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Review

Metabonomic approaches to nutrient metabolism and future molecular nutrition

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ABSTRACT

Metabonomics provides access to the environmental, diet, genetic and metagenetic integrative metabolic phenotype of individuals. Recent advances in spectroscopic and chromatographic techniques can capture metabolites and nutrients within a broad dynamic range. Applications to nutrition sciences have addressed nutrient metabolism and diet-related phenotypes under healthy and pathological conditions. Future molecular stratified nutrition requires development of comprehensive, quantitative profiling of nutrients to match the individual's specific requirements and metabolic peculiarities (metabolic phenotype) to improve health and dietary management of medical conditions.

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1. Introduction

Population aging and the pandemic of chronic diseases related to impaired metabolic, gastrointestinal and neurological functions represent a major burden for healthcare systems. Recent progress in understanding the relationships between nutrition and health has inspired the preventive role of diet in the onset of diseases and the management of medical conditions with medical foods. However, determining the dietary nutrient profile that would be adequate for an individual is challenged by the complexity of food composition and the biological range of human's physiological responses. Nutrition research had thus evolved from the typical measurements of the effects of single or a few nutrients to more analysis of the system, including genes, transcripts, proteins, and metabolites. Integration of this biological information is of paramount importance to delineate the ultimate metabolic nutritional phenotype of individuals. However, studies are naturally made complex by the large number of intrinsic and extrinsic factors at play, such as environmental stressors, drugs, diet, lifestyle, stress, and microbiome modulations [1,2].

The advent of omics technologies has made it possible to collect high-density biological readouts related to physiological and pathological processes. Their applications are driving a rapid shift from clinic-style investigations to large molecular epidemiology studies,

Abbreviations: GC, Gas chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; LC, Liquid chromatography; MS, Mass spectrometry; NMR, Nuclear magnetic resonance.

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aiming to enhance our understanding of the role of genetics, environmental factors and their interactions on individual susceptibility to disease [3].

Metabonomics is uniquely suited to measure the real endpoints of the physiological regulatory processes that result from molecular interactions between host and gut microbiota, environmental factors and diet [4]. Moreover, holistic profiling is now being applied to food analysis through the recently introduced foodomics, opening new analytical possibilities to connect food composition to nutrition and health at the molecular level [5].

Ultimately, application of metabonomics to nutrition sciences (i.e. nutritional metabonomics) and foodomics are foreseen as providing the molecular phenotypic basis resulting from the interplay between host, gut microbiota, environment and nutrient interactions. Such nutritional phenotypes would build the scientific foundations of future targeted nutrition matching specific nutrient requirements of the individual to maintain or improve health status or quality of life.

This article reviews nutritional metabonomics with respect to different analytical technologies, applications to nutrition studies and nutrition-related diseases in gastrointestinal, metabolic and brain health. We also provide perspectives on the development of the next generation of nutrient profiling that is expected to enable stratified nutrition at the system level.

2. Analytical approaches for nutritional metabonomics

Metabonomics measures metabolite concentrations and dynamics in cells, tissues, and circulating biological fluids, revealing not only the end products of enzyme expression and activity, but also the ultimate information contained in the genetic code [6,7]. Because specific physiological states, gene expression and environmental stressors can cause changes in the steady state of a biological system, monitoring the resulting metabolic variations provides unique insights into intra-cellular and extra-cellular regulatory processes involved in metabolic homeostasis.

Metabonomic applications extend from cellular systems to animal tissues and biofluids [8]. Metabonomic studies of biofluids show strong potential for clinical nutrition research. Metabonomics relies on the exploitation of high-density metabolic profiles generally collected from urine and blood plasma/serum samples by a broad range of statistical methods, usually catalogued into either supervised or non-supervised approaches to allow the recovery of the statistically and biologically relevant information. Metabolic profiles can be generated more or less comprehensively and quantitatively depending on the chosen analytical technique and method. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) have become analytical standards in nutritional metabonomics studies offering a broad panel of complementary techniques to analyze metabolic variations or metabolic fluxes in complex living systems and elucidate the molecular structure of metabolites (Table 1).

2.1. High-resolution NMR spectroscopy

NMR spectroscopy offers the unique prospect to profile holistically hundreds of metabolites with no *a priori* selection in an analytically robust manner and with no or very limited sample preparation [9,10]. Usually, parallel analysis of urine and blood plasma metabolic profiles captures complementary information on time-averaged and instantaneous homeostatic processes, respectively. More interestingly, NMR profiling of urine samples encapsulates and accumulates information on the metabolic activity of gut microbiota. When available, intact tissue samples can also be profiled by high-resolution magic angle spinning NMR spectroscopy using minimal sample preparation. Proton NMR spectroscopy is commonly used for sensitivity reasons, while the carbon-13 nucleus can also be measured, often for confirming molecular identity or even for structure elucidation purposes using multidimensional techniques.

2.2. Mass spectrometry (MS)

MS is commonly employed for global or targeted profiling [11,12]. It can be coupled to gas chromatography (GC) or liquid chromatography (LC), including at the nL scale, to enable highly sensitive metabolite analysis using a range of ionization techniques, but requiring preliminary sample preparation. A broad panel of methods is available for measuring classes of various metabolites and nutrients, such as amino acids (AAs), fatty acids, organic acids, vitamins and phytonutrients. Thanks to recent technological advances, MS analytical performance in terms of sensitivity, mass accuracy, scan rate and resolution improved to the point of allowing metabolic profiling of biological samples even in the absence of a preliminary chromatographic step, such as in lipid analysis (i.e. lipidomics) [13].

Table 1
Comparative summary of the main NMR and MS techniques applied in nutritional metabonomics

Technique	Main application	Advantage	Limitation
NMR	Global metabolic profiling, structural elucidation of metabolite*	Sample preparation, robustness, holistic, throughput (proton), structural data, can be quantitative	Sensitivity**, signal overlaps (resolution)
HRMS	Global metabolic profiling, structural elucidation of metabolite*	Sensitive, direct infusion, chromatography coupling, can be quantitative	Matrix effects (ion suppression), robustness§, data filtering required†
Targeted MS	Metabolic panel	Sensitive, quantitative, can be metabolic pathway specific	Prior knowledge on analytical targets‡, sample preparation, internal standards required for absolute quantitation
Stable Prior	isotopes knowledge on analytical targets, infusion/intake of stable isotopes required, in vivo isotopic dilution	Metabolic fluxes	Sensitive, quantitative, metabolic reaction/pathway specific

HRMS, High resolution mass spectrometry; NMR, Nuclear magnetic resonance.
* Structural elucidation often requires both NMR and HR mass data.
** Relative to MS.
§ Significant inter-instrument variations.
† HRMS-generated metabolic profiles may require tedious data filtering (e.g., peak alignment and removal of ion adducts) prior to statistical analysis.
‡ Metabolites of interest need to be predefined.