13C NMR and cerebral biochemistry

EDITORIAL
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13C NMR approaches have recently made it possible to study cerebral metabolism in more detail than with radioactive or nuclear medicine methods. Improvements in the technology now permit us to obtain in vivo, localized 13C NMR spectra from rodent or human brain with similar quality to those obtained earlier only under in vitro conditions, providing in this way a wealth of information on neurotransmitter recycling and cerebral bioenergetics in situ. Simultaneously, high-resolution 13C NMR approaches using cerebral extracts, brain slices or neural cell cultures are now yielding large amounts of detailed information on cerebral metabolic compartmentation and neuronal–glial interactions. These important advances are distributed in a plethora of publications in journals with very different profiles, making it difficult
for the general scientific community to understand and integrate the abundant interdisciplinary information obtained in this field. This circumstance inspired me to prepare a special issue of NMR in Biomedicine on '13C NMR Studies of Cerebral Metabolism', which aimed to provide from an integrative perspective, a comprehensive
analysis of the 'state of the art' of in vivo and in vitro 13C NMR approaches and their contribution to our current understanding of cerebral function.

Most neuroscientists would wish to start this issue by discussing whether 13C NMR entails sufficient advantages over more classical methodologies for investigating cerebral metabolism and if, as a consequence, 13C NMR methods have contributed any relevant information on cerebral function. To address this question properly it is
important to remark here that the general concepts of cerebral metabolism were established much earlier than 13C NMR methodologies became available. Using conventional biochemical methods, it was possible to show that plasma glucose is the main substrate for the adult mammalian brain, providing both the energy and the carbon skeletons.

Most previous methodologies for investigating cerebral glucose metabolism in vivo used 2-deoxyglucose, either labeled with radioactive isotopes such as 14C, or with positron emitting isotopes such as 18F.4,5 Both procedures are based in the fact that 2-deoxyglucose, a glucose analog transported to neural cells similarly to glucose, yields after intracellular phosphorylation the virtually unmetabolizable intermediate 2-deoxyglucose 6-phosphate. The corresponding 14C or 18F label accumulations detected by autoradiography or positron emission tomography (PET) make it possible to obtain spatially resolved measurements of glucose uptake or cerebral metabolic rates in different brain regions in vivo.

More recently, functional magnetic resonance imaging (fMRI) has been able to determine indirectly the increases in cerebral activity through blood oxygenation level-dependent (BOLD) MRI contrast, a phenomenon thought to be caused by local changes in hemodynamics and in the oxygenation state of hemoglobin in those brain areas under motor or sensory activation. However, fundamental limitations of these traditional methodologies become apparent when considering the astroglial or neuronal location of glucose and energy metabolism, how these two different neural cell environments are functionally coupled and how this metabolic coupling supports global cerebral function and neurotransmission. Notably, autoradiography, PET or fMRI do not have the ability to determine the neuronal or glial origin of the increases in substrate and oxygen consumption supporting glutamatergic or GABAergic neurotransmissions. It is precisely in this respect where 13C NMR approaches have been recently shown to become considerably powerful. In particular, in vivo and in vitro 13C NMR methods have provided novel information on many important aspects of modern neurochemistry, including the activity of the neuronal and glial tricarboxylic acid cycles and the operation of the intercellular glutamate–glutamine–GABA cycle in vivo, 8 on carbohydrate metabolism with emphasis on cerebral glycogen turnover, 9 on the biochemical basis of some neurological disorders in humans, on some novel cerebral metabolic pathways such as the pyruvate recycling system, on the exchange of metabolites between neurons and glial cells, on the subcellular compartmentation of neurotransmitter amino acids and many others.

It should noted here that the admitted advantages of the 13C NMR approach do not imply that it is devoid of drawbacks. Indeed, 13C NMR is severely limited by its inherently low sensitivity, and its human applications remain at the academic level because of the considerable cost of the equipment and the 13C-enriched isotopes required. These adverse circumstances hamper the spatial localization of events occurring in small cerebral structures, preclude the resolution in time of fast metabolic processes and make it difficult to extend 13C NMR studies to the increasingly cost-conscious clinical scene. Despite these disadvantages, the continuous increases in field strength of modern spectrometers, the development of more sensitive forms of indirect 1H-observed 13C NMR spectroscopy, the use of the faster timescale of 13C detected hydrogen turnover, and the increasing demand for 13C isotopes and clinical high field magnets promise important improvements in spatial or temporal resolution, as well as in cost, of the 13C NMR examinations in the near future.

The present issue of NMR in Biomedicine covers in several review articles the current status of in vivo and in vitro 13C NMR methods, providing in addition, a series of original papers addressing key aspects of modern neurochemistry. Review articles begin with a reflection on the application of 13C NMR to studies of cerebral metabolism (see Morris and Bachelard), followed by authoritative descriptions of the state of the art of in vivo (Gruetter et al. and de Graaf et al.) or in vitro 13C NMR (Zwingmann and Leibfritz), and illustrative applications in both rodent models of neurological diseases (Sonnewald and Kondziella) and clinical studies in humans (Lin et al.). The original papers address important and unresolved issues in cerebral biochemistry such as the use of LC Model to interpret quantitatively dynamic changes in 13C isotopomer populations from 13C NMR spectra obtained in vivo (Henry et al.), the turnover and role of NAA in cerebral metabolism (Karelson et al.) or the mechanisms of metabolic coupling and substrate selection in neurons and astrocytes in normal and diseased brain (Serres et al. and García-Espinosa et al.). To compile this issue I looked for the assistance of recognized specialists in the various a spects of cerebral 13C NMR. I am deeply indebted to the many friends and colleagues who accepted my invitation and devoted their time and effort to writing reviews and research articles. My gratitude is extended also to the Editorial Board of NMR in Biomedicine and John Wiley and Sons for their always enthusiastic support in the production of this issue.

Finally, many important aspects of cerebral metabolism remain incompletely understood. These involve among others, the quantitative role of glial cells supporting, modulating or even contributing to cerebral activation and neurotransmission, the precise metabolic coupling mechanisms between neurons and glial cells and their corresponding energetics or the metabolic basis of most neurodegenerative and psychiatric disorders. I sincerely hope that readers of this volume will find in its pages sufficient impetus to fulfill these challenges and extend the use of 13C NMR to other areas of neurochemistry, contributing even more fundamental advances to cerebral metabolism than the ones presented here.