The effect of valproic acid and omega-3 fatty acids on brain membrane in bipolar disorder patients

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Introduction

Numerous studies have demonstrated that changes in phospholipid membrane fluidity affect several neuronal functions such as signal transduction, membrane protein interactions, surface-receptor binding, ion exchange, and mitochondrial functioning (1, 2). Interestingly, additional research has indicated that many current treatments for bipolar disorder (manic depressive illness) can be achieved by modifying one or more of these neuronal functions, thus highlighting alterations in membrane fluidity as a possible common mechanism of action.

We have previously shown that effect of omega-3 fatty acids (ω3FAs) may be assessed through differences in brain water proton T2 values (3). We hypothesized that administration of Valproic acid (VPA), which is structurally similar to ω3FAs and which is known to increase membrane fluidity, would decrease T2 values in subjects with bipolar disorder. This abstract communicates our preliminary findings.

Materials & Methods

Fifty-two subjects (38.1±12.6 years of age) meeting DSM IV criteria for bipolar I or II disorder on clinical interview were enrolled in the MR T2 study before and after a 4-week treatment of medication-dietary supplement. Among them, 10 received valproic acid (depakote), 19 received ω3FAs and the rest received standard mood stabilizers. Twenty-seven healthy comparison subjects (29.0 +/- 6.8 years in age) were recruited to undergo two identical MR examinations at 4-week intervals (54 total scans). These comparison subjects reported no history of medical, neurological, or psychiatric illness at clinical interview.

Subjects underwent brain T2 measurement using a 1.5-T MR scanner and a quadrature head coil for transmit and receive. The T2 measurement was conducted using 32 spin echo EPI images in axial view with initial TE of 32ms and TE increment of 4 msec in each consecutive image through the basal ganglia. Linear least square regression was used to calculate a single T2 relaxation time for each pixel. The subjects were also underwent evaluation of standardized mood rating scales and assigned to mood state groups (manic, depressed, mixed, or euthymic) based upon HAM-D and YMRS scores by an investigator who was blind to the MRI results.

Results

There was a significant negative correlation in the general study population between age and T2; as subject age increased, T2 value decreased ($z=-2.74$, $p=0.006$). This association also remained significant in the bipolar cohort alone ($z=-2.04$, $p=0.041$). Consequently, all subsequent study calculations were adjusted for the effect of age on T2.

Among the bipolar subject cohort, the T2 values of individuals on valproic acid (depakote) were significantly lower than T2 of those on other conventional treatment (Figure 1, $p=0.003$). More specifically, the negative correlation between VPA administration and T2 was significantly stronger than that between lithium administration and T2 ($p=0.001$) and between the drug naïve state and T2 ($p=0.0085$). As expected, bipolar subjects taking ω3FAs also had significantly lower T2 values than those who did not take ω3FAs (Figure 2, $p=0.034$). Furthermore, the negative correlations between VPA administration and T2 and ω3FA administration and T2 were of approximately equal strength ($p=0.8059$).

Our data also suggested a trend toward decreasing T2 values and increasingly antidepressant mood states. According to a multivariate analysis of the bipolar cohort, individuals in the depressed and mixed mood states tended to have higher T2 values than patients in the euthymic state ($z=1.18$ and $z=2.39$, respectively), while individuals experiencing mania tended to have lower T2 values than euthymic patients ($z=-1.86$).

Discussion

VPA and ω3FAs are incorporated into neuronal cell membranes both in phospholipids and neutral lipids, thereby reducing the symmetry of the resulting molecule (6). Perlman and Goldstein have shown that VPA and other short-chain fatty acids have membrane-disordering properties, which are linked to the ability to cause sedation (7). In addition, Perlman et al have shown that membrane-disordering properties of VPA and alcohol as determined by EPR spectroscopy (7). It has been shown that the T2 value of ethanol protons increased as fluidity of brain membrane decreased (8). This effect indicates that fluidity changes of brain membrane may influence T2 of water protons in a similar way.

Decreased T2 values observed in the brains of bipolar subjects taking VPA could be caused by increased blood flow or increased neuronal membrane fluidity. However, multiple studies examining the effects of VPA on cerebral blood flow (CBF) have actually demonstrated decreased blood flow in association with VPA administration (4, 5), which would likely result in T2 increase. Consequently, the decreased T2 values found in subjects taking VPA is likely a consequence of increased membrane fluidity as opposed to an increase in CBF. This is consistent with our recent finding that changes in T2 values of rat brains fed with ω3FAs had a strong correlation with membrane fluidity measured with fluorescence anisotropy (manuscript in preparation).

Conclusions: In subjects with bipolar disorder, both VPA and ω3FA treatments appear to decrease brain water T2 value, and this effect may be mediated by changes in membrane fluidity. Furthermore, these decreases in brain water T2 may be associated with progressively antidepressant changes in mood.

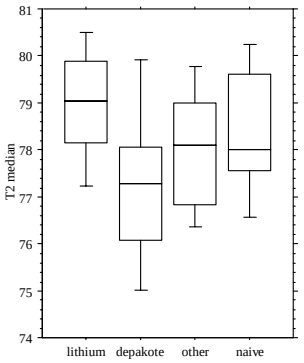

Fig. 1 T2 Median by Mood Stabilizers

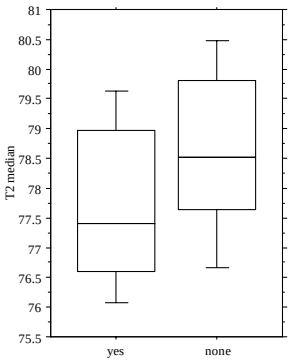

Fig.2 T2 Median by ω3FA Administration

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