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Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients☆

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Abstract

Cortical glutamate/glutamine (Glx) metabolism seems to be affected by a major depressive disorder. Recently, a Glx deficit was detected by proton magnetic resonance spectroscopy (^{1}H-MRS) in the bilateral anterior cingulum of depressives. The aim of this study was to assess the effect of successful electroconvulsive therapy (ECT) on Glx levels in the anterior cingulum. The left anterior cingulum of 17 severely depressed unipolar patients was measured by ^{1}H STEAM spectroscopy before and after ECT, and the results were compared with those for 17 age- and gender-matched controls. We observed significantly reduced Glx levels in the patients' left cingulum compared to healthy controls. In ECT responders, in contrast to non-responders, Glx levels normalized ($P=0.04$) and then did not differ statistically from controls. Severe depression seems to be associated with a Glx deficit and increasing Glx may be an important mechanism of ECT action.

Keywords: Proton magnetic resonance; Spectroscopy; Electroconvulsive therapy; Major depressive disorder; Excitatory amino acids; Glutamate

1. Introduction

There is some evidence drawn from neurochemical studies that severe depression is accompanied by perturbation of the metabolism of excitatory amino acids, especially of glutamate (Glu) (Altamura et al., 1993). Normal glutamate metabolism depends on intact neuronal and glial cell function (Gallo and Ghiani, 2000; Magistretti et al., 1999). Both cell types showed distinct histomorphological alterations in the anterior cingulum of depressives (Ongur et al., 1998; Rajkowska, 2000). Recently, a significant reduction of glutamate/glutamine (Glx) in the bilateral anterior cingulum in severely depressed patients was demonstrated by means of proton magnetic resonance spectroscopy (^{1}H-MRS) (Auer et al., 2000). MRS provides a unique opportunity to assess brain metabolite levels in

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Table 1
Clinical characteristics of patients

	Unipolar depressed patients ($n=17$)
Age (years)	61.0 ± 11.2
Gender	12 female
Diagnosis	Major depressive disorder
Duration of illness (years)	14.9 ± 11.9
Number of hospitalizations	3.8 ± 2.9
Number of depressive episodes	5.3 ± 5.4
Duration of index episode (months)	12.9 ± 9.3
Hypertension	$n=7$ (41.2%)
Off-medication days	5.1 ± 2.7
Number of sufficient antidepressant trials in index episode	2.3 ± 1.1
Pre-ECT: MADRS	37.7 ± 8.8
Post-ECT monotherapy: MADRS	Non-responders: 26.4 ± 5.6 ($n=7$) Responders: 7.1 ± 4.7 ($n=10$)
Number of ECTs[a]	Non-responders: 9.7 ± 3.3 Responders: 9.8 ± 2.9

[a] After completion of ECT monotherapy.

vivo (Maier, 1995). If reduced Glx metabolism were pivotal for depression, effective electroconvulsive therapy (ECT), well known for its strong antidepressive effect, should be able to reverse the Glx deficit. We, therefore, investigated 17 severely depressed patients referred for ECT due to treatment resistance. MRS was used to assess metabolic changes in the left anterior cingulum before and after ECT. The left cingulum was chosen, since it was demonstrated by Drevets et al. (1997) that abnormalities in metabolism are left lateralized and we, therefore, expected effects of ECT on glutamate metabolism to be pronounced in this region.

2. Methods

2.1. Patients

Seventeen patients fulfilling the diagnostic criteria for severe recurrent unipolar major depressive disorder (American Psychiatric Association, 1994) were enrolled in this study. Diagnosis was made independently by two experienced psychiatrists, only one of them (N.M.) directly involved in this study, employing a checklist for DSM-IV diagnosis (Hiller et al., 2000). All but one of the patients were off medication 5.1 ± 2.7 days prior to MRS. Only lorazepam, which was shown not to influence brain metabolism as measured by ^{1}H-MRS (Brambilla et al., 2002), was allowed at a maximum dosage of 3 mg/day. Alcohol, drug abuse, or dementia as exclusion criteria were ruled out by careful psychiatric evaluation of subjects and by interviewing close relatives.

During the index episode, one patient took lithium, eight patients benzodiazepines, one patient valproic acid and eight patients neuroleptics in addition to antidepressants. Antidepressant response was defined as a Montgomery–Åsberg rating scale (MADRS) reduction $>60\%$ of baseline scores. For clinical details, see Table 1.

Patients were examined by MRS within 24–48 h after the last ECT (response) or after the last ECT monotherapy (non-response). They were always measured at the same time in the evenings (20.00–22.00 h). Non-responders and responders to ECT monotherapy received approximately the same number of ECT applications (Table 1).

Seventeen age- and gender-matched healthy controls (mean age: 60.1 ± 10.9 years; 12 female, five male) were enrolled after a standardized interview designed to rule out any psychiatric condition. The study was approved by the Ethics Committee of