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Review

A big picture view of precision nutrition: from reductionism to holism

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ABSTRACT

Purpose: This review describes the historical changes in nutrition philosophy from a reductionist to a holistic approach during the 20th century. Also, the role and efficient use of a holistic approach to precision nutrition are discussed. **Results:** Over the past century, significant progress has been made in human nutrition research, unraveling fundamental mechanisms of single nutrients on single targets or pathways. This kind of a reductionist approach has helped to save populations from nutrient deficiency diseases and improve associated health outcomes in large parts of the world. However, a new set of nutrition problems, like obesity and diet-related chronic diseases, are growing each year worldwide, increasing the financial burden on the health care system. A linear cause-effect association between single nutrients and a single physiologic effect, is insufficient to solve the complex nutrition-health relationships. Research that involves a more holistic rather than reductionist approach is needed to tackle a new set of nutrition problems. Recent advances in technology, informatics, and statistical methods are enabling an understanding of the diversity of individuals and the complex interactions between foods and human bodies, leading to the concept of "precision nutrition." **Conclusion:** The emerging goal of precision nutrition is to provide tailored dietary advice for maintaining health and preventing obesity and diet-related chronic diseases. The parts are already being installed. To grab the complexity, reductionism and holism must be used interdependently.

KEY WORDS: reductionism, holism, nutrient deficiency disease, diet-related chronic disease, precision nutrition

Introduction

Within 100 years since the description and naming of the first vitamin, nutrition research using a reductionist approach has achieved remarkable advances in knowledge of the chemistry, biology, and metabolism of vitamins [1]. Reductionism tends to explain the complex phenomenon with simple and tractable units, advocating that the whole can be defined by the sum of its parts [2]. However, the relationship between diets and health is complex and varies among individuals. Moreover, these factors may act in a synergy that cannot be adequately described using a reductionist approach [3]. This situation applies to the obesity epidemic and diet-related chronic diseases, which we are now facing as a new set of nutrition problems [4]. With the increase in theoretical life expectancy and a growing prevalence of obesity and diet-related chronic diseases, the number of life years with chronic diseases is continuously increasing [5]. For example, life expectancy in the Republic of Korea was up to 82 y (85 y for women and 79 y for men) in 2017, but healthy life years decreased from 65.7 (in 2012) to 64.9 y (in 2016), leaving more than 15 years of life in a chronic disease state with increasing human and financial burdens [6].

In systems theory, it has long been recognized that "the whole is more than the sum of its parts." Therefore, to handle these new nutrition predicaments, an alternative philosophy is needed to guide nutrition research [3]. A holistic approach may complement the existing reductionist approach and succeed to tackle new emerging nutrition challenges, by understanding diverse and complex nutrition-health interactions [4]. Recent advances in high-throughput omics technology and computational and statistical tools are now leading to the concept of precision nutrition that enables researchers to explore the current issues [7].

This review is divided into two parts. The first part discusses the historical events that have shifted nutrition philosophy from a reductionist to a holistic approach that occurred in the 20th century. The second part discusses the role and the efficient use of a holistic approach

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particularly regarding precision nutrition.

Philosophy Shifts in Nutritional Science from a Reductionist to a Holistic Approach

Nutritional Science in the First Half of the 20th Century: Reductionism

It was less than 100 years ago when Casimir Funk first introduced the idea of "vital amine" in food, by writing about the anti-beriberi factor extracted from polished rice. By the mid-20th century, all major vitamins and minerals had been isolated and synthesized. Also, biochemists and nutritional scientists excelled in understanding the roles of these micro-nutrients in preventing single nutrient deficiency diseases, conducting extensive research [8]. In 1933, Leslie Harris reviewed that nearly 1,000 papers had been published on vitamins in just 12 months [9]. The intervention studies generally focused on proving a simple cause-effect relationship between a particular nutrient and a specific nutrient deficiency disease, by removing and reintroducing single nutrients into cells, animals, and humans [10]. Epidemiological studies were performed usually to quantify the associations between a single nutrient or food intake and a given disease or health status, using the method to compare the results between the highest and the lowest or no consumption group [3,11].

With the success of the intervention and epidemiological studies, a new strategy that reduced the process into smaller, simpler, and, thus, more tractable entities became the predominant paradigm of nutritional science [12]. Since the methods are "reduced" into isolated entities, this technique has been termed "reductionism" [12]. Reductionism worked well, unraveling key roles of nutrients on the human body functions. Based on the linear cause-effect relationship between a single nutrient and a particular deficiency disease, the reductionism approach achieved a revolutionary success in saving millions of lives, through the development of dietary strategies to tackle serious nutrient deficiency diseases, such as beriberi, scurvy, pellagra, rickets, anemia, and xerophthalmia [8,10].

The reductionism approach also initiated the era of quantifying nutritionism [13]. Foods were fractionated and quantified into their essential nutrients, i.e., macro- and micro-nutrients, which parallels with the concept of nutritional recommendations [14]. The first recommended dietary allowances (RDAs) were announced in 1941 at the National Nutrition Conference on Defense, providing new guidelines for total calories, protein, calcium, phosphorus, iron, vitamin A, B_1, C, and D, riboflavin, and nicotinic acid. RDAs aimed to quantify nutrient intake levels for avoiding nutrient deficiency diseases but maintaining normal body function and growth [15]. In 1962, under the leadership of the Food and Agricultural Organization (FAO) Regional Office in Korea, the Korean RDAs were also initiated for total calories, protein, calcium, iron, vitamin A, D, C, B_1, and B_2, and niacin [16].

Nutritional Science in the Second Half of the 20th Century: Limitation of Reductionism

During the second half of the 20th century, economic development and technical advances in food processing allowed a significant reduction in the global incidence of calorie and protein malnutrition, and specific vitamin deficiencies. At the same time, however, obesity and non-communicable diseases, such as diabetes, cancer, and cardiovascular diseases, have emerged as new public health concerns [10]. Despite the success of reductionist nutrition research advocating the linear cause-effect relationship between a single nutrient and a specific deficiency disease, it was not applicable to obesity and diet-related chronic diseases [8]. The limitations of reductionism are mostly derived from the oversimplification of the reality [17]. Since the nutrition-health relations have complex features in nature and obey non-linear and multi-causal relationships, only investigating the effect of parts or the combination of some parts, at most, is not sufficient to explain the whole [2,14].

One good example of such a limitation related to the application of reductionism in nutritional research can be found in prospective studies investigating the effects of isolated antioxidant vitamin intake and cancer development [18,19]. The results were not without controversy. Although antioxidants become pro-oxidative after exerting their antioxidant effect in *in vitro* systems, the pro-oxidant formation is rapidly dampened by recyclable chain reactions involving glutathione in the human body [20]. However, at a super high dose, antioxidant vitamins may lead to toxic pro-oxidant actions, indicating non-existence of the linear cause-effect association [20]. In other words, as a network, antioxidants exert different, complementary, and synergic effects that cannot be fully understood solely by analyzing single targets.

Meanwhile, isolated vitamins may not act similarly as vitamins contained in raw, natural foods. Fardet *et al.* [21] insisted that food health potential depends on both the nutrient composition and food structure properties, often leading to contradictory findings. It is akin to the story of the blind men and an elephant: six blind men were each attempting to explain what an elephant looked like after touching the different parts of an elephant's body. Therefore, it was anticipated that a more holistic perspective of antioxidant potential would likely address some various aspects of antioxidants with the considerations of synergistic, antagonistic, or additive effects of multiple components and multiple targets.

Nutritional Science in the 21st Century: Holism

The ultimate goal of nutritional science is to help people make educated choices about their diets and lifestyles to achieve a long and healthy life without diseases [3,22]. What we learn during the second half of the 20th century may well indicate that the marked variation associated with food, human health and individuals, and the complexity of their interactions cannot be sufficiently described using a reductionist approach [4]. So how should complex human disorders and nutrient responses encountered while using a reductionist approach be addressed? Research that integrates a more holistic approach is needed in nutritional science to gain insights into understanding the multiorgan-involved complex physiological processes that occur in response to diets.

The reductionist nutrition approach prospered by using the tools of analytical chemistry and experimental biology. As such, recent advances in high-throughput omics technology, and computational and statistical tools may enable scientists to explore the current challenges effectively, by providing global measures reporting the diversity of individuals and complex interactions between foods and human bodies [3, 4, 23]. High-throughput omics technology includes genomics, transcriptomics, proteomics, metabolomics, and metagenomics. Nutrigenomics, or genomics in nutrition, refers to the study of how genes and dietary components interact to alter phenotype [24]. The three genomic categories where knowledge building is critically needed are human genomics, commodity plant and animal genomics, and microbial genomics [4]. Nutrigenomics encompasses an understanding about how the response to food components depends on an individual's genetic background (nutrigenetics), nutrient-induced changes in DNA methylation and chromatic alterations (nutritional epigenetics), and nutrient-induced changes in the expressions of genes (nutritional transcriptomics) and proteins (nutritional proteomics) [24]. Metabolomics is one of the newest omics and has been defined as a comprehensive analysis of the changes in many low molecular weight compounds and their fluxes through human metabolism in response to dietary treatments [4]. Metagenomics refers to studies of the combined genome of microbial communities using next-generation DNA sequencing, which accounts for differences in community structure among sampling sites, among individuals, and between healthy versus diseased states [25].

A Holistic, Multivariate Approach to Precision Nutrition

Large-scale high-throughput omics technologies and wearable devices are already being used to generate high-volume, multi-dimensional data related to health and diet, leading to precision nutrition [26]. Moreover, the computationally-intensive statistical methods, bioinformatics software, and custom software and algorithms are now available to integrate data from emerging technologies and traditional assessments, and data from single omics platforms with the multiple omics platforms and, ultimately, to systems biology [27]. This kind of holistic approach allowed insights into how foods and their constituents exert synergistic effects by interacting with biological targets and pathways to influence human health in a randomized clinical trial [28].

The development of a holistic approach to nutrition research has also led to the concept of "personalized nutrition." Nonetheless, challenges persist regarding the characterization of phenotypic differences between individuals that contribute to health status [4]. Nutrigenetics refers to the analysis of genetic variations and the response to specific foods [29]. Following the completion of the Human Genome Project, many efforts were made to investigate the role of single nucleotide polymorphisms in chronic diseases and to predict the response of individuals to different dietary interventions [30]. In some countries, including the Republic of Korea, nutrigenetic services are currently available, at least partially. However, any nutrition-related health outcome is not likely to be predicted based on differences between just one or several genetic profiles, because environmental, cultural, and behavioral factors may have overwhelming influences on genotypic variation in common non-communicable diseases [31]. Meantime, metabolomics has begun to receive academic attention, serving as a useful alternative or complement to reveal the complex effects of diet on health [4]. Although limitations still exist, metabolomics also provides new opportunities to detect prognostic markers for predicting the responders to nutritional interventions [32].

Concluding Remarks

A reductionist approach in nutrition research led to the remarkable advances in our understanding of the metabolism of nutrients and non-nutrient components in foods, explaining their functions within human organisms and, consequently, contributing to the prevention of nutritional deficiencies. However, reductionism seems to be insufficient to justify the complex system characteristics of diet-health associations. When considering the dynamic interaction of the parts, it is not surprising that “the whole is more than the sum of its parts.” With the advances in nutrition knowledge, high-throughput omics technologies, computational tools, wearable devices, and research strategies, we are now equipped to implement a holistic approach and, thus, overcome the limitation of a reductionist analysis. Reductionism and holism must be used interdependently and complementarily to tailor dietary advice for maintaining health and preventing obesity and diet-related chronic diseases, which is the emerging goal of precision nutrition.

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