Complications in major depressive disorder therapy: a review of magnetic resonance spectroscopy studies

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Summary

Advanced magnetic resonance imaging techniques, such as proton magnetic resonance spectroscopy (H-MRS), have helped to further understanding of the pathophysiology of major depressive disorder (MDD) and to shed light on mechanisms underlying the therapeutic response. Potential complications of MDD therapy constitute an important area of research. Interruption of the absorption of serotonin reuptake inhibitors (SSRIs) is associated with discontinuation syndrome, while electroconvulsive therapy (ECT) can lead to transient and persistent anterograde amnesia.

This paper reviews studies, since 1994, that have used H-MRS to evaluate adverse effects and complications of MDD treatment, either with ECT or SSRIs. Three articles have been published on adverse effects and complications of MDD treatment and H-MRS. Two focused on the ECT-induced memory deterioration and showed no sign of hippocampal atrophy in MDD patients with a residual memory deterioration after ECT, but a significant mean increase of the signal from Cho-containing compounds bilaterally, possibly due to an alteration of membrane turnover in the hippocampal region. The third paper showed that placebo-day Cho/Cr metabolite ratios were decreased in subjects with discontinuation syndrome, a finding that possibly reflects the dynamics of rostral anterior cingulate function.

In spite of the limits deriving from the small number of papers published, our review demonstrated that H-MRS could be a useful instrument not only in evaluating therapy efficacy, but also for offering new insights into mechanisms underlying MDD treatments.

KEY WORDS: advanced MRI technique, major depression disorder, spectroscopy, therapy.

Introduction

Major depressive disorder (MDD) is one of the most frequent psychiatric disorders and because of its considerable impact on social and work functioning, it is a major illness in primary care settings. MDD is currently considered to be the consequence of a malfunction of multiple circuits that connect the limbic system with the prefrontal cortex, the brain stem and the hypothalamus. These areas are responsible for many basic functions, such as sleep, appetite, and libido. Recent developments in the neurosciences have given us many insights into MDD aetiology, in particular significant breakthroughs have been achieved in the fields of genomics, neurobiology and neuroimaging (1). Current research efforts are aimed at shedding light on the pathophysiology and mechanisms underlying the therapeutical response to pharmacological approaches (selective serotonin reuptake inhibitors, SSRIs), and also to antidepressant stimulation techniques, such as electroconvulsive therapy (ECT) (2,3).

New advanced magnetic resonance imaging (MRI) techniques, in particular proton magnetic resonance spectroscopy (H-MRS), make it possible to study in vivo numerous metabolites connected with brain neurotransmitters crucial in understanding this complex pathology, which it would otherwise be impossible to evaluate directly due to their rapid removal. As well as treatment efficacy, potential complications are an important aspect of MDD therapy. Interruption of SSRIs absorption, as consequence either of non-compliance or prescribed “drug holidays”, is associated with a discontinuation syndrome, characterised by symptoms including dizziness, dysphoria and gastrointestinal upset (4). Moreover, known adverse effects of ECT are transient anterograde amnesia, involving rapid forgetting of newly-learned information, and retrograde amnesia for information learned before treatment, which might be persistent or permanent (5,6).

This aim of this paper was to review studies that, since 1994, have used H-MRS to evaluate adverse effects and complications of MDD treatment, either with ECT or SSRIs.
Methods

In May 2008, we searched the PubMed database for clinical articles dealing with neuroimaging and adverse effects and complications of MDD therapy, published since 1994. In order to limit the results to relevant articles, the strategy combined, without language restriction, the MeSH term magnetic resonance spectroscopy AND [the major MeSH term major depressive disorders / drug therapy (SH*) OR the major MeSH term major depressive disorders / therapy (SH*)].

All the manuscripts selected were then hand-searched for further relevant publications. In order to qualify for inclusion in this review, studies had to: i) have been an original paper in a peer-reviewed journal; ii) have included a group of subjects with unipolar MDD; iii) have studied subjects using H-MRS; iv) have studied subjects before and after an antidepressant treatment protocol; and v) have provided explicit subject inclusion and exclusion criteria.

Results

Our search of the literature identified only three articles, whose main features are summarised in Table I. Two papers (7,8) focused on ECT-induced memory deterioration, which is thought to be connected to hippocampal atrophy or cell death caused by ECT. In the short evaluation times considered (30 hours to 10 days after ECT), no changes in N-acetylaspartate (NAA), lactate or lipid levels were observed. A significant mean increase of 16% of the signal from choline-containing compounds after five or more ECT treatments was described bilaterally, in spite of the fact that ECT application was mostly unilateral (7). The long-term follow up showed that the NAA signal tended to be stable, while an initially significantly increased Cho signal reversed to values close to those recorded pre-ECT (8). The third paper focused on metabolite variations in the rostral anterior cingulate during discontinuation syndrome due to substitution of medication with active SSRIs or placebo. Placebo-day Cho/Cr (choline/total creatine) metabolite ratios were decreased in subjects meeting discontinuation syndrome criteria, compared with asymptomatic subjects (9).

Discussion

The adverse effects and complications of MDD therapy can be considered in relation to two main syndromes: a classic amnestic syndrome involving anterograde and retrograde amnesia in association with ECT, and discontinuation syndrome, which is a potential complication of SSRI treatment. Ende and colleagues (7) expressed doubt on possible ECT-induced hippocampal atrophy or cell death, since such effects would be suggested by a decreased NAA signal, whereas in their short-term evaluation they found no change in NAA, which seems to suggest that ECT does not produce axonal damage. Furthermore, recent studies on the effects of ECT report data which support a possible role of ECT in the expression of brain growth factors, as well as functional and structural alterations in certain neuron populations: ECT could even reverse the atrophy of stress-vulnerable neurons or protect them from further damage, through regulation of neurotrophic factors (10). These results seem to be concordant with previous animal studies showing that long-term ECT administration induces sprouting of granule cell mossy fibre pathways in the hippocampus, in the absence of neuronal loss. This induced effect could contribute to the therapeutic action of ECT (11,12). Moreover, the observation of an increased signal of Cho-containing compounds, in association with a normal NAA signal, supports the hypothesis of ECT-induced mossy fibre sprouting, reflected in spectroscopy data as an increased membrane turnover.

Obergriesser and colleagues (8) re-evaluated patients around 20 days after the last ECT and corroborated the hypothesis that ECT has no influence on the NAA signal, given that this value was found to be stable also in long-term follow up. From this perspective, amnestic effects do not seem to be due to detectable structural damage to hippocampal neurons or to reduced neurogenesis. On the other hand, the increase in Cho signals observed soon after treatment (from lower than normal levels pre-ECT to normal values immediately post-ECT) reversed over time. The authors support the idea of a strong link between these alterations and the therapeutic effect of ECT, which could act either by inducing sprouting of serotonergic axons in the hippocampus or by increasing an underlying reduced state-dependent neuronal plasticity in MDD patients.

These articles on ECT presented several limitations. First, H-MRS data were not correlated to clinical evaluation of memory function impairment; moreover, due to well-known technical limitations associated with H-MRS, single-voxel analysis focused only on the hippocampus, and was performed with a voxel size which cannot differentiate between different hippocampal subregions (CA1-CA3). The only study dealing with discontinuation syndrome was the paper by Kaufman and colleagues (9), describing a “rostral anterior cingulate Cho/Cr metabolite ratio decrease that may reflect dynamics of rostral anterior cingulate function.” This finding seems to be consistent with the reduced Cho levels in the basal ganglia and hippocampus observed in MDD patients, levels that tend to normalise after treatment (7,13). These results are discordant with those of Auer et al. who did not report any Cho alteration in the anterior cingulate region in MDD subjects (14). Kaufman et al. (9) suggested that astrocytes may contribute to Cho metabolism changes. In fact, there seems to be a relationship between glial abnormalities in specific brain regions such as the anterior cingulate cortex and thus a role of glial cells in the pathophysiology of MDD. From this perspective, even the hippocampal Cho metabolite increase observed after ECT (7) could be explained not only by the neuronal sprouting hypothesis: neuronal and astrocyte membrane alteration might also be associated with Cho metabolite changes following ECT.

Concluding remarks

Recently, H-MRS has been used to investigate some adverse effects connected with MDD treatment. In par-
MR spectroscopy in major depressive disorder

**Table I - Results of the search.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Objective</th>
<th>Treatment</th>
<th>Protocol timing</th>
<th>H-MRS</th>
<th>Markers</th>
<th>Region of interest</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman MJ et al. 2003 (Ref. 9)</td>
<td>Correlation between SSRI treatment discontinuation and rostral anterior cingulate Cho metabolite ratios</td>
<td>SSRI</td>
<td>Patients continued on their own SSRI except for days 5-7 of study weeks 2 and 6. On those days patients were administered placebo or their own SSRI, in a randomised and double-blinded manner. Each subject was rated and scanned twice, on the 7th day (3rd day of blinded substitution) of study weeks 2 and 6.</td>
<td>Multi-voxel; 1.5T; TE=65</td>
<td>Cho/Cr, NAA/Cr, Cho/NAA</td>
<td>Rostral anterior cingulate</td>
<td>Placebo-day Cho/Cr metabolite ratios were decreased in subjects meeting DS criteria</td>
</tr>
<tr>
<td>Obergriesser T et al. 2003 (Ref . 8)</td>
<td>Follow up of the quantitative changes in Cho and NAA signals in the hippocampal region of patients who remitted from MDD after a course of ECT</td>
<td>ECT</td>
<td>Patients previously studied with H-MRS pre- and post-ECT were re-evaluated after a mean of 20±8.6 months after the last ECT</td>
<td>Single-voxel; 1.5T; PRESS, TE=135</td>
<td>Cho, Cr, NAA</td>
<td>Left and right hippocampus</td>
<td>No changes in hippocampal NAA signal; the initially significant increase in the Cho signal reversed to values close to pre-ECT levels</td>
</tr>
<tr>
<td>Ende G et al. 2000 (Ref . 7)</td>
<td>Monitoring of quantitative changes in the NAA and Cho signals in the hippocampal region of patients during the course of repeated sessions</td>
<td>ECT</td>
<td>At least 2 datasets were acquired from each patient: one before ECT started and a second after 5 or more ECT treatments, within 30 hours to 10 days of ECT.</td>
<td>Single-voxel; 1.5T; PRESS, TE=135</td>
<td>Cho, Cr, NAA</td>
<td>Left and right hippocampus</td>
<td>No changes in the hippocampal NAA signal after ECT; significant mean increase of Cho-containing compounds</td>
</tr>
</tbody>
</table>

Abbreviations: MDD=major depressive disorder; DS=discontinuation syndrome; ECT=electroconvulsive therapy; SSRI=selective serotonin reuptake inhibitor; NAA=N-acetyl aspartate acid; Cho=choline; Cr=creatine


6. Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson ER, Snow J, Staib LH, Charney DS, Brenner JD. Hippocampal volume, memory, and cortisol status...