A Nuclear Magnetic Resonance Advance

Imaging Fluorinated Anesthetics in the Brain

In a technologically intense research manuscript in this issue of the Journal, Xu et al.\(^1\) describe the use of advanced magnetic resonance imaging (MRI) and spectroscopy (MRS) to rapidly obtain regional intensity plots of sevoflurane, a fluorinated anesthetic, in the brains of rats. This is the first time that fluorine-19 (\(^{19}\)F) nuclear magnetic resonance (NMR) imaging has shown a meaningful distribution of a general anesthetic in brain. Although \(^{19}\)F MRI techniques have been used \textit{in vitro} experimentally to image: (1) the distribution and oxygenation state of perfluorocarbon blood substitutes,\(^2\),\(^3\) (2) regional cerebral blood flow,\(^4\),\(^5\) and (3) fluorodeoxyglucose uptake,\(^6\),\(^7\); previous attempts by various prominent investigators all found resulting NMR signal strengths for anesthetics in brain parenchyma to be too small for significant regional imaging.\(^8\),\(^9\)\(^,\)\(^1\)\(^0\)\(^,\)\(^9\)\(^1\)\(^1\) The technical details here are complex. Prominent medical journals, as part of general attempts to encourage literacy in modern science, have published basic review articles about NMR imaging for physicians.\(^12\),\(^13\) Nevertheless, the mastery of numerous subtle NMR principles is often an elusive goal, even for the most ambitious science students. A bit of background for the uninitiated is called for.

First, as a point of conceptual clarity regarding basic principles of NMR spectroscopy (Xu et al. provide a review of NMR physics in a technical appendix), we note that many people do not appreciate that NMR spectroscopy is \textit{absorption} spectroscopy.\(^14\) Although NMR imaging and spectroscopy require that radiofrequency electromagnetic energy be pumped into a sample, there are no emitted “resonance signals” that subsequently are radiated by the sample to detectors in the spectrometer—as in fluorescence spectroscopy. Instead, what is measured in NMR spectroscopy is the frequency specificity of energy lost to an NMR coil that is loaded with a sample. As Abrahams has written, “The simplest description of the NMR phenomenon is that of absorption by the nuclear spin system of electro-

magnetic energy provided by a radiofrequency generator.” Although some pumped-in magnetic excitation energy goes into flipping nuclear spins at NMR resonance frequencies, such excitation energy ultimately dissipates within the sample during magnetic relaxation, primarily \textit{via} radiationless transitions, resulting in heat. (Some of the pumped-in radiofrequency electrical energy causes electrical currents in the sample and thus is directly lost in the form of heat.)

Second, a few words about Xu et al.’s \(^{19}\)F NMR methods are indicated. They strategically chose a special fluorine resonance for imaging. The radiofrequency magnetic field that excites this resonance causes concurrent flips in six structurally identical \(^{19}\)F nuclei, these being symmetrically located in every sevoflurane molecule. (There is a seventh \(^{19}\)F nucleus in sevoflurane, but its NMR resonance is not used in this particular imaging process.) The amplitude of the \(^{19}\)F signal measured for each small spatial region (pixel) in the image is affected by both fluorine density and rapidity of NMR resonance decay (relaxation times, \(T_1\) and \(T_2\)). This last point should be without surprise. It is well known that conventional, clinical MRI is based on the detection of the NMR resonance for protons (\(^{1}\)H) in water, and MRI intensities strongly depend not only on the spatial density of water but also on various tissue relaxation times (\(T_1\) and \(T_2\)). Furthermore, in routine clinical proton MRI, image contrast often is enhanced by exploiting differences in proton \(T_1\) and \(T_2\) that are peculiar to variations in tissue type and tissue condition. \(T_1\) is the “spin-lattice” relaxation, and \(T_2\) is the “spin-spin” relaxation. These are also referred to as “longitudinal” and “transverse” relaxation, respectively. In conventional \(T_1\)- or \(T_2\)-weighted proton MRI, contrast enhancement is obtained by exploiting differences in the extent to which there was longitudinal or transverse relaxation. As Xu et al. explain, to date, the greatest obstacle to \(^{19}\)F NMR imaging in brain tissue has been an exceptionally small \(T_2\) value, typically 2–5 ms for fluorinated anesthetics. For the human brain, water proton \(T_2\) values are approximately 30 times larger, \textit{i.e.}, \approx 75 ms in 1.5 Tesla systems. If water proton transverse relaxation times are as short as the brain’s \(^{19}\)F \(T_2\) relaxation time, conventional NMR pulse

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sequences would not produce an image. Thus, a tremendous achievement by Xu et al. was their development of a technique for detecting short-$T_1$ $^{19}$F nuclei in brain parenchyma. The authors also had to contend with the fact that $^{19}$F nuclei are just outside brain parenchyma, e.g., in muscle, bone marrow, or fat. $^{19}$F's $T_2$ is approximately 10–20 times larger, or 100 to 130 ms. Thus a fixed group of sevoflurane molecules would appear brighter in an image if they were outside the brain. Although the images of Xu et al. are a trifle fuzzy, they represent a major advance. This paper demonstrates a path to better radiofrequency coil design and better radiofrequency pulsing. $^{19}$F NMR brain images should be better in the future, because it is clear that these methods can be further improved. Additionally, because sodium ($^{23}$Na) NMR relaxation times are typically 5–10 times larger than those for $^{19}$F, the work by Xu et al. strongly suggests the feasibility of conducting rapid, $^{23}$Na NMR imaging of the brain. Sodium imaging of the brain has potential for monitoring areas of brain edema and infarct in experimental and clinical stroke.

Third, a point of interest relates to the use of NMR techniques for detection of different in vivo compartments of anesthetics. In a brilliant $^{19}$F NMR paper 20 yr ago, Trudell and Hubbell were the first to demonstrate (using an in vitro model system) that halothane molecules are in rapid exchange between different molecular compartments. This means that halothane molecules jump back and forth several hundred times per second between hydrophobic and hydrophilic environments. Because spin sampling times in NMR experiments are typically tens of a second, NMR measurements of physical properties reflect an average over the two environments. In vivo, hydrophobic and hydrophilic environments for $^{19}$F are often characterized by different longitudinal and transverse relaxation times. Because Xu et al. were able to measure NMR signal strength as a function of echo delay, they could detect a biexponential decay pattern for the sevoflurane resonance they followed, which meant that this resonance corresponded to excitation of sevoflurane in two molecular compartments. This clever NMR method, implicit in fundamental NMR work by Carr and Purcell9 and Melboom and Gill,20 was recently applied explicitly in in vitro NMR studies of anesthetic interactions with excised brain and specific protein binding.21–23

More generally, the work by Xu et al. suggests that advanced NMR pulsing techniques can be used to make in vivo distinctions between different molecular compartments. Additionally, the approach by Xu et al. can be modified to search for compartmentation that not only is characterized by different relaxation times but also or instead is characterized by other physical/chemical properties, such as different diffusion times or different metabolic rates.

Fourth is a comment on pharmacokinetics. Very early work with $^{19}$F NMR spectroscopy suggested there might be an excessive accumulation of general anesthetics in the brain after short periods of general anesthesia.24 Although subsequent work seemed to resolve disagreements,5,25 this accurate study by Xu et al. shows better than ever that there is agreement between invasive measures of vapor pharmacokinetics and NMR measures. As was thought, there should be no worry about ambulatory surgery patients going home after general anesthesia with hidden, uneliminated deposits of clinically significant quantities of vapor anesthetic.

Xu et al. additionally point out that the ability to image anesthetics also permits studies in which the monitoring of regional anesthetic distributions might be of concern—as in focal cerebral ischemia. An ability to measure regional anesthetic distributions would seem to be potentially helpful to other types of NMR studies, in which brain perfusion, brain edema, metabolic rates, or functional activity are being measured.

In summary, the paper by Xu et al. demonstrates an impressive advance. Although the manuscript is charged with NMR terminology, both the terminology and associated conceptual issues are likely to be around for some time. An effort to appreciate what is happening should, apart from being enjoyable, also prepare the reader for keeping up with future advances in today's changing biomedical world.

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