

Metabolic response to injury and role of anabolic hormones

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Purpose of review

To provide a short review of the literature describing the hypermetabolic response to injury and potential treatments. Associated findings include changes in inflammatory mediators and secreted hormones.

Recent findings

Treatments should be aimed at decreasing the response and potentially the use of anabolic agents. Of note, recent interest in the hyperglycemic response to injury and insulin treatment will be highlighted.

Summary

The current metabolic care of the burned patient including nutrition is now being unfolded. It is relatively clear that anabolic treatment should be considered in all those with severe injury. Timing of the treatment, however, is still a topic of discussion.

Keywords

anabolic agents, hypermetabolism, insulin, severe burn

Introduction

The past few decades have witnessed great advancements in the care of severe burns. Improvements in resuscitation management to preserve organ function while avoiding the complications of volume overloading, early and adequate enteral nutrition, and, most notably, early excision of the burn wound with immediate coverage by autograft, allograft or synthetic skin have all contributed to decreased morbidity and mortality. The metabolic derangements associated with severe burn, however, continue to be a nemesis and are an area of intense research. Once recovered from the acute illness phase, the hypermetabolic and catabolic state of the patient may persist for 9 months or more [1,2]. Appreciation of this metabolic response will continue to guide further study and enable us to impact patient care in both the acute-phase and long-term outcomes in the severely burned.

Acute response to injury

The initial response to severe burn is mediated through a cascade of proinflammatory cytokines, acute-phase proteins and hormonal changes inducing a hypermetabolic state (Fig. 1). Presumably, this response is an attempt to restore homeostasis [3,4], and is characterized by increased energy expenditure with elevated temperature [5], hyperdynamic circulation described as 'ebb and flow' physiology, hyperglycemia, protein catabolism and free fatty acid liberation from adipose tissue [6].

In response to skin injury, proinflammatory cytokines are released by innate mechanisms as a defense to the insult. Activated platelets and macrophages initiate this cascade with the release of mediators from the tumor necrosis factor and interleukin (IL) families. Tumor necrosis factor- α , IL-6 and IL-8 were all noted to be elevated in the plasma after severe burn [7–9]. To control a robust proinflammatory state, antiinflammatory cytokines are elaborated to help regulate and inhibit a potentially excessive inflammatory and immune response. IL-4 and IL-10 [10,11], soluble tumor necrosis receptors [12], IL-1 receptor antagonist [13], and transforming growth factors [14] were all found to be elevated above normal levels after burn in both the injured tissue and in the systemic circulation, potentially leading to immunosuppression. Similar to proinflammatory cytokines, excessive and prolonged elaboration of antiinflammatory cytokines is associated with the development of sepsis and/or death.

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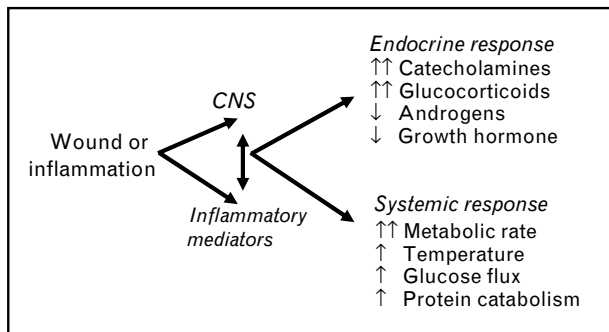
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Abbreviation

IL interleukin

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Figure 1 Schematic of the initial response to injury that results in hypermetabolism

CNS, central nervous system.

Simultaneously, a hormonal response exists to the insult in an attempt to return the patient to homeostasis. Release of catecholamines, glucagon, prolactin, growth hormone and cortisol are all detectable early after the injury [15] (Fig. 2). Catecholamines appear to be the primary mediator of the hypermetabolic response and urinary catecholamine levels correspond to burn severity [16]. Prolactin is stimulatory to the immune system and elevated levels after injury correlate with the extent of burn [15]. Cortisol concentrations are also increased after severe burn and are proportional to the degree of injury. Plasma corticotrophin, however, was not elevated, suggesting that classic endocrinologic control may not be at play. Investigators of this response suggested that although the cortisol findings were significant, they paled in effect in comparison to catecholamines in the same study [17].

Hypermetabolic response

The metabolic response to severe burn typically displays the classic 'ebb and flow' physiology initially described

by Moore [18]. Adequate resuscitation and nutrition is necessary for the clinical signs of hypermetabolism to manifest [19]. Hyperdynamic circulation with elevated cardiac output occurs with initiation of resuscitation and by 6–12 h will already begin to exceed preburn levels [20]. The increased energy expenditure to cope with this insult necessitates mobilization of large amounts of substrate from fat stores and active muscle for repair and fuel, leading to catabolism. Hyperpyrexia associated with this response adds to the cost. Upregulation of acute-phase proteins and a decrease in constitutive proteins leads to the potential detriment of structure and function of essential organs [21]. Another clinical manifestation is hyperglycemia.

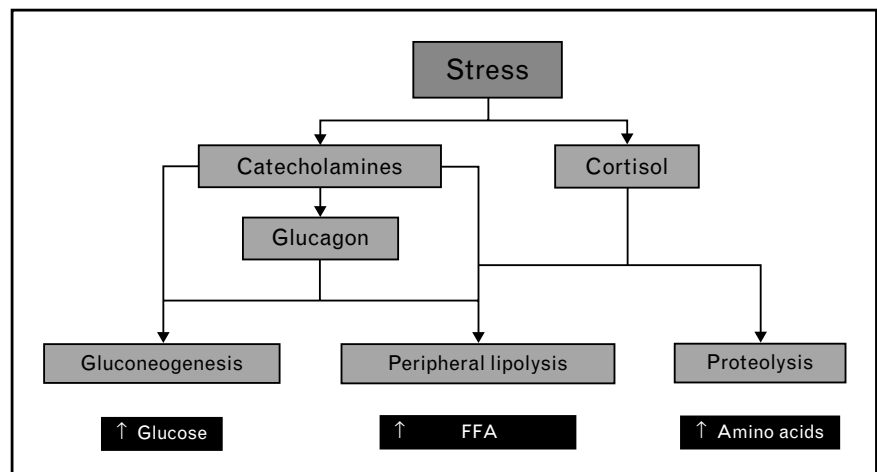
Hyperdynamic circulation and substrate cycling

In burns greater than 50% of the total body surface area, the metabolic rate increases in proportion to the burn wound to a maximal response of 70–75 kcal/m²/h [22]. More recent studies show a maximal response in burns as small as 20% with further increases related to burn size only in ambient temperatures below thermoneutrality [23]. It also appears that increases in resting energy expenditure are maximized at approximately 40% total body surface area burned in the age of aggressive early excision, where the unburned parts of the body are now wounds associated with donor sites, thus the wound area approaches 100% [24]. Hypermetabolism and increases in metabolic rate are also associated with increased cardiac output. Much of this appears to be from catecholamine stimulation of heart rate and contractility through the β -receptors. Catecholamine levels are highly stimulated after severe burn [16,25] and the cardiac effects can be beneficially limited with β -blockade [26].

Associates of hypermetabolism are increases in substrate cycling, particularly of glucose and the fatty acids. A

Figure 2 Hypermetabolism and the endocrinologic response to injury

FFA, free fatty acid.



substrate cycle exists when opposing, nonequilibrium reactions catalyzed by different enzymes are operating simultaneously, with at least one of the reactions involving the hydrolysis of ATP. Thus, a substrate cycle both liberates heat and increases energy expenditure without any beneficial effect. In severe burns, the total rates of triglyceride–fatty acid and glycolytic–gluconeogenic cycling without effective product were 450 and 250%, respectively, over normal controls.

In conjunction with the fat cycling described above, catecholamine and glucagon secretion are associated with significant lipolysis of fat stores [27]. Free fatty acids are liberated into the plasma and are efficiently removed by the liver, as high levels are toxic to neurons. Once in the hepatocyte, the free fatty acids are re-esterified into triglyceride. Normally, this product is transported into very-low-density lipoprotein particles that are excreted from the liver and are removed from the bloodstream primarily by lipocytes. After severe burn, however, the formation of very-low-density lipoprotein particles in the hepatocyte is inefficient. The triglyceride stays in the liver to result in hepatic steatosis. Even in the face of high carbohydrate feeding, far and away the greatest component of re-esterified triglyceride is from the periphery rather than de-novo synthesized fatty acid [28]. Therefore, hepatic steatosis associated with injury is due to fat substrate cycling from the periphery to the liver with inefficient transport back to the periphery; feeding with carbohydrate or fat with de-novo synthesis of fat plays only a very minor role. For treatment, one should consider decreasing lipolysis rather than changing the feeding regimen.

Muscle catabolism

Accelerated net protein catabolism occurs after injury – this protein catabolism is one of the major hormonal responses to injury and is the most detrimental in terms of delayed recovery. When compared to normal fasted subjects [29], protein breakdown and subsequent efflux of amino acids from muscle are elevated almost two-fold after severe burn [30]. The principal defect is an accelerated rate of protein breakdown with a failure of compensatory synthesis, resulting in a decrease in net protein synthesis (muscle protein synthesis minus muscle protein breakdown) [31].

Hyperpyrexia

Burn patients have an elevated core temperature 1–2°C higher than normal [32]. This is unrelated to septic episodes or cool ambient temperatures, which will further elevate the core temperature by increases in catecholamine secretion among other responses. The hyperpyrexia after severe burn is due to a homeostatic elevation in the hypothalamic ‘set-point’ evidenced by the higher ambient temperature which burn patients find com-

fortable compared to normals. The normal physiologic response to cooler ambient temperature is by vasoregulation to decrease heat loss through the skin. Burned skin and wounds, however, lose this ability, and are characterized by vasodilation bringing increased oxygen, nutrients and cellular elements to the damaged tissue.

Acute-phase proteins

Under threats such as severe burn, homeostasis is upset by a coordinated sequence of systemic changes and local disturbances aimed at recovery. This response, termed the acute-phase response, is realized in the liver by increased production of many plasma proteins, known as the acute-phase proteins, and decreased production of constitutive proteins. We define acute-phase proteins as those whose concentration increases in response to inflammation and a constitutive protein as one that decreases. Acute-phase proteins such as C-reactive protein, serum amyloid A, α_1 -acid glycoprotein, α_1 -antitrypsin, fibrinogen, haptoglobin and α_1 -chymotrypsin are synthesized exclusively in the liver, and are assumed to play important roles in restoring normal homeostasis based on known functions and on logical speculation about how these might serve useful purposes. It is presumed that upregulation of acute-phase proteins serves to stimulate the wound-healing process and protect from damage by hemostatic effects.

Hyperglycemia

Glucose-dependent tissues are assured an energy source by increased hepatic gluconeogenesis and peripheral resistance to insulin. While this is beneficial, to a point, numerous studies showed hyperglycemia is associated with worse outcome in intensive care unit and burned patients associated with impaired immune function, poor wound healing and exacerbation of protein muscle catabolism [33,34]. The development of hyperglycemia is not surprising as it is associated with dramatic increases in gluconeogenesis and glucose substrate cycling. In addition, insulin resistance associated with decreased insulin signaling is present after severe burn. What is thought to occur after severe burn is that residues on insulin receptor substrate-1 (relatively proximal in the signal transduction sequence) are phosphorylated, thus rendering them the signal less robust.

Treatment of hyperglycemia generally includes exogenous insulin to reach euglycemia. As mentioned above, several studies of continuous insulin treatment in the intensive care unit [34], including burns [35,36], have shown benefit. These benefits appear to be due to decreased infections as well as improved amino acid metabolism [30,37]. Several investigators have asked the question of whether the improvements were due to prevention of hyperglycemia or due to pharmacologic effects of insulin on pathways indirectly associated with

glucose disposal. This question has not been answered to any real effect yet and will undoubtedly be the focus of future investigations.

Metformin as an oral hypoglycemic has been shown to augment the effects of insulin in the severely burned. Gore *et al.* [38] elegantly showed that metformin use was associated with lower endogenous glucose production and glucose oxidation. When given with glucose, it improved glucose disposal, and when given with additional insulin, improved glucose uptake. In a later study, they showed associated improvements in net muscle protein synthesis, thus showing an anabolic effect similar to that seen with insulin [39]. Mechanisms discussed included improved insulin sensitivity and thus greater insulin effects rather than direct effects on glucose transporter-4 activity or effects on net protein synthesis.

Recently, the peroxisome proliferator-activated receptor- γ agonists, known as thiazolidinediones, have been shown to have effects in this area. These agents have been used in those with type II diabetes mellitus as insulin sensitizers, thought to be effective through suppression of peripheral lipolysis and redistribution of triglyceride stores to peripheral fat. It was shown that fenofibrate treatment decreased serum levels of glucose and improved insulin-stimulated glucose uptake. More studies will be required before treatment with hypoglycemic agents in addition to insulin can be widely adopted.

Treatment for hypermetabolism

The hypermetabolic state cannot persist indefinitely without adversely affecting the patient's outcome. Several aspects of care can either attenuate or reverse this response leading to a more anabolic state to facilitate and promote wound healing. Ameliorating the deleterious effects of this ongoing state is beneficial; however, reversing this condition to an anabolic one is even more desirable. Two strategies can be considered: (1) to decrease the response by antagonism and (2) to stimulate anabolism through pharmacologic means primarily through anabolic hormones.

Antagonizing the response

A few years ago we performed a series of studies in severely burned adults and children with the intent to determine which clinical factors were most highly associated with increased muscle catabolism measured by net protein balance across the leg. In this study of 123 patients, we found that catabolism was associated with admission weight, burn size, time to excision, resting energy expenditure and sepsis [24]. Therefore, an effective means of treatment would be prevention of associated conditions. Those which are amenable to conscientious clinical treatment are time to definitive treatment and avoidance of sepsis (also associated with early treat-

ment of the wounds). Early excision with prevention of infection and subsequent sepsis is crucial towards minimizing the full expression of the hypermetabolic response. Modern burn care has shifted from topical treatment of extensive burns to early excision and closure with biologic dressings. Total excision within 48 h significantly decreased invasive wound infections and sepsis in pediatric patients with 40% or more total body surface area burns [40].

Another measure that can be taken to decrease hypermetabolism and catabolism in severe burns is to direct temperature regulation. As stated previously, burned patients have a higher set point for temperature regulation. Attempts to decrease temperature to normal levels will only result in increased metabolism for heat production until the new set point is reached, which is typically between 38 and 38.5°C. The converse is also true, however, in that hyperpyrexia in excess of 39°C is likely associated with increased caloric expenditure that might be controlled to spare substrate.

Stimulation of anabolism

Pharmacologic adjuncts are often utilized to convert these catabolic patients to an anabolic state. While they may reach this point on their own, these therapeutic interventions can shorten the infirm period and improve recovery. The adjuncts can be broken into two major classes, i.e. soluble protein hormones and the anabolic steroids.

Soluble proteins

Growth hormone was the first agent used clinically to ameliorate hypermetabolism after injury. As stated previously, Cuthbertson [41] used doses of growth hormone to improve protein balance in a leg fracture model. Gore *et al.* [42], using protein kinetics data measured in an isolated limb, showed that burned adolescents given recombinant human growth hormone increased protein synthesis. This study also showed that insulin, by itself, has a similar effect. Enthusiasm for the use of growth hormone to treat hypermetabolism was severely diminished, however, by the findings of Takala *et al.* [43], who demonstrated that the use of growth hormone in critically ill adults was associated with increased mortality.

Insulin-like growth factor can be given to produce anabolism without the direct catabolic effects seen with growth hormone. Cioffi *et al.* [44] gave insulin-like growth factor-1 to burned patients, and they found a decrease in protein oxidation and a promotion of glucose uptake while not altering resting energy expenditure. This study, however, was plagued by the appearance of hypoglycemia in some of the subjects. This effect can be diminished by giving insulin-like growth factor-1 with its principal binding protein insulin-like growth factor-1 binding protein-3 that retained its anabolic effect on

leg muscle which was found mostly in those who were most catabolic [45]. A similar effect was seen in adults given insulin-like growth factor-1/insulin-like growth factor-1 binding protein-3, but several of these subjects developed peripheral neuropathies, again quelling any enthusiasm for widespread use of this agent in this population [46].

Insulin is a very potent anabolic agent, which has been shown to induce improved protein and amino acid kinetics in the severely burned [47]. The first of these studies performed with high-doses of insulin (above 30 units/h) given for 3–5 days showed improvements in inward transport of amino acids as well as improved protein synthesis by more than 200% [37]. Other studies with lower doses were also effective [30]. It was also associated with increased lean body mass and decreased length of hospital stay without increased caloric delivery [35].

Androgenic steroids

Testosterone is the major androgenic steroid produced by the testes of men, although a small amount is also produced in women. Testosterone levels are extremely diminished after severe injury [48]. When testosterone was given to severely burned men to normalize these levels, it was found that protein synthetic efficiency improved over two-fold and protein breakdown decreased. The authors concluded that testosterone could be used to ameliorate muscle catabolism after injury [49].

Oxandrolone is an analogue of testosterone which has been used clinically to treat muscle wasting in convalescing burned adults [50]. Oxandrolone is purported to have a much greater anabolic potential than testosterone with one-sixth of the androgenic effects [51]. All of these studies showed that oxandrolone use is safe, and was efficacious when given to burned adults to improve nitrogen balance and decrease weight losses [52]. Similar effects were seen in children [53]. When oxandrolone's effect on muscle protein kinetics was studied in burned patients using stable isotopic methodology, oxandrolone treatment was shown to improve net protein synthesis [54]. Most recently, a multicenter trial on the use of oxandrolone in the severely burned showed a decrease in acute hospital stay with its use without significant side effects. This was associated with a decreased number of operations for wound closure [55**].

Conclusion

Severe burn is perhaps the most striking example of hypermetabolism. The response is homogenous and thus can be studied carefully. Investigators have shown several associates of the effect, i.e. increases and/or decreases in cytokine levels and increases/decreases in certain hormones or their agents, thus all of these are associated signals for the development of hypermetabolism. One of

the caveats of hypermetabolism is the development of alterations in substrate metabolism, perhaps the most difficult being muscle protein catabolism, which leaves survivors of the injury weak and unable to participate fully in recovery activities, even at a time when they are most needed. Some agents have been tested in this population which show promise, but more research needs to be done. In particular, more attention to actual functional effects should be highlighted in future studies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 368).

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