Clinical Nutrition xxx (2017) 1–8

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

The 2017 Sir David P Cuthbertson lecture. Amino acids and muscle protein metabolism in critical care

Robert R. Wolfe

University of Arkansas for Medical Sciences, Department of Geriatrics, 4301 West Markham Street, Slot 806, Little Rock, AR 72205-7199, USA

ARTICLE INFO

Article history:
Received 8 December 2017
Accepted 14 December 2017

Keywords:
Catabolic state
Anabolic resistance
Hypermetabolism
Essential amino acids
Amino acid transmembrane transport

SUMMARY

In this short review, our current understanding of key aspects of the catabolic response are presented in the context of the seminal contributions of Sir David Cuthbertson.

Studies have confirmed that an increase in resting energy expenditure occurs in almost all forms of critical illness and injury. However, meeting the resulting increase in caloric requirement is not an insurmountable problem. The primary focus of nutritional support should be the net loss of body protein. Increased intake of dietary protein may ameliorate, but usually will not entirely reverse, the accelerated loss of body protein because of anabolic resistance. Anabolic resistance is due, at least in part, to impaired inward transport efficiency of amino acids from blood into muscle. Simultaneous consumption of excess non-protein calories in an anabolic resistant state provides minimal additional benefit, and may cause potentially adverse effects, including accumulation of liver fat and excess production of carbon dioxide. Because of the limited effectiveness of dietary protein and non-protein caloric intake, it is likely that traditional nutritional support alone will not reverse the net loss of body protein in the catabolic state. The reversal of the catabolic response can only be accomplished in many patients by combining reasonable nutritional support with appropriate metabolic control. Metabolic control may be achieved with the use of a number of pharmacological approaches, including propranolol, insulin or testosterone. Regardless of the approach, ensuring an adequate availability of dietary essential amino acids is necessary for pharmacologic therapy to result in an increased rate of protein synthesis.

1. Introduction

Sir David Cuthbertson had a remarkable career in which he excelled in a number of areas. He made research contributions in different disciplines, and had a successful and important administrative career in directing the Rowett Institute [1]. Perhaps the most notable contributions of Sir David were his seminal observations on the response to serious injury and other patho-physiological conditions that together can be referred to as the catabolic state. While his observations were largely based on the response to femur fracture and to bed rest, over time we have come to realize that his insights were relevant to most forms of trauma and critical care. In a review article published in 1950 [2] Sir David outlined several fundamental aspects of the response to trauma that have formed the framework of current research in the field. The key points in that article with regard to the response to trauma were the following:

1. After an initial period of shock, the metabolic rate rises.
2. The catabolic response includes a rapid loss of nitrogen.
3. Muscle is the source of catabolized material.
4. Muscle catabolism is the source of amino acids for the healing process in the absence of food.
5. Negative nitrogen balance persists during the catabolic period despite a substantial increase in a diet rich in protein and calories.

All of these points have been investigated extensively since originally put forward by Sir David. This article highlights selective research advances relevant to each of the points.

1.1. "After an initial period of shock, the metabolic rate rises"

The so-called "hypermetabolism" of trauma and critical illness became a major research focus in the 1950s and 1960s. The rapid loss of lean body mass observed in these patients was largely attributed to "hypermetabolism". In the 1960s and especially the

E-mail address: rwolfe@uams.edu.

https://doi.org/10.1016/j.clnu.2017.12.010
0261-5614/

1970's, methods became available to deliver large amounts of calories to critically ill patients via parenteral and enteral nutrition, so that meeting energy requirements became possible. However, administering large amounts of calories and amino acids did little to stem the rate of loss of lean body mass. Further, adverse effects of excessive caloric intake, particularly in the form of glucose became evident. For example, we found that glucose given at rates in excess of caloric requirement stimulated fat synthesis in the liver [3], which, when coupled with a high rate of delivery of free fatty acids to the liver from accelerated endogenous lipolysis [4], led to significant lipid accumulation in the liver [5]. An extensive increase in liver fat in critically ill patients presents at least two major problems related to ventilation: the liver can become so enlarged with fat that movement of the diaphragm is physically impaired [5], and the net synthesis of fat from glucose causes an increased production of CO_2 [6]. This is because the respiratory quotient of fat synthesis is well above 1.0, meaning that CO_2 production exceeds the rate of O_2 consumption during periods of net lipid synthesis. The combination of these factors can prolong the requirement of artificial ventilation due to retention of CO_2.

The potential adverse effects of excessive caloric intake led us to examine the true metabolic requirements of severely hypermetabolic patients. We performed studies in severely burned children. These patients represent among the most hypermetabolic critically ill patients. In a study of 57 patients we found that resting energy expenditure (REE) determined by indirect calorimetry was 30% higher than the corresponding predicted basal metabolic rate [7]. However, while the REE was elevated, the REE was not increased sufficiently to explain the extent of loss of lean body mass. The inability to attribute the loss of lean body mass to an elevated REE was particularly relevant because of the minimal daily activity of these patients. We evaluated the relationship between the REE and total energy expenditure determined by the doubly-labeled water technique [8]. The doubly labeled water technique measures the energy expenditure over several days, and includes the contributions from all physical activity in addition to the resting and basal rates of energy expenditure [9]. In 15 severely burned children, total energy expenditure was 1.18 times the REE [8]. Total energy expenditure usually exceeds REE by 1.3 or 1.4 times or more. Thus, while catabolic patients are “hypermetabolic” as reflected by an elevated REE, a decrease in activity counterbalances the increased REE. The results of this study indicated that caloric requirements of catabolic patients can be met by consumption of about 20% more calories than REE [7].

The results of the studies defining the relationship between REE and total energy expenditure in catabolic patients contributed to a realization that the caloric demands of the hypermetabolic response can be easily met, and that potentially adverse effects of excessive caloric intake are of more concern than failing to meet all caloric requirements. They also validate Cuthbertson's recognition that factors other than or accompanying the hypermetabolic response were responsible for the extensive loss in lean body mass.

1.2. “The catabolic response includes a rapid loss of nitrogen”

Nitrogen (N) is the defining element of protein, so a rapid loss of body N in the catabolic state reflects a rapid loss of body protein. At any time the amount of body protein is a function of the balance between the rate of protein synthesis and breakdown. The whole body rates of protein synthesis and breakdown can be measured with the use of stable isotope tracers. We have had the opportunity to determine the rates of whole body protein synthesis and breakdown in the post-absorptive state in a number of forms of catabolic stress. The highlights are presented in Fig. 1.

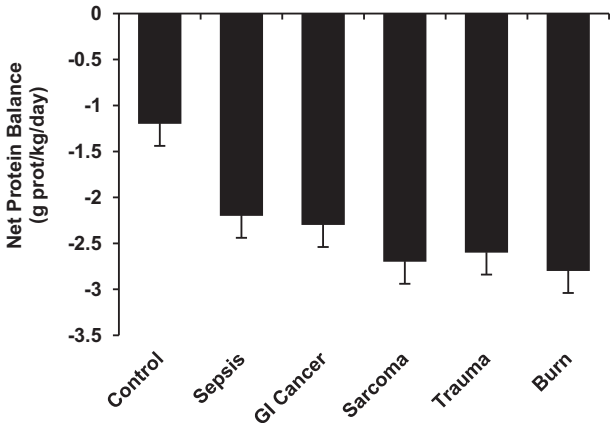

Fig. 1. The balance between whole body protein synthesis and breakdown measured in the post-absorptive state using stable isotope methodology in a variety of catabolic patients. From references [10–14].

The rate of protein breakdown exceeds the rate of protein synthesis at the whole body level in the post-absorptive state in all circumstances, including in normal subjects. Protein breakdown will always exceed the rate of protein synthesis in the post-absorptive state because the essential amino acids (EAAs) that are required for protein synthesis cannot be produced in the body. In the post-absorptive state the only source of EAAs is protein breakdown, and some of the EAAs released from protein breakdown are oxidized and thus not available as precursors for protein synthesis. The obligatory oxidation of some of the EAAs released from protein breakdown explains the negative protein balance in the control values of 36 normal men and women shown in Fig. 1. Regardless of the catabolic state, there is a significant acceleration of whole body protein breakdown relative to the rate of synthesis in the post-absorptive state (Fig. 1) [10–14]. On average, the net loss of body protein is approximately doubled in the catabolic state. The clinical management of catabolic patients must therefore place a high priority on maintaining the body protein pool with adequate nutritional and metabolic support to balance the potential adverse effects of a rapid loss of lean body mass.

1.3. “Muscle is the source of catabolized material”

In severely catabolic states the loss of muscle is so dramatic that it can be evident by physical exam. Although it is difficult to directly measure muscle mass in catabolic states, indirect measurements of body composition by using methods such as DEXA analysis support the notion of the preferential loss of muscle [15]. The net loss of body protein can be so extensive in catabolic states that both acute as well as long-term recovery is adversely affected. Consequently, understanding the mechanisms responsible for accelerated net loss of muscle protein is essential for devising targeted metabolic strategies.

There are several key aspects of muscle protein metabolism that are involved in the catabolic response. Most importantly, the rates of muscle protein synthesis and breakdown determine the net loss or gain of muscle protein. Other rates of importance in the regulation of muscle protein metabolism include the rates of transport of amino acids from blood into the intracellular space, and the rates of movement of amino acids from the intracellular pool into blood. Our current understanding of the catabolic response of muscle protein metabolism can be attributed to a large extent to the development of a stable isotope tracer method to quantify all of the rates shown schematically in Fig. 2 [16].

Please cite this article in press as: Wolfe RR, The 2017 Sir David P Cuthbertson lecture. Amino acids and muscle protein metabolism in critical care, Clinical Nutrition (2017), https://doi.org/10.1016/j.clnu.2017.12.010