1

Core Concepts of Nutrition

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Key messages

• The change in body reserves or stores of a nutrient is the difference between the intake of that nutrient and the body’s utilisation of that nutrient. The time-frame necessary to assess the body’s balance of a particular nutrient varies from one nutrient to another.
• The concept of turnover can be applied at various levels within the body (molecular, cellular, tissue/organs, whole body).
• The flux of a nutrient through a metabolic pathway is a measure of the rate of activity of the pathway. Flux is not necessarily related to the size of the pool or pathway through which the nutrient or metabolite flows.
• Nutrients and metabolites are present in several pools in the body. The size of these metabolic pools varies substantially for different nutrients/metabolites, and a knowledge of how these pools are interconnected greatly helps us to understand nutrition and metabolism.
• Darwinian theory of evolution implies a capacity to adapt to adverse conditions, including adverse dietary conditions. Many such examples can be cited. Some allow for long-term adaptation and others buy time until better conditions arrive.

1.1 Introduction

This textbook on nutrition and metabolism covers macronutrient aspects of nutrition in an integrated fashion. Thus, rather than considering the macronutrients separately, this book brings together information on macronutrients and energy in relation to specific states or topics (e.g. undernutrition, overnutrition, cardiovascular disease). Before considering these topics in detail it is necessary to outline the core concepts that underlie nutritional metabolism. The core concepts to be covered in this chapter are nutrient balance, turnover and flux, metabolic pools, and adaptation to altered nutrient supply.

1.2 Balance

As discussed in Chapter 3, nutrient balance must be considered separately from the concepts of metabolic equilibrium or steady state. In this chapter, the concept of balance is considered in the context of the classical meaning of that term, the long-term sum of all the forces of metabolic equilibrium for a given nutrient.

The concept of nutrient balance essentially restates the law of conservation of mass in terms of nutrient exchange in the body. It has become common practice to refer to the content of the nutrient within the body as a ‘store’ but in many cases this is not appropriate and the term ‘reserve’ is better. Thus, the idea of nutrient balance is summarised by the equation:

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\text{nutrient intake} - \text{nutrient utilisation} = \text{change in body nutrient reserves}
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The above equation can have three outcomes:

• zero balance (or nutrient balance): intake matches utilisation and reserves remain constant
• positive balance (or positive imbalance): intake exceeds utilisation and reserves expand
• negative balance (or negative imbalance): utilisation exceeds intake and reserves become depleted.

In relation to macronutrient metabolism, the concept of balance is most often applied to protein (nitrogen) and to energy. However, many research
Nutrition and Metabolism

studies now subdivide energy into the three macronutrients and consider fat, carbohydrate and protein balance separately. This separation of the macronutrients is valuable in conditions of altered dietary composition (e.g. low-carbohydrate diets) where a state of energy balance might exist over a few days but be the result of negative carbohydrate balance (using the body’s glycogen reserves to satisfy the brain’s requirement for glucose) matched in energy terms by positive fat balance.

Balance is a function not only of nutrient intake but also of metabolically induced losses. Fat balance is generally driven by periods where energy intake exceeds energy expenditure (positive energy balance) and by periods when intakes are deliberately maintained below energy expenditure, such as in dieting (negative energy balance). However, nutrient balance can also be driven by metabolic regulators through hormones or cytokines. For example, the dominance of growth hormone during childhood ensures positive energy and nutrient balance. In pregnancy, a wide range of hormones lead to a positive balance of all nutrients in the overall placental, foetal and maternal tissues, although this may be associated with a redistribution of some nutrient reserves from the mother to the foetus (Chapter 6). By contrast, severe trauma or illness will dramatically increase energy and protein losses, an event unrelated to eating patterns.

Balance is not something to be thought of in the short term. Following each meal, there is either storage of absorbed nutrients [triacylglycerol (TAG) in adipose tissue or glucose in glycogen] or a cessation of nutrient losses (breakdown of stored TAG to non-esterified fatty acids or amino acid conversion to glucose via gluconeogenesis). As the period of post-prandial metabolism is extended, the recently stored nutrients are drawn upon and the catabolic state commences again. This is best reflected in the high glucagon to insulin ratio in the fasted state before the meal and the opposite high insulin to glucagon ratio during the meal and immediate post-prandial period. However, when balance is measured over a sufficient period, which varies from nutrient to nutrient, a stable pattern can be seen: zero, positive or negative (Figure 1.1). It is critically important with respect to obesity that the concept of balance is correctly considered. While at some stage energy balance must have been positive to reach an overweight or obese stage, once attained most people sustain a stable weight over quite long periods.

In the context of the present chapter, it is worth reflecting on the reasons why the period to assess energy balance correctly varies for different nutrients.

**Fat and adipose tissue (Chapter 5)**
- There is a very large capacity to vary the body’s pool of adipose tissue. One can double or halve the level of the fat reserves in the body.
- The capacity to vary the level of TAG in blood en route to and from adipose tissue can vary considerably.
- Almost all of the TAG reserves in adipose tissue are exchangeable.

**Calcium and bone (Chapter 12)**
- The human being must maintain a large skeleton as the scaffold on which the musculature and organs are held.
- There is a very strict limit to the level of calcium that can be transported in blood. Excess or insufficient plasma calcium levels influence neural function and muscle function, since calcium is also centrally associated with both.
Only a small fraction (the miscible pool) of bone is available for movement into plasma.

Because of these differences, calcium balance will require months of equilibrium while fat balance could be equilibrated in days or at most a few weeks.

1.3 Turnover

Although the composition of the body and of the constituents of the blood may appear constant, this does not mean that the component parts are static. In fact, most metabolic substrates are continually being utilised and replaced (i.e. they turn over). This process of turnover is well illustrated by considering protein metabolism in the body. Daily adult dietary protein intakes are in the region of 50–100 g, and the rates of urinary excretion of nitrogen match the protein intake. However, isotopically derived rates of protein degradation indicate that approximately 350 g is broken down per day. This is matched by an equivalent amount of protein synthesis per day, with most of this synthesis representing turnover of material (i.e. degradation and resynthesis) rather than being derived *de novo* from dietary protein (Chapter 4).

Similar metabolic turnover occurs with other nutrients; glucose is a good example, with a relatively constant blood glucose concentration arising from a matching between production by the liver and utilisation by the tissues (Chapter 3).

The concept of turnover can be applied at various levels within the body (molecular, cellular, tissue/organs, whole body). Thus, within a cell the concentration of adenosine triphosphate (ATP) remains relatively constant, with utilisation being matched by synthesis. Within most tissues and organs there is a continuous turnover of cells, with death and degradation of some cells matched by the production of new ones. Some cells, such as red blood cells, have a long lifespan (c. 120 days), while others, such as platelets, turn over in a matter of 1–2 days. In the case of proteins, those with very short half-lives have amino acid sequences that favour rapid proteolysis by the range of enzymes designed to hydrolyse proteins. Equally, those with longer half-lives have a more proteolytic-resistant structure.

A major advantage of this process of turnover is that the body is able to respond rapidly to a change in metabolic state by altering both synthesis and degradation to achieve the necessary response. One consequence of this turnover is the high energy cost of continuing synthesis. There is also the potential for dysfunction if the rates of synthesis and degradation do not match.

The consequences of a reduction in substrate synthesis will vary between the nutrients, depending on the half-life of the nutrient. The half-life is the time taken for half of the material to be used up, and is dependent on the rate of utilisation of the nutrient. Thus, if synthesis of a nutrient with a short half-life is stopped, the level of that nutrient will fall quickly. By contrast, a nutrient with a long half-life will disappear more slowly. Since proteins have the most complex of structures undergoing very significant turnover, it is worth dwelling on the mechanism of this turnover. Synthesis is fairly straightforward. Each protein has its own gene and the extent to which that gene is expressed will vary according to metabolic needs. In contrast to synthesis, a reasonably small array of lysosomal enzymes is responsible for protein degradation.

1.4 Flux

The flux of a nutrient through a metabolic pathway is a measure of the role of activity of the pathway. If one considers the flux of glucose from the blood to the tissues, the rate of utilisation is approximately 2 mg/kg body weight per minute at rest. However, this does not normally lead to a fall in blood glucose because it is balanced by an equivalent rate of glucose production by the liver, so the net flux is zero. This concept of flux can be applied at the cellular, tissue/organ or whole body level, and can also relate to the conversion of one substrate/nutrient to another (i.e. the movement between metabolic pathways). Flux is not necessarily related to the size of the pool or pathway through which the nutrient or metabolite flows. For example, the membrane of a cell will have several phospholipids present and each will have some level of arachidonic acid. The rate at which arachidonic acid enters one of the phospholipid...
pools and exits from that phospholipid pool is often higher in the smaller pools.

### 1.5 Metabolic pools

An important aspect of metabolism is that the nutrients and metabolites are present in several pools in the body (Figure 1.2). At the simplest level, for a given metabolite there are three pools, which will be illustrated using the role of dietary essential fatty acids in eicosanoid synthesis.

In the **functional pool**, the nutrient/metabolite has a direct involvement in one or more bodily functions. In the chosen example, intracellular free arachidonic acid, released from membrane-bound stores on stimulation with some extracellular signal, is the functional pool. It will be acted on by the key enzyme in eicosanoid synthesis, cyclo-oxygenase.

The **storage pool** provides a buffer of material that can be made available for the functional pool when required. Membrane phospholipids store arachidonic acid in the sn-2 position at quite high concentrations, simply to release this fatty acid when prostaglandin synthesis is needed. In the case of platelets, the eicosanoid thromboxane A₂ is synthesised from arachidonic acid released into the cytoplasm by stimuli such as collagen.

The **precursor pool** provides the substrate from which the nutrient/metabolite can be synthesised. Linoleic acid represents a good example of a precursor pool. It is elongated and desaturated in the liver to yield arachidonic acid. Thus, the hepatic pool of linoleic acid is the precursor pool in this regard. Not all nutrient pools should be thought of in the concept of the precursor, storage and functional pool model outlined above. The essential nutrients and the minerals and trace elements do not have a precursor pool. Nevertheless, no nutrient exists in a single homogeneous pool and an awareness of the existence of metabolic pools is essential to an understanding of human metabolism. For example, one might expect that a fasted individual would show a fall in all essential nutrient levels in the plasma pool. In many instances this is not the case initially because of the existence of storage pools, such as liver stores of iron or vitamin A. In the case of folic acid, fasting causes a rise in blood folic acid levels and this is explained by the concept of metabolic pools. A considerable amount of folic acid enters the gut via the bile duct and is reabsorbed further down the digestive tract. Thus there is an equilibrium between the blood folate pool and the gut folate pool. Fasting stops gallbladder contraction and thus the flow of folate to the gut, and hence folate is redistributed from one pool to another.

Another example of how an awareness of metabolic pools helps us to understand nutrition and metabolism is the intracellular free amino acid pool. This is the functional pool from which protein is synthesised. As this pool is depleted in the process of protein synthesis, it must be repleted, otherwise protein synthesis stops. Moreover, it is not just the intracellular pool of amino acids that matters but the intracellular pool of essential amino acids or, more precisely, the intracellular pool of the most limiting essential amino acid. Calculations show that if the pool of the most limiting amino acid in mammalian cells was not replenished, protein synthesis would cease in under 1 h. This highlights the need to transfer the limiting amino acid across the cell membrane, which raises the question of how that pool is replenished. Effectively, it can only be replenished if there is a comparable rate of protein degradation to provide the key amino acid, assuming the balance is zero. Thus there are links between the protein pool of amino acids and the extra- and intracellular pools of amino acids.

The size of these various pools varies substantially for different nutrients and metabolites. When studying the activities of metabolic processes within the body, it is often necessary to measure or estimate the size of the various pools in order to derive quantitative information about the overall rates of the processes. In addition, the actual situation may be more complex than the simple three-pool model described.

**Figure 1.2** The pools in the body in which nutrients and metabolites may exist.
above. Nutritional assessment often involves some biochemical assessment of nutritional status. Blood is frequently the pool that is sampled and even there, blood can be separated into:

- erythrocytes, which have a long lifespan and are frequently used to assess folic acid status
- cells of the immune system, which can be used to measure zinc or ascorbic acid status
- plasma, which is used to ascertain the levels of many biomarkers
- fractions of plasma, such as cholesteryl esters used to ascertain long-term intake of polyunsaturated fatty acids.

In addition to sampling blood, nutritionists may take muscle or adipose tissue biopsies, or samples of saliva, buccal cells, hair and even toenails. Knowledge of how a nutrient behaves in different metabolic pools is critically important in assessing nutritional status. For example, the level of folic acid in plasma is determined by the most recent intake pattern and thus is subject to considerable fluctuation. However, since erythrocytes remain in the circulation for about 120 days, a sample of erythrocytes will represent very recently synthesised cells right through to erythrocytes ready for recycling through the turnover mechanism previously described. As erythrocytes do not have a nucleus, they cannot switch on genes that might influence folate levels, and so the cell retains the level of folate that prevailed at the time of synthesis. Thus, erythrocyte folate is a good marker of long-term intake. The free form of many minerals and trace elements is potentially toxic, and for this reason their level in the plasma is strictly regulated. Hence, blood levels are not used to assess long-term intake of selenium, but toenail clippings can be used.

### 1.6 Adaptation to altered nutrient supply

In many circumstances, the body is able to respond to altered metabolic and nutritional states in order to minimise the consequences of such alterations. For example, the brain has an obligatory requirement for glucose as a substrate for energy and it accounts for a significant part of resting energy expenditure. During undernutrition, where glucose input does not match glucose needs, the first adaptation to the altered metabolic environment is to increase the process of gluconeogenesis, which involves the diversion of amino acids into glucose synthesis. That means less amino acid entering the protein synthesis cycle of protein turnover. Inevitably, protein reserves begin to fall. Thus, two further adaptations are made. The first is that the brain begins to use less glucose for energy (replacing it by ketones as an alternative metabolic fuel). The second is that overall, resting energy expenditure falls to help sustain a new balance if possible (Chapter 8). Stunting in infants and children, reflected in a low height for age, can be regarded as an example of successful adaptation to chronic low energy intake. If the period of energy deprivation is not too long, the child will subsequently exhibit a period of accelerated or catch-up growth (Chapter 7). If it is protracted, the stunting will lead to a permanent reprogramming of genetic balance. In many instances, the rate of absorption of nutrients may be enhanced as an adaptive mechanism to low intakes. Some adaptations appear to be unsuccessful but work for a period, effectively buying time in the hope that normal intakes will be resumed. In essential fatty acid deficiency the normal processes of elongation and desaturation of fatty acids take place but the emphasis is on the wrong fatty acid, that is, the non-essential 18-carbon monounsaturated fatty acid (oleic acid, C18:1 n-9) rather than the deficient dietary essential 18-carbon polyunsaturated fatty acid (linoleic acid, C18:2 n-6). The resultant 20-carbon fatty acid does not produce a functional eicosanoid. However, the body has significant reserves of linoleic acid which are also used for eicosanoid synthesis and so the machinery of this synthesis operates at a lower efficiency than normal. Eventually, if the dietary deficiency continues then pathological consequences ensue. In effect, adaptation to adverse metabolic and nutritional circumstances is a feature of survival until the crisis abates. The greater the capacity to mount adaptations to adverse nutritional circumstances the greater the capacity to survive.

### 1.7 Perspectives on the future

These basic concepts of nutrition will remain forever but they will be refined in detail by the emerging
subject of nutrigenomics (Chapter 2). We will develop a greater understanding of how changes in the nutrient content of one pool will alter gene expression to influence events in another pool and how this influences the flux of nutrients between pools. We will better understand how common single nucleotide polymorphisms will determine the level of nutrient intake to achieve nutrient balance in different individuals.

Further reading


Websites

health.nih.gov/search.asp?category_id=29
http://themedicalbiochemistrypage.org/