THE EFFECT OF ELECTROCONVULSIVE THERAPY ON PLASMA CYCLIC-AMP, NON-ESTERIFIED FATTY ACID, TRYPTOPHAN AND TYROSINE IN DEPRESSION

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ABSTRACT

Electroconvulsive therapy (ECT) was applied to nine endogenous depressed patients and the concentrations of cyclic-AMP (c-AMP), free (non-albumin bound) tryptophan, total tryptophan, non-esterified fatty acid (NEFA) and tyrosine in the plasma were measured before and after the first single ECT. As for six patients that could be followed after a course of ECTs, the change of these components and clinical assessments with rating scales was also measured. The content of c-AMP was significantly increased at 1 min, 5 min, 10 min and 30 min after the first single ECT and returned to 121% on the average by 1 hr. As to the maximum content of free tryptophan of each patient from 1 min to 10 min after ECT, a significant increase was noted. Total tryptophan levels were significantly decreased at 5 min and 10 min after the first single ECT and gradually returned to the original level by 1 hr. The content of tyrosine was significantly increased just after the first single ECT and, conversely, a significant decrease was noticed at 1 hr after ECT. NEFA was significantly decreased at 1 min and 5 min after the first single ECT. As for the six patients that could be followed concerning the changes of various components and clinical assessments, all six patients showed dramatic and significant improvement in both subjective and objective rating scales. Percent free tryptophan tended to increase significantly in these patients, but there was no significant change in c-AMP, total tryptophan, NEFA, and tyrosine values.

INTRODUCTION

Endogenous depression is a psychosis of unknown cause, and it is now mainly treated with antidepressants, especially tricyclic antidepressants. Electroconvulsive therapy (ECT) was created in 1938 (Cerletti and Bini)¹, and had been used

as the epoch-making treatment for depression and schizophrenia until the 1950s. But since the advent of the drug therapy, and because of erroneous uses and side effects such as temporary memory losses etc., ECT has been used less year by year. As it is often the quickest and surest way of relieving depression, however, it is still applied to severe depressed patients with suicidal motivation or stupor, or patients unresponsive to medication or with protracted depression. The mechanism of action of ECT, however, is not known though there have been many theories proposed.

The author applied ECT to patients diagnosed as endogenous depressive and measured the concentration of amino acids in the plasma after the first single ECT. The compounds measured included tyrosine, the precursor of catecholamines; tryptophan, the precursor of indoleamines; cyclic-AMP (c-AMP); and, non-esterified fatty acid (NEFA), which had the possibility to change the level of these amino acids. Furthermore, in a smaller group of patients, the change of clinical manifestations was assessed with rating scales and the changes of these various components in the plasma were determined before and after a course of ECTs.

SUBJECTS AND METHODS

1) Subjects

The subjects were nine patients, diagnosed as endogenous depressives following ICD 9 (296.1, 296.3) that were admitted to the neuro-psychiatric ward in Fujita-Gakuen University. Sex, age, type of depression, number of phase, medication, reason for indication of ECT, period before ECT since the onset of that phase and the beginning of medication, number of ECTs given and responses to ECT are presented in Table 1. Either the patients or their families consented to ECT and blood collection in all cases.

2) ECT administration

Each ECT was given at 10:00 am three times a week following the method of Yasukoti et al.² with fasting for over 17 hr. and 500 mg of amobarbital was administered intravenously at 30 min before ECT.

3) Blood collection

The blood was collected from the cubital vein 7 times, i.e. just before anesthesia—9:30, 9:55, just after ECT—approximately 10:01, 10:05, 10:10, 10:30, and 11:00 am. Each sample was divided into two tubes with EDTA-4Na for c-AMP assay and heparin for amino acids and NEFA. Immediately after blood collection, blood was centrifuged at 1000 g for 15 min at ice cold, and the plasma was kept frozen at -20°C till measurement.

4) Measurement of various components in the plasma

The content of c-AMP was measured using radioimmunoassay (YAMASA Cyclic AMP Assay Kit®) (Honma et al.³); NEFA was measured spectrophotometrically (NEFA Test WAKO®) (Laurell et al.⁴). The contents of free (non-albumin bound) tryptophan and total tryptophan were determined spectrofluorometrically (Denckla et al.⁵). The sample for free tryptophan was obtained by the centrifugation of 1 ml plasma through Amicon Centriflo Membrane Cone CF50A® at 1000 g for 30 min at 37°C (Knott et al.⁶). The content of tyrosine was spectrofluorometrically measured (Wong et al.⁷).

5) Clinical assessment

Clinical assessment was done with the self-rating depression scale (SDS) (Zung⁸) written by the patients themselves from 8:30 to 9:00 am and with Hamilton's⁹ and Bojanovský's¹⁰ rating scales checked by the doctor while the patients were lying down from 9:00 to 9:30 am.

6) Medication

During the course of ECT 80 to 150 mg of amitriptyline was used in eight patients (clomipramine in one patient) and a sleep inducer of benzodiazepine group was administered in two patients but their doses were scarcely changed.

Calculation of t-test and correlation coefficient was done using PDP 11 (Digital Equipment Corporation).

RESULTS

1) Changes of various components in the plasma before and after the first single ECT (Figure 1, 2, 3, 4, 5)

Figs. 1 to 5 show the changes of various components in the plasma before and after the first single ECT by converting the absolute value at 9:55 am into 100%. The difference between the percent values of each time and that at 9:55 was tested (t-test; two-tailed).

Though the content of c-AMP in the plasma varied in each patient (18.4 to 35.5 pmole/ml) at 9:30 am just before anesthesia, it became tolerably steady (16.1 to 27.5 pmole/ml; mean $\pm$ SD = 20.4 ± 3.7 pmole/ml) at 9:55 am. At 1 min, 5 min, 10 min, and 30 min after ECT, the percent change of c-AMP became significantly increased ($p < 0.01$, $p < 0.05$, $p < 0.01$, $p < 0.05$ respectively), and returned to 121% on the average by 1 hr. This change is depicted in Fig. 1.

The content of free tryptophan in the plasma at 9:55 ranged between 1.81 and 5.89 nmole/ml (mean $\pm$ SD = 3.92 ± 1.23 nmole/ml). Concerning the percent values a significant increase was found just after ECT ($p < 0.05$) and more sig-

Table 1
Properties of patients studied

Case	Sex	Age	Type of Depression	No. of Phase	Medication mg/day AMT Benzodiazepines	Reason of Indication of ECT	Period before ECT	No. of ECTs	Response to ECT
■	F.	20 ys.	U-P	2	80 (-)	substupor	1.5 M.	3	markedly improved
■	F.	52 ys.	U-P	2	80 (-)	unresponsive to medication	6 M.	15 (4+11)	markedly improved
■	F.	46 ys.	U-P	1	70~80 (-)	unresponsive to medication	4 M.	5	markedly improved
■	F.	52 ys.	B-P	17	55 (-)	unresponsive to medication	1.5 M.	10 (5+5)	markedly improved
■	M.	28 ys.	U-P	2	80 (-)	unresponsive to medication; urgency	2 M.	1	markedly improved
■	M.	51 ys.	U-P	1	80 diazepam 6 estazolam 2	agitated; suicidal idea	4.5 M.	4	markedly improved (but recurred)
■	M.	36 ys.	U-P	2	70~105 (-)	protracted	6 M.	4	markedly improved
■	F.	33 ys.	U-P	1	80~105 (-)	unresponsive to medication; protracted	6.5 Y.	3	improved
■	M.	48 ys.	U-P	5	clorimi- pramine 80	estazolam 2 unresponsive to medication	1 M.	1	improved

U-P=Unipolar depression (296.1 in ICD 9);

B-P=Bipolar depression (296.3 in ICD 9);

unresponsive to medication=without any clinical change even over 4 weeks later;

AMT=amitriptyline.

Fig. 1 The percent changes of the plasma level of c-AMP before and after the first single ECT
 Different to values at 9:55 * $p < 0.05$
 ** $p < 0.01$ Each point is the mean of nine patients and vertical lines indicate SD.

Fig. 2 The percent changes of the plasma level of free tryptophan before and after the first single ECT
 Different to values at 9:55 * $p < 0.05$.

nificant increase was found on the maximum value from 1 min to 10 min after ECT for each patient ($p < 0.01$). This change is presented in Fig. 2.

The content of total tryptophan in the plasma at 9:55 ranged between 45.2 and 124.5 nmole/ml (mean $\pm$ SD = 69.7 ± 22.5 nmole/ml). As for the change of percent value, a distinct significant decrease was found at 5 min and 10 min after ECT ($p < 0.01$ in both). This change gradually returned to the original level by 1 hr. This change is displayed in Fig. 3.

Fig. 3 The percent changes of the plasma level of total tryptophan before and after the first single ECT
Different to values at 9:55 ** $p < 0.01$.

Fig. 4 The percent changes of the plasma level of tyrosine before and after the first single ECT
Different to values at 9:55 * $p < 0.05$.

The content of tyrosine in the plasma at 9:55 ranged between 3.75 and 6.35 $\mu\text{mole/dl}$ (mean $\pm$ SD = $5.06 \pm 0.8 \mu\text{mole/dl}$). Regarding the percent values, a significant increase was noticed at 1 min after ECT ($p < 0.05$), and it fell to the original level at 5 min after ECT and a significant decrease was found at 1 hr. after ECT ($p < 0.05$). This change is presented in Fig. 4.

The content of NEFA at 9:55 ranged between 0.83 and 1.071 mEq/L (mean $\pm$ SD = $0.450 \pm 0.245 \text{ mEq/L}$). A significant decrease was noticed at 1 min and 5 min after ECT ($p < 0.01$) and at 10 min after ECT ($p < 0.05$) in the percent change. This change is displayed in Fig. 5.

Fig. 5 The percent changes of the plasma level of NEFA before and after the first single ECT
Different to values at 9:55 * $p < 0.05$
** $p < 0.01$.

A series of varied values of each component before and after ECT was paired for each patient and correlation coefficient was calculated. Significant correlation ($p < 0.05$; $r > 0.754$) was noticed in two of nine patients between c-AMP and free tryptophan ($r = 0.768, 0.844$ respectively), in one of nine between free tryptophan and tyrosine ($r = 0.780$), and in one of nine between NEFA and tyrosine ($r = 0.798$); a significant reverse correlation was found in one of nine between c-AMP and total tryptophan ($r = -0.816$). As a whole there was not any significant correlation, however any two of the various components were paired. In respect of the patient M.M., blood glucose and cortisol were also measured. Though correlation coefficient was calculated including them, there was no sig-

nificant correlation.

2) Changes of various components in the plasma and clinical manifestations before and after a course of ECTs (Fig. 6)

As to the six patients that could be followed on the changes of these various components and clinical assessments at 9:30 am before and after a course of ECTs, all six patients became dramatically and significantly improved in SDS, Hamilton's and Bojanovský's depression scales ($p < 0.01$ in all).

The level of c-AMP was increased in two patients, unchanged in one and tended to decrease in three. Free tryptophan became increased up to 137 to 168% in four patients, correlated with the clinical improvement. On the absolute values

Fig. 6 The changes of the plasma level of c-AMP, free tryptophan, total tryptophan, tyrosine and clinical assessment before and after the course of ECTs
Different to values before ECT * $p < 0.01$.

statistical significance was not found but tendency to increase was noticed on the percent values ($p < 0.1$, one-tailed). Total tryptophan tended to decrease in four and to increase in two. Tyrosine became increased in four and tended to decrease in two. No consistent tendency was found in the change of NEFA.

DISCUSSION

There are still many recent reports about the fact that ECT is an evidently useful and effective treatment (Avery et al.¹¹; Freeman et al.¹²). Two recent reviews indicated that ECT is more effective than antidepressant drug therapy (Barton¹³; Royal College of Psychiatrist¹⁴). In spite of numerous empirical studies indicating that ECT is really effective, the mechanism of action of ECT is not yet known.

In this study the contents of c-AMP, free tryptophan, total tryptophan, tyrosine and NEFA in the plasma were measured before and after the first single ECT in depressive patients, and clinical assessment was done with the measurement of these components before and after a course of ECTs.

Though the content of c-AMP was found to be increased significantly by 30 min after the first single ECT, there have been no reports of c-AMP content in the plasma following ECT. It was found that urinary excretion of c-AMP/24 hr. increased up to 310% on the day of ECT compared with before ECT (Hammadah et al.¹⁵). Brown et al.¹⁶ and Moyes et al.¹⁷, however, insisted that they could not find a significant increase of the urinary excretion of c-AMP. The origin of c-AMP in the urine is more obscure than that in the plasma. It was reported that 60% of urinary c-AMP was from glomerular filtration (Broadus et al.¹⁸). The distinct and significant increase of c-AMP in the plasma during a period of 30 min after ECT could have been diluted in the urine for 24 hr. As it was suggested that c-AMP in the plasma might be a good indicator of the activity of the sympathetic nervous system (Honma et al.¹⁹), it was assumed that ECT might strongly activate the sympathetic nervous system. This appears to confirm the results of Weil-Malherbe²⁰ and Havens et al.²¹, in which catecholamines in the blood were found to be increased just after ECT.

NEFA is generally thought to increase with the activation of hormone sensitive lipase due to the excitation of the sympathetic nervous system (Mallov et al.²²). As NEFA was significantly decreased at 1 min and 5 min after ECT in this study, though the sympathetic nervous system might be strongly activated by ECT, it appears that re-esterification from NEFA was activated more through a certain mechanism with ECT, and overcame the increase of NEFA due to hydrolysis from lipoprotein.

It was reported that NEFA was increased up to 122% and free tryptophan up to 134% at 1 min after ECT (Stelmasiak et al.²³). They suggested that ECT

increased NEFA and so increased free tryptophan through a mechanism whereby free tryptophan was released from albumin by NEFA, which competed with free tryptophan in binding to albumin (Curzon et al.²⁴; Knott et al.⁶). They reported further that the increase of free tryptophan in the plasma caused the increase of tryptophan and then the increase of 5-HT turnover in the brain (Curzon et al.^{25,26}; Tagliamonte et al.²⁷), and that ECT might improve depression through the same mechanism. As the free tryptophan level was definitely increased at 1 min after ECT, as Stelmasiak found, though NEFA was significantly decreased at 1 min and 5 min after ECT, this increase presumably is related to a mechanism other than theirs.

In this study the level of free tryptophan tended to increase in accordance with clinical improvement. This result was consistent with the report by Coppen et al.²⁸ and might be important in the mechanism of action of ECT and the pathophysiology of depression in association with the indoleamine hypothesis of depression (Coppen²⁹; Coppen et al.³⁰). The content of total tryptophan became significantly decreased at 5 min and 10 min after ECT. There have been no previous reports of this phenomenon, and the mechanism and the metabolic meaning of this result is not clear.

On the other hand, tyrosine, the precursor of catecholamines, was also significantly increased. There have been no reports of this phenomenon. It is important to investigate the mechanism of this phenomenon and its meaning in the effectiveness of ECT in association with catecholamine hypothesis of depression (Schildkraut³¹) and further study its relationship with indoleamine metabolism.

In this study intravenous anesthesia, amobarbital, was used. Although it was thought to influence the level of various components in the plasma, especially c-AMP, free tryptophan and NEFA. At 9:30 the levels of c-AMP, free tryptophan and NEFA were 24.9 ± 5.3 pmole/ml, 3.82 ± 1.46 nmole/ml and 0.569 ± 0.287 mEq/L respectively and at 9:55 20.4 ± 3.7 pmole/ml, 3.92 ± 1.23 nmole/ml and 0.450 ± 0.245 mEq/L respectively. As the contents of c-AMP and NEFA were significantly decreased ($p < 0.05$) and SD of the levels of these components were decreased after anesthesia, these levels were thought to become stabilized in 25 min after anesthesia. Furthermore, in the cases A.K., M.O. and Y.T. the contents of c-AMP, free tryptophan and NEFA during amobarbital anesthesia without ECT were measured for the same period of time as ECT. There was no consistent and significant change of the contents of these components.

There remain several questions in this study: 1) Are these changes specific in depression or non-specific change following ECT? 2) What is the indispensable change to improve depression? 3) What about the improved patients who did not show significant change? 4) How much does the real convulsion and the temporary hypoxia during ECT influence these results? 5) How do the temporary

changes sustain the clinical improvement even after a course of ECTs? 6) Were these subjects in this study only a subgroup of depressive patients unresponsive to medication? As the level of various components in the plasma is related to the sum of synthesis, degradation, influx and efflux, how these changes in the plasma influence the metabolism in the brain and behavior must be investigated further in animal experiments, now in progress.

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