

Anterior Cingulate Proton MRSI in Unipolar Major Depression: Choline Metabolite Changes During SSRI Discontinuation

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Introduction

The anterior cingulate cortex appears to play an important role in major depression (1). Several laboratories have recently reported that the [¹H]MRS brain choline resonance is abnormal in patients with unipolar (2-5) or bipolar major depression (6). Presently, we conducted proton magnetic resonance spectroscopic imaging ([¹H]MRSI) to assess whether the anterior cingulate choline/creatine (Cho/Cr) ratio is altered in mood-stabilized patients with unipolar major depression. Measurements were made at baseline and 2 days after selective serotonin reuptake inhibitor (SSRI) withdrawal in patients stabilized with paroxetine (Paxil) or fluoxetine (Prozac). Paroxetine but not fluoxetine termination typically results in a withdrawal syndrome (7-9). This is probably a result of more rapid elimination kinetics for paroxetine (9). We exploited the differences between these two SSRIs to selectively promote a transient withdrawal state in paroxetine-medicated subjects, and assessed anterior cingulate metabolite ratios (Cho/Cr, choline/Nacetylaspartate (Cho/NAA) and NAA/Cr) and mood state ratings. We hypothesized that placebo substitution would be associated with an elevated anterior cingulate Cho/Cr ratio, but that this would occur only in paroxetine-withdrawn subjects.

Methods

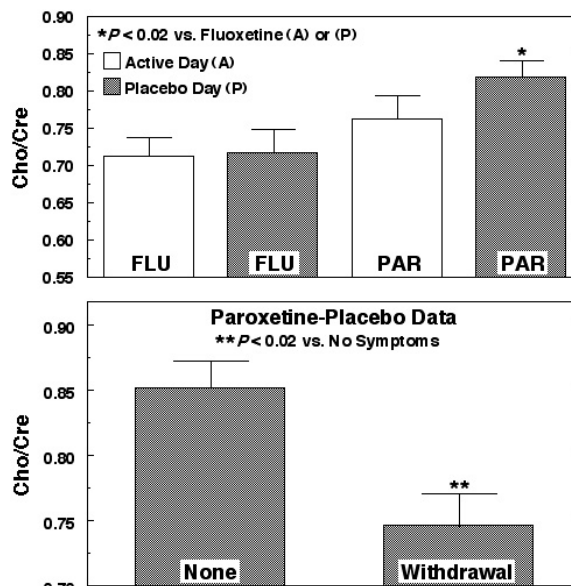
Thirteen patients stabilized on fluoxetine (20 mg/d, >9 months) and thirteen stabilized on paroxetine (20 mg/d, >8 months) participated and provided written informed consent. All subjects met DSM-III-R criteria for a diagnosis of unipolar major depression. In this 6 week study, subjects were administered their active drug for the balance of the time. On study weeks 2 and 5, they were administered either active drug or placebo (randomized, double-blind design). MRSI and mood ratings data were acquired 2 days after medication substitution. On both study days, subjects were administered the 21 item Hamilton rating scale for depression (HAM-D)(10). Subjects were considered to have experienced withdrawal if their placebo study day mood rating scores increased by 6 or more points over active drug ratings.

MRI and MRSI were conducted on a 1.5 Tesla Signa Scanner (General Electric, Milwaukee, WI) using a quadrature volume headcoil. An internal landmark voxel registration procedure was used to optimize MRSI voxel coregistration for the two scan days. The superior/inferior and right/left axis head positioning between scan day variance was $3.1 \pm 2.2^\circ$ and $2.7 \pm 2.0^\circ$, respectively. MRSI was prescribed through the middle of the rostral anterior cingulate cortex. A water suppressed PRESS pulse sequence was used: TR=2000 ms, TE=65 ms, field of view=20.2, number of points=1024, total scans=2. A single spectrum was extracted from the midline of the rostral anterior cingulate cortex. Spectra were fit to Gaussian lineshapes by an experienced rater, blind to treatment conditions, using VARPRO/MRUI. The data were expressed as metabolite ratios (e.g., Cho/Cr, NAA/Cr, Cho/NAA). Tissue segmentation was performed on the axial images acquired to localize the MRSI voxel, which had been edited to apply the MRSI voxel dimensions. All measurements and analyses were completed under double-blind conditions.

Results

There were no differences in MRSI voxel tissue contents between scan days. ANOVA with a repeated measures model revealed statistical equivalence of the NAA/Cr ratio in both paroxetine (PAR) and fluoxetine (FLU) treatment groups on both scan days. The Cho/NAA metabolite ratio was slightly though not significantly ($F_{1,24}=2.7$, $P<.12$) elevated in the paroxetine group. The Cho/Cr ratio was elevated in the paroxetine group ($F_{1,24}=6.6$, $P<.02$). This resulted primarily from an elevated Cho/Cr ratio on the paroxetine-placebo treatment day (Figure, top). Post-hoc ANOVAs revealed that the paroxetine-placebo Cho/Cr ratio was elevated versus both fluoxetine scan days ($F_{1,24}>7.5$, $P<.02$). The paroxetine-placebo Cho/Cr ratio was slightly but not significantly elevated compared with the paroxetine-active day ratio ($F_{1,12}>1.6$, $P<.023$). We also found a trend toward statistically elevated HAM-D ratings on the paroxetine-placebo

day ($F_{1,11}=4.6$, $P<.06$). In 4 subjects experiencing a withdrawal syndrome, a post-hoc ANOVA revealed a significantly lower Cho/Cr ratio than the rest ($n=9$) of the paroxetine-withdrawn group ($F_{1,11}=9.0$, $P<.02$, Figure, bottom).



Discussion

Paroxetine subjects had slightly higher Cho/NAA ratios and significantly higher Cho/Cr ratios than fluoxetine subjects, suggesting a group difference in choline-containing metabolites. Additionally, the Cho/Cr ratio was increased on the paroxetine-placebo day. No changes in metabolite ratios were noted in the fluoxetine group. This is likely attributable to an expected 10% reduction of fluoxetine brain levels over the 2 day withdrawal period (9). Accordingly, the fluoxetine group appears to be an appropriate referent population, and provides a good reliability estimate for the Cho/Cr ratio (Spearman $\rho=.736$, $P=0.01$).

Within the paroxetine group, the majority exhibited an increased Cho/Cr ratio upon placebo substitution, while the subgroup experiencing withdrawal symptoms had a lower Cho/Cr ratio. We interpret this to suggest that the ratio reflects dynamic anterior cingulate function as it adapts to a new neurochemical milieu (SSRI withdrawal), and more specifically might indicate a relative inability to adapt in patients who experience withdrawal symptoms. Interestingly, we have previously reported that the basal ganglia Cho/Cr ratio is elevated in fluoxetine responders but not in nonresponders (4). Thus, the Cho/Cr ratio seems to constitute a neurochemical measure that is related to mood state change in major depression. Exploring differences in the anterior cingulate Cho/Cr ratio will help to determine its functional significance in relation to mood state, and ultimately, this measure might assist in antidepressant treatment optimization.

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Supported by MH58681, DA00329, and Eli Lilly and Co.