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Review

Metabolic self-destruction in critically ill patients: Origins, mechanisms and therapeutic principles

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ABSTRACT

Objectives: The aim of this study was to describe the evolution and nature of self-destructive metabolic responses observed in critically ill patients, and to analyze therapeutic principles on how best to avoid or diminish these responses.
Methods: We electronically identified articles through a search of PubMed and Google Scholar.
Results: Metabolic reactions associated with surgical injury or infections comprise hyperglycemia, insulin resistance, increased hepatic glucose production, and muscle protein breakdown. From an evolutionary perspective, these responses have been necessary and successful to overcome spontaneously survivable insults (minor surgical trauma). If prolonged and exaggerated, however, these reactions may become self-destructive, causing secondary metabolic damage. There is overwhelming evidence that extreme metabolic responses have not been selected by evolution, but are brought about by modern medicine enabling survival of severe, otherwise lethal insults and giving patients the chance to develop such exaggerated self-destructive metabolic reactions. Poorly adapted metabolic responses to severe insults, however, may have persisted because of unavoidable evolutionary constraints. Self-destructive metabolic responses cannot be prevented by adjuvant therapies such as artificial nutrition, which may only help to ameliorate secondary metabolic damage.
Conclusions: Minor surgical trauma is associated with a beneficial adaptive metabolic response. After a severe insult, however, emergence of self-destructive responses will be unavoidable if the patient survives the acute phase. Effective treatment is only possible by an aggressive therapy of underlying pathologies (such as shock, trauma or infection) thereby interrupting secondary metabolic trigger mechanisms at an early stage.

Introduction

The human substrate (fat, carbohydrate, and protein) metabolism is a complex operational system that controls numerous interactive metabolic reactions, creating a dynamic equilibrium within and between different organs. A dense network of positive and negative feedback mechanisms maintains metabolic homeostasis, thereby ensuring the survival of the individual and, consequently, of the species. Scientists committed to metabolism research continually are impressed by the complexity of substrate metabolism and by its remarkable power to adapt itself in response to nutrition and environment [1].

Compared with physiological adaptions to variations in food supply or composition, however, the metabolic responses to a severe disturbance of homeostasis are not nearly as impressive, and may be regarded as middling at best. Indeed, a significant portion of morbidity and mortality that is observed in response to severe shock, injury, or in infection, most likely is mediated by endogenous secondary metabolic reactions impairing immunologic functions and causing cachexia [2–4]. Within these undesired metabolic reactions, two phenomena are of particular clinical importance: an exaggerated hepatic glucose production, which is associated with hyperglycemia and insulin resistance, and a progressive loss of muscle mass. Even during times of an apparently optimal nutritional support, patients with severe sepsis/systemic inflammatory response syndrome are suffering from a protracted loss of muscle protein. After 3 wk, this loss amounts to 10% to 15% of the initial protein content [5,6]. Consequently, after a severe disturbance of homeostasis, substrate metabolism does not react adequately and contains

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self-destructive elements. Awareness of this potentially fatal situation is not new. More than 3 decades ago, Cerra et al. already created the term *septic auto-cannibalism*, which impressively describes the inability of human protein metabolism to adequately adapt to a severe insult [7].

In the following article, we describe the origins of this detrimental metabolic scenario from an evolutionary perspective. We differentiate between extremely quick fatal injuries that did not allow selection, and severe to moderate injuries that allowed the selection of adaptive metabolic responses. We discuss the use and purpose of adaptive metabolic reactions throughout phylogeny. From this, we investigate how modern medical care has affected the usefulness of these adaptive reactions that may become self-damaging when out of control. We show that qualitatively there are no “good secondary” and “bad secondary” responses. Rather, detrimental effects relate to the quantity of these responses, reflecting the magnitude of a certain response over a certain period of time. All of these insights should finally allow us to draw conclusions relevant for patient management.

The importance of evolution for developing adaptive secondary metabolic reactions

Metabolism of vertebrates must be viewed as the result of countless generations of refinement via natural selection. In theory, evolvement of mechanisms optimizing secondary pathophysiological reactions after a severe insult would, as a first step, require a quantitatively reasonable selection among those individuals exposed to such a disturbance. Simultaneously, genetic variability is a prerequisite for natural selection. Surviving organisms should possess superior secondary reactions, and should be able to pass the underlying genetic information to future generations. Two major factors have, however, limited and do still limit the selection pressure for beneficial responses to a severe disturbance of homeostasis. First is the likelihood of surviving a severe insult (polytrauma, hemorrhagic shock, severe infection) in the absence of modern medical intervention, and second is the age of the patient [8].

In the past, when man sustained a severe insult, natural selection may not have been able to act because variance in outcome was virtually nonexistent. Severe disturbances of homeostasis caused by polytrauma, severe infections, or hemorrhagic shock were usually fatal in the absence of emergency therapy or long-term critical care. It is only by sophisticated modern medical care that, for example, shock-related mortality has been reduced to a low percentage of the extraordinary high mortality that occurred during World War I [9,10]. If, however, an advanced health care infrastructure is absent (as it still is in many of today’s developing countries), mortality rates for severe disturbances of homeostasis (polytrauma) will still be prohibitively high [11]. Thus, before the advent of modern medical care, most affected individuals died from severe damage to their physical integrity. Therefore, in the past such a low chance of survival made it almost impossible for evolution to select appropriate adaptive reactions after a severe insult.

Additionally, even if individuals survive severe disturbances of homeostasis and can be regarded as positively selected, a future successful reproduction will be highly unlikely. First, it is well known that critically ill patients who have been successfully treated and who have overcome multiple organ failure, suffer from a decreased sexual motivation and performance [12]. Second, an additional factor limits the passing on of positively selected genetic information. Surviving critically ill patients, whose adaptation to a severe insult may be regarded as successful, are mostly of an age (on average 65 y), in which fertility is usually reduced (men) or absent (women).

A further limitation arises from the different life expectancy of individuals in contemporary and historic populations. In contrast to the average age of contemporary critically ill patients, the average lifespan in hunter–gatherer societies can be conservatively estimated at approximately 28 y, even after adjusting for elevated infant mortality [13,14]. Even if survivable severe insults occur in these traditional settings, the vast majority of our ancestors would have never had an insult at an age corresponding to that of the mostly geriatric, contemporary critically ill patients. Therefore, it is unlikely that elderly patients of today would profit from a positive selection that had taken place in our younger ancestors.

Therefore, it is fairly safe to conclude that the amplifications of the metabolic responses, which may be observed nowadays after a severe insult in a typical patient in the intensive care unit, have not been shaped by evolutionary selection. From this, however, it also is logical to conclude that mild secondary metabolic responses to a less severe insult (which may be survived even without modern medical care, and which may not be associated with detrimental long-term effects) have been fine-tuned by evolution. Consequently, in modern man, secondary metabolic reactions to a “spontaneously” survivable, minor disturbance of homeostasis may be viewed as the optimal result of countless selection processes. For a deeper understanding of the benefits of adaptive responses, however, it is first necessary to consider the environmental conditions in which organisms were living that had sustained a minor, possibly survivable disturbance of homeostasis.

Framework and setting of evolutionary processes shaping adaptive metabolic responses

There are good reasons to assume that strategies selected to overcome an insult had to develop in the absence of nutrient or fluid supply. For early vertebrates, which surfaced long before the advent of man in evolution, two environmental conditions limited the access to food or fluids:

1. A nurturing or caregiving behavior as it is known, for example, in primates including Homo sapiens, did not exist among mature organisms, meaning that individual organisms had to rely on themselves when struggling for survival [15].
2. It is highly likely that the most common survivable disturbances of homeostasis either affected the musculoskeletal system (injuries to the extremities or wings) or the digestive tract.

Even today, in wild or farmed mammals, fractures or soft tissue injuries at the extremities, and acute enteric disorders still dominate the pattern of insults [16,17]. If fatal, infections were the main cause of death pointing to the need for strategies to prevent them at any price [15].

Musculoskeletal injuries will acutely impair access to food or water by reduced mobility that prevents effective hunting or gathering of nutrients. Furthermore, moving or foraging may be dangerous when ill or injured. Digestive diseases usually are associated with an ineffective utilization of consumed nutrients. Both conditions will lead to a state of nutrient or fluid deficiency. In the simultaneous absence of nurturing by other members of the species, the organism will be forced to use its own resources