The effect of electroconvulsive shock on the neurochemical profile in the live rat: Neurogenesis & Glutamate

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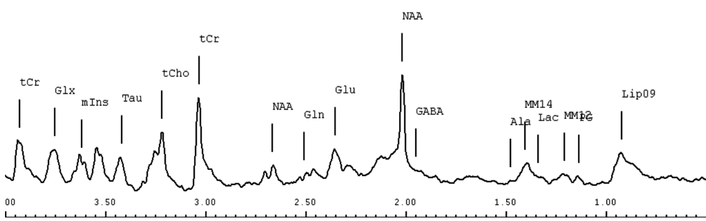
Introduction: Major depression is associated with memory impairment, dysregulation of the hypothalamic-pituitary axis (HPA) and hippocampus volume reduction. Electroconvulsive therapy (ECT) in patients with depression offers rapid relief of symptoms and HPA normalization but the mechanism underlying its therapeutic action is still poorly understood. The hippocampus has been a structural focus in depression and ECS research for several reasons including its 1) sensitivity to stress, 2) inhibitory control of the corticotrophin releasing cells of the hypothalamus, 3) involvement in memory formation, 4) susceptibility to excitotoxicity and 5) persistent neurogenesis. In regards to depression and excitotoxicity, glutamate antagonists have recently received increased attention as anti-depressants (1). Further, animal studies have repeatedly demonstrated that electroconvulsive shock (ECS) (mimicking human ECT), significantly increases the number of progenitor cells in the hippocampus signifying the importance of neurogenesis in the therapeutic process of ECT. In a previous study ^{1}HMRS was used to indirectly demonstrate the increase in neurogenesis in the hippocampus following ECS by tracking a biomarker characterized by a spectral signal at 1.28ppm shown to be enriched in neural stem cells which was quantified using singular value decomposition (SVD) based spectral analysis (2). *Herein, we characterized several additional metabolites in the live rat hippocampus before and after ECS using ^{1}HMRS and LCModel software. Specifically, we tested the hypotheses that 1) the ECS-induced 1.28ppm NSC biomarker increase could be tracked using LCModel software and 2) that ECS being an effective anti-depressant treatment in human suffering from major depression would result in changes in glutamate detectable by LCModel software.*

Material & Methods: The animal studies were approved by the institutional animal care and review committee. Fifteen Sprague Dawley rats were divided into Group 1 (n=9) and Group 2 (n=6). All rats were anesthetized with Nembutal (40mg/kg i.p.) and received a baseline ^{1}HMRS scan. Group 1 and 2 rats were exposed to ECS or Sham treatments, respectively and subsequently received a repeat ^{1}HMRS scan. Prior to the repeat scan all rats received an i.p. injection of chlordeoxyuridine (CldU) (128mg/kg) for post-mortem analysis of neuronal progenitor cells. ^{1}HMRS was performed using a 9.4T MRI instrument controlled by a Bruker console with an operating system of Paravision 5.0. First, anatomical localizers were performed in three orthogonal planes for precise positioning of the ^{1}HMRS hippocampus voxel. ^{1}HMRS was performed on each animal in the dentate gyrus of the hippocampus using a voxel size of 8 ml. Data were acquired using a PRESS sequence (TE=12ms, TR=2000ms, nex=1496) with VAPOR water suppression. All spectra were processed offline using the LCModel software package. Metabolite concentrations were estimated using the unsuppressed water signal from the same voxel, which served as an internal standard. Statistical analysis: To test our hypothesis that major cerebral metabolites changes with ECS treatment a multivariate analysis of variance (MANOVA) was performed on the two groups. Post-hoc repeated measures ANOVA for individual metabolites were then carried out only if the MANOVA was significant ($p<0.05$).

Results: LCModel via simulation analyzes for the 1.28ppm component and is referred to as 'Lip13a+Lip13b'. The Cramer-Rao-Lower-Bounds (CRLB) of Lip13a+Lip13b in all the acquired ^{1}HMRS spectra were >30% and could therefore not be used for accurate concentration estimations. Inter- and intra-group analysis of total creatine (=Cr+PCr) demonstrated no differences and all data are therefore presented as metabolite:tCr. The table below shows the average levels ± SD of metabolites, lipids and MMs (CRLB<30%) from Group 1 and 2 rats which demonstrated statistical significant changes; and shows that ECS resulted in significant increases in glutamate in addition to NAA decreases. Interestingly, we observed significant increases in levels of MM20 in the ECS group only when compared to pre-ECS baseline control levels. Preliminary histological analysis demonstrates a 4-fold increase in neuronal progenitor cells in agreement with the literature. Figure 1 shows a typical ^{1}HMRS acquired from the dentate gyrus after preprocessing involving correction for center frequency drift, 5Hz line broadening, phase and baseline adjustments.



Experimental Group	Condition	Glu/[tCr]	NAA/[tCr]	Glx/[tCr]	MM20/[tCr]
1 (n=9)	Baseline	1.09 ± 0.08	1.09 ± 0.04	1.56 ± 0.08	0.75 ± 0.16
	ECS	1.20 ± 0.08***	0.92 ± 0.04**	1.66 ± 0.10*	1.01 ± 0.28#
2 (n=6)	Baseline	1.02 ± 0.17	1.05 ± 0.11	1.51 ± 0.14	0.83 ± 0.24
	Sham	1.15 ± 0.06	1.05 ± 0.11	1.68 ± 0.10	0.85 ± 0.16

Data are average ± SD. ***p=0.0015;**p=0.0029;*p=0.014;#p=0.008;##

Conclusion: Analysis of the ^{1}HMRS spectra from the dentate gyrus demonstrate that the concentration of the 1.28ppm-equivalent is too low to be detected by LCModel. However, careful analysis of major metabolites revealed significant increases in the concentration of glutamate and decreases in NAA in rats exposed to ECS but not in sham-treated rats. Interestingly, we also observed significant increases of MM20 in the ECS rats when compared to their baseline control levels. The ECS-induced glutamate increases has never before been reported and should be further investigated considering the known anti-depressant effect of ECS.

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2. Manganas LN, et al. (2007) Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. *Science*. 318:980-985.