NMR of lipids and membranes

Ewa Swiezewska*[a] and Jacek Wójcik[a]
DOI: 10.1039/9781849734851-00320

1 Introduction

The chapter on NMR of lipids and membranes summarizes the literature published between June 2010 and May 2011. The reviewed material has been arranged in thematic sections which are focused on selected aspects of lipidology, *i.e.* proteins/peptides – lipids interactions in the membranes, covalently lipidated proteins, non-covalent lipoprotein complexes, lipids in the membranes and glycolipids. A separate section devoted to metabonomic studies is finally followed by a brief summary of the new NMR methods designed to study peptides/proteins and lipids. We included in our review only those papers which were accessible, peer-reviewed and printed. Finally, we would like to admit that because of the space limits this review covers only a selection of the published data.

2 Proteins/peptides – lipids interactions in the membranes

Studies on interactions of peptide/proteins with lipids are still a big challenge in spite of the development of many new NMR techniques. Various approaches employing simplified model lipid-protein interacting systems and also natural partners interactions are summarized below.

a Effect on lipid

Static NMR (^{2}H and ^{31}P) and rotational-echo double-resonance NMR (^{13}C REDOR) spectroscopy has been applied to probe the structure and motion of model lipid membranes with bound human immunodificienct virus (HIV) fusion peptide by Gabrys *et al.*[1]

Cheng *et al.*[2] have used solid-state ^{31}P NMR to determine the mode of action of several aurein (antimicrobial peptide) mutants on mechanically aligned POPC/POPG bilayers. Dudkina *et al.*[3] have elucidated incorporation of water-soluble proteins into the PC liposomes using ^{31}P NMR spectra. Solid-state ^{31}P and ^{2}H NMR has been used by Sherman *et al.*[4] to investigate the effect of antimicrobial peptide fallaxidin on the dynamics of physpholipid multilamellar vesicles (mammalian-like DMPC and bacterial-like DMPC/DMPG). The ^{31}P and ^{2}H NMR solid state experiments have been used by Fernandez *et al.*[5] to show the differences in the interactions of the synthetic P5 antimicrobial peptide with the DPMC and anionic (DPMC/DPMG) bilayers. Changes in membrane dynamics of DPME/DPMG system upon addition of the antimicrobial maculatin 1.1 have been characterized by Sani *et al.*[6] with ^{31}P MAS spectra.

The selectivity of antimicrobial peptides, PG-1 and IB484 against Gram-positive and Gram-negative bacteria has been studied by Su *et al.*[7] The LPS-rich and POPE/POPG membrane disorder caused by these

[a]*Institute of Biochemistry and Biophysics, Polish Academy of Sciences, ul. Pawińskiego 5a, Warszawa, Poland 02-106. E-mail: ewas@ibb.waw.pl*

arginine rich peptides have been observed using a range of solid-state heteronuclear NMR experiments, including ^{31}P MAS, ^{13}C CP-MAS, ^{13}C-^{13}C DARR, DIP-SHIFT and ^{13}C-^{31}P REDOR.

Farver *et al.*[8] have elucidated the effect of pulmonary surfactant protein B (N-terminal 25 amino acids) on lipid organization and polymorphism *via* solid-state ^{31}P and ^{2}H NMR.

Haney *et al.*[9] have reviewed techniques, including 2D NMR and ^{31}P NMR, to study antimicrobial peptides-lipids interactions that produce positive or negative membrane curvature or cubic lipid phases.

b Effect on peptide/protein

Ieronimo *et al.*[10] have analyzed the effect of antimicrobial peptide with a selectively ^{19}F labelled 4-CF_3-phenylglycine from *Xenopus laevis* on the protoplast membrane from bacterium *Micrococcus luteus* and from human erythrocytes using ^{19}F NMR.

Buer *et al.*[11] have examined the feasibility of application of solution phase ^{19}F NMR to study peptide-membrane interaction using the antimicrobial peptide MSI-78 labelled with trifluoroethylglycine and model vesicles.

^{15}N solid-state NMR spectroscopy has allowed Salnikov and Bechinger[12] to find that antimicrobial peptide, magainin 2 exhibits stable in-plane alignments associated with the surface of DPMC/DPMG membranes whereas PGLa adopts a number of different topologies within the membrane depending on lipid composition.

Bojko *et al.*[13] have analyzed the effect of fatty acid on interactions of theophyline (diuretic, cardial stimulant and asthma medicament) with human serum albumin by means of ^{1}H NMR. The effect of phosphorylation on the structure of phospholamban (transmembrane protein that regulates the cardiac cycle) incorporated into DOPC/DOPE mechanically oriented membranes has been elucidated by Chu *et al.*[14] by static ^{15}N solid-state and ^{31}P NMR. The same group, Chu *et al.*,[15] has analyzed the effect of N27A mutation on phospholamban dynamics by ^{2}H and ^{15}N solid-state NMR.

Mineev *et al.*[16] have analyzed the spatial structure of the heterodimeric complex formed by transmembrane domains of ErbB1 and ErbB2 receptors embedded into DMPC/DHPC bicelles by solution NMR (2D and 3D $^{1}H^{15}N$ and $^{1}H^{13}C$ HSQC, TOCSY, HNCA, HN(CO)CA, HNCACB and CBCA(CO)NH, HCCH-TOCSY, ^{1}H NOESY experiments).

Franzoni *et al.*[17] have compared the structure and binding properties of the main cytosolic retinol carriers – cellular retinol-binding proteins types I and II (CRBP-I and II) using 2D TOCSY, NOESY, HSQC and 3D NOESY-HSQC spectra.

Structural studies on the ABC transporter ArtMP from *Geobacillus stearothermophilus* in native lipid environment have been performed by Lange *et al.*[18] by ^{13}C MAS NMR. Using ^{1}H spin diffusion solid-state NMR experiments with ^{13}C and ^{31}P detection, Luo and Hong[19] have determined the water accessibility of the M2 transmembrane domain (of influenza A virus) in virus-envelope-mimetic lipid membranes.

Shi *et al.*[20] have applied ss MAS NMR (3D NCOCX, NCACX, CONCA nd 4D CONCACX experiments) to characterize bacterial light-driven retinal-binding proton pump – proteorhodopsin) in DMPC/DMPA liposomes.

2D NMR has been used by Yamamoto *et al.*[21] to elucidate the structures of a series of designed α-helical peptides of various degrees of hydrophobicity and stability, and to study their influence on the formation of two lipid domains in an anionic liposome; by Zheng *et al.*[22] to study the structure of core peptide, CP, in aqueous solution and in DPC micelles; by Mishra *et al.*[23] to determine the structure of a 10-residue class G* peptide from apolipoprotein J in DPC micelles; by Grace and Cowsik[24] to solve the conformation of non-mammalian tachykinin physalaemin in DPC micelles where lipid-induced α-helix has been found from Pro^4 to the C-terminus; by Toke *et al.*[25] to determine a helix-break-helix conformation of maximin-4 in SDS micelles; by Saravanan and Bhattacharjya[26] to solve 3D structure of 22-residue peptide derived from fowlicidin-1, VK22 in DPC micelles; by Walrant *et al.*[27] to investigate the secondary structure of three basic cell penetrating peptides (R9, RW9 and RL9) in DPC or SDS micelles; by Plesniak *et al.*[28] for initial structural characterisation of the *Y. pestis* Ail membrane protein in DPMC, DHPC and LPG micelles (the β-barrel has been found and additionally confirmed with SSNMR measured in bilayers); by Metcalf *et al.*[29] to explore dynamic behaviour of the cross-linked αIIb and β3 cytoplasmic domains in DPC micelles.

2D heteronuclear solution NMR spectra of an 18-residue N-terminal fragment of SP-B, unmodified and with oxidized tryptophan in the presence of SDS or DPC have been measured by Sarker *et al.*[30] The solution as well as solid state ^2H NMR POPC bilayers data have indicated that tryptophan oxidation causes substantial disruption in helical structure of the peptide and lipid interactions.

It has been shown by Lorieau *et al.*[31] that charge-dipole interactions between the N-terminal amino group (Gly^1) and the second helix additionally stabilize helical hairpin structure of influenza hemagglutinin fusion peptide in DPC micelles. From pH dependence of ^{15}N and ^{13}C chemical shifts of Gly^1 measured with the 3D HACAN CH_2-TROSY experiment pK value of 8.73 has been estimated. The structure of bombolitin II (BLT2), the heptadecapeptide from the venom of bumblebee bound to DPPC membrane has been studied by Toraya *et al.*[32] ^{13}C NMR and ^{15}N REDOR spectra revealed that the structure of BLT2 is a straight rod of α-helix. ^{15}N solid-state NMR spectroscopy has allowed Heinzmann *et al.*[33] to confirm that maximin-4 in DPMC/DPMG micelles preserves the kinked conformation found for this peptide in the solution.

T-state structural topology of phospholamban (PLN) pentamer in lipid bilayers has been confirmed by Verardi *et al.*[34] using a hybrid solution and solid-state NMR method. For this purpose 3D NMR solution spectra have been measured for PLN with DPC micelles; 2D DARR MAS and 2D ^1H,^{15}N-PISEMA spectra have been measured for PLN with mechanically aligned DOPC/DOPE bilayers.

^2H NMR spectra have been used by Gu *et al.*[35] to monitor the average indole ring orientations and motions in doubly Phe-substituted gramicidin A analogues, [Phe13,15]gA and [Phe9,11]gA in DPMC oriented samples: different backbone conformations have been found, the single stranded $\beta^{6.3}$-helical channel and double stranded, respectively.

Ordered conformation of distinctin on the surface of the membrane has been documented by Verardi *et al.*[36] using ^{15}N, ^{31}P, [^1H-^{15}N]-HSQC and

SAMPI4 SSNMR; POPC/DOPE and POPC/DOPA bilayers have been used for this purpose.

Grasnick *et al.*[37] have studied the conformation, aggregation and dynamics of five selective CF_3-Phg and four selective D_3-Ala labels of the HIV fusion peptide embedded in phospholipid model membranes using ^{19}F and ^{2}H solid state NMR.

$^{1}D_{HN}$ residual couplings, relaxation rate constants R_1 and R_2 and ^{1}H-^{15}N NOE's have been measured by Stewart *et al.*[38] for the wild type C1B domain of protein kinase Cα, C1Bα and its Y123W mutant. The differences in the conformational behaviour between both proteins have been localized to the hinge regions of diacylglycerol binding loops that may account for the >100 fold increase in the mutant binding affinity to lipid membranes containing DAG.

^{1}H,^{13}C and ^{1}H,^{15}N HSQC spectra have been used by Gustavsson *et al.*[39] to investigate conformational changes upon chemical unfolding of unphosphorylated monomeric phospholamban (AFA PLN) and its phosphorylated form (pS16-AFA-PLN) in the presence of DPC micelles. In addition the [^{1}H,^{15}N] SEA-CLEANEX spectra have been measured for the peptides and for other pseudophosphorylated S16D-AFA-PLN, and S16E-AFA-PLN mutants. The resulting exchange data, averaged [^{1}H,^{15}N]–NOE and normalized chemical shifts have been shown to correlate linearly with inhibition of each peptide.

Lu *et al.*[40] have found that the peptide corresponding to the single transmembrane segment of APP exists partially in nonhelical conformations in POPC bilayers; ^{13}C NMR have been used in these studies.

The presence of the multiple resonances per site of membrane bound transmembrane domain of M2 in ^{15}N and ^{13}C SSNMR spectra measured under different conditions has been attributed by Hu *et al.*[41] to different conformational states of the peptide.

Using ^{13}C solid-state NMR and $^{13}C_1$-Val_1 gramicidin in DPMC bilayers Jones *et al.*[42] have demonstrated that the valine residue exist in two slowly exchanging conformations with lifetimes of several seconds.

Molecular segments engaged in fast, large amplitude fluctuations (so-called '*J*-residues') of proteorhodopsin in DMPC/DMPA bilayer have been identified using high-resolution solid-state NMR by Yang *et al.*[43] The influence of lipid bilayer properties, water and temperature on the protein dynamics has been studied using a broad range of 1D and 2D *J*- and dipolar coupling-based experiments, *i.e.* CC-INEPT-TOBSY, CC-DARR, ^{13}C-CP, ^{13}C-INEPT, HC-INEPT-HETCOR and WISE spectra.

McDonald *et al.*[44] have studied orientation and dynamics of three helical polypeptides comprising GpATM dimerization motifs in POPC bilayers; ^{2}H NMR spectra have been measured for this purpose.

Vostrikov *et al.*[45] have studied importance of outer tryptophans in Ac-GWW$(LA)_n$WWA-NH_2 peptides on the peptide tilt within lipid bilayer membranes. In these studies the peptides of the sequence Ac-GXALW-$(LA)_6$LWLAXA-NH_2 (where X = W, K, R or G) and DLPC, DMPC and DOPC bilayers have been used. With the aid of ^{2}H NMR it was found that W5 and W19 determine the direction of the tilt.

It has been shown by Kalli *et al.*[46] that mutations in the four basic residues in the talin F2 domain reduce the affinity of the talin head (F2-F3,

Tal2$_{198\text{-}408}$) domain for the membrane and change its relative orientation in the bilayer. These findings have been supported by monitoring shift perturbations in ^{1}H-^{15}N HSQC NMR spectra of mutated versus wild type domains in the presence of liposomes.

The effect of binding of palmitic acid on the structure and dynamics of the Sterol Carrier Protein of mosquitoe *Aedes aegipty* has been analyzed by Singarapu *et al*.[47] by a series of two- and three-dimentional heteronuclear NMR spectra, *e.g*. ^{1}H-^{15}N HSQC, HNCO, HNCACB, CBCA(CO)NH, ^{15}N-resolved ^{1}H-^{1}H NOESY, ^{13}C,^{15}N-filtered/^{15}N-edited ^{1}H-^{1}H NOESY, ^{13}C,^{15}N-filtered/^{13}C-edited ^{1}H-^{1}H NOESY, ^{13}C-filtered ^{1}H-^{1}H TOCSY.

The mechanism of binding interaction between lysozyme and liposomes composed of phosphatidylcholine and cholesterol has been investigated with the aid of ^{31}P NMR by Witoonsaridsilp *et al*.[48]

Fatty acid binding protein has been studied by He *et al*.[49] who have exploited ^{15}N-edited HSQC signal formed during stepwise ligand (oleate) titration to yield the stoichiometric characterization of the complex.

Płoskoń *et al*.[50] have analyzed the involvement of bacterial acyl carrier protein (ACP) in fatty acid biosynthesis by acquiring the ^{1}H-^{15}N sensitivity enhanced HSQC, HNCACB, CBCA(CO)NH, HCCH-TOCSY NMR spectra of intermediates covalently bound to ACP.

Lowden *et al*.[51] have used ^{1}H, ^{13}C and 2D TOCSY, NOESY, HMQC and HMBC spectra to prove the presence of *cis*-palmitoleate (16:1) bound to the pocket in the N-terminal domain of ToxT (*Vibrio cholerae* transctription factor).

Pettersson-Kastberg *et al*.[52] have elucidated how the lack of native three-dimentional structure in the α-lactalbumin protein positively contributes to the selective *in vivo* tumoricidal activity of the complex of this protein with oleic acid; 1D ^{1}H and diffusion NMR spectra were obtained.

The structure of p7 protein of hepatitis C virus (forming ion channel) incorporated into the 14-O-PC/6-O-PC bicelles has been studied by Cook and Opella[53] by solid state NMR (1D ^{15}N, 2D SAMMY spectra). Cook *et al*.[54] have also established an efficient protocol for p7 overproduction in *E. coli*; and Cook and Opella[55] have suggested a model of the architecture of p7 in magnetically aligned DHPC micelles using solution NMR (^{1}H,^{15}N HSQC, HNCA, ^{1}H,^{15}N NOE experiments) and a solid-state NMR.

It has been shown by Fan *et al*.[56] that it is possible to obtain solid state NMR spectra of a eukaryotic 7TM helical protein in lipids (DMPC/DMPA) with the resolution leading to the assignment of majority of backbone and side-chains resonances.

Several 3D SSNMR experiments have been employed by Shi *et al*.[57] to solve the structure of a seven-helical transmembrane photosensor, sensory rhodopsin from *Anabaena sp*. PCC 7120 in lipid environment. A number of notable structural differences have been found in comparison to X–ray data.

Two dimensional ^{1}H,^{15}N-TROSY spectra of hVDAC1 in LDAO have been measured by Villinger *et al*.[58] The protein dynamics was analyzed in detail and compared with its X-ray structure.

Concepts and novel developments in oriented solid-state NMR used for investigation of membrane associated polypeptides have been reviewed by Bechinger *et al*.[59] Hong and Su[60] have reviewed solid-state NMR techniques

used to study the structure and dynamics of cationic memebrane peptide and proteins.

Investigation of transmembrane alignment of host defence peptides with the aid of ^{15}N solid-state NMR spectra has been reviewed by Bechinger.[61]

Chicken ileal bile-acid-binding protein 3D structure has been solved by Guariento *et al.*[62] with the aid of 3D heteronuclear NMR spectroscopy and its interactions with glycocholic and glycochenodeoxycholic acids have been monitored with ^{1}H,^{15}N HSQC spectra.

c Simultaneous elucidation of the effects on lipid and protein

Butterwick and MacKinnon[63] have used 2D (TROSY HSQC) and 3D NMR (TROSY, NOESY) to determine the structure and phospholipid interface of the voltage-sensor domain from the voltage-dependent K^+ channel (from bacteria *Aeropyrum pernix*); association of bilayer-forming phospholipids was analyzed (fast HSQC spectra) using paramagnetically labelled compounds (16-doxyl PSPC).

Walther *et al.*[64] have used solid-state ^{31}P and ^{15}N NMR to resolve the membrane alignment of the pore-forming $TatA_d$ (subunit of translocase responsible for protein export in *Bacillus subtilis*) and subsequent membrane lipid orientation in DMPC/DMPG/6-O-PC bicelles; high-resolution 2D separated local field method – polarization inversion spin exchange at the magic angle (SAMMY) experiment was used.

Solid-state 2D ^{1}H-^{13}C and 3D ^{1}H-^{13}C-^{13}C MAS NMR has been applied by Kijac *et al.*[65] to examine lipid-protein interface in POPC nanodiscs containing truncated membrane scaffolding protein (MSP1) and to determine the gel-to-liquid crystal lipid phase transition.

Schmick and Weliky[66] have determined the fraction of parallel structure in membrane (14-O-PC/14-O-PG/cholesterol) -associated N-terminal region of gp41 by solid-state ^{13}C MAS NMR (REDOR experiment).

The effect of anesthetics (halothane or isoflurane) on the structure and dynamics of transmembrane domain T2 of the neuronal nicotinic acetylcholine receptor incorporated into DMPC/DHPC bicelles has been investigated by Cui *et al.*[67] using solid-state ^{2}H and 2D ^{15}N-^{1}H PISEMA NMR experiments; the effects of anesthetics on the lipid bilayers have been followed too.

Pedò *et al.*[68] have performed NMR investigation (^{1}H,^{15}N TROSY, ^{1}H,^{15}N HSQC, 2D ^{15}N-edited NOESY) on the role of membranes (DMPG liposomes) in the binding of bile acids to bile acid binding protein.

Stark *et al.*[69] have suggested the biological function of YndB of *Bacillus subtilis* by NMR titration experiment (2D ^{1}H,^{15}N HSQC) following the *in silico* screen of lipid ligands. The structure and alignment of the cationic antimicrobial peptide arenicin incorporated into POPC or POPE/POPG membranes have been evaluated by Salnikov *et al.*[70] using ^{31}P and ^{15}N solid-state NMR (1D and 2D PISEMA experiment). Mao *et al.*[71] have elaborated a *E.coli*-based Single-Protein-Production system for solid-state ^{13}C MAS NMR analysis of uniformly ^{13}C, ^{15}N enriched ATP synthase subunit c in natural bacterial membrane. Park *et al.*[72] have characterized the local and global dynamics of the chemokine receptor CXCR1 using a combination of solution NMR (^{1}H,^{15}N HSQC, TROSY, 3D ^{15}N-edited

NOESY-HSQC, HNCA, HNCOCA experiments in isotopic bicelles) and solid-state NMR (1D stationary and MAS ^{15}N spectra using magnetically oriented and unoriented bicelles).

Interaction of *de novo* synthesised K4 peptide with phospholidpids has been analyzed by Legrand *et al.*[73] with the ^{31}P and PSGE NMR experiments.

Thennarasu *et al.*[74] have studied the interaction of the synthetic peptide $(KFAKKFA)_3$-NH_2, MSI-367 with the POPC bilayers using ^{2}H and ^{31}P NMR and found that the peptide is localized at the membrane surface.

The effects of peptide hydrophobicity on its incorporation in phospholipid membrane have been investigated by Orädd *et al.*[75] using three variants of the antimicrobial peptide CNY21, POPE or POPC membranes and ^{2}H and PSGE NMR spectroscopy.

Sugawara *et al.*[76] have investigated interaction of several catestatin-derived peptides with POPC/POPS micelles. It appears that these peptides adopt partially α-helical structure whereas the ^{31}P and ^{15}N solid-state NMR data indicate that this short helix causes disordering at the level of the membrane phospholipid head groups.

^{31}P NMR spectra measured by Cheng *et al.*[77] for POPC/POPG and CL/POPG bilayers interacting with aurein 2.2 and its variants have revealed the importance of membrane composition for functioning of the aurein peptides.

$^{13}C[^{31}P]$-REDOR SSNMR spectra have been measured by Hughes *et al.*[78] for PLM38-72, the phospholemman cytoplasmic domain with kidney membrane revealing peptide-lipid interactions. Kobashigawa *et al.*[79] have proposed phosphoinositide-incorporated lipid-protein nanodiscs as a tool for studying protein-lipid interactions with the aid of proton and ^{31}P NMR.

He *et al.*[80] have used 3D heteronuclear NMR spectra to solve the structure of the FAPP1 pleckstrin homology domain and ^{1}H,^{15}N HSQC spectra to monitor on the molecular level interaction of the protein with phosphatidyloinositol 4-phosphate. The same type of experiments has been used by Ankem *et al.*[81] to demonstrate the C2 domain of Tollip binding to phosphoinositides in the presence of Car^{2+} and by Zhang *et al.*[82] to monitor binding of the ^{15}N-labelled Grp1 PH to different 5-stabilized phosphatidyloinositol 3,4,5-triposphate analogues. ^{1}H,^{15}N HSQC spectra have served Fernandes *et al.*[83] to study interactions of the matrix protein of HIV-1 with phosphatidylinositol phosphates.

The S227-245 segment of glycosyltransferase atDGD2 has been evaluated by Szpryngiel *et al.*[84] as the possible site involved in lipid interactions. The induced α-helical structure of the segment in DPC micelles has been found using 2D NMR techniques and the interactions of the peptide with zwitterionic or anionic bicells have been checked by measurement of diffusion coefficients in PFG NMR experiments.

Hydrodynamic radii of wt, nit-Y39F and Y125/133/136D α-synuclein have been measured by Sevcsik *et al.*[85] using PFG NMR in the studies of long-range interactions in this protein and their importance for the membrane binding ability.

Binding of palmitic acid to CD4 has been well documented with 1D STD NMR experiments by Lee *et al.*[86]

Raschle *et al.*[87] have reviewed recent developments on nonmicellar systems with a particular focus on their application to solution NMR studies of membrane proteins. NMR studies demonstrating differences between two viroporins: p7 of HCV and Vpu of HIV1 have been summarized by Cook *et al.*[88] The emergence of solution NMR spectroscopy as a powerful tool for the structural characterization of membrane-associated protein domains involved in transmembrane signaling has been presented by Call and Chou.[89]

3 Lipidated proteins and peptides

Covalent lipidation of proteins is a biological phenomenon with various chemical and physiological implications. It is substantial for protein hydrophobicity and is thought to be crucial for the association of lipidated protein with the cellular membranes as well as for protein-protein interaction, protein folding and stability. Several recent papers have been focused on these topics.

Liu *et al.*[90] have reported a high-resolution NMR structure of full-length myristoylated yeast Arf1 protein in a complex with DMPC/DHPC bicelles.

Theisgen *et al.*[91] using ^{2}H solid-state and ^{1}H-^{15}N HSQC solution spectra have shown that both myristolyated and non-myristolyated GCAP-2 proteins have very similar binding energies to phospholipid bilayers.

The structure of antifungal cyclic heptapeptides lipidated (with 16:0 to 18:0 alkyl side chain) of *Bacillus amyloliquefaciens* has been estimated by Romano *et al.*[92] by 1D ^{1}H and ^{13}C and 2D NMR (COSY, HOHAHA, HSQC, HMBC).

Spanedda *et al.*[93] have used NMR to characterize four new water soluble lipidopeptidic immunoadjuvants.

2D ^{1}H NMR spectra of LPT1b, a post-translationally modified form of barley lipid transfer protein with lipid like adduct on the side chain of Asp7, have been measured by Mills *et al.*[94] before and after heating to 100 °C. It has been shown that the protein refolds back after heating. The hydrodynamic radii of the studied species have been obtained from the PFG NMR measurements.

^{2}H NMR has been used by Penk *et al.*[95] to show that N-terminal lipid modifications of transmembrane α-helices are membrane-inserted. The study was performed using LV16ac peptides in POPC and DLPC membranes.

Theisgen *et al*. have reviewed the studies on the applications of solid-state NMR to analyze the N-terminus of the myristoylated proteins.

4 Lipoproteins (non-covalent complexes)

Lipoprotein complexes are involved in intercellular lipid transport which is a prerequisite of lipid (cholesterol, triacylglycerols and others) homeostasis in human. For this reason many studies are focused on elucidation of lipoprotein structure and metabolism.

^{1}H NMR spectra of human plasma samples have been analyzed for determination of lipoprotein subclasses (size and concentration) by Muth *et al.*,[96] by Tejero *et al.*,[97] by Al-Shahrouri *et al.*[98] in connection with type 2

diabetes diagnostics, by Arsenault *et al.*,[99] by Kostara *et al.*[100] as a prediction of coronary heart disease, by Chung *et al.*[101] as diagnostic measure of atherosclerosis in patients with rheumatoid arthritis. ^{1}H NMR spectra of human plasma samples have also been acquired by Schmelzer *et al.*[102] to analyze the effect of ubiquinol supplementation on the level of LDL.

Rat serum metabolic profile has been investigated by Zhao *et al.*[103] using ^{1}H NMR-based metabolomic in order to follow the effect of quercetin, flavonoid component of the diet, on lipoprotein profile.

New structural details of the nascent High-Density Lipoproteins have been described by Gogonea *et al.*[104] using ^{31}P NMR in combination with various biophysical platforms together with molecular dynamics.

Bancells *et al.*[105] have used ^{1}H NMR to monitor LDL fusion and to evaluate the degradation of phospholipids.

2D HR NMR (^{1}H-^{13}C HSQC) has been employed to characterize the surface-exposed lysine residues of the apolipoprotein (apo)B-100 protein in LDL subfractions by Blanco *et al.*[106]

Gómez *et al.*[107] have employed ^{1}H NMR to check an eventual fusion of LDL particles in their oxidation with Cu and Fe ions.

Systemic dyslipidemia and lipoprotein modification caused by acrolein consumption have been shown by Conklin *et al.*[108] in acrolein-fed mice. The examinations of lipoproteins were carried out with the aid of NMR.

DOSY has been applied by Coles *et al.*[109] for accurate measurement of particle size of lipopetides.

5 Lipids and membranes

Cellular and organellar membranes are dynamic structures that trigger many aspects of cell function. Studies on various aspects of lipid interactions and membrane dynamics are summarized below.

a Lipid structure and dynamics

The structure of 7-hydroperoxycholesterol (synthetic standard and food component) has been identified by Nogueira *et al.*[110] using ^{13}C NMR.

Gao *et al.*[111] have used ^{1}H and ^{13}C NMR for identification of the structure of six titanocenyls functionalized with steroids – potential anticancer drugs. The structure of metabolites of 3-substituted ergosterol formed by microbial degradation (anologs of vitamine D) has been analyzed by Dovbnya *et al.*[112] using ^{1}H NMR. Yamazaki *et al.*[113] have used ^{1}H and ^{13}C NMR (HSQC, NOESY) to analyze the structure of pentacecilides, inhibitors of lipid droplet formation in macrophages, produced by *Penicillium cecidicola*. ^{1}H and ^{13}C NMR have been used for analysis of polyhydroxylated sterols of sponge *Callyspongia fibrosa* with an antimalarial activity by Rao *et al.*[114] while analogous derivatives of starfish *Asterina pectinifera* with antiviral and cytotoxic activities have been studied by Peng *et al.*[115] (in the latter case ^{1}H-^{1}H COSY and HMBC spectra were also collected). Vílchez *et al.*[116] have elucidated the structure of *trans*-2-decenoic acid, a novel interkingdom-signaling molecule inhibiting the yeast-to-hyphal transition of *Candida albicans* using ^{1}H and ^{13}C NMR. The structute of new cytotoxic steroidal alkaloids from *Kibatalia laurifolia* has

been elucidated by Phi *et al.*[117] using 1D ^{1}H and ^{13}C and 2D COSY, HSQC and NOESY experiments. The structure of tuberatolides, meroterpenoid antagonists of the Farnesoid X Receptor isolated from *Botryllus tuberatus* has been established by Choi *et al.*[118] using 1D ^{13}C and 2D HMBC and DEPT experiments. Jarret *et al.*[119] have used time domain NMR for eavaluation of the seed oil content of 1100 accessions of okra. The structure of sixteen plakortolides (containing bicyclic poroxy-lactone ring) isolated from sponge *Plakinastrella clathrata* has been established by Yong *et al.*[120] by 1D ^{1}H and 2D NMR (HMBC, HSQC, NOESY experiments). Structures of two new eicosanoids with a unique isovalerianic acid ester moiety from the gorgonian *Dichotella gemmacea* have been established by Wang *et al.*[121] using 1D ^{1}H and ^{13}C and 2D COSY, HMQC, HMBC and DEPT experiments. Eighteen new diterpenes have been structurally characterized by Hayes *et al.*[122] using 1D ^{1}H and ^{13}C and 2D COSY, ROESY and HMBC experiments. Antibacterial sphingolipids and steroids of black coral *Antipathes dichotoma* have been isolated and characterized by Al-Lihaibi *et al.*[123] using 1D ^{1}H and ^{13}C and 2D COSY, HMQC, HMBC and DEPT experiments. The structure of novel prenyl bibenzyls of liverwort *Marsupidium epiphytum* has been established by Toyota *et al.*[124] using 1D ^{1}H and ^{13}C and 2D COSY, HMBC and NOESY experiments.

^{31}P NMR has been used in combination with different analytical techniques by Lobasso *et al.*[125] to analyze the lipids present in total extracts of olfactory neuroepithelium.

Heteronuclear NMR spectra have been used to solve the structure of three bioactive acylphloroglucinols isolated from the aerial parts of *Hypericum densiflorucm* Pursch by Henry *et al.*;[126] of six meroterpenoids of chromene class isolated from *Sargassum siliquastrum* by Lee and Seo.[127]

The solution structure of 4′-phosphopantetheine-GmACP3 from *Geobacter metallireducens* has been solved by Ramelot *et al.*[128] using restraints obtained from NMR spectra.

The presence of two major phosphatidylserine headgroup conformations in calcium-induced clusters of this lipid in POPS/POPC bilayer has been demonstrated by Boettcher *et al.*[129] using 2D SSNMR ^{13}C-^{13}C, ^{15}N-^{13}C and ^{31}P-^{13}C spectra.

Leftin and Brown[130] have reported a database with experimental NMR parameters for membrane phospholipids which may be useful for validation of molecular simulations.

The structures of chemically randomized (sodium methoxide treated) oils from seal blubber and menhaden with modified positional distribution of fatty acids have been investigated by Wang *et al.*[131] using quantitative ^{13}C NMR. Lessig and Fuchs[132] have examined the hypochlorous acid-induced plasmalogen degradation in a model mixture of polyunsaturated plasmalogens using HR ^{31}P NMR. The structure of the alkaline degradant of Ezetimibe, a selective inhibitor of intestinal cholesterol absorption has been established using ^{1}H and ^{13}C NMR by Gajjar and Shah.[133] Side chain cholesteryl polymers (mesogen-like) have been sythesized and evaluated structurally with ^{1}H NMR by Wang *et al.*[134] Magnusson *et al.*[135] have applied ^{1}H NMR to evaluate the regiopurity of the synthesized 72 ether lipids of 1-*O*-alkyl-2,3-diacyl-sn-glycerol type. Vaique *et al.*[136] have

synthesized a set of triacylglycerols with *n*-3 polyunsaturated fatty acids; their purity has been checked by ^{1}H and ^{13}C NMR.

Xu *et al.*[137] have isolated and characterized over a dozen oxysterols formed in the free radical oxidation of 7-DHC using 1D and 2D NMR.

Griesser *et al.*[138] using ^{1}H NMR have identified two cyclic hemiketal eicosanoids as the major products of the nonenzymatic rearrangement of the diendoperoxide.

Blanco *et al.*[139] have synthesised 6-methylnitroarachidonate and characterized the structure of this nitro-fatty acid using heteronuclear 2D NMR.

Quantitative ^{31}P NMR spin trapping has been used by Zoia *et al.*[140] to study the mechanism of enzymatic oxidation of linoleoic acid by soybean lipoxygenases-1.

Indentification of soybean lipoxygenase-1 products by Zheng and Brash[141] with the aid of 1D ^{1}H and 2D COSY NMR has permitted its biochemical characterization as a bifunctional enzyme.

The structure of paleic acid, an antibiotic obtained from a fermentation broth of *Paenibacillus* sp., has been elucidated by Kurata *et al.*[142] by means of 1D ^{1}H and ^{13}C and 2D NMR (DEPT, HMQC, COSY, TOCSY and HMBC spectra).

Osipova *et al.*[143] have characterized substrate specificity of plant lipoxygenases by identification the structure of their oxylipin products using ^{1}H NMR and 2D COSY.

Time-resolved ^{31}P MAS direct polarization and cross polarization techniques have been used by Ullrich *et al.*[144] to simultaneously follow ATP hydrolysis and the DGK (diacylglycerol kinaze) catalyzed phosphorylation of DOG (1,2-dioctanoylglycerol) in DOPC bilayers.

The structure of fatty acid derivatives as components of glandular trichome exudates of *Ibicella lutea* and *Proboscidea louisiana* have been elucidated by Asai *et al.*[145] by means of ^{1}H and ^{13}C NMR.

The polar lipids of *Clostridium tetani*, the causative agent of tetanus, have been examined using 1D ^{1}H, ^{13}C, ^{31}P and 2D COSY, HMQC, HMBC NMR by Johnston *et al.*[146]

Metabolic relationship between the synthesis of polyhydroxyalkanoic acid and rhamnolipid (two biotechnologically important compounds) in *Pseudomonas aeruginosa* has been analyzed by Choi *et al.*[147] *via* quantitative ^{13}C NMR following the metabolic labelling with [1-^{13}C]octanoic acid. Tsukada *et al.*[148] have studied the biosynthesis of jasmonic acid in a plant pathogenic fungus *Lasiodiploidia theobromae* using metabolic labelling with [$^{2}H_6$]linolenic acid followed by ^{2}H NMR.

Maatooq *et al.*[149] have used proton and carbon homo- and hetero-correlated NMR spectra to identify seven metabolites of biotransformation of 18β-glycyrrhetinic acid.

Gylfason *et al.*[150] have analyzed the lipid content of extracts of lipid rafts from Atlantic cod intestinal enterocytes by ^{31}P NMR.

The structures of *N*-acylated bacteriohopanehexol-mannosamides from the thermophilic bacterium *Alicyclobacillus acidoterrestris* have been solved by Řezanka *et al.*[151] with the aid of ^{1}H and ^{13}C NMR. Monolysocardiolipin has been characterised with ^{1}H NMR by Kim and Hoppel[152] as a preferential product of cardiolipin hydrolysis in methanol. The sizes of

DPhPC/DPhPE vesicles have been determined by Andersson *et al.*[153] using NMR diffusion experiments.

Equivalence of dehydration and osmotic pressures in lipid membrane deformation has been demonstrated by Mallikarjunaiah *et al.*[154] using solid-state ^{2}H NMR and DPMC bilayers.

Frankel[155] has reviewed analytical methods used for the authentication of extra virgin olive oil. This includes ^{1}H, ^{13}C, ^{31}P NMR used in studies of EVOO adulteration.

b Lipid – lipid interactions

Mihailescu *et al.*[156] have shown that addition of cholesterol to poly-unsaturated lipid bilayers (18:0-22:6n3-PC) increases the order parameters of DHA and stearyl acid chain; ^{2}H NMR and ^{13}C-MAS NMR have been used in this study.

Scheidt *et al.*[157] have used a combination of solid-state NMR methods (^{2}H, ^{1}H MAS, 2D ^{1}H MAS) to investigate the membrane orientation and transversal distribution of 17β-estradiol in model POPC membranes. The phase behaviour of mixtures of palmitic acid and various sterols has been characterized by ^{2}H NMR at different pH by Cui *et al.*[158]

The effect of *E,Z* isomers of monoenoic fatty acids on the DMPC membrane fluidity (the supramolecular lamellar structure during gel – fluid transition) has been analyzed by Filippelli *et al.*[159] using ^{2}H NMR.

Teixeira *et al.*[160] have checked the solubility of oleanolic acid in melted stearic acid by means of ^{1}H NMR.

The effect of cholesterol on the magnetic induced orientation of sphingomyelin/cholesterol multilamellar vesicles has been examined using static solid-state ^{31}P MAS NMR by Castello and Alam.[161] The effect of cholesteryl sulfate on the stability of DMPC/DHPC bicelles has been tested by Shapiro *et al.*[162] by NMR measurement of ^{2}H quadrupole splittings in D_2O, while the utility of the cholesteryl sulfate containing bicelles has been tested using ^{15}N HSQC-IPAP NMR following the addition of ^{15}N-ubiquitin. The mode of tocotrienol entrapment/association with the lipid nanoparticles (four high melting point lipids were tested) has been evaluated by Ali *et al.*[163] by ^{1}H NMR.

Guillermo *et al.*[164] have used ^{13}C HR CPMAS and PFGSTE experiments for morphological characterisation of two lipid-based formulations of lip gloses, D014 and D019.

^{13}C CPMAS NMR has been used by Shih *et al.*[165] to study the-conformations of two steroid hormones, dehydroepiandrosterone and spironolactone in the DPMC/DHPC mixture.

Unilamellar liposomes made up of DOTAP, DOPE and a novel amphiphile lauroyl uridine have been characterized with ^{1}H NMR by Cuomo *et al.*[166]

c Lipid – drug interactions

2D ^{1}H MAS NMR (NOESY) analysis has been applied by Hoffmann *et al.*[167] to visualize the direct insertion of polyprenylated acylphloro-glucinolhyperforin, the modulator of phospholipase A_2 activity, into POPC liposomes. Ma *et al.*[168] have studied the structure of inclusion

complexes of cyclodextrins with cortisone acetate (steroidal drug) by means of 2D ^{1}H NMR(ROESY). The effect of sodium bicarbonate (pharmaceutical formulation excipient) on the interaction of fluvastatin (anticholesterolemic drug) with membrane phospholipids (DMPC/DMPS mixture mimicking the gut cell membranes) has been investigated by Larocque *et al.*[169] using ^{1}H NMR. Jensen *et al.*[170] have studied interaction of cisplatin (anticancer drug) with POPS liposomes using a broad range of solid-state NMR techniques. *i.e.* ^{13}C MAS, ^{31}P, ^{15}N and ^{15}N{^{31}P}REDOR experiments. Smith *et al.*[171] have used SSNMR to gain insight into the structure of the DMPC-dendrimer (poly(amidoamine) polymer for targeted drug delivery) complex; static ^{31}P and ^{14}N and MAS R-PDLF, NOESY, RFDR and ^{1}H NMR spectroscopies have been used.

The effect of quipazine and LY-165,163, two serotonin receptor 1a agonists on the phase behaviour of DPPC/cholesterol bilayers has been studied by Batchelor *et al.*[172] using ^{1}H MAS NMR spectra.

The encapsulation of doxorubicin or vinorelbine into PEG/PE micelles has been proved by Wang *et al.*[173] using 2D ^{1}H NOESY spectra.

Su *et al.*[174] have investigated the interaction of PMX30016 with POPC, POPG, POPS, DPMC, DPMG and 6-O-PC. Orientation, depth of insertion and dynamics of this antimicrobial arylamide in bilayers have been determined with ^{19}F and ^{31}P solid state NMR.

Sharma *et al.*[175] have reviewed the investigations of drug binding to three conductance domains of viral porins (M2 proteins from influenza A and B, and viral protein 'u' from HIV-1) and their mutants, performed with PISEMA spectra in bilayers.

6 Glycolipids

The structure of various natural glycolipids has been analyzed using NMR.

Lin *et al.*[176] have identified two sterol glycosides inhibiting the cancer cell growth in the red alga *Peyssonnelia*. Ono *et al.*[177] have elucidated the structure (1D ^{1}H and ^{13}C NMR spectra) of oligoglycosides of hydroxy fatty acid methyl esters isolated from seeds of *Pharbitis nil*.

Paściak *et al.*[178] have established the structure of glycolipids from *Arthrobacter scleromae* and *A.globiformis* utilizing 1D ^{1}H and ^{13}C and 2D NMR (COSY, TOCSY, ROESY, HSQC-DEPT and HMBC experiments).

2D NMR spectroscopy has been used by Silipo *et al.*[179] to elucidate the structure of the carbohydrate backbone of the core-lipid A region of the lipooligosaccharide from *Halmonas* sp.; by Morando *et al.*[180] to reveal structural features of the Nod factor synthetic analogues; by Layre *et al.*[181] to identify in the wild-type strain of *Mycobacterium tuberculosis* new di-acylated sulfoglycolipids esterified by simple fatty acids and mono-acylated sulfoglycolipids bearing hydroxyphthioceranoic acid; by Jang *et al.*[182] to elucidate the structures of lipoteichoic acids isolated from *Lactobacillus plantarum*.

Konishi *et al.*[183] with the aid of proton and carbon NMR have determined the structure of biosurfactant produced by *Pseudozyma hubeiensis* SY62. The major product has been identified as 4-*O*-[4′-*O*-acetyl-2′,3′-di-*O*-alka(e)noil-β–D-mannopyranosyl]-D-erythritol.

A specific interaction of new synthetic amphiphilic glycolipids (antisepsis agents) with CD14 have been proved by Piazza *et al.*[184] with the aid of STD NMR spectroscopy.

The influence of the concentration of deep rough mutant ReLPS from *E. coli* strain WBB06 on the size of raft domain in membranes composed of a phospholipid (DEPE), cholesterol and sphingomyelin (egg-SM) has been studied by Nomura *et al.*[185] using ^{13}C and ^{31}P solid state NMR.

7 Metabonomic studies

The high-throughput studies on cellular metabolom are continuously being developed. Metabolomic approaches open new perspectives for the development of new diagnostic tools and speed up the progress in therapy of various metabolic disorders. The number of NMR applications for metabonomic *in vitro* and *in vivo* studies has significantly increased during recent year. Selected papers are summarized below.

^{1}H NMR spectra of urine samples have been utilized by Kim *et al.*[186] for metabolomic profiling of cholesterol and low-density lipoproteins. A similiar approach has been used by Lu *et al.*[187] to follow the metabonomic pattern after oral administration of polychlorinated bifenyls and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (endicrine disruptors). ^{1}H NMR spectra of rat urine, serum and ^{1}H MAS NMR spectra of liver have been used by Bollard *et al.*[188] to identify biomarkers of liver regeneration folowing partial hepatectomy.

^{1}H NMR (1D, 2D COSY, TOCSY, HSQC) based metabolic profiling of mouse feces has been carried out by Martin *et al.*[189] in different microbiome mouse models (including gnotobiotic mouse inoculated with a model of human baby microbiota). The effects of probiotics on colonic inflammation has been assessed by Hong *et al.*[190] by metaboling profiling of the fecal extracts of mice using ^{1}H NMR with NOESYPR pulse sequence and 2D TOCSY, HMBC, HSQC experiments.

^{1}H NMR supported with different types of statistics has been used in analysis of metabolic profiles of the diabetic nephropathy streptozotocin induced in rats by Zhao *et al.*;[191] of lipidome and metabolome of rat cardiomyocytes after EPA or DHA supplementation by Righi *et al.*;[192] of metabolic profiling of serum of accelerated aging mice ($ERCC1^{d/-}$) by Nevedomskaya *et al.*;[193] of lipid profiles in urine and plasma of inbred rat strains by Pontoizeau *et al.*;[194] of metabolites including lipids in rabbit aqueous humour after the glucocorticosteroids administration by Song *et al.*;[195] of alternations in the levels of LDL/VLDL in patients with renal cell carcinoma by Zira *et al.*;[196] of levels of lipid moieties in patients with minimal hepatic encephalopathy by Jiménez *et al.*;[197] of the levels of lipid metabolites in serum in kidney transplant recipients with cyclosporine A- or tacrolimus-based immunosuppresion by Kim *et al.*;[198] of mucosal colonic biopsies, colonocytes, lymphocytes and urine from patients with ulcerative colitis by Bjerrum *et al.*;[199] of LDLp and HDLp in patients with coronary artery endothelial dysfunction by Ford *et al.*;[200] of lipid profiles in extracts of gallbladder tissues in chronic cholecystitis and cancer by Jayalakshmi *et al.*[201]

^{1}H NMR metabolic phenotyping has been developed to identify biomarkers of rheumatoid arthritis (cholesterol and other lipids) by Lauridsen *et al.*,[202] to identify chronic lymphocytic leukaemia disease-state biomarkers by MacIntyre *et al.*,[203] to reveal progression axes for glucose intolerance and insulin resistance statuses by Zhang *et al.*[204]

^{1}H HRMAS NMR (1D NOESYPR and 2D TOCSY) has been applied to unravel the effects of three natural marine products with antineoplastic activity in intact human MCF7 breast cancer cells by Bayet-Robert *et al.*[205] The same group, Bayet-Robert *et al.*[206] has designed a method for quantitative 2D ^{1}H HRMAS NMR metabolite profiling of intact human cancer cells and response to chemotherapy.

Fernando *et al.*[207] have elucidated the effect of ethanol-induced fatty liver by ^{1}H and ^{31}P NMR analysis of lipids from rat plasma and liver.

A robust method for the simultaneous quantification of major biliary lipids has been deviced by Ijare *et al.*[208] using ^{1}H NMR spectroscopy. ^{1}H and ^{31}P NMR analysis (1D and 2D COSY and TOCSY) of lipid components in the tissue, serum and cerebrospinal fluid has been performed by Srivastava *et al.*[209] to develop a diagnostic tool for evaluation of brain tumours.

Triba *et al.*[210] have used ^{1}H HR-MAS NMR for elucidation of antiproliferative drugs (doxorubicin and bisphosphonates) on metabolic (lipid) profiles of whole B16 melanoma cells.

Lutz and Cozzone have performed multiparametric studies aimed at optimization of ^{31}P NMR measurements of brain phospholipids in crude tissue extracts focused on the effects on chemical shift[211] and on the line width and spectral resolution.[212]

In vivo single-voxel MRS and *ex vivo* ^{1}H HR NMR have been used by Mosconi *et al.*[213] to study the composition of adipose tissues in Zucker obese and lean rats.

To examine a potential link between the choline metabolism and phosphoinositide 3-kinase/Akt signalling Romanska *et al.*[214] have compared the metabolic profiles of murine pluripotent embryonic stem cells and the embryonal carcinoma cell using ^{1}H NMR spectra of cell extracts.

^{1}H NMR-based (1D PRESAT and spin-echo spectra) metabonomic analysis of human serum has been developed by Mao *et al.*[215] to follow the progresssion of critically ill patients from Systemic Inflammatory Response Syndrome to Multiple Organ Dysfunction Syndrom.

Quantitative ^{1}H NMRmetabolomics has been applied by Xu *et al.*[216] to follow the specific mitochondrial toxicities *in vitro* in myotube cells.

1D, COSY and TOCSY ^{1}H NMR and 1D ^{31}P NMR spectra of serum lipids in Duchenne muscular dystrophy patients have been measured and quantified by Srivastava *et al.*[217] ^{1}H and ^{13}P NMR metabolomics have been applied by van Patot *et al.*[218] to quantify lipid metabolites in human placental tissue biopsies. The study has shown the presence of labour oxidative stress in placentas from pregnancies at sea level but not in those at 3100 m. Hepatic lipid composition in patients with chronic hepatitis C has been analysed *in vitro* and *in vivo* by Cobbold *et al.*[219] using ^{1}H MRS. The results show significant dependence of the lipids profile on the disease severity.

Levels of lipoproteins and lipids in serum of more than 4000 healthy adults have been measured by Würtz *et al.*[220] with ^{1}H NMR and used in the analysis of metabolic phenotypes associated with subclinical atherosclerosis. The results of metabonomic studies carried out by Inouye *et al.*[221] with the aid of ^{1}H NMR for a large population-based cohort combined with transcriptomic and genomic analysis have revealed that the lipid-leukocyte module has a prominent role in over 80 serum metabolites including lipoprotein subclasses and lipids. Chasman *et al.*[222] have performed a genome-wide association studies (GWAS) for 22 lipoprotein measures derived from NMR-based and conventional assays in a population of more than seventeen thousand women. 43 genetic loci involved in lipoprotein metabolism have been found in these studies.

Signals from intra- and extra-myocellular lipids have been assigned in 1D ^{1}H and L-COSY NMR spectra collected for human soleus muscle *in vivo* at 7T by Ramadan *et al.*[223] It has been shown that at this field strength all signals from multiple lipid compartments are shifted by 0.20 to 0.26 ppm.

Metabolic fingerprinting of medicinal plant extracts (leaf and root of *Withania somnifera*) has been elucidated by Chatterjee *et al.*[224] with the aid of ^{1}H NMR including ^{1}H-^{13}C HSQC experiment. Lipid composition of intact algal cells which are used for biodiesel production has been analyzed by Beal *et al.*[225] by means of a liquid state ^{13}C and liquid state ^{31}P NMR. Bunescu *et al.*[226] have performed *in vivo* ^{1}H HRMAS NMR metabolic profiling of the cladoceran *Daphnia magna* of different physiological status.

Szeto *et al.*[227] have observed inherent biological variation of ^{1}H NMR metabolic profiles of yeast and nematode model systems. Szeto *et al.*[228] have also examined exometabolome of the yeast *Saccharomyces cerevisiae* mutants defective in succinate dehydrogenase (model of mitochondrial dysfunction) using ^{1}H NMR.

Metabolites obtained from *Caenorhabditis elegans* using twelve combinations of different techniques of tissue extraction and disruption have been compared by Geier *et al.*[229] ^{1}H NMR has been used for detection of lipids. Micro-Raman spectroscopy for quantitative determination of the unsaturation index in mammal fat tissues has been calibrated against ^{1}H HR NMR by Giarola *et al.*[230] The usage of Raman spectroscopy does not require chemical extraction of the lipid component.

8 New NMR methods

a For peptides/proteins

Chu *et al.*[231] have developed a new tool to study membrane proteins which permits to determine the membrane immersion depth of a spin-labelled probe using paramagnetic relaxation enhancement (PRE) in solid-state ^{31}P NMR; a DOXYL spin labelled PSPC was used.

Gopinath *et al.*[232] have presented new sensitivity enhanced schemes for heteronuclear correlation spectroscopy (HETCOR) in solid-state NMR of oriented systems.

Lu *et al.*[233] have established a general assignment method for oriented sample solid-state NMR of proteins based on correlation of resonances through heteronuclear dipolar couplings in samples aligned parallel and perpendicular to the magnetic field.

Jayanthi *et al.*[234] have presented a new sequence named 2_4-SEMA for obtaining reliable dipolar couplings in membrane proteins oriented in lipid bilayers and liquid crystals. Under off-resonance conditions intensities of signals from the new sequence are several folds higher than that from PISEMA.

Well resolved spectra of proton detected solid-state NMR H/N correlations of perdeuterated and partially proton-back-substituted membrane proteins have been demonstrated by Linser at al.[235] The method has been validated using the outer membrane protein G in perdeuterated *E. coli* lipid bilayer and bacteriorhodopsin.

Using virtual NMR data Esteban-Martín *et al.*[236] have demonstrated that dynamic data analysis of peptides in membrane depends critically on the choice of isotope labelling scheme. For example: ^{15}N labels accommodated within the peptide backbone will yield nearly correct peptide helix tilt angle whereas CD_3 or CF_3 groups attached to the C_α–C_β bond will yield this angle severely underestimated.

Several new approaches that combine cell-free expression and different labelling strategies for preparing a membrane protein sample for solid-state NMR measurements have been overviewed by Abdine *et al.*[237] These approaches will hopefully lead to a protein structure determination in the solid state using NMR technique.

b For lipids

Kupce and Freeman[238] have proposed a fast-PANACEA experiment (combination of three standard NMR pulse sequences INADEQUATE, HSQC and HMBC into a single entity) for fast analysis of cholesterol.

A novel self-oriented system made of a fatty acid hexagonal phase has been established by Douliez[239] using ^2H solid-state NMR. Kashima and Okabayashi[240] have developed a system with an on-line immobilized enzyme reactor integrated into liquid chromatography-NMR for identification of enzymatic reaction products with application of ^1H and 2D ^1H-^1H NMR.

It has been shown by Yamamoto *et al.*[241] that the inclusion of Cu^{2+} ions in bicelles results in a 10-fold reduction of T_1 and in 6.2 fold decrease in MAS experimental time.

Kielar *et al.*[242] have designed a bis-substituted DOTA derivative Gd^{III} complex and shown that, incorporated into liposomes, it causes significant enhancement of relaxivity.

Diffusion-weighted ^1H MRS spectroscopy has been implemented by Zietkowski *et al.*[243] to monitor mobile lipids in cervical tissue biopsies.

The lipid composition of human muscle has been measured by Webb *et al.*[244] in a 7T system with a coil producing a longitudinal travelling wave. It was possible to obtain localized proton spectra with the coil placed 30 cm away from the region of interest.

9 Miscellaneous

Gao *et al.*[245] have used ^1H NMR to show formation of hydrogen bonding between molecules of a new gelator (cholesterol based and sugar containing).

Lee *et al.*[246] have applied *in vivo* ^{1}H NMR (STEM spectra) for detection of early responses to radiation that precede tumour volume changes.

Quintero *et al.*[247] have elucidated the compartmentalization of the biosynthesis of triacylglycerols in C6 rat glioma cells by acquiring the 2D HMQC NMR spectra of the total lipid extracts of cells upon labelling with [1-^{13}C]glucose.

The interactions of poxvirus particles with small unilamellar vesicles composed of DPPG, the main component of pulmonary surfactant, have been studied by Debouzy *et al.*[248] using ^{1}H NMR.

Pages *et al.*[249] have applied fast-recording diffusion-diffraction (pulsed field-gradient spin-echo, PGSE) ^{1}H NMR to follow the change of erythrocyte shape, from an echinocytic stage to normal discocytic shapes due to the modulation of Mg^{2+}; simultaneusly ^{31}P NMR was used to report on metabolism during the shape reversion, while the membrane phospholipid distribution of the cells was investigated with ^{1}H spin-echo NMR.

The loss of *N*-oleoylethanolamine during tissues extractions has been proved by Skonberg *et al.*[250] who have identified the product of its reaction with chloroform with the help of ^{1}H NMR.

Freikman *et al.*[251] have studied the influence of oxidative stress on membrane lipid composition using ^{1}H NMR.

Oxygen distribution across the MLMPC bilayer has been monitored by Al-Abdul-Wahid *et al.*[252] using ^{13}C paramagnetic chemical shift perturbations for 18 different sites of this lipid.

Using ^{129}Xe NMR Meldrum *et al.*[253] have characterized the interactions of the xenon-cryptophane-A cage molecular sensor with lipid vesicles under different conditions.

The rate of phosphocreatine recovery after exercise have been measured by van den Broek *et al.*[254] with ^{31}P MRS *in vivo* and found to be a sensitive measure of skeletal muscle mitochondrial function.

Water and fat thermal MRI has been demonstrated by Soher *et al.*[255] using water-fat fanthoms. This approach may be applied for accurate tumour and normal tissue temperature measurements in hypothermic treatment.

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