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AJNR Am J Neuroradiol 1993, 14 (5) 1038-1042
http://www.ajnr.org/content/14/5/1038.citation

Commentary

Measurement of Psychoactive Drugs in the Human Brain In Vivo by MR Spectroscopy

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The success of magnetic resonance (MR) imaging has led to considerable interest in MR spectroscopy (MRS) as a noninvasive probe of in vivo brain biochemistry for neuropsychiatric applications (1–3). Most work has used [^{31}P]MRS and [^{1}H]MRS to measure relative concentrations of endogenous metabolites. [^{31}P]MRS can probe tissue pH, energy metabolites such as phosphocreatine and adenosine triphosphate, and the precursors and degradation products of phospholipid metabolism (4). [^{1}H]MRS can measure certain metabolites of low molecular weight and amino acids such as choline, creatine, glutamate, and N-acetylaspartate. The last compound occurs primarily in neurons and appears to be a marker for neuronal density (5). The article by Gonzalez et al (6) in this issue of the *American Journal of Neuroradiology* describes measurements of brain lithium (Li) concentrations in vivo using MRS and highlights the ability of MRS to monitor exogenous agents, an important feature that has received less attention than the use of MRS to measure endogenous metabolites in vivo.

MRS of Drugs In Vivo

Although monitoring of therapeutic (or toxic) agents and their metabolites in blood or urine is convenient and relatively inexpensive, it may not be ideal. The magnitude of the pharmacologic or toxic effect of a drug depends on the concentration at the receptor sites in the target tissue. For example, the concentration in serum may not always reflect the concentration in brain, where highly water-soluble compounds can be excluded by the blood-brain barrier. Alternatively, a drug may accumulate to a high level in tissue with long-term administration, whereas levels in serum remain at a relatively constant lower level. Therapeutic (and/or toxic) response, the ultimate measure of correct dosage, might be expected to correlate better with concentration in tissue than in blood or urine. Moreover, drug metabolism in the target tissue may differ substantially from that in the liver. An in vivo probe of drug concentration in tissue may have utility for psychiatric illnesses, in which accurate diagnosis is often problematic, therapeutic response can be difficult to measure, and drug levels in serum often are inadequate predictors of response.

Because it is noninvasive, MRS can be used repetitively, permitting pharmacokinetic studies. In principle, the drug concentration can be measured at separate locations in the body or organ. Because MRS is performed on one magnetically active isotope (eg, ^{7}Li, ^{19}F) at a time, there is no interference from background signals if the drug contains a label not normally found at significant levels in the body. The sensitivity of MRS to molecular structure may permit simultaneous monitoring of the parent drug and its metabolites. The possibility of simultaneously measuring the level of a drug in tissue and its local metabolic effects (with ^{31}P or ^{1}H spectra) is unique to MRS.

On the other hand, the low sensitivity of MRS and the low concentrations of most drugs in tissue, except perhaps when taken in overdose, limit in vivo studies to a handful of compounds. Most drugs do not have a convenient MRS handle such as fluorine, and can only be studied by [^{1}H] MRS or perhaps by [^{13}C]MRS. Metabolites that can be resolved in spectra of extracts or whole biological fluids in vitro usually cannot be resolved in vivo because of the broader lines encountered and the lower magnetic fields used. Moreover, it is currently not possible to distinguish drug in different compartments (ie, the intracellular and extracellular spaces), which may be important for correlating concentration in tissue with clinical response.

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Index terms: Drugs, psychoactive; Magnetic resonance, spectroscopy; Magnetic resonance, experimental; Brain, measurements; Brain, magnetic resonance; Commentaries

AJNR 14:1038–1042, Sep/Oct 1993 0195-6108/93/1405–1038

In Vivo ^{7}Li MRS

Lithium, which is normally present at trace levels in the body, is the treatment of choice for acute manic illness and prophylaxis in bipolar disorder (7). Treatment typically consists of a daily oral dose of 900 to 1800 mg of Li_2CO_3, and the Li level in serum is maintained in the demonstrated therapeutic range between 0.5 and 1.2 mEq/L. Levels in serum above ~2 mEq/L are usually toxic. Although it is accepted that the therapeutic efficacy of Li can be monitored by the concentration in serum, approximately 30% of patients do not respond adequately when therapeutic concentrations in serum are maintained. Others develop neurotoxicity at nominally therapeutic levels of Li in serum. This suggests that Li concentration in serum is not a totally adequate measure of Li efficacy and that Li concentration in brain may be a better measure. Li concentrations in brain are on the order of 0.5 mEq/L, but they had never been measured precisely in humans in vivo until the application of MRS.

The ^{7}Li isotope is relatively favorable for MRS studies, with a sensitivity 27% that of ^{1}H. In biologic systems, the spectrum typically is a single, narrow line arising from the Li cation in both the intracellular and extracellular environments.

The article by Gonzalez et al (6) describes detailed technical procedures for obtaining Li concentration in brain with high precision and accuracy using [^{7}Li]MRS. The work represents a technical advance over previous in vivo [^{7}Li]MRS studies in humans (8–12), which are reviewed in the article (6) with one exception (12). Early work in humans (8, 9) emphasized technique feasibility and the pharmacokinetics of Li uptake and elimination in individuals, as well as the measurement of absolute concentrations and correlation with levels in serum. Perhaps the most significant finding of clinical relevance in the early work was that Li crosses the blood-brain barrier relatively rapidly, on the order of an hour, and not over days, as had long been suggested, based on the delayed therapeutic effect of Li. Li concentrations in brain of 0.2 to 0.9 mEq/L were found in previous work (8–11), consistent with the work of Gonzalez et al (6). Kato et al (12) studied 10 bipolar patients on Li therapy. Levels in brain were about half those in serum, also consistent with the reports of other workers (6, 8–11). Interestingly, serial measurements indicated that Li concentration in brain increased substantially during a manic episode (12).

Among the several improvements to the [^{7}Li] MRS approach, Gonzalez et al (6) use a very long pulse repetition time (TR) of 25 s to eliminate differential saturation effects caused by possible variations in spin-lattice relaxation time (T1). This approach, although not of optimal efficiency for signal detection, is justified for quantitative purposes. Evidence is accumulating that in vivo T1 values can vary substantially, even under nominally constant conditions. To date ^{7}Li T1 values of 3.4 ± 0.5 ($n = 4$) (11), 4.2 ($n = 2$) (6), and 4.6 ($n = 1$) (13) have been measured for human head. Although in vivo T1 values are difficult to measure precisely for Li (and other drugs), the above variations may represent real differences, perhaps because of variations in Li concentration in tissue. We have found that the ^{19}F T1 of the antidepressant fluoxetine in human brain can vary among individuals by about a factor of 4 and that T1 weakly correlates with tissue concentration ($r = 0.62$, $n = 10$) (Komoroski et al, unpublished results).

Rather than provide an average concentration over a volume of head, Gonzalez et al (6) measure brain volume by computerized morphometric analysis and then correct for contributions from Li in muscle, cerebrospinal fluid, and blood. Morphometric analysis adds considerable difficulty to the procedure, even when the software is available. Corrections for muscle and cerebrospinal fluid are problematic in that the individual Li concentrations are unknown and may vary substantially. This is probably of little consequence except for muscle, where Li concentrations can be substantially greater than those in brain (14). A better long-term solution might be to sample a large volume totally restricted to brain with three-dimensional localization.

To limit errors due to instrumental deficiencies, adiabatic pulses were used to ensure uniform excitation throughout the brain, and corrections were made for receiver spatial inhomogeneities. The use of adiabatic pulses is becoming more common, but nonuniform excitation and reception can be minimized with coils of higher radiofrequency field homogeneity, as mentioned previously (6).

Gonzalez et al (6) report brain-to-serum concentration ratios for 10 patients in the range of 0.50 to 0.97 mEq/L, which is in general agreement with results from previous work. They do not mention the dose schedules or the delays between the time of data acquisition and of the

last dose, which can affect the brain-to-serum concentration ratio (9).

It is noted that the Li concentration probably varies with brain location and that this possibility is, of necessity, ignored in this analysis. Multivoxel localized ^{7}Li spectroscopy of reasonable spatial resolution ($4 \times 4 \times 4$ cm^3 voxel) is possible (13) but not fully developed, and interpretable ^{7}Li images of rat brain have been reported (14). Such information on local Li concentrations may shed light on the neurotoxicity and mechanism of action of Li. Further technique development to measure local Li concentration in the brain is warranted (13).

One complication not considered by Gonzalez et al (6) is the possible multicomponent signal behavior of ^{7}Li. For nuclei such as ^{23}Na, ^{39}K, and ^{7}Li, the MRS signal for a single biochemical environment can consist of two components, one narrow and one broad, when ionic brownian motion is restricted. Depending on the degree of motional restriction and on data acquisition conditions, the broad component may not be detected, resulting in lower apparent concentrations. For ^{23}Na and ^{39}K, the effect is well documented and often substantial (up to 60% intensity loss) (15). The unique relaxation behavior of ^{7}Li makes this effect less severe than that for ^{23}Na or ^{39}K, but it may not be negligible (16). Results for erythrocytes suggest that at the low concentrations encountered therapeutically, about 15% signal loss may occur (16). The size of the intensity loss, if any, is not known in vivo and would be difficult to measure.

One last issue of importance is compartmentation of the ion in vivo. Even ignoring the different cell types, the ratio of the intracellular-to-extracellular Li concentrations is not known for brain. Although Li presumably works intracellularly in the brain and about 80% of the volume of the brain is intracellular, the intracellular concentration may be substantially lower than the extracellular concentration, as is the case for Na. Thus, the in vivo ^{7}Li signal may primarily represent *nonactive* Li, although a measure of total brain Li could still prove useful. Although possible in principle, it is not yet clear if ^{7}Li MRS in vivo can provide separate measures of intracellular and extracellular Li in practice. Compartmentation issues will probably be resolved by in vivo perfusion studies of cultured cells.

It is difficult to assess the long-term significance of the improvements implemented by Gonzalez et al (6). Given the ambiguities surrounding localization, compartmentation, and signal visibility, their rigorous procedures may represent some overkill for ^{7}Li. Less-precise data from a smaller but well-localized region in the brain is possible and may be preferable for ^{7}Li MRS, which is of relatively limited application in any event. Nevertheless, their more exacting approach should yield benefits for more difficult and important applications using in vivo MRS of nuclei such as ^{19}F.

[^{19}F]MRS In Vivo

[^{19}F]MRS has been used to study a number of drugs in vivo (17). The isotope has very favorable MRS properties with a sensitivity 83% that of ^{1}H and relatively short T1 values; it is not present in biologic systems to any significant extent. Many drugs, including numerous psychoactive agents, have fluorine as a part of their molecular structure (18). However, only a few reach sufficient concentration in the brain to be detectable by MRS in vivo. Most work has centered on the antipsychotic agents trifluoperazine and fluphenazine and the antidepressant fluoxetine (18–24).

For example, trifluoperazine, which has a trifluoromethyl group, can be detected without localization in the head for individuals on relatively large oral doses of 60 to 120 mg/d (18, 22), for whom concentrations in brain were estimated to be on the order of 1 to 5 μg/ml. The [^{19}F]MRS signal intensity correlated with dose for six individuals responding to treatment. Interestingly, no signal was detected for a nonresponding patient at a dose of 120 mg/d. Sensitivity improvements are necessary to study lower doses of trifluorinated antipsychotic agents or common monofluorinated agents such as haloperidol.

The sensitivity limitation is not as severe for the common antidepressant fluoxetine, which can be readily detected by [^{19}F]MRS in the head for individuals receiving typical clinical doses of 20 to 40 mg/d for 2 weeks or longer (18, 22–24). The drug apparently occurs at a higher relative concentration in the brain and has a lower fluorine equivalent weight than do the antipsychotic agents. More than 30 patients have been studied (22–24), and it has been demonstrated that the drug accumulates in the brain relative to plasma. T1 measurements were described above, and crude spectroscopic localization indicates that most of the ^{19}F signal is from the brain and not from surrounding tissue (Komoroski et al, unpublished results). Preliminary results suggest that

[^{19}F]MRS could serve as a useful, albeit expensive, measure of patient compliance.

Certain aspects of the approach of Gonzalez et al (6) would undoubtedly improve [^{19}F]MRS studies of psychoactive drugs.

[^{1}H]MRS of Drugs

On the basis of considerations of sensitivity and general applicability, it might be expected that [^{1}H]MRS would be the preferred approach for detecting drugs in brain in vivo. However, the small range of chemical shift, the necessity of eliminating the very large water signal, and the presence of endogenous metabolites at about 1 mmol/L or greater make [^{1}H]MRS less promising in this regard. One exception has been for ethanol, which has been detected in vivo in human brain (25, 26). By using [^{1}H]MRS, it may be possible to detect certain drugs that have a low therapeutic index (ie, drugs administered in relatively large amounts by weight) or that accumulate in the brain. Many drugs contain aromatic rings in their molecular structure, and this region of the ^{1}H spectrum is relatively free of background signal.

Future Enhancements

The major limitation of in vivo MRS studies of drugs is low signal-to-noise ratio. Increases in sensitivity by better coil design and higher magnetic fields (3 to 5 T) will permit lower concentrations or smaller localized regions to be detected. The limits in concentration and spatial resolution depend on the drug and the nucleus of interest. Clinical MRS will continue to progress, even with the introduction of functional MR (27), which is not a *biochemical* measure of tissue status. The work of Gonzalez et al (6) represents another step in the progress of clinical MRS.

Acknowledgment

I thank Dr. J.E.O. Newton for his careful reading of the manuscript.

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