Compounds Containing Cytosolic Choline in the Basal Ganglia: A Potential Biological Marker of True Drug Response to Fluoxetine

Shamsah B. Sonawalla, M.D., Perry F. Renshaw, M.D., Ph.D., Constance M. Moore, M.Sc., Ph.D., Jonathan E. Alpert, M.D., Ph.D., Andrew A. Nierenberg, M.D., Jerrold F. Rosenbaum, M.D., and Maurizio Fava, M.D.

Objective: Studies have identified two types of antidepressant response: true drug response and placebo pattern response. This study examined the relationship between true drug response and choline-creatine ratios in the basal ganglia of depressed patients treated with fluoxetine. **Method:** The authors evaluated drug-free outpatients with major depression before (N=41) and after (N=15) 8 weeks of fluoxetine treatment, 20 mg/day, by using proton magnetic resonance spectroscopy. **Results:** There was a significant difference in the degree of change from baseline to week 8 in choline-creatine ratios between the true drug response group (N=8) and the placebo pattern response/nonresponse group (N=7); the true drug response patients had a 20% increase in choline-creatine ratios, and the placebo pattern response/nonresponse patients had a 12% decrease in choline-creatine ratios. **Conclusions:** These data suggest that true drug response to fluoxetine treatment in depression may be associated with an increase in choline-creatine ratios in the basal ganglia.

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Studies using pattern analysis have distinguished between true drug response and the placebo pattern of response (1). While true drug response is characterized by a 2-week delay in onset followed by persistent improvement, placebo pattern response is characterized by early, transient, or nonpersistent improvement (1). Biological markers of true drug response, however, are lacking.

Two studies (2, 3) demonstrated the feasibility of applying localized proton magnetic resonance spectroscopy (MRS) to patients with depression and control subjects as a means of noninvasively detecting cytosolic-choline-containing compounds in the brain (4, 5). Specifically, Charles and co-workers (2) found an 18% elevation in choline-creatine ratios in the subcortical gray matter structures (including the basal ganglia and the thalamus) of older patients with major depression in comparison with older subjects without depression. Renshaw and colleagues (3) found significantly lower choline-creatine ratios in the basal ganglia of patients with depression than in those of nondepressed subjects. The subjects with depression in the Renshaw et al. study were younger than those in the Charles et al. study. Morphometric magnetic resonance imaging studies have noted that caudate and putamen volumes are smaller in elderly patients with depression than in matched control subjects (6). This leads to different proportions of gray and white matter within the volumes of interest and thereby potentially confounds localized proton MRS results because choline and creatine have a different signal intensity in gray matter than in white matter. This may explain the difference in the results between the two studies (7).

The purpose of this study was to evaluate the relationship between basal ganglia choline-creatine ratios, as measured by in vivo localized proton MRS, among patients with a true drug response compared to those without a true drug response following antidepressant treatment.

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METHOD

After complete description of the study to the subjects, written informed consent was obtained before participation in this study. The subjects with depression were outpatient participants in a standardized treatment trial. Patients were requested to undergo localized proton MRS before and after an 8-week open trial with fluoxetine, 20 mg/day.

Forty-one drug-free patients with depression between 19 and 56 years of age who met the criteria for major depressive disorder on the Structured Clinical Interview for DSM-III-R—Patient Edition (8) and received an initial 17-item Hamilton Rating Scale for Depression (9) score of 16 or greater were included in the study. The exclusion criteria for this study were as described previously (3).

All patients underwent in vivo localized proton MRS by means of a Signa 1.5-T scanner (General Electric Medical Systems, Milwaukee) equipped with a level-4.8 operating system. Spectra were acquired by means of an 8-cm^3 voxel centered on the head of the left caudate and the putamen. Methods for localized proton MRS are described in detail elsewhere (3). Fifteen of these 41 patients underwent the same MRS assessment at the end of 8 weeks of fluoxetine treatment, 20 mg/day.

Patients were assessed weekly by using the Clinical Global Impression (CGI) (10) severity and improvement scales. On the basis of identification of patterns of improvement by Stewart et al. (1), a score of 1 ("very much improved") or 2 ("much improved") on the CGI improvement scale in any week was considered improved.

One-factor analysis of variance (ANOVA) was used to compare choline-creatine and *N*-acetylaspartate-creatine ratios at baseline and after 8 weeks of fluoxetine treatment among patients with true drug response and patients with placebo pattern response/nonresponse.

RESULTS

The mean age of the 41 patients was 38.9 years (SD=9.4) (44% women, N=18). All but one of the 41 depressed patients was strongly right-handed, as assessed by the Edinburgh inventory (11). The mean 17-item Hamilton depression scale baseline score was 20.8 (SD=3.8). Of the 41 patients, 24 had never before been treated for depression, and treatment data were unavailable for four patients. In the 13 patients who received previous treatment, the mean drug-free period was 2.3 years (SD=2.2). There were no significant differences between the true drug response group and the placebo pattern response/nonresponse group across demographic factors, including age and gender, and across pretreatment 17-item Hamilton depression scale scores. ANOVAs revealed no statistically significant differences in the baseline choline-creatine and *N*-acetylaspartate-creatine ratios in the basal ganglia between the true drug response group and the placebo pattern response/nonresponse group. Of the 15 patients who underwent a repeat MRS at the end of 8 weeks, eight patients had a true drug response, four patients had a placebo pattern response, and three patients had no response. There were no significant differences in age, CGI severity scores, and baseline choline-creatine and *N*-acetylaspartate-creatine ratios between the two groups (one with baseline MRS only [N=41] and the other with both baseline and repeat MRS [N=15]). However, there was a statistically significant difference in the degree of change from baseline in choline-creatine ratios between the true drug response group (N=8) and the placebo pattern response/nonresponse group (N=7), with the true drug response patients having a 0.14 (20%) increase in choline-creatine ratios from baseline and the placebo pattern response/nonresponse patients having a 0.09 (12%) decrease in the choline-creatine ratios at week 8 (table 1). There was no significant difference change in *N*-acetylaspartate-creatine ratios between the two groups after 8 weeks of treatment with fluoxetine (F=1.13, df=1, 13, p=0.3).

TABLE 1. Choline-Creatine Ratios in the Basal Ganglia at Baseline and After 8 Weeks of Fluoxetine Treatment for Depressed Patients With True Drug Response or With Placebo Pattern Response or Nonresponse to Fluoxetine

	Choline-Creatine Level					
	Patients With True Drug Response (N=8)		Patients With Placebo Pattern Response or No Response (N=7)		ANOVA (df=1, 13)	
Time Point	Mean	SD	Mean	SD	F	p
Baseline	0.69	0.16	0.74	0.09	0.61	0.45
End point (after 8 weeks of fluoxetine treatment)	0.83	0.11	0.65	0.19	5.34	<0.05
Difference between baseline and end point	0.14	0.20	–0.09	0.22	4.78	<0.05

DISCUSSION

To our knowledge, this is the first study evaluating the relationship between basal ganglia choline-creatine ratios, as measured by in vivo localized proton MRS, and patterns of response to antidepressant medication.

The findings of our study are limited by the small number of patients involved and by the fact that nonresponders and placebo pattern responders were lumped together. We are also aware of the limitations involved in using metabolite ratios. In particular, a change in choline-creatine ratios may reflect either a change in ratios of choline-containing compounds or a change in ratios of creatine and phosphocreatine or both. This error could be compounded if different amounts of gray and white matter were contributing to the measured volumes of interest because choline and creatine ratios are different in gray and white matter (12, 13).

Within the framework of these limitations, these pilot data suggest that true drug response to fluoxetine treatment in depression may be associated with an increase in choline-creatine ratios in the basal ganglia.

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