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# Nuclear Magnetic Resonance in Bipolar Affective Disorders

Ricardo A. Rangel-Guerra,<sup>1</sup> Hector Perez-Payan,<sup>2</sup> Lawrence Minkoff,<sup>3</sup> and Luis E. Todd<sup>4</sup>

**Nuclear magnetic resonance produced by a FONAR QED 80 whole-body scanner with measurement in vivo of T<sub>1</sub> proton relaxation time was used in 20 patients with the clinical diagnosis of bipolar affective disorder. Diagnoses were based on Research Diagnostic Criteria, Diagnostic Statistical Manual III code 296.66, and on Schedule for Affective Disorders and Schizophrenia. Proton T<sub>1</sub> relaxation times were measured in all patients and in 18 normal controls before and after lithium carbonate treatment. Normal values of T<sub>1</sub> in frontal and temporal lobes were 210 ± 10 msec. All but three patients had prelithium T<sub>1</sub> values higher than the controls (264 ± 8.8 msec). After lithium therapy of 900 mg/day for 10 days, serum lithium levels were in the therapeutic range of 0.5–1.5 mEq/L, and patient T<sub>1</sub> values were near normal levels (208 ± 8.0 msec). One patient with a prelithium level within normal range proved to have cyclothymic disorder and not bipolar affective disorder; two patients did not complete the study. This study shows a statistically significant difference (*p* < 0.01) in the behavior of hydrogen protons in bipolar affective disorder, which has not previously been reported in medical literature.**

The diagnosis and treatment of mental illness have been hampered by the inability of physicians to directly observe the chemical state of human brain tissue in vivo. This paper presents findings about the chemistry of normal and abnormal human brain function obtained noninvasively and without the use of radioactive tracers through the use of nuclear magnetic resonance (NMR).

Damadian [1] proposed NMR for tumor detection in 1971. He observed, and subsequent experiments have confirmed [2–7], that malignancies in general have longer proton relaxation times than corresponding normal tissues [8, 9]. The prediction that NMR would be able to discriminate between normal and malignant tissue was based on a comprehensive investigation by Damadian of the role of sodium, potassium, and water in the origin of the electrical activity of living tissue [10–13]. According to these findings, we hypothesized that the well known effect of lithium carbonate in relieving the symptoms of manic-depressive patients might be the result of the lithium ion acting on the water structure of brain tissue in a manner analogous to its demonstrated effect on aqueous water [10].

In 1973, Damadian [14] showed that L<sub>1</sub><sup>+</sup>, by virtue of its tendency to increase the ordering of liquid water structure, shortened the T<sub>1</sub> relaxation time (fig. 1) of water protons. Accordingly, if lithium were

achieving its effect in the manic-depressive patient through its power to order water structure and decrease the T<sub>1</sub> relaxation time, it seemed reasonable that, using the whole-body NMR scanner [15], the shortening of the T<sub>1</sub> relaxations of water would be demonstrable in the brain tissue of lithium-treated patients. This paper confirms that theoretical expectation, and observes that the manic-depressive patient may have an elevated proton relaxation time as a characteristic biochemical alteration of this disease.

## Subjects and Methods

All patients were referred to the Unidad de Resonancia Nuclear Magnética, Hospital Universitario, Monterrey, Mexico, by that institution's psychiatry department. All patients were diagnosed as having bipolar affective disorder through clinical evaluation with the use of different scales, mainly the Research Diagnostic Criteria (RDC); Diagnostic Statistical Manual III (DSM III), code 296.66; and Schedule for Affective Disorders and Schizophrenia (SADS). Serum lithium levels were measured to check that none of the subjects had received this drug prior to scanning. Most patients were in the depressive phase of their bipolar disorder.

The patients were then scanned on a FONAR QED 80 whole-body NMR scanner. This machine permitted direct focusing down on specific regions of the brain, and quantitative measurements of T<sub>1</sub> in the selected tissue volumes (about 64 mm<sup>3</sup>). For purposes of this study we chose to investigate the frontal and temporal lobe tissues after first identifying and locating the regions of interest in the cross-sectional color images provided by the QED 80. The T<sub>1</sub> measurements were a 13 point discrimination of T<sub>1</sub> made by the progressive saturation method of Freeman and Hill [16], which is a standard feature of the FONAR QED 80 dual mode whole-body scanner. The FONAR QED 80 operates at a frequency of 1.7 MHz and a magnetic field strength of 500 G.

Eighteen normal controls were chosen from medical student volunteers. They received lithium carbonate at the same dosage as the patients (900 mg/day for 10 days). All were subjected to the same battery of diagnostic tests (RDC, DSM III, and SADS).

After initial scanning, patients were started on lithium carbonate therapy at the dosage of 300 mg three times daily. After 10 days of treatment, the battery of diagnostic psychiatric tests was given again to the patients, and they were rescanned with the NMR machine (table 1). Serum lithium levels were measured and deter-

<sup>1</sup> Division de Neurología, Hospital Universitario U.A.N.L., Apartado Postal 1-4469 Mitras, Monterrey, Nuevo León, México. Address reprint requests to R.A. Rangel-Guerra.

<sup>2</sup> Departamento de Psiquiatría, Hospital Universitario U.A.N.L., Monterrey, Nuevo León, México.

<sup>3</sup> FONAR Corporation, Melville, NY 11211.

<sup>4</sup> Unidad de Resonancia Nuclear Magnética, Hospital Universitario U.A.N.L., Monterrey, Nuevo León, México.

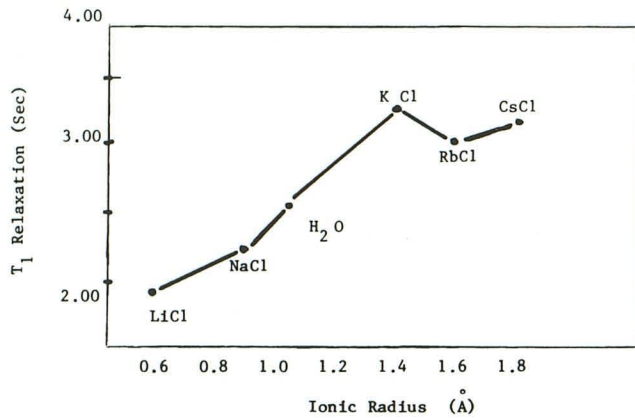


Fig. 1.—Plot of  $T_1$  relaxation times of water protons versus crystal radius of alkali cations in aqueous solutions of alkali halides. Study performed at NMR frequency of 100 MHz on 4 M solutions of alkali chlorides.

TABLE 1: Results of Psychiatric Tests before and after Lithium Therapy

Case No. (age, gender)	SADS		Code DSM III
	Prelithium	Postlithium	
1 (42, M)	60	66	296.66
2 (20, F)	45		296.66
3 (25, F)	65	72	296.66
4 (48, F)	60	75	296.66
5 (42, F)	67	76	296.46
6 (46, F)	70	75	296.66
7 (23, M)	72	80	301.13
8 (28, F)	42	55	296.66
9 (26, M)	40	54	296.66
10 (54, F)	48	60	296.36
11 (23, F)	50		296.66
12 (23, M)	42	50	296.66
13 (46, F)	55	60	296.66
14 (23, F)	50	56	296.66
15 (59, F)	58	60	296.66
16 (56, F)	46	50	296.66
17 (45, M)	46	56	296.66
18 (57, M)	66	70	296.66
19 (52, F)	45	56	296.66
20 (33, F)	60	70	296.66

mined to have reached the therapeutic level known to be effective (0.5–1.5 mEq/L). The patients were positioned for all initial and follow-up  $T_1$  measurements by means of the laser positioner and computer control bed of the FONAR QED 80, which controls bed position with an accuracy of  $\pm 1$  mm. No other drug treatment was administered to the patients during the period of study.

**Results**

Table 2 is a summary of the  $T_1$  measurements made on the manic-depressive patient group (20 patients) before and after lithium therapy. The administration of lithium to the control group did not produce any changes in the  $T_1$  relaxation times of the water protons of the brain (temporal lobe).

The mean  $T_1$  value of all patients tested before the administration of lithium carbonate was  $277 \pm 10.5$  msec. Ten days after treatment

TABLE 2: Results of  $T_1$  Measurements before and after Lithium Therapy

Case No. (age, gender)	Mean $T_1$ in msec (no. of readings)		Serum Lithium Level (mEq/L)
	Prelithium	Postlithium	
1 (42, M)	240 (3)	195 (3)	0.8
2 (20, F)	209 (1)		
3 (25, F)	251 (1)	244 (2)	0.2
4 (48, F)	272 (2)	225 (2)	0.9
5 (42, F)	244 (2)	205 (3)	1.0
6 (46, F)	314 (2)	222 (3)	0.8
7 (23, M)	217 (2)	198 (2)	0.5
8 (28, F)	241 (3)	186 (1)	1.2
9 (26, M)	226 (3)	158 (2)	0.6
10 (54, F)	285 (2)	180 (3)	1.0
11 (23, F)	249 (1)		
12 (23, M)	268 (2)	201 (4)	0.8
13 (46, F)	349 (2)	212 (3)	0.9
14 (23, F)	283 (1)	217 (1)	1.1
15 (59, F)	336 (1)	287 (2)	1.2
16 (56, F)	269 (2)	198 (2)	1.0
17 (45, M)	367 (3)	183 (3)	0.8
18 (57, M)	264 (2)	215 (2)	0.6
19 (52, F)	347 (2)	222 (2)	1.1
20 (33, F)	219 (2)	213 (2)	1.2

Note.—Mean  $T_1$  prelithium =  $277.3 \pm 10.5$  msec; mean  $T_1$  postlithium =  $208.9 \pm 6.6$  msec.

the  $T_1$  had fallen to  $208.9 \pm 6.6$  msec in the patient group with no significant change in the control group. The mean of the normal value in the control group was  $210 \pm 8$  msec.

The probability that the difference in the means of the treated and untreated patients is not significant is less than 0.01. The probability that the difference in the means of the normal group and the untreated manic-depressive group is not significant is also less than 0.01. In the control group there was no significant difference in the mean  $T_1$  value before and after lithium treatment.

All patients reported that their symptomatology improved with the lithium treatment. This was also shown in their profiles on the psychiatric scales used (table 1). Cases 2 and 11 did not complete the study; case 7 proved to have cyclothymic disorder.

The control group was enlisted from medical student-volunteers. None had previous history of any mental disorder. Therapeutic concentrations of lithium have no psychotropic effect in a normal individual. It is not a sedative, antidepressant, or a stimulant, which separates lithium from all other psychotropic drugs [17]. The mechanism of action of lithium carbonate as a mood stabilizing agent was heretofore unknown [18].

**Discussion**

The reduction in the  $T_1$  relaxation time of the water proton due to the administration of lithium may be accounted for by the physicochemical effect of this ion on water. The lithium ion is the smallest of the alkali metal ions (group 1A), and salts of this monovalent cation have many similarities to salts of the physiologic alkali cations, sodium, and potassium. It is the effect of the alkali cations on the structure of solvent water that is of interest here [10, 18]. Alkali cations with atomic numbers larger than sodium (i.e., potassium, rubidium, and cesium) elevate the  $T_1$  of distilled water (fig. 1). Sodium and lithium decrease the relaxation time of distilled water, and apparently increase the average time required for the rotation or translation of solution water molecules.  $K^+$ ,  $Rb^+$ , and  $Cs^+$  decrease the required time of the equivalent hydrodynamic fluctuation

(correlation time). The  $T_1$  maximum of this in vitro study appears consistently at potassium, suggesting that potassium induces the greatest motional freedom of solution water molecules. The  $T_1$  minimum at lithium suggests that this ion reduces the motional freedom of water the most.

This is in agreement with the calculation of Samoilov [19] of the energy required for a water molecule to escape from the hydration atmosphere of an ion. Water molecules in the hydration shells of lithium and sodium ions exchange less frequently than water molecules in the pure water phase. Water molecules in the hydration atmospheres of  $K^+$ ,  $Rb^+$ , and  $Cs^+$  exchange more rapidly than water molecules in bulk phase. Krestov [20] obtained similar results in his observations of the motional entropy of water in the vicinity of alkali cations and pure water. Motional entropy of water molecules in the vicinity of  $K^+$ ,  $Rb^+$ , and  $Cs^+$  was greater than that of surrounding water, whereas motional entropy of water in the vicinity of  $Li^+$  and  $Na^+$  was less than that of the surrounding water.

Studies of cell water generally agree with the results of Krestov and Samoilov for simple aqueous solutions [10, 21]. The lithium reduction of  $T_1$  in brain tissue water in manic-depressive patients is consistent with the effect of this ion on aqueous solutions. The elevated water proton  $T_1$  relaxation in the untreated patients further suggests a reduction in the "ordering" of tissue water structure in the manic-depressive state. Such a change in tissue solvent structure could alter chemical reactions dependent on those solvents, such as those that require direct participation of a molecule of water in the overall reaction (e.g., pyruvate kinase, carbonic anhydrase, and peptidases), as well as altering bioelectric events [13].

As presented in the data, the manic-depressive patients have  $T_1$  proton relaxation times elevated relative to normal. It is possible, therefore, that the cell water in the brains of patients with this disease has an abnormally high degree of motional freedom which is reduced toward normal by lithium treatment.

Of the 20 patients studied who were thought to be suffering from manic-depressive illness (bipolar affective disorder) 17 had clearly longer  $T_1$ s than normal, and three (cases 2, 7, and 20) had  $T_1$ s close to normal. Case 7 had been diagnosed as the cyclothymic disorder, which is a variant of affective disorder (DSM III 301.13).

The identification of a tissue chemical parameter, which can be measured and quantified in a whole-body NMR Scanner and linked to a treated illness such as manic-depression, leads to the hope that NMR can also be used to reveal the chemical underpinnings of other mental disorders. For the case of manic-depressive disorders, the  $T_1$  discrimination suggests the possibility of a method for screening patients who would respond to lithium therapy. These findings can be used in the future as a diagnostic procedure in mental illness, to help differentiate affective disorders from schizophrenia or borderline states.

#### Editor's note:

The prolongation of  $T_1$  of brain tissue has been observed in areas of gliosis following surgery. The results reported by the authors may not be unique or characteristic of bipolar affective disorder. The observations made by the authors are of great interest, but their significance and specificity need to be investigated further.

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