Hippocampal N-Acetyl-Aspartate in Generalized Anxiety Disorder Patients Treated with Riluzole: a Proton Magnetic Resonance Spectroscopic Imaging Study

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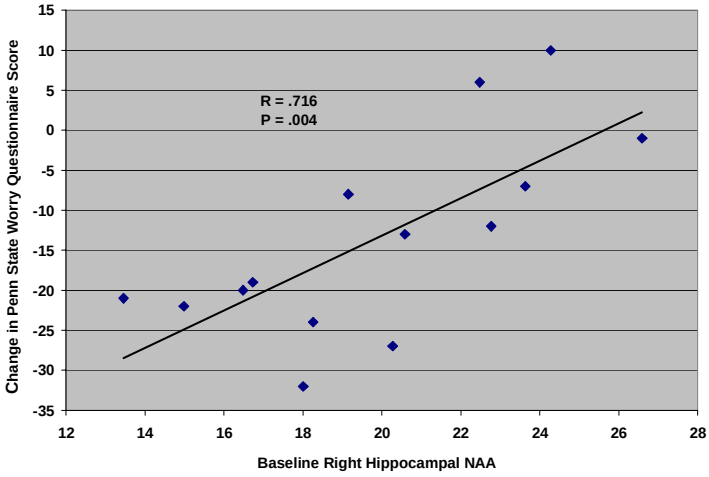
INTRODUCTION. There is a need to identify novel, pathophysiologically-based pharmacotherapies for anxiety disorders. Impairments in neuronal plasticity and resilience have been implicated in the pathophysiology of stress-related psychiatric conditions, including mood and anxiety disorders. Inhibition of excessive glutamatergic activity in specific regions, a medication approach that might impact favorably on neuroplasticity, has resulted in therapeutic benefit for patients with severe, recurrent mood disorders.[1,2] However, much less is known about the role of glutamate and its impact on neuroplasticity in primary anxiety disorders. Given the extensive lifetime comorbidity between anxiety and mood disorders, and the suggestion that early-onset anxiety disorder is a risk factor for the subsequent development of mood disorders, we conducted a trial of the glutamate release inhibitor riluzole in adult patients with generalized anxiety disorder (GAD) and tested its impact on a putative *in vivo* measure of neuroplasticity. Proton magnetic resonance spectroscopic imaging (^{1}H MRSI) was used to measure levels of N-acetyl-aspartate (NAA), a marker of neuronal viability/integrity, at three time points: (1) immediately before treatment, when patients were acutely ill; (2) after 1 day of treatment (50 mg BID), to assess the *acute effect* of riluzole on NAA; and (3) after 8 weeks of riluzole, to assess the *chronic effect* of treatment.

Hypothesis. We predicted that chronic treatment with riluzole would result in increased NAA in hippocampus, a brain region vulnerable to glucocorticoid-mediated excitotoxicity. We evaluated relations between baseline hippocampal NAA and response to treatment at 8 weeks.

METHODS. A total of 14 medication-free patients (6 males, 8 females; mean age=31.7, SD=9.6) with a primary diagnosis of GAD (DSM-IV criteria) were administered open-label monotherapy treatment with riluzole (100 mg/day) for 8 weeks. GAD patients had a mean duration of illness of 14.4 years, SD=9.9. Exclusion criteria for the GAD sample included: major depressive episode or substance abuse/dependence within 6 months of study entry; lifetime history of psychotic, bipolar, obsessive-compulsive, PTSD, or eating disorder; mental retardation or learning disability; autism; and significant medical or neurological conditions requiring daily medication treatment. No patient had psychotropic exposure for at least 2 weeks prior to baseline scan. Immediately following the baseline scan, the first dose of riluzole (50 mg p.o.) was administered. Patients took the second dose of 50 mg riluzole 3 hours prior to the day 1 scan; thus they had the equivalent of 100 mg/day riluzole prior to scan # 2. After scan #2, they entered the clinical trial, which consisted of weekly visits for 8 weeks, medication compliance checks, and adverse events monitoring. No psychotherapy or additional psychotropic medications were allowed during the 8 week study. At endpoint, while the patient was on drug, scan #3 was performed. The primary efficacy measures were the Hamilton Anxiety Rating Scale (HAM-A) score and Penn State Worry Questionnaire at endpoint. Seven untreated, medically-healthy volunteers (2 males, 5 females; mean age= 27.4; SD= 4.2) received ^{1}H-MRSI scans at these same time intervals. There were no differences between GAD patients and controls in mean age, IQ, or educational level (all p's > 0.20).

MRSI Methods. All scans were performed on a 1.5 T GE Signa MR system. Following sagittal scout images, a 4-section T1-weighted axial/oblique localizer image, angulated parallel to the Sylvian fissure, was acquired, with a slice thickness of 15 mm and an inter-slice gap of 3.5 mm, matching the subsequent ^{1}H MRSI scan. Next, multislice ^{1}H MRSI scan was performed using the method of Duyn *et al*.[3] to record the data, with TE/TR 280/2300 ms, FOV 240 mm, 32x32 circularly sampled k-space phase-encoding steps, and 256 time-domain points. The strong pericranial lipid resonances were suppressed using octagonally-tailored outer volume suppression pulses, and water was suppressed with a single CHESS pulse followed by spoiler gradients. The raw data were separated into individual slices and then processed by the standard fast Fourier transform algorithm. The mean of the peak areas for each metabolite within the ROI was computed from fitted spectral data. The *a priori* metabolite of interest was the NAA peak level expressed relative to root-mean-square (rms) of background noise (NAA/rms), and secondary analyses were performed with the NAA/Cr ratio.

RESULTS. Response rates to riluzole at week 8 were 80%, while the week 8 remission rate for trial completers was 53%. The median time to response was 2.5 weeks (range 1-6 weeks). The mean HAM-A score decreased from 20.0 (SD=3.4) at baseline to 7.5 (SD=5.3) at week 8, while mean PSWQ score decreased from 64.6 (SD=8.3) to 51.0 (SD=12.6) [paired t=3.37, df=26, p<0.001). Analysis of variance indicated significant improvement in HAM-A score occurred from week 1 onward for trial completers (F=17.34, df=1,7, p<0.0001). For the primary ROIs in right/left hippocampus, there were no group-by-time interactions for either NAA/rms or NAA/Cr. For left hippocampus NAA/rms, there was a trend for a group effect [F(1,19)=3.48, p=0.07], with visual inspection revealing decreased NAA/rms concentrations at all 3 MRS assessments for the GAD group. This trend for a group effect was not observed when Cr was used as the denominator (p=0.25).



Baseline Group Comparisons and Correlations with Clinical Symptoms. At baseline, patients did not differ from controls in NAA/rms or NAA/Cr in either the right or left hippocampus. Severity of worry, as reflected by PSWQ, trended toward negatively correlating with right hippocampal NAA/rms (r=-0.398) across all subjects. This pattern was not as pronounced in left hippocampus (r=-0.266).

Relationship Between NAA and Symptom Change in GAD Patients. We examined whether concentrations of NAA before treatment was associated with symptom severity in response to treatment at 8 weeks for riluzole treated GAD patients. The magnitude of NAA/rms in right hippocampus was found to strongly predict treatment response. Those patients with relatively decreased NAA at baseline showed the greatest improvements in worry scores as obtained from the PSWQ at endpoint. There was a significant negative correlation between baseline right hippocampal NAA and change in PSWQ (r=0.72, p=0.004) (Figure).

Exploratory Analyses in Other ROIs. There was a group-by-time interaction for Cr/rms in anterior cingulate, such that the difference between the GAD and control conditions was greater at the endpoint scan (week 8) than at either the baseline or day 1 scan [F(2,32)=3.65, p=0.037]. Post-hoc t test revealed that patients had lower endpoint cingulate Cr/RMS concentrations than controls, which were significantly different than baseline differences between groups, at a trend level (p=0.09).

CONCLUSION. The glutamate antagonist riluzole appears to be an effective, well-tolerated, and rapidly-acting anxiolytic medication in some patients with GAD. GAD patients did not differ from healthy volunteers in baseline measures of bilateral hippocampal NAA, using either rms or Cr as denominator, and there were no group-by-time interactions suggesting a differential effect of riluzole on these measures. However, in GAD patients, impaired neuronal viability or integrity in right hippocampus was a robust predictor of treatment responsivity to riluzole. The findings suggest that therapeutic strategies that subserve a neuroprotective function can be beneficial to anxiety disorder patients who display relative impairments in one measure of neuronal resilience. The regional specificity and persistence of these findings awaits evaluation in larger placebo-controlled studies of longer duration with additional brain imaging correlates of neuronal function.

REFERENCES.

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