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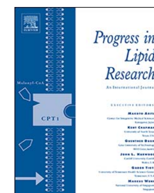

Review

Applications of nuclear magnetic resonance in lipid analyses: An emerging powerful tool for lipidomics studies

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ABSTRACT

The role of lipids in cell, tissue, and organ physiology is crucial; as many diseases, including cancer, diabetes, neurodegenerative, and infectious diseases, are closely related to absorption and metabolism of lipids. Mass spectrometry (MS) based methods are the most developed powerful tools to study the synthetic pathways and metabolic networks of cellular lipids in biological systems; leading to the birth of an emerging subject lipidomics, which has been extensively reviewed. Nuclear magnetic resonance (NMR), another powerful analytical tool, which allows the visualization of single atoms and molecules, is receiving increasing attention in lipidomics analyses. However, very little work focusing on lipidomic studies using NMR has been critically reviewed. This paper presents a first comprehensive summary of application of ^{1}H, ^{13}C & ^{31}P NMR in lipids and lipidomics analyses. The scientific basis, principles and characteristic diagnostic peaks assigned to specific atoms/molecular structures of lipids are presented. Applications of 2D NMR in mapping and monitoring of the components and their changes in complex lipids systems, as well as alteration of lipid profiling over disease development are also reviewed. The applications of NMR lipidomics in diseases diagnosis and food adulteration are exemplified.

1. Introduction

The suffix "*-om-*" originated as a *back-formation* from "genome". Because "genome" refers to the complete genetic makeup of an organism, people have made the inference that there exists some root, "*-ome-*", of Greek origin referring to *wholeness* or to *completion,* but such root is unknown to most or all scholars. Because of the success of large-scale quantitative biology projects such as genome sequencing, the suffix "*-om-*" has migrated to a host of other contexts. As research scientists increasingly sought to integrate biology with information science, they took up the use of omics. For biologists, -omics easily conveyed a key concept, the implications of a complex systems approach, an approach that is closely tied to study of networks, emergent properties and encapsulation concepts of theoretical computer science. "Proteomics" has been well accepted as a term for studying the proteome. Thereafter, scientists have proposed other "-omics" which are becoming accepted as well within biology field (http://omics.org/index.php/Omes_and_Omics). "Lipidomics" is one of the concepts. Based on the history and definition of "-omics", lipidomics is the study of the structure and function of the complete set of lipids (the lipidome) produced in a given cell or organism as well as their interactions with other lipids, proteins and metabolites (http://www.nature.com/subjects/lipidomics). Through the detailed quantification of a cell's lipidome, the kinetics of lipid metabolism, and the interactions of lipids with cellular proteins, lipidomics has already provided new insights into health and disease. However, the true power and promise of lipidomics is only beginning to be realized [1].

Quantitative techniques are essential for the lipidomics. Both normal and reversed phase high performance chromatography (HPLC) systems have been developed since 1970s for lipids quantification [2–5]. However, these procedures could not meet the requirements for the application of lipidomics to the study of human disease because

Abbreviations: MS, mass spectrometry; NMR, nuclear magnetic resonance; HPLC, high performance chromatography; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PG, phosphatidylglycerol; PS, phosphatidylserine; PA, phosphatidic acid; SM, sphingomyelin; LC-NMR, liquid chromatography-NMRs; SPE, solid phase extraction; TOCSY, total correlation spectroscopy; TAG, triglycerides; DHA, docosahexaenoic acid; NOE, nuclear overhauser effect; EPA, eicosapentaenoic acid; GC, gas chromatography; HSQC, ^{1}H, ^{13}C heteronuclear single quantum coherence; TLC, thin-layer-chromatography; PLs, phospholipids; CAD, coronary artery disease; AD, Alzheimer's disease; PUFAs, polyunsaturated fatty acids; FTIR, Fourier transform infrared spectroscopy; EDTA, ethylenediaminetetraacetic acid; D_2O, deuterium oxide; CDTA, cyclohexane diamine tetraacetic acid; CDCl3, chloroform-*d*; MeOH, methanol; $CHCl_3$, chloroform; Cs, cesium; $Cr(acac)_3$, chromium(III) acetylacetonate; SDS, sodium dodecyl sulfate; HDL, high density lipoprotein; LDL, low density lipoprotein; PEe, alkyl ether-linked phosphatidylethanolamine; DHSM, dihydrosphingomyelin

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they were plagued by cumulative errors from multistep chromatographic procedures [1]. Moreover, HPLC based lipidomics is not very informative because only limited lipids can be quantified from an individual run.

Mass spectrometry (MS) is an extraordinary sensitive tool for the detection of various classes, subclasses, and individual molecular species of lipids in a biological sample [1]. MS-based lipidomics has been extensively studied and reviewed by many scientists [6–9]. The limitations of most MS-based lipidomic methods include the differing abilities of lipid species to form ions and hence varying signal intensity as well as ion-quenching phenomena, in which the signal from poor ionizing lipids is quenched by more easily ionized species suppressing the former signal, which requires the prior separation of lipid species for accurate quantitation or the use of specialized MS. These factors result in a loss of sensitivity for many of the nonpolar lipid metabolites, as exemplified in a study of tuberculosis bacilli [10]. MS also destroys the sample during analysis and thus the sample cannot be recovered for other complementary analyses.

Compared to the MS method, NMR-based lipid analytical methods are less sensitive and typically limited by overlapping signals in either the ^{1}H NMR or ^{31}P NMR, and the low natural abundance of ^{13}C for ^{13}C NMR [11]. Additionally, NMR generally has a poor separation of signals, which produces crowded spectra when acquired as a 1D spectrum, hampering discrimination of resonances from the various compounds in complex mixtures [12]. Saturated fatty acyl residues (such as in PC 14:0/16:0 compared to PC 16:0/16:0) can be easily differentiated by MS while this is very difficult by NMR. However, the NMR-based methods have their own advantages compared to MS-based methods. In Table 1, we list a comparison between NMR and MS lipidomics methods. The main advantages of the NMR-based methods are: 1) no destruction of the sample; 2) high analytical reproducibility; 3) easy identification of molecular moieties; 4) high robustness of instruments; 5) possibility to obtain molecular dynamics information; and 6) direct quantitative information. With these advantages, the NMR-based methods have the potential as a powerful tool for lipidomics analysis.

Thousands of individual lipid molecular species are present in cells. This complexity implies that no single technique can effectively study all the lipid species. Therefore, even though the NMR-based method is not as sensitive as MS, it can still serve as a complementary method of MS to gain additional information and finally realize the global mapping of the lipidome. Especially, the development of 2D ^{1}H,^{1}H NMR [13], ^{1}H,^{13}C NMR [10] and ^{31}P,^{1}H NMR [14] techniques may bring new vitality for NMR in lipidomics analysis [15]. Although it is highly possible that the NMR-based methods could be used widely in lipidomics studies, until now the relevant studies are not a lot. Consequently, no relevant review has been published.

In this paper, we attempt to review the recent development of NMR-based methods for lipid analysis. Specifically, the applications of ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR and combinations of them are revisited. The authors would expect, to some extent, to attract more attention of the NMR-based lipidomics through this review.

Table 1
Comparison of NMR and MS based methods.

	NMR	MS
Detection limits	Low-micromolar at typical observation frequencies (600 MHz), but nanomolar using cryoprobes for ^{1}H NMR. Larger amount of sample (around 200 mg) for ^{13}C NMR. 10 mg for ^{31}P NMR. Lower amounts of sample loading can be compensated by more number of scans	Picomolar with standard techniques, but can be much lower with special techniques
Universality of metabolite detection	If metabolite contains hydrogens, carbons, or phosphorus, it will be detected, assuming the concentration is sufficient or no overlapping of chemical shift spins	Usually needs a more targeted approach. There can be problems with poor chromatographic separation; with the loss of metabolites in void volumes; with ion suppression (but this is reduced when using UPLC); lack of ionization; ability to run both + ve and − ve ion detection gives extra information
Sample handling	Whole sample analyzed in one measurement for ^{1}H NMR and ^{13}C NMR, while ^{31}P NMR sometimes needs different solvent; deuterated solvents needed	Different LC packings and conditions for different classes of metabolite; usually samples have to be extracted into a suitable solvent; samples have to be aliquoted but some recent studies have avoided the need for chromatography
Sample recovery	Nondestructive. Can be used for other analysis thereafter	Destructive but only small amounts needed
Analytical reproducibility	Very high	Fair
Sample pre-preparation	Simple and rapid [37]	
Ease of molecular identification	High, both from databases of authentic material and by self-consistent analysis of 1D and 2D spectra between ^{1}H and ^{13}C, or ^{1}H and ^{31}P	Difficult, often only the molecular ion is available; this needs extra experiments, such as routine tandem MS; GC–MS is generally better with accurate retention times and comprehensive databases of spectra
Time to collect data	1 min for 1D ^{1}H NMR. Around 60 min for 1D ^{13}C NMR. Less than 10 min for ^{31}P NMR	10 min for UPLC-MS run. At least 60 min for ESI-MS run
Robustness of instruments	High	Low
Molecular dynamics information	Yes, from T1, T2 relaxation time and diffusion coefficient measurements	No
Analysis of tissue samples	Yes, using MAS NMR	No
Availability of databases	Not yet comprehensive but increasing; several are available freely on the web; some commercial products also exist	Comprehensive databases for electron impact MS allow spectral comparisons; For electrospray ionization, as is usual in LC-MS, only mass values can be compared
Reliable and reproducible quantitative data of phospholipids	Yes	Unreliable. Different phospholipids have quite different response factors in ESI source and a direct comparison among all these classes is often hindered by several other factors. Neutral membrane lipids (PC, pPC, ePC, SM) are usually detected and quantified in positive ESI ion-mode whilst anionic membrane lipids (PE, PS, PG, PI, CL) require negative ESI ion-mode conditions. It is not a major disadvantage with modern MS devices that switch very rapidly between positive and negative polarity
Resolution for the same class of lipids [37]	Weak. Almost the same ^{1}H- and/or ^{31}P NMR spectra irrespective of the acyl chain length, number and position of unsaturation	High
Derivation needed	No	Yes. For GC–MS

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