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

Marc J. Kaufman1, Michael E. Henry1, Blaise deB. Frederick1, John Hennen1, Rosemond A. Villafuerte1, Eve Stoddard1, Bruce M. Cohen1, Perry F. Renshaw1

1Brain Imaging Center, McLean Hospital, Harvard Medical School, Belmont, MA USA.

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/Cre) 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 on 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, NAA/Cr, Cho/NAA and NAA/Cr) and mood state ratings. We hypothesized that placebo substitution would be associated with an elevated anterior cingulate Cho/Cre ratio, but that this would occur only in paroxetine-withdrawn subjects.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 scale for depression (HAMD) was greater than 15 points above their baseline study day (F1,11=4.6, P<0.06). 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 (F1,11=9.0, P<0.02, Figure, bottom).

Discussion
Paroxetine subjects had slightly higher Cho/NAA ratios and significantly higher Cho/Cre ratios than fluoxetine subjects, suggesting a group difference in choline-containing metabolites. Additionally, the Cho/Cre 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/Cre ratio (Spearman rho=.736, P<0.01).

Within the paroxetine group, the majority exhibited an increased Cho/Cre ratio upon placebo substitution, while the subgroup experiencing withdrawal symptoms had a lower Cho/Cre 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/Cre ratio is elevated in fluoxetine responders but not in nonresponders (4). Thus, the Cho/Cre ratio seems to constitute a neurochemical measure that is related to mood state change in major depression. Exploring differences in the anterior cingulate Cho/Cre ratio will help to determine its functional significance in relation to mood state, and ultimately, this measure might assist in antidepressant treatment optimization.

References

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