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Original Articles

The Effect of ECT on Plasma Cyclic Nucleotides: A Simulated ECT Controlled Study in Melancholic Patients

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Summary. Concentrations of cAMP and cGMP in plasma were measured in 20 drug-free melancholic patients during a simulated electroconvulsive treatment (SECT) and a bilateral ECT session. Blood samples were taken every 15 min beginning 15 min before and ending 60 min after the SECT or the ECT. Two-way ANOVA and paired *t*-test demonstrated a significant and greater fall in cAMP over time following SECT. ECT induced a marginal increase ($P < 0.05$) at 45 min postictally. It is postulated that ECT causes an increase in cAMP levels which is masked by the decrease observed during SECT, caused presumably by the anaesthetic medication. The plasma cGMP levels were increased gradually and significantly after SECT and the same rise was observed during ECT. These effects are discussed in relation to changes in adrenergic-cholinergic activities induced by the medication and the electrical stimulus.

Key words: Electroconvulsive treatment – Cyclic 3′,5′adenosine monophosphate – Cyclic 3′,5′guanosine monophosphate – Major depressive disorder

Introduction

Electroconvulsive treatment (ECT) has been used for decades and is still an impressively effective treatment in major depression (Consensus Conference 1980). Despite this, the neurobiological mechanisms underlying this treatment have not as yet been delineated. Among other variables that can give information on the mode of ECT action is cyclic 3′,5′adenosine monophosphate (cAMP), which can be measured in body fluids. This nucleotide acts as a second messenger of many hormones. It possesses the same key role in the central and peripheral neural transmission, mediating the action of catecholaminergic neurotransmitters (Nathanson 1977), which have been implicated in the pathophysiology of affective disorders. Animal studies have shown that electroconvulsive shock (ECS) and several convulsant drugs (Opmeer et al. 1976; Rodnight 1979) increase the levels of cAMP and of cyclic 3′,5′guanosine monophosphate (cGMP) (another nucleotide with a second messenger role in cholinergic systems) in brain. In human studies, a series of ECTs did not significantly alter the levels of cAMP in depressed patients (Geisler et al. 1976; Post et al. 1977). An increasing effect of ECT on cAMP in the urine of depressed patients was suggested in one (Hamadah et al. 1972) and denied in another report (Moyes and Moyes 1976).

The aim of the present study was to obtain information about the acute effect of a single ECT on cAMP and cGMP levels in plasma of melancholic patients. The study also included measurement of cyclic nucleotides following simulated ECT (SECT), where general anaesthesia with muscle relaxant was given but current was not passed.

Subjects and Methods

All patients were hospitalized at the Psychiatric Clinic of the Athens University Medical School, Eginition Hospital. Patients were selected from those referred for ECT after being diagnosed as having major depressive disorder, provided that their depressive episode had melancholic features (DSM-III criteria). Twenty patients were in the study sample (2 men, 18 women, mean age 53.0 ± 7.8 years, range 35–63). Eighteen of them had unipolar and 2 bipolar disorder. Seven patients (1 man, 6 women) met DSM-III criteria for major depressive episode with psychotic features, mood congruent. All patients scored more than 17 points on the first 17 items (mean value ± SD: 30.4 ± 7.2, range 22–42) of the Hamilton Rating Scale for Depression (HDRS; Hamilton 1960). Patients had been free of any drugs at least 2 weeks before and during the trial with the exception of small doses of benzodiazepines given to all 20 patients. Excluded from the study were those with medical, neurological or endocrinological illness. Consent for ECT was obtained from patients and relatives. ECT was administered between 8.30 and 9.30 a.m. after an overnight fast. Premedication for ECT included intravenous administration of atropine (0.6 mg) 5 min before ECT, followed by pentothal anaesthesia (250–350 mg), succinylcholine (25–40 mg) and oxygenation.

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Bilateral ECT was applied in all patients. The characteristics of the electrical stimulus were: partial sine wave stimulus starting at maximum (90 Hz) and through rectification the half-way frequency was 50 Hz, peak current intensity 400–450 mA, and current flow time 2–3 s. The cuff method was used to estimate duration of seizures (Fink et al. 1982), which was more than 20 s in all sessions. Blood samples were taken into tubes containing EDTA, during the first two ECT sessions, 15 min prior to and immediately before the electrical stimulus was delivered, and 15, 30, 45 and 60 min post-ECT. Plasma was then separated by centrifugation and was kept at −30°C until analysed. To compensate for order effects, SECT was done at the first treatment of 12 patients while ECT was done at the first treatment of 8 patients. At the second treatment, which took place 2 days later, the subgroup of 12 patients received ECT and the subgroup of 8 patients received SECT. We then compared pre-ECT cAMP and cGMP levels with those before SECT (zero time values) in each one of patient subgroups. No significant differences were found. Cyclic AMP and cGMP were measured with the protein binding kits of Amersham. Initially we studied 8 melancholic patients where only cAMP was estimated. Thereafter it was decided to enlarge our sample and to estimate both nucleotides. We thus have data from 20 patients for cAMP and from 12 of them for both nucleotides.

Interassay variations in the mean (duplicates of the measurements of cyclic nucleotides) were around 8%. Biochemical estimations were made without knowledge of the clinical state.

Data were analysed statistically using the two-way ANOVA with factors time (−15 +15 +30 +45 +60 min) and treatment (SECT vs ECT), and their interaction (time × treatments). The *t*-test for unpaired and paired observations and Spearman's correlation coefficient were also used.

Results

The pretreatment HDRS score was mean ± SD = 30.4 ± 7.2, range 22–42. Pretreatment cAMP and cGMP levels did not correlate with age or initial HDRS score.

The mean values of cAMP and cGMP during SECT and ECT are given in Table 1.

A two-way ANOVA demonstrated that cAMP alters significantly over time: $F = 3.73$, $df = 19$, $P = 0.003$ (Table 1). It was shown that SECT induced a significant decrease in plasma cAMP at 30 min ($P < 0.05$), 45 min ($P < 0.0025$) and 60 min ($P < 0.005$). After ECT, cAMP levels were also reduced but not significantly (at 45 min $P < 0.1$). By treatment (SECT vs ECT) two-way ANOVA showed that SECT affects cAMP levels to a significantly different degree compared with ECT: $F = 7.15$, $df = 19$, $P = 0.008$. In fact, the fall in cAMP was stronger after SECT than ECT, as also shown above by paired *t*-test. The interaction term of two-way ANOVA was not significant.

The results of two-way ANOVA for cGMP ($n = 12$) showed no significant differences by treatment (SECT vs ECT): $F = 0.24$, $df = 11$, P: NS, while by time a significant change of values at zero times during SECT and during ECT was found: $F = 3.73$, $df = 11$, $P = 0.0032$ and $F = 2.43$, $df = 11$, $P = 0.0379$ respectively). In particular, cGMP increased significantly 30 min following SECT ($P < 0.05$) and this increase continued at 45 min ($P < 0.025$) and 60 min ($P < 0.025$) (Table 1). Similar results were obtained after ECT administration except that the significant increase was shown 15 min later, i.e. at 45 min ($P < 0.05$) and 60 min ($P < 0.05$).

Table 1. Mean values and standard deviations of cAMP and cGMP in plasma of melancholic patients during a simulated (SECT) and a real electroconvulsive therapy (ECT)

Time (min)	Cyclic AMP pmol/ml ($n = 20$)		Cyclic GMP pmol/ml ($n = 12$)	
	After SECT	After ECT	After SECT	After ECT
−15	17.5 ± 4.7	18.2 ± 4.5	3.54 ± 1.45	3.70 ± 1.78
0	16.8 ± 4.8	17.3 ± 4.9	3.52 ± 1.47	3.60 ± 1.91
15	15.4 ± 4.5	17.2 ± 4.7	3.67 ± 1.19	3.72 ± 1.22
30	14.6 ± 4.2	16.4 ± 5.6	4.07 ± 1.51[c]	4.03 ± 1.34
45	13.5 ± 3.9[a]	15.3 ± 4.6	4.37 ± 1.33[d]	4.73 ± 1.98[c]
60	13.0 ± 3.8[b]	15.8 ± 4.7	4.61 ± 1.23[e]	4.77 ± 2.18[c]

[a] $P < 0.005$, compared with zero values, paired *t*-test
[b] $P < 0.001$
[c] $P < 0.05$
[d] $P < 0.025$
[e] $P < 0.01$

Two-way ANOVA: (a) cAMP by treatment (SECT vs ECT): $F = 7.15$, $df = 19$, $P = 0.008$; by time: $F = 3.73$, $df = 19$, $P = 0.0032$; interaction term: $F = 0.89$, $df = 19$, P: NS. (b) cGMP by treatment: $F = 0.24$, $df = 11$, P: NS; by time: $F = 2.43$, $df = 11$, $P = 0.0379$; interaction term: $F = 0.05$, $df = 11$, P: NS

Finally there were no significant correlations of the pretreatment values of cAMP and cGMP with the age, or duration of illness on HDRS.

Discussion

The present study revealed a significant fall in cAMP levels during SECT, which was obviously caused by the drugs administered as pre-ECT medication. After ECT no significant change from the baseline was shown. Interpretation of these results is related to the problem of origin of cAMP in plasma. Several tissues including CNS, liver, kidney, myocardium, lung, adipose tissue, adrenals and blood cells are considered as contributors of plasma cAMP concentrations but not one has been identified as a major source (Broadus et al. 1970; Wehmann et al. 1974). Broadus et al. (1970) have suggested (and it has been verified by others; Strange et al. 1974; Wehmann et al. 1974) that changes in plasma cAMP reflect intracellular levels of this nucleotide, perhaps because of increased membrane permeability (Gill et al. 1975) and that changes in plasma concentrations of some hormones can alter the rate of passage through membranes (Kaminsky et al. 1970; Taylor et al. 1970). In view of the above, one cannot assume that the changes of plasma cAMP in melancholic patients following SECT and ECT simply reflect similar changes in the brain of these patients.

Information on the effect of succinylcholine used for muscle paralysis on plasma cAMP is not available, and atropine, as shown in one study, seems not to exert a significant effect on plasma cAMP in rats (Honma and Yi 1978). It has been reported that barbiturates inhibit cAMP accumulation in depolarizing brain tissue (Ferrendelli and Kinscherf 1979). They also depress trans-

mission in sympathetic ganglia (Harvey 1980) and the production of cAMP (Nathanson 1977). It has also been demonstrated that barbiturate premedication suppresses the elevated plasma levels of adrenaline and noradrenaline following ECT (Weil-Malherbe 1955; Havens et al. 1959). Injection of catecholamines increases the levels of plasma cAMP in normals (Ball 1972). Thus, the lowering effect of barbiturates on cAMP could be the result of decreased sympathetic activity cause by these drugs. The contribution of succinylcholine to the lowering of cAMP levels remains to be investigated in further experiments. After ECT, plasma cAMP concentrations were found to be decreased to a significantly lesser degree compared with SECT. Considering the marked and stronger decrease in cAMP concentrations over time with anaesthetic medication and its slight decrement postictally, we may postulate that ECT failed to elicit a clear-cut rise in cAMP because of the severe fall of cAMP caused by pre-ECT medication. Clearly ECT restrained this fall. This point could be clarified with results obtained from patients given unmodified ECT. However, this was considered unacceptable for ethical reasons. It is noteworthy that Moyes and Moyes (1976) reported two cases of depressed patients who received unmodified ECT without significant effect in urine cAMP excretion. The same was found in their patients receiving modified ECT. In contrast, Hamadah et al. (1972) reported increased cAMP excretion in depressed patients on the day of treatment. Data derived from animal studies have shown a rise in cAMP content both in brain and CSF after ECS (Myllyla et al. 1976a; Clarenbach et al. 1978). Yet, CSF cAMP levels in epileptic patients were found to be increased after a generalized fit (Myllyla et al. 1976b). As mentioned above, infusion of catecholamines has been shown to increase cAMP in plasma (Ball et al. 1972) and elevation of endogenous catecholamines in cardiac infarction runs parallel to the increase of cAMP in plasma (Strange et al. 1974). It has been shown from animal experiments that ECT increases catecholamine levels in brain (Lerer 1988, for review). Human studies have also demonstrated peripheral catecholamine increases with ECT (Weil-Malherbe 1955; Havens et al. 1959; Khan et al. 1985). Since cAMP acts as a second messenger for catecholamines it may be that the enhancement of cAMP in plasma after ECT is the result of the heightened sympathetic activity accompanying seizures.

The plasma cGMP concentrations increased gradually and significantly after SECT. This unexpected change is difficult to explain at present, since animal studies (Honma and Yi 1978) have shown that atropine lowers plasma cGMP levels, while in humans it does not affect its baseline plasma concentrations (Okada et al. 1982). Further, barbiturates like pentobarbital decrease cGMP in mouse brain (Opmeer et al. 1976). No information is available regarding the possible effects of succinylcholine, but hexamethonium, a ganglionic blocking agent, reduces plasma cGMP in rat (Honma and Yi 1978).

Enhanced plasma cGMP concentrations were also found after a single ECT. This change could be explained on the basis of a stimulation of cholinergic and α-adrenergic receptors occurring during ECT (Pitts 1982) and the finding of raised plasma cGMP levels in humans induced by cholinergic agonists like metacholine (Okada et al. 1982) and by α-adrenergic agonists like adrenaline and noradrenaline (Ball et al. 1972; Belmaker et al. 1981; Okada et al. 1982). However, the ECT-induced rise in cGMP was nearly of the same magnitude as that induced by SECT. Thus, one could argue that this rise apparently reflects the SECT effect on cGMP, whereas ECT has no influence.

Summarizing, this study has shown once more the necessity for appropriate control for revealing the mechanisms underlying ECT. If the study was of real ECT only, the results would show no influence on cAMP but an increase in cGMP, while the actual findings (SECT controlled) are that ECT increased cAMP concentrations and had no influence on cGMP levels.

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