The Impact of Metabolic Flexibility on Determining Nutrient Requirements

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Abstract

In determining nutrient requirements, we may be relying on the animal's ability to adapt or accommodate to different intakes. Accounting for nutritional adaptation can be challenging from a scientific point of view but has practical implications when determining nutrient requirements. How does metabolic flexibility impact the methods we use and our ability to determine nutrient requirements? Protein and amino acid metabolism will largely be used as examples as it is one of the more complex metabolic pathways and a frequently discussed topic.

Glossary of Abbreviations
AMDR: Acceptable Macronutrient Distribution Range
AP: Adequate Protein
DIAAS: Digestible Indispensible Amino Acid Score
DM: Dry Matter
DRI: Dietary Reference Intakes
HP: High Protein
LP: Low Protein
ME: Metabolizable Energy
MP: Medium Protein
RQ: Respiratory Quotient

What Is Metabolic Flexibility?

Phenotypic flexibility in physiological, morphological and behavioral traits can allow an organism to cope with environmental changes. Flexibility with respect to energy needs is important as it reflects the minimal energetic costs of living and is a primary characteristic in organism performance.[1] Metabolic flexibility is the capacity of an organism, tissue or cell system to alternate readily between fuel types.[2] From an evolutionary point of view, this type of flexibility may have provided an advantage with respect to growth, reproduction and even disease in an environment of changing food availability.[1] More currently, in the face of climate change, this flexibility may provide many advantages.[1]

Any conversation on metabolic flexibility should include two terms often used in the same conversation: adaptation and accommodation. The former is defined as the "modification of an organism or its parts that make it more fit for existence under the conditions of its environment."[3] This adjustment can be temporary or permanent, acquired through short-term or life-long processes, and may include behavioral, cultural, genetic, physiological, or structural changes designed to improve the organism's functional performance in the face of an ever-changing environment.[4] One of the key points of adaptation is that it represents a new or steady state compared to a similar system not required to adapt.[5] Second, it is important to note that adaptation does not leave all body functions unaffected, thus it involves choices between maintaining some functions at the expense of others.[6] The difference between adaptation and homeostasis is that homeostasis represents the same steady state, relying on regulatory factors that resist any imposing changes.[5] Homeostasis also happens on a different time scale than adaptation. Homeostasis occurs minute to minute or hour to hour, whereas adaptation is a slower response to the external environment.[5] The outcome of adaptation is often homeostasis.

Waterlow has summarized the concepts of nutritional adaptation as eight succinct points: 1) All animals adapt to their environments, otherwise they would not survive. 2) Adaptation often involves overspecialization and therefore loss of adaptability. 3) The adapted state is a sustainable state. 4) Adaptation and normal are two sides of the same coin. 5) Adaptation has a cost. 6) For every function there is a range of acceptable or sustainable states; adaptability keeps function within the acceptable range. 7) We need to define the acceptable range. 8) When applying these principles to humans and possibly animals, we cannot escape value judgments.[37]

In contrast, Frisancho defines accommodation as "responses to environmental stresses that are not wholly successful because even though they favor survival of the individual, they also result in some significant losses in some important functions."[4] Accommodation is used to describe a response that is not fully successful or one in which the preservation of a function of interest has not been achieved.[6]

How Is Metabolic Flexibility Measured?

There are a variety of ways one can scientifically evaluate metabolic flexibility. One general approach is the use of

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indirect calorimetry, which gives information regarding the amount of energy an animal uses. Indirect calorimetry also provides a respiratory quotient (RQ) (sometimes referred to as a respiratory exchange ratio). The respiratory quotient is calculated as the ratio of the volume of CO_2 produced to the volume of O_2 consumed. Respiratory coefficients for animals range from 1.0 (the value for pure carbohydrate oxidation) to ~0.7 (the value for pure fat oxidation). A value between these numbers represents a mixed diet composed of both carbohydrate and fat. A respiratory quotient may exceed 1.0 for an animal metabolizing carbohydrate to synthesize fat (as some animals do during hibernation). The respiratory quotient can include a contribution from protein; however, due to the complexities of amino acid metabolism, no single respiratory quotient can be assigned to the oxidation of protein in the diet.

When it comes to evaluating metabolic flexibility with regard to protein and amino acid metabolism and requirements, other approaches also are considered, but are not limited to, nitrogen balance, body composition, muscle strength, amino acid kinetics, 3-methyl histidine, and measurement of urea cycle enzymes. Many of these will be discussed in the context of various research studies in these proceedings.

Why Is Metabolic Flexibility Important?

Metabolic flexibility is important as it allows us to adapt or accommodate to nutrient availability in both health and disease. The availability of energy and other nutrients varies greatly over time. Physiologic, metabolic and environmental conditions change routinely, and organisms must adapt in kind. Scientific data supports that dogs adapt respiratory quotient to variations in carbohydrate and fat concentrations.[7] Several studies underscore the metabolic flexibility in cats fed wide variations in dietary protein, providing minimal protein requirements were met.[8,9,10]

Using indirect calorimetry, Russell, et al. (2002) investigated substrate oxidation when cats were fed moderate (35% ME) or high-protein (52% ME) diets.[9] Protein oxidation increased when cats were consuming a high-protein diet. The authors concluded that cats are more capable at adjusting protein metabolism than reported based on previously published enzyme data. However, only diets exceeding the minimum requirement for protein were evaluated, and adaptation to these protein concentrations could have been easily explained by allosteric and substrate/intermediate level regulation of the urea cycle and/or change in liver size.[8]

A second study evaluated protein oxidation in cats fed diets with protein concentrations below, at and above their requirement in order to test their ability to adapt substrate oxidation to dietary macronutrient concentration.[8] Semi-purified diets were fed containing protein at 7.5% (low protein, LP), 14.2% (adequate protein, AP), 27.1 % (medium protein, MP), and 49.6% (high protein, HP) of the calories. Using indirect respiration calorimetry and nitrogen balance, the ratio of protein oxidation:protein intake was highest when cats consumed the LP diet.[8] Protein oxidation approximated protein intake, provided the diet met the cat's minimum protein requirement.[8,9,10] Overall, the results supported the hypothesis that cats adapt protein oxidation to dietary intake provided protein requirements are met. However, the cats were unable to decrease protein oxidation to maintain nitrogen balance if fed diets below their protein requirement.[8]

Taken together, the cat demonstrates metabolic flexibility, albeit limited, to adapt to low-protein diets. This may be the result of evolutionary adaptation to a natural diet consisting of primarily protein.[11] The ability to upregulate urea cycle activity is a protective mechanism against ammonia toxicity after a high-protein meal and allows the utilization of amino acid carbon skeletons for gluconeogenesis.[8] High rates of protein oxidation only become a detriment when dietary protein content is below the cat's minimum requirement. Consequently, the cat exceeds its ability to adapt and faces a negative nitrogen balance, whereas most omnivores would continue to thrive.[8]

One study evaluating urea kinetics in the cat reported protein turnover to be one-half to one-third that in other mammals.[12,13] The results of this study did not explain the cat's need to catabolize amino acids at the high rates reported in numerous other studies.[12,13,14] Based on this finding, the authors concluded that the high-protein requirement is probably not due solely to their inability to downregulate hepatic protein catabolism in response to variations in dietary protein intake.[10,12,13,14]

More recently a model was proposed to explain the cat's high-protein requirement.[14] In summary, the model says that "... cats do not have a high-protein requirement per se, but rather a secondarily high elevated protein requirement in response to a high endogenous glucose demand ..."[14] The hypotheses that serve as the basis of this model include: 1) For its size, the cat has a relatively large brain and, secondarily, a high metabolic demand for glucose. Despite consuming a low-carbohydrate diet, the cat has developed metabolic strategies to meet a high-glucose requirement that does not include hyperketonemia. 2) Amino acids are directed to gluconeogenesis independent of dietary carbohydrate intake (obligatory gluconeogenesis). 3) Obligatory amino acid-based gluconeogenesis results in endogenous nitrogen losses that exceed the amount predicted for the cat's size, thereby explaining why the cat has a minimum protein requirement above that of other noncarnivorous species.[14]

While some may consider the capacity to upregulate urea cycle enzymes to assist with nitrogen disposal as metabolic flexibility, others may see this as a potential impairment. Indeed, Eisert rejects the idea that obligate gluconeogenesis reduces metabolic flexibility and leaves the cat incapable of adapting to a low-protein diet. The author instead offers the hypothesis that the risks of a transient negative nitrogen balance in a cat consuming a high-protein diet are relatively small compared to a possible compromise in brain function or other organ systems due to low glucose concentrations.[14]

What Happens when Metabolic Flexibility Is Impaired?

There are other examples in the scientific literature of metabolic inflexibility. The concept of metabolic inflexibility was originally proposed as a phenomenon of impaired fuel switching in skeletal muscle in obesity and diabetes but applies equally to fuel selection in the heart.[2] Cardiac muscle has a high-energy requirement and a preference for fatty acids as a fuel source. Therefore, it might be a natural conclusion that obesity-related differences in fatty acid availability and uptake might be detrimental to the heart. In support of that hypothesis, many studies report increases in myocardial fatty acid uptake and utilization in the physiological states of obesity and insulin resistance.[2,15] Further, it is apparent that the increased fatty acid uptake can contribute to impairments in myocardial function.[16,17]

How Do We (or Should We) Consider Metabolic Flexibility when Determining Nutrient Requirements?

It may help to consider the concepts of metabolic flexibility, adaptation and accommodation in relation to amino acid oxidation and protein metabolism and requirements by considering a few studies. One is an experiment designed to determine the effects of leucine metabolism and body protein turnover in healthy adult humans.[18] Subjects were fed leucine intakes of 30 mg/kg/day or 7 mg/kg/day for three weeks. The lower amount fed in this study, 7mg/kg/day, was suggested as the mean requirement based on earlier nitrogen balance studies.[19] The rate of protein turnover, as determined by the rate of nonoxidative leucine disappearance (or uptake into proteins), was significantly lower after three weeks for those subjects consuming 7 mg/kg/day. However, leucine balance was similar and approached equilibrium at both intake amounts. The investigators interpreted their findings to suggest that the lower leucine intake (7 mg) was below the limit of adaptive mechanisms and was, in fact, an accommodation to achieve body leucine balance at the expense of leucine uptake (protein synthesis) and protein turnover. The difficult question is whether the similar leucine balance between the two groups is equivalent in terms of health given that leucine uptake was diminished (and presumably reflects a lower rate of total body protein turnover) in subjects consuming 7 mg/kg/day.

It has been postulated that whole body protein turnover is important as it is associated with a change in the turnover of skeletal muscle proteins, which play a pivotal role in adaptation to inadequate nutritional conditions, trauma or illness.[20,21] Evidence supports that a high rate of protein turnover also is beneficial. Crabtree and Newsholme proposed that high-substrate passage through metabolic pathways ensured a precise and sensitive control mechanism to assure metabolic intermediates can be readily derived when cell or tissue demands were increased.[22,23] These same investigators went on to demonstrate that glutamine, derived from protein or amino acid metabolism in muscle where branch-chain amino acids provided the nitrogen for glutamine synthesis, was necessary for lymphocytes and other rapidly dividing cells.[24] A high rate of protein turnover would assure continued glutamine availability to meet lymphocyte function. Speculatively, a reduced rate of protein turnover (and availability of glutamine) might have adverse consequences. This example underscores the need to account for the principles of metabolic regulation when it comes to determining nutrient requirements. In particular, it highlights some of the changes in the systems responsible for maintenance of protein and amino acid balance at reduced protein intakes, which include: 1) reduced amino acid oxidation, 2) a decline in protein synthesis, and 3) changes in protein degradation.[6]

It also is important to acknowledge the interdependency of energy intake and protein requirements.[25] Energy balance has a significant effect on nitrogen balance. Increasing energy intake at a fixed quantity of nitrogen increases nitrogen retention. It has been documented in the scientific literature that different combinations of protein and energy restriction can result in different biochemical changes and clinical signs.[6,26] Furthermore, it appears there is a reduced efficiency of energy retention (utilization) in rodents and monkeys consuming protein-restricted diets.[27,28] Young and Marchini have speculated that the less-efficient retention in energy may offer an adaptive capacity to ingest more of the low-protein diet, thereby obtaining more nitrogen and amino acids to meet requirements.[6]

A more recent example in cats illustrates the discrepancy in protein requirements using nitrogen balance and assessment of lean body mass.[29] Adult male, neutered cats were adapted to a 36.6% protein (DM) extruded diet for one month and then either a low-(21.9% DM), moderate- (28.2% DM), or high-protein (36.6% DM) diet for two months after which time nitrogen balance and lean body mass were assessed. Weight loss increased in a linear manner with decreasing protein intake despite no significant differences in energy intake. Nitrogen requirements based on nitrogen balance were 1.5 g protein/kg body weight versus 5.2 g protein/kg body weight using lean body mass. The authors concluded that nitrogen balance studies are inadequate for determining optimum protein requirements. Moreover, cats can adapt to low dietary protein intakes and maintain nitrogen balance while depleting lean body mass.

This study raises the need to consider several possible methods of adaptation to low-protein diets. The first is simply the reduction in obligatory nitrogen loss. Obligatory nitrogen losses are defined as all nitrogen losses on a protein-free diet and are assumed to represent the minimal metabolic demands for nitrogen and amino acids.[30] The second is an increased efficiency of protein utilization. The efficiency of protein utilization is the slope of the line relating nitrogen balance to intake. Efficiency of utilization is a critical component in determining nutrient requirements. Nutrient requirements = metabolic demand (obligatory nitrogen losses)/ efficiency of utilization. It has been shown that dogs depleted of nitrogen used dietary nitrogen more efficiently than comparable control dogs.[31] It is assumed that variation in efficiency of utilization exists even within like populations and that this variation can be significant. The variation also may reflect highly variable biological values for protein sources thought to be of high quality.

A third adaptation is reflected in lean body mass. Waterlow (1985) has stated that a person on a submaintenance intake, provided it is not too low, will eventually achieve nitrogen equilibrium at the expense of loss of lean body mass.[32] However, he proceeds to raise the question, "At what point does this loss begin to matter in functional terms?" It has been suggested that there is probably an upper limit to lean body mass beyond which it will not increase regardless of protein intake.[32] Below this limit, there must be a range of levels that are functionally adequate and acceptable.[33] While functionality was not tested in their study, Laflamme and Hannah postulated that loss of lean body mass or reduced protein turnover can have adverse health consequences.[29,34,35,36] As lean body mass is lost, a pattern emerges. Brain is preserved, as are liver and other organs partly preserved, at the expense of lean body mass and skin. It has been suggested that we should consider titrating loss of lean body mass to special functions to find breakpoints and where adaptation fails.[37] Waterlow surmised, "There are likely numerous factors that promote adaptation to lower protein intakes. They may be small and difficult to measure, but their integrated result may be significant."[5]

As enumerated in the above examples, protein intake can vary widely, but the benefits and costs of that variation are not well-defined. The traditional model for determining nutrient requirements has been to define requirements for maintenance (using nitrogen balance) and then to account for various life stages such as growth, gestation or lactation. This is, however, controversial, especially regarding how adaptation should be considered when evaluating nitrogen balance data.[38] An adaptive metabolic demand model has been put forth to try to address protein requirements.[38] In summary, the model identifies metabolic demands for amino acids as a small but fixed component. It also incorporates a variable, adaptive component characteristic of habitual intake, representing amino acid oxidation rates and not impacted by acute protein intake. The adaptive component varies slowly with sustained changes in intake allowing nitrogen equilibrium to be reached.[38] In this model the protein requirements are the minimum intake that meets metabolic demands and maintains appropriate body composition/growth rates after accounting for any inefficiency of digestibility and metabolic needs.[39]

Several other outcomes emerge from this model that require consideration. Many studies examining nitrogen balance report efficiency of utilization of dietary proteins to be about 50%, even for high-quality proteins. In the metabolic demand model, efficiency of use is higher as metabolic demand is not assumed to be constant. Assessment of protein quality by amino acid scoring is complex. The model is fluid so the relationship between metabolic demand for essential amino acids and protein quality is complex and ever-changing. In fact, it is further complicated because: 1) Postabsorptive protein loss requiring replacement will vary daily, 2) Not all amino acids liberated postabsorption will be completely oxidized (i.e., lysine and leucine), and 3) Postprandial protein deposition will vary with dietary amino acid composition.[38] Considered together, these points suggest a complex response to varying intakes of nitrogen and amino acids. Contrast this to the traditional model in which the amino acid requirement pattern is consistent and measurable. The traditional approach enables amino acid scoring and determination of biological value. Utilization can then be predicted from protein digestibility-corrected amino acid scoring.[40] Complete details of the model can be found in a variety of references.[38,39,41,42]

Currently, dieticians and health care professionals are translating their own dietary guidelines into practice with a special focus on meeting protein requirements in a widely diverse population.[43] The most recent dietary reference intakes (DRI) for macronutrients contain expanded guidance for determining protein needs while also considering the relation of total calorie intake to protein, fat and carbohydrates.[43] This model also emphasizes the interrelatedness and interdependence of protein, fat and carbohydrate in diets. One underlying goal of this approach is the prevention of chronic disease. The interaction between macronutrients is reflected in the acceptable macronutrient distribution range (AMDR). Similar to points raised by Millward in his adaptive metabolic demand model, they also are considering not only protein quantity but also quality. The digestible indispensible amino acid score (DIAAS) accounts not only for the amount and distribution of essential amino acids in a protein source but also digestibility.

The purpose of setting nutrient requirements is twofold.[38] The first is to be able to formulate safe, effective diets by recommending appropriate amounts of nutrients. The second is to establish the framework for indicators of risk in populations (versus the individual). Defining protein requirements for any species continues to be controversial, in part, due to how metabolic flexibility enters into the equation. In discussions regarding the establishment of nutrient requirements, adaptation has been proposed to be central to the design and interpretation of outcomes pertaining to nitrogen and amino acid requirement studies.[38] In a relatively recent review, Hegsted wrote, “If the requirement of any nutrient is to be defined, the subjects must be allowed time to adapt. Otherwise, one simply estimates the nutrient supply in the current diet, which is of little nutritional significance.”[44] That said, how does one approach accounting for metabolic flexibility and/or adaptation in a practical and meaningful way? While suggestions on how to achieve this goal have been and continue to be proposed, clear consensus on a path forward has not been forthcoming. Clearly, this area deserves further investigations but is difficult, in part, due to the likely need to impose artificial conditions to try to answer many of the proposed questions. Future research should emphasize biochemical and metabolic responses to protein and amino acid intakes.[45]

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