome and lessen the consequences of protracted intensive care. Recent trials concerning, corticotropin, somatotropin, insulin, and neuroimmunomodulation axes show some promise that there may be room for endocrine intervention in protracted critical illness. This review intends to incorporate these studies in a review of the metabolic processes of the critically ill.

Growth Hormone

Of all the hormones in the neuroendocrine axis, somatotropin has been the most controversial over the past decade. Its virtues were first extolled in demonstrating reduced catabolism in patients with burns (17), sepsis (18), trauma (19), previous surgery (20), and critical illness (21). It has been demonstrated to improve graft healing (22, 23), preserve muscle mass and grip strength (24), and improve weaning from ventilation (25). These results were found using supranormal continuous intravenous dosing of growth hormone (GH). Even with the above benefits, however, decreases in mortality, days on the ventilator, and days in the ICU were difficult to prove. Much of the GH debate was put to rest in 1999 when Takala et al. (26) reported the results of a randomized, double-blinded, prospective trial that showed significant increase in mortality with administration of GH. Since this trial, understandably, much skepticism surrounds medical intervention in the somatotropin axis.

GH is secreted from the pituitary gland during normal activity in a pulsatile manner. Its release is augmented by GH releasing hormone and attenuated principally by somatostatin (27, 28). Of note, some peripheral stimulators are dopamine, α - and β -agonists and high pro-

tein meals, malnourishment, and insulin-induced hypoglycemia. Peripheral inhibitors include glucocorticoid excess, hypoglycemia, leptin, and β -agonists. These demonstrate the complexity of GH regulation and represent the forces at play in critical illness. Nearly all of these factors are seen in the critically ill, particularly glucocorticoid excess, beta and alpha agonism, and malnourishment. When GH is allowed to act fully, it is known to directly increase lipolysis and lipid oxidation, antagonize insulin, and indirectly stimulate protein synthesis. GH, however, in protracted critical illness, does not act accordingly.

After trauma, GH is typically elevated. The normal pulsatile flow of GH is characterized by undetectable troughs, yet in acute insult, that trough is summarily raised to a detectable and typically constant level (29, 30). Although the peaks do not increase, the total amount of excreted hormone is increased. The causes of this are suspected to be immune in nature or perhaps nutritionally stimulated (31, 32), although this has yet to be made clear. It seems that overall GH retains its lipolytic and insulin antagonistic effect while losing its anabolic properties (33, 34). This is in accordance with the acute need to mobilize building blocks to aid in manufacturing acute phase reactants and immune modulators.

The chronic phase is somewhat different. The pulsatile phase recedes to reveal a tonic subnormal GH activity. Whereas the acute phase was characterized by GH resistance (elevated GH with limited GH activity), the chronic phase demonstrates more hypothalamic inactivity (33, 34). This has been shown true with work with GH secretagogues (35). Pulsatile GH activity was shown to return with the administration of GH releasing hormone (36, 37), demonstrating hypothalamic inactivity instead of presupposed GH resistance. Ghrelin, a newly discovered biological GH releasing hormone analog produced in the stomach, has been shown to be a more potent secretagogue than GH releasing hormone, further solidifying a link between nutritional stimuli and GH activity (35). These late discoveries shed light onto controversy surrounding GH. It is possible that by using only high-dose GH to elicit anabolism instead of restoring natural pulsatile GH activity, the benefit of GH was subverted. Moreover, the acute and chronic phases of critical illness are not differentiated in many previous studies. By ad-

ministering GH during the acute phase of critical illness, marked by continued pulsatile activity, the effects are unknown and possibly detrimental.

Insulin-Like Growth Factor

As intimated previously, insulin growth factor (IGF) should be included with any discussion of GH. Its involvement in the metabolic processes of the critically ill continues to evolve. IGF-1, also known as somatomedin, is an 8 kD, single-chain polypeptide with a structure similar to proinsulin. IGF-1 is produced by hepatocytes in response to GH stimulation. Many of the effects of GH have been attributed to IGF-1 (38). When IGF-1 and GH are given concurrently, the metabolic consequences are greater than if these two agents are given individually. This is explained by GH's ability to sensitize target cells to IGF-1 and stimulate hepatocytes to produce IGF-1's key binding protein, IGF binding protein-3 (IGFBP3) (39).

IGF-1's mechanisms for promoting a beneficial metabolic profile include promoting protein synthesis and attenuating proteolysis. During conditions of catabolism, IGF-1 infusion stimulates the uptake of amino acids and promotes the assembly of these amino acids into proteins (40). A unique and beneficial property of IGF-1 is its ability to bind to both its own receptor and the insulin receptor. This feature allows the uptake of insulin and improved glucose oxidation in patients who are typically insulin resistant (41). In addition, IGF-1 stimulates cellular differentiation and cell division (40, 42).

Significant loss of lean muscle mass is a common feature after significant burn injury, which results in loss of physical strength, decreased resistance training, and diminished aerobic capabilities. Patients are predisposed to an increased rate of hospital-acquired infections and prolonged duration of mechanical ventilation. Administration of IGF-1 reduces this catabolic response after injury (43–45). Cioffi and Rue (43) documented a reduction in protein oxidation in burn patients treated with IGF-1. IGF-1 administration, both *in vivo* and *in vitro*, prevented the catabolic responses associated with thermal injury (46, 47). This IGF-1-mediated reduction in catabolism occurs by inhibiting lysosomal and ubiquitin-proteasome-dependent mediated pathways of protein degradation (48).

IGF-1 given alone rapidly loses its effectiveness. IGF-1 has six binding proteins. The most relevant of these binding proteins is IGFBP3. IGF-1, when bound to IGFBP3, has a prolonged half-life and increased biological effectiveness (41). Several investigators have demonstrated improved protein balance in catabolic burn patients after administration of IGF-1/IGFBP3 complexes (41,49).

Considering these recent developments, IGF-1's role in intervention is yet to be clearly defined, but it plays an essential role in decreasing catabolism in concert with GH. Future trials must demonstrate its effectiveness in the acute vs. prolonged phase of critical illness.

Insulin

Recent developments concerning insulin demand its inclusion in a discussion of the metabolic processes of the critically ill. It has previously been viewed as a metabolic force only. Not only has its significance burgeoned over time, but its scope as an anti-inflammatory agent has as well (50). Insulin is a pancreas-derived hormone that regulates the uptake of glucose by adipose and muscle tissues. During periods of stress, the liver's ability to generate glucose, gluconeogenesis, is under the influence of insulin. Hyperglycemia is commonly seen in critical illness or after serious injury in patients without any history of diabetes mellitus (48, 51, 52). Insulin resistance is characterized by elevated levels of: serum glucose free fatty acids, glycerol, and lactate levels. The impaired actions of insulin are a result of decreased insulin-stimulated phosphorylation of the insulin receptor and many of the secondary messengers (53). As alluded to previously, insulin's ability to regulate blood glucose levels has been overshadowed by some fascinating and important anabolic and anti-inflammatory properties.

Multiple investigations in normal, human volunteers have demonstrated that insulin possesses anabolic properties (54–56). Insulin promotes the uptake of amino acids and synthesis of new proteins (34). The administration of insulin induces these beneficial metabolic changes with only minimal hypoglycemic response (30). In addition to augmenting anabolism, researchers have determined that the administration of insulin will decrease the rate of proteolysis (57, 58).

The exciting recent observations by Van den Berghe et al. (59) demonstrated

that intensive insulin therapy resulted in significant decreases in mortality and morbidity in critically ill patients maintained on mechanical ventilatory support. Insulin therapy with maintenance of plasma glucose levels between 80 and 100 mg/dL resulted in a near 50% drop in mortality (from 8.0% to 4.6%) compared with patients whose blood glucose was maintained at 180–200 mg/dL. Intensive insulin therapy also reduced mortality in patients with bacteremia from 29.5% to 12.5%, and it also reduced the frequency of episodes of sepsis by 46%.

Infusion of insulin improves outcomes in cardiac patients. Both the American College of Cardiology and the American Heart Association have recommended a regiment of glucose, insulin, and potassium, also known as GIK therapy, to patients with acute myocardial ischemia, especially for patients who are high risk for anticoagulation or thrombolytics (53). Both insulin and glucose inhibit the effects of TNF α and production of migration inhibitory factor in a dose-dependent fashion (60–62). In models of cardiac ischemia, glucose, insulin, and potassium may prevent coronary artery thrombosis by enhancing the activity of nitric oxide synthesis (49). Insulin increases the production of NO that subsequently promotes vasodilatation and decreased platelet aggregation.

The mechanism of this protective effect has not been well identified. In animal studies, treatment with insulin resulted in beneficial changes in leukocyte adherence and migration (43, 42) and could inhibit TNF α production and the proinflammatory effects of TNF α in a dose-dependent manner (63). Nuclear factor- κ B is the principle mediator of TNF α induced inflammation. TNF α and IL-1 produce a breakdown of inhibitor factor- κ B, and a subsequent increase in nuclear factor- κ B. Nuclear factor- κ B is the mediator responsible for the proinflammatory actions attributed to TNF α . Insulin acts as an anti-inflammatory molecule by decreasing nuclear factor- κ B in mononuclear cells and increasing inhibitor factor- κ B. These molecular changes result in a net decrease in the production of oxygen free-radicals (64) and to stimulate endothelial NO synthesis (65). Insulin also suppresses the production of the pro-inflammatory molecule macrophage migration inhibitory factor. Once the insulin is removed, the anti-inflammatory changes revert back to normal (66).

Hyperglycemia has also been implicated in the pathogenesis of the inflammatory responses. For example, exposure of monocytes to high plasma glucose levels induced IL-6 and TNF α expression and secretion (67), and the alteration of the redox status in muscle cells by decreasing the expression of the rate-limiting enzyme of glutathione synthesis, γ -glutamylcystein synthetase (68). In humans, hyperglycemia is known to impair the phagocytic function of neutrophils, and this might be attributed to induction of a monocyte adhesion molecule, mac-1 (69). Irrespective of the etiology, the study by Van den Berghe et al. (59) attests to the importance of tight control of plasma glucose levels in the critically ill patient. Additional studies to determine the optimal doses of insulin used and the optimal blood glucose levels to be achieved are needed.

Neuroimmunomodulation

This concept was briefly discussed in the introduction but has, during the last 5 yrs, received more acclaim and, in turn, deserves more profound exposure. The endocrine system is known to interact with the immune system, but the extent to which this happens is much more than at first apparent. The hypothalamic-pituitary axis reacts to systemic inflammatory mediators released during initial stress. One of the effects of this reaction is to increase systemic corticosteroids. This in effect mitigates the immune response so that the entire body is not mutilated in its wake. However, the interaction between the neurologic and immune system is quite complex. The major immunoregulatory organs have immense autonomic innervations (70). Animals with known hypothalamic deficiency are more susceptible to chronic immunologic insults like arthritis. Intraventricular injection of endotoxin inhibits function of systemic immunologic machinery (71). Deficiency of GH leads to atrophic thymus that is reversed by administration of GH (72).

Most of the previous discourse about neuroimmunomodulation concerns humoral interaction between the neuroendocrine framework and the peripheral immune system. A second route of exchange has been demonstrated by direct neural-catecholaminergic stimulation (73). In the acute phase of stress response, increased sympathetic outflow stimulates a surge of catecholamines, in-

More work is needed to answer questions about catabolism, cachexia in the face of adequate nutrition, and stunted immune response, but we believe this review begins to shed light on these problems.

creasing as much as 10-fold (74, 75). They are a well-known participant in acute stress response and help to increase cardiac output (76), increase basal energy expenditure (77) and attenuate normal anabolic activity, and increase breakdown of skeletal muscle (78, 79) for the manufacturing of acute-phase proteins. Herndon et al. (80, 81) demonstrated that beta blockade can interfere with long-term catabolism of severely burned patients and decreasing heart rate (82, 83). In addition, norepinephrine and epinephrine have been demonstrated in animals and human models to have immune capabilities by enhancing expression of immune mediators and exhibiting effects on T-helper cells (84–90).

Sympathetic activity, primarily because of its association with the stress response, has received most of the attention from researchers, but parasympathetic activity during stress has recently been discovered to attenuate the stress response as well. Afferent activity has been demonstrated to enhance cytokine to brain activation of the immune response (91–93). Efferent activity has also been shown to decrease systemic levels of TNF α and prevent lethal hypotension (94). Acetylcholine, just like catecholamines, has immuno-active capabilities. It actively inhibits release of inflammatory interleukins like IL-6 and IL-18, but not IL-10, which is an anti-inflammatory protein (94). In addition, studies show that nicotine might be an effective tool in fighting inflammatory bowel disease, and there is less inflammatory activity in the bowel mucosa of smokers (95–97). The real impact of sympathetic and parasympathetic innervation to the immune response is yet to be illumi-

nated, but there is ample activity trying to do so.

Even less is known about the long-term effects of autonomic stimulation during a stress response. Because of the difficulty of studying long-term critical illness in both human and animal models, it is easy to see why there is more information about the acute phase. Some have generally postulated that continued stimulation of reactionary systems by long-term stress results in an attenuated response (98, 99). This has been demonstrated in lifetime stress and aging (99), but diminished activity of the autonomic nervous system during critical illness has yet to be shown.

Critical illness continues to present challenges, even when therapies improve. If physicians were not successful in treating initial insults, protracted critical illness would not be an issue. It is previously mentioned experimentation that differentiates acute from chronic illness and the array of metabolic processes involved. More work is needed to answer questions about catabolism, cachexia in the face of adequate nutrition, and stunted immune response, but we believe this review begins to shed light on these problems.

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1

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