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Early increase in marker of neuronal integrity with antidepressant treatment of major depression: $^1$H-magnetic resonance spectroscopy of N-acetyl-aspartate

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Abstract

Increasing interest surrounds potential neuroprotective or neurotrophic actions of antidepressants. While growing evidence points to important early clinical and neuropsychological effects of antidepressants, the time-course of any effect on neuronal integrity is unclear. This study used magnetic resonance spectroscopy to assess effects of short-term treatment with escitalopram on N-acetyl-aspartate (NAA), a marker of neuronal integrity. Thirty-nine participants with major depression were randomly assigned to receive either 10 mg escitalopram or placebo daily in a double-blind, parallel group design. On the seventh day of treatment, PRESS data were obtained from a 30 $\times$ 30 $\times$ 20 mm voxel placed in medial frontal cortex. Age and gender-matched healthy controls who received no treatment were also scanned. Levels of NAA were significantly higher in patients treated with escitalopram than in either placebo-treated patients ($p<0.01$) or healthy controls ($p<0.01$). Our findings are consistent with the proposition that antidepressant treatment in depressed patients can produce early changes in neuronal integrity.

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Key words: Antidepressant, depression, magnetic resonance spectroscopy, N-acetyl-aspartate.

Introduction

There is increasing interest in the potential neuroprotective or neurotrophic action of antidepressant treatments (Schmidt & Duman, 2007). N-acetyl-aspartate (NAA) is a marker of neuronal integrity, synthesized within neuronal mitochondria (Moffett et al. 2007), that can readily be measured using the safe, non-invasive technique of magnetic resonance spectroscopy (MRS). If antidepressant treatment acts via a neurotrophic mechanism, increased levels of NAA might be observed. Indeed, in animal studies, it has been found that antidepressant treatment can prevent stress-induced decreases in NAA (van der Hart et al. 2002). In addition, some clinical reports have noted increases in NAA in frontal cortex with antidepressant treatment over periods of several weeks (Gonul et al. 2006; Huang et al. 2010; Jang et al. 2006) although there are also some negative findings (Henigsberg et al. 2011; Kaymak et al. 2009).

Clinical trial evidence shows that antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have an early onset of clinical effects detectable with standard rating scales within 1 wk (Taylor et al. 2006). Consistent with this, early effects on behavioural and neural aspects of emotional processing are observed after even a few days administration of antidepressants (Harmer et al. 2004). If neurotrophic effects are mechanistically important in therapeutic response, they should also be evident after short-term treatment of depression with an SSRI. Escitalopram is a clinically effective antidepressant and the most selective of the SSRIs for the serotonin transporter. We hypothesized that 7 d treatment with escitalopram...
would lead to an increase in cortical NAA levels. Accordingly, the aim of the present study was to compare the neurochemistry of the medial prefrontal cortex in two groups of depressed patients, one unmedicated and one who had received short-term treatment with the SSRI, escitalopram.

Method

Design

Drug-free depressed patients were randomly assigned to receive 10 mg escitalopram or placebo daily for 7 d in a double-blind, parallel group design. Both groups were then scanned on the seventh day of treatment. The escitalopram dose was chosen as this is the manufacturer’s recommended treatment dose for major depressive episodes. The elimination half-life after multiple dosing is about 30 h. Ratings of mental state were obtained using the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1967), Beck Depression Inventory (BDI; Beck et al. 1961) and the State-Trait Anxiety Inventory (Spielberger et al. 1970). An age and gender-matched group of healthy controls were scanned on a single occasion and received no treatment.

Participants

Thirty-nine participants with major depression and 27 healthy controls completed the MRS protocol. Controls were recruited through university volunteer lists and advertising in local newspapers. Depressed patients were recruited from a number of sources, including newspaper advertisements as well as referral from other clinicians. All participants were assessed for the presence of current and past psychiatric disorder with the Structured Clinical Interview for DSM-IV (First et al. 2002). The depressed patients met criteria for a primary diagnosis of major depressive disorder. Exclusion criteria for the study were as follows. For depressed patients: suffering from psychosis or substance dependence as defined by DSM-IV; being at clinically significant risk of suicidal behaviour; having contraindications to escitalopram treatment; or being treated with psychotropic medication <3 wk before the study (5 wk in the case of fluoxetine). For healthy volunteers: current or past history of Axis I disorder as defined by DSM-IV. For both groups: major somatic or neurological disorders; pregnancy or breast-feeding; contraindications to magnetic resonance imaging or concurrent medication, which could alter emotional processing. No minimum HAMD-17 score was required. The study was approved by the Oxford Research Ethics Committee and all participants gave written informed consent. Participants were reimbursed for their time and any other expenses.

MRS methodology

Scanning was performed on a 3T Siemens Trio (Erlangen, Germany) system with a head gradient coil (Magnex Scientific, Oxford) and a 12 channel head-only receive array RF coil. Data were acquired from a 30 x 30 x 20 mm voxel placed in the medial prefrontal cortex anterior to the genu of the corpus callosum (Supplementary Fig. S1). The voxel was positioned manually by reference to an axial T1-weighted gradient-echo image.

PRESS data (Bottomley, 1987) with water suppression were acquired (TE 30 ms, TR 3 s, 64 averages). PRESS data were analysed with LCModel (Provencher, 1993) using a set of simulated metabolite basis spectra. Concentrations relative to creatine (Cr) were obtained for NAA, the total of NAA and N-acetylaspartylglutamic acid (NAA+NAAG), choline, inositol and total combined glutamate and glutamine (Glx). Concentration estimates with Cramer–Rao lower bounds (CRLB) >20% were rejected as unreliable. In a subset of participants (29 patients, 15 controls) PRESS-J data (Hurd et al. 2004) were also acquired (TE 35–185 ms, 10 ms increments, total 128 acquisitions, TR 3 s). Estimates of glutamate relative to Cr were obtained using AMARES (Vanhamme et al. 1997). Estimates with damping factor >55 were excluded. T1-weighted structural images of whole brain were acquired with 1 mm³ voxel resolution. FSL FAST was employed to segment the structural brain images into grey matter, white matter and cerebrospinal fluid, to allow estimation of voxel composition. Group differences were tested using the general linear model in PASW Statistics v18 (SPSS Inc., USA) employing analysis of variance or analysis of covariance as appropriate with post-hoc t test. Results were tested for sensitivity to the inclusion or exclusion or age, gender and voxel grey matter content as covariates. A conventional two-tailed statistical significance threshold of p = 0.05 was applied throughout.

Results

The three groups were demographically similar (Table 1). After 1 wk of treatment, there was no significant difference in rating scale scores between those patients receiving placebo and those receiving
escitalopram (HAMD-17 \( p = 0.59 \); BDI \( p = 0.93 \); state anxiety \( p = 0.49 \); Table 1).

A significant effect of group was seen on NAA + NAAG/Cr (placebo 1.07 ± 0.16, escitalopram 1.18 ± 0.18, healthy 1.06 ± 0.16, \( p = 0.03 \)) and NAA/Cr (placebo 0.99 ± 0.16, escitalopram 1.13 ± 0.19, healthy 0.96 ± 0.18, \( p < 0.01 \); Fig. 1) but not on other metabolites measured (\( p > 0.35 \) in all cases). Levels of NAA/Cr were higher in patients randomized to 7 d treatment with escitalopram than in those receiving placebo (\( p < 0.01 \)) or in healthy controls (\( p < 0.01 \)). The same effect was seen with the more conservative NAA + NAAG/Cr measure (\( p < 0.05 \) both cases). There was no difference between NAA/Cr or NAA + NAAG/Cr levels between the placebo group and healthy controls (\( p > 0.7 \) both cases).

A small but statistically significant inverse effect of age on NAA/Cr was observed (\( r = -0.26, p = 0.03 \)) across the entire group. No age \( \times \) group interaction on NAA/Cr was observed and the group effect remained with age as a covariate (\( p < 0.01 \)). No effect was seen of age on NAA + NAAG/Cr (\( p = 0.19 \)). No group effect on Glx/Cr was observed, but there was an inverse correlation between baseline depression rating scale score and Glx/Cr in the depressed group (\( r = -0.39, p = 0.015 \)).

Metabolite estimates were obtained with a high degree of confidence. Mean CRLB for NAA + NAAG/Cr estimates was 3.65% and for NAA/Cr estimates was 4.94% (see Supplementary Table S1).

**Discussion**

The main finding of this study was that after 7 d treatment of depression with escitalopram, elevated levels of NAA are observed in the medial frontal cortex. As NAA is one of the major peaks on proton MRS spectrum (Supplementary Fig. S1), quantitation can be

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**Table 1. Participant characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (( n = 19 ))</th>
<th>Escitalopram (( n = 20 ))</th>
<th>Healthy (( n = 27 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>32.4 (12.0)</td>
<td>30.6 (8.5)</td>
<td>31.4 (11.1)</td>
</tr>
<tr>
<td></td>
<td>range 18–56</td>
<td>range 19–51</td>
<td>range 19–58</td>
</tr>
<tr>
<td>Gender</td>
<td>9 male/10 female</td>
<td>8 male/12 female</td>
<td>9 male/18 female</td>
</tr>
<tr>
<td>HAMD-17: baseline</td>
<td>23.2 (4.6)</td>
<td>24.2 (5.7)</td>
<td>0.5 (0.7)</td>
</tr>
<tr>
<td>7 d</td>
<td>20.4 (4.2)</td>
<td>19.3 (7.9)</td>
<td>–</td>
</tr>
<tr>
<td>BDI: baseline</td>
<td>31.5 (9.7)</td>
<td>30.8 (9.6)</td>
<td>1.1 (1.3)</td>
</tr>
<tr>
<td>7 d</td>
<td>25.1 (9.0)</td>
<td>24.8 (12.0)</td>
<td>–</td>
</tr>
<tr>
<td>STAI state: baseline</td>
<td>49.2 (17.7)</td>
<td>47.5 (23.6)</td>
<td>27 (5.3)</td>
</tr>
<tr>
<td>7 d</td>
<td>47.3 (10.5)</td>
<td>49.9 (11.8)</td>
<td>–</td>
</tr>
<tr>
<td>Voxel grey-matter</td>
<td>43 (5)</td>
<td>43 (4)</td>
<td>42 (5)</td>
</tr>
<tr>
<td>percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voxel CSF percentage</td>
<td>21 (5)</td>
<td>22 (3)</td>
<td>21 (4)</td>
</tr>
</tbody>
</table>

HAMD-17, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; CSF, cerebrospinal fluid. Values are mean (s.d.). No significant differences between patient groups.
achieved with high accuracy, lending confidence to this result.

An increase in NAA in similar brain regions has been reported after longer-term response to a variety of antidepressants for major depression (Gonul et al. 2006) and after 12 wk treatment of obsessive–compulsive disorder with citalopram (Jang et al. 2006). However, not all have reported similar findings (Henigsberg et al. 2011; Kaymak et al. 2009), suggesting that patient heterogeneity might be a factor. For example, a significant proportion of our patients were drug naive and none was treatment-resistant. It should also be noted that we did not observe any effect on NAA in previous studies of citalopram in healthy volunteers (Taylor et al. 2008, 2010), which suggests there may be an interaction of treatment and underlying disease factors.

No difference in NAA levels was seen here between placebo-treated depressed patients and healthy controls. A lack of effect of depression itself on observed NAA levels is consistent with many prior studies that have found no significant effect of depression on NAA in this region (Yildiz-Yesiloglu & Ankerst, 2006). More recently, some studies have found decreased NAA in medial prefrontal cortex in particular populations. One study found decreased NAA + NAAG in chronic and relapsing–remitting subgroups, but not in the early phases of the illness (Portella et al. 2011). Decreased NAA was also found in a group of patients prior to electroconvulsive therapy treatment (Merkl et al. 2010). Thus, as with the effects of treatment on NAA, it is possible that a difference could have been observed if the patients studied had different clinical characteristics.

NAAG is a neuropeptide synthesized from NAA and glutamate and also found localized within neurons (Moffett et al. 2007). There is substantial overlap of MRS signal from NAA and NAAG. While the total combined signal is readily measured using MRS, errors in correctly attributing components of that signal to NAA or NAAG are a possible cause of erroneous findings. In these data, effects were observed whether NAA or NAA + NAAG was considered, which lends support to the effect seen.

The effect here was demonstrated in medial prefrontal cortex. Future studies could investigate a wider range of brain structures because effects on hippocampal and amygdala function are likely to be important in antidepressant actions (Schmidt & Duman, 2007). While one recent study of paroxetine for generalized anxiety found no effect on hippocampal NAA levels (Mathew et al. 2010), increases in hippocampal NAA with extended SSRI treatment have now been described in other patient populations (Duan et al. 2011; Huang et al. 2010).

This study reported concentrations relative to Cr, which is conventional. It is possible that apparent changes in NAA:Cr ratio could be explained by alterations in Cr levels. This seems unlikely to explain the effect seen here, since no change was observed in other metabolites, also referenced to Cr. Nevertheless, future studies could also reference concentrations to tissue water, to avoid this potential confound. The major methodological limitation of our study is the cross-sectional design. Thus, although we have a reasonable sample size, it is possible that the difference in NAA, which we detected at 7 d, is actually due to baseline differences between the subject groups. Clearly a further study with longitudinal design is necessary to control for this possibility and to allow for investigation of any link between the early neuronal effects observed here and eventual clinical response. Within these limitations, our findings are consistent with a neurotrophic hypothesis of antidepressant action.

Some investigations have reported lower levels of Glx in anterior brain regions in depressed patients but not all studies are in agreement (YükSEL & ÖNGÜR, 2010). No group effect on Glx was observed here, but the inverse correlation between depression severity and Glx suggests that an effect might have been seen if a more severely depressed group of patients had been studied. However, the correlation observed would not have survived correction for multiple comparisons, so interpretation of the finding needs to be cautious. We used PRESS-J to derive a measure of glutamate separate from Glx in a subgroup of patients but again found no difference between the depressed patients and controls. There is evidence from the study of Portella et al. (2011) that lowered Glx levels may be more apparent in patients with chronic depression, which might make such a change less likely to be detected in our particular patient group (see above). Better measures of glutamate in larger patient groups will be needed to address this issue more definitively.

The lack of effect of short-term SSRI treatment on glutamate and Glx in anterior brain regions is consistent with our previous studies in healthy volunteers (Taylor et al. 2010). Our findings are consistent with the proposition that antidepressant treatment in depressed patients can produce early changes in neuronal integrity. Future studies should clarify whether an early change in NAA could be a possible early biomarker of treatment effect in depressed patients.
Supplementary material
For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145712000272.

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Statement of Interest
Professor Cowen has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth and Xytis and has been a paid lecturer for Eli Lilly, Servier and GlaxoSmithKline. He has received remuneration for scientific advice given to legal representatives of GlaxoSmithKline. Dr Taylor’s spouse is an employee of GlaxoSmithKline.

References

Early antidepressant effect on NAA 1545


