The effect of electroconvulsive therapy (ECT) on serum tryptophan metabolites

Tore Ivar Malmei Aarsland (1,2), Ieva Leskauskaite (3,*), Øivind Midttun (4), Per Magne Ueland (5), Arve Ulvik (4), Leif Oltedal (6,7), Ketil Oedegaard (2,3,6), Jan Haavik (1,2,3), Ute Kessler (3,6)

(1) Department of Biomedicine, University of Bergen, Bergen, Norway, (2) K.G. Jebsen Center for Neuropsychiatric Disorders, University of Bergen, Bergen, Norway, (3) Division of Psychiatry, Haukeland University Hospital, Bergen, Norway, (4) Bevital A/S, Bergen, Norway, (5) Section for pharmacology, Department of Clinical Science, University of Bergen, Bergen, Norway, (6) Department of Clinical Medicine, University of Bergen, Bergen, Norway, (7) Department of Radiology, Haukeland University Hospital, Bergen, Norway. (*) Presenting author

BACKGROUND

Prior studies suggest that neuroinflammation and the tryptophan catabolism via the kynurenine pathway may be involved in the pathophysiology of depression. This includes the immune-modulated activation of the tryptophan degrading enzyme indoleamine 2,3 dioxygenase (IDO), which is diverting the metabolism of tryptophan into kynurenine and further potentially neurotoxic kynurenine metabolites, such as 3-hydroxy kynurenine (HK) and quinolinic acid (QA) [1,2]. Electroconvulsive therapy (ECT) is a highly effective treatment of major depressive episodes. However, there is still limited knowledge about the mechanisms of action of ECT. Preliminary studies suggest that ECT may down-regulate immune activation [3]. There is only a limited number of studies, which have investigated the possible impact of ECT on the tryptophan-kynurenine pathway [4,5]. Findings so far indicate that ECT might alter the tryptophan catabolism towards catabolites with neuroprotective properties [5]. One prior study demonstrated a reduced level of QA, an N-methyl-D-aspartic acid (NMDA) receptor agonist with neurotoxic properties which previously has been implicated in the pathogenesis of depression [4].

The aim of this study was to investigate serum concentrations of tryptophan and catabolites in the kynurenine pathway in patients with treatment-resistant major depression in comparison with healthy controls. Further we aimed to explore the effect of ECT on the kynurenine pathway.

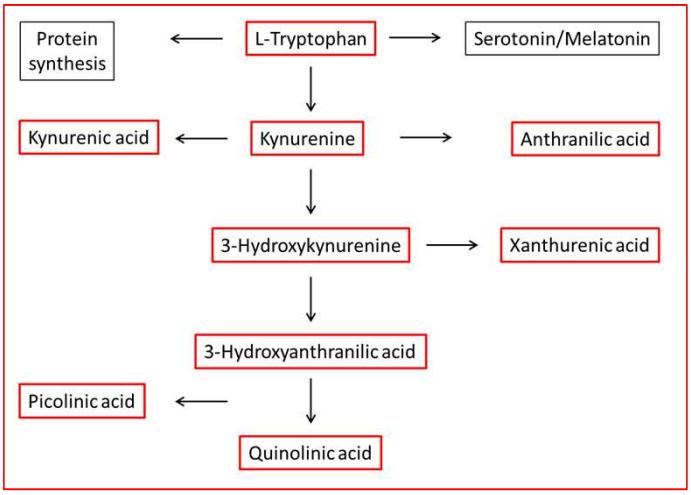

Figure 1: Simplified kynurenine pathway of tryptophan degradation

METHODS

Blood samples were collected prior to treatment and within one week after completed ECT-series from 23 patients with major depression and 12 healthy, age-matched controls (same time frame without ECT-treatment). ECT was administered three times a week with right unilateral electrode placement. Serum concentrations of tryptophan, kynurenine, 3-hydroxykynurenine (HK), kynurenic acid (KA), xanthurenic acid (XA), anthranilic acid (AA), 3-hydrocyanthranilic acid (HAA), quinolinic acid (QA), picolinic acid, and neopterin, were measured using liquid chromatography-tandem mass spectrometry by Bevital (www.bevital.no). All patients improved; the mean depression rating (Montgomery and Åsberg Depression Rating Scale) was 33.0 (SD 6.6) before and 14.0 (SD 8.8) after treatment.

Table 1: Demographics and clinical features for 23 patients with major depression

Gender (female), *n* (%)	13 (56.5 %)
Age in years, mean ± SD (range)	48.26 ± 15.12 (24 - 78)
Unipolar major depressive episode, *n* (%)	16 (69.6 %)
Bipolar major depressive episode, *n* (%)	7 (30.4 %)
Illness duration, years since the first affective episode, mean ± SD (range)	22.52 ± 15.58 (1 - 49)
Prior hospitalizations due to depressive episodes, mean ± SD (range)	3.61 ± 3.70 (0 – 15)
Duration of current depressive episode in weeks, mean ± SD (range)	52.61 ± 44.12 (4 – 156)
MADRS pre ECT, mean ± SD (range)	33.04 ± 6.55 (18 – 46)
MADRS post ECT, mean ± SD (range)	14.00 ± 8.75 (0 – 30)

RESULTS

Demographic and illness characteristics are presented in Table 1. At baseline, independent sample *t*-tests of log- transformed data showed significantly lower serum concentrations of XA and picolinic acid and a higher level of neopterin in depressed patients compared to the healthy control group. In addition, the KA/QA ratio was reduced in the patient group. Based on repeated-measures analyses of variance of log-transformed variables with assessment time (pre- vs. posttreatment) as the within-group variable, treatment with ECT resulted in an increase of KYN, HK, KA, AA, HAA, and picolinic acid, as well as, KYN/TRP and KA/QA compared to the healthy control group, as shown in Table 2. Contrary to previous findings [4], Tryptophan, Kynurenine and QA were not reduced after ECT.

CONCLUSION

Preliminary analyses support an altered kynurenine pathway in major depression and suggest an increase in tryptophan catabolism after ECT. The study is limited by its small sample size and the biological and analytical variation of biomarker testing.

Measure	Patients (*n* = 23)		Healthy controls (*n* = 12)		*t*-test for baseline values		Mixed model ANOVA								
							Group			Time			Group × Time		
	Pretreatment[a]	Posttreatment[a]	Timepoint 1[a]	Timepoint 2[a]	*t*	*p*[b]	F[c]	*p*	η^2	F[c]	*p*[b]	η^2	F[c]	*p*[b]	η^2
Tryptophan (Trp)	1.84 (0.09)	1.85 (0.07)	1.90 (0.06)	1.87 (0.06)	−1.67	0.10	1.94	0.17	0.06	1.85	0.18	0.05	2.89	0.10	0.08
Kynurenine (Kyn)	0.19 (0.11)	0.21 (0.14)	0.18 (0.09)	0.15 (0.10)	0.59	0.56	0.86	0.36	0.03	0.11	0.75	0.00	4.65	**0.04**	0.12
3-hydroxykynurenine (HK)	1.55 (0.18)	1.63 (0.17)	1.58 (0.72)	1.54 (0.11)	−0.25	0.80	0.51	0.48	0.02	0.58	0.45	0.02	5.33	**0.03**	0.14
Kynurenic acid (KA)	1.62 (0.23)	1.68 (0.26)	1.68 (0.12)	1.61 (0.16)	−0.83	0.41	0.01	0.93	0.00	0.10	0.75	0.00	6.42	**0.02**	0.16
Xanthurenic acid (XA)	1.00 (0.23)	1.08 (0.22)	1.19 (0.13)	1.14 (0.19)	−3.55	**<0.01**	3.97	0.06	0.11	0.31	0.59	0.01	3.05	0.09	0.09
Anthranilic acid (AA)	1.19 (0.12)	1.22 (0.16)	1.28 (0.13)	1.21 (0.09)	−0.92	0.36	0.91	0.35	0.03	0.89	0.35	0.03	5.32	**0.03**	0.14
3-hydroxyanthranilic acid (HAA)	1.46 (0.17)	1.56 (0.20)	1.55 (0.13)	1.49 (0.17)	−1.65	0.11	0.07	0.79	0.00	0.33	0.57	0.01	6.28	**0.02**	0.16
Quinolinic acid (QA)	2.56 (0.22)	2.59 (0.24)	2.50 (0.11)	2.50 (0.12)	1.32	0.20	1.26	0.27	0.04	0.32	0.56	0.01	0.99	0.33	0.03
Picolinic acid	1.40 (0.14)	1.50 (0.18)	1.53 (0.13)	1.50 (0.14)	−2.55	**0.02**	2.46	0.13	0.07	1.52	0.23	0.04	4.49	**0.04**	0.12
Neopterin	1.28 (0.23)	1.38 (0.19)	1.19 (0.10)	1.21 (0.14)	2.30	**0.03**	4.20	0.05	0.11	9.07	**0.01**	0.22	3.82	0.06	0.10
Kyn/Trp	0.10 (0.06)	0.12 (0.07)	0.10 (0.05)	0.08 (0.05)	1.72	0.09	1.06	0.31	0.03	0.08	0.78	0.00	4.64	**0.04**	0.12
KA/QA	0.63 (0.05)	0.65 (0.07)	0.67 (0.03)	0.64 (0.06)	−3.52	**<0.01**	1.05	0.31	0.03	0.34	0.56	0.01	5.78	**0.02**	0.15

[a]Reported values are mean and standard deviation of logtransformed serum concentrations. [b]Bold: $p<0.05$. [c]Degrees of freedom: 1, 33.

Table 2: Pre-and posttreatment serum concentrations for Tryptophan metabolites accompanied by statistics for *t*-tests and Mixed model ANOVA

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CONTACT:
Ieva Leskauskaite; ieva.leskauskaite@helse-bergen.no

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HELSE BERGEN Haukeland University Hospital