Indian J. Psychiat., 1997, 39 (4), 272-277

ECT AND PLATELET 5HT UPTAKE IN MAJOR DEPRESSION

P.K. DALAL, NAROTTAM LAL, J.K. TRIVEDI, P.K. SETH, A.K. AGARWAL & ABDUL KHALID

ABSTRACT

Several studies have reported decreased platelet 5-HT uptake in patients of major depression. The mechanism of antidepressant action of ECT is not clear. The present work was undertaken with the aim to study the active platelet 5-HT uptake and the effect of ECT on it in patients of major depression. 15 patients of major depression (DSM-III-R) and equal number of age and sex-matched controls were included in the study. Active platelet 5-HT uptake was determined before ECT, after a course of ECT and 7 days after last ECT. Platelet 5-HT uptake was significantly lower in depressives than normal controls. After ECT treatment there was significant increase in 5-HT uptake which came down to pretreatment level after 1 week of last ECT. The effect of ECT on serotonergic system is discussed.

Key words : Active platelet 5-HT uptake, major depression, ECT, serotonin

Dysfunction of brain serotonergic system may be a factor responsible for mood and behavioural disturbances associated with depression. Major depression, or at least a subcategory thereof, is thought to be associated with disturbances in the serotonin (5-HT) system as indicated by, for example, low cerebrospinal fluid concentrations of the 5-HT metabolite 5-hydroxy indoleacetic acid (Asberg et al., 1984). Studies showing a low 5-HT uptake (Vmax) into blood platelets (Tuomisto et al., 1976; Coopen et al., 1978; Meltzer et al., 1981; Malmgren et al., 1981), a low number of 3H-impramine binding sites (Bmax) in platelets (Briley et al., 1980; A'sarch et al., 1980; Paul et al., 1981; Wagner et al., 1985) and a low concentration of 5-HT in platelets or whole blood (Coppen et al., 1976; LeGuen et al., 1984; Sarrias et al., 1987) also support this assumption.

Platelet serotonin measures represent indirect but easily obtainable indices of brain serotonin function (Sheline et al., 1995). The human platelet 5-HT_2 receptor may resemble a peripheral model of central 5-HT_2 binding sites and has been linked by changes in 5-HT_2 receptor function in depression (Steckler et al., 1993). Several studies have reported decreased platelet 5-HT uptake in depressed patients (Hallstrom et al., 1976; Scott et al., 1979; Ehsanullah, 1990; Born et al., 1980; Jeffery et al., 1982).

The mechanism of antidepressant action of electroconvulsive therapy (ECT) is still a matter of controversy. Shapira et al. (1992) showed that ECT enhances central serotonergic responsivity. Subramanyam (1975) reported that ECT produced a sustained increase in the synthesis and turn over of amines in the brain. Jori et al. (1975) reported that ECT caused significant increase in CSF 5-HIAA at the time of recovery than at the beginning of the treatment. Costain et al. (1979) reported that ECT potentiates 5-HT effects in

test animals (rats).

The present study was undertaken with the aim to find out active platelet 5-HT uptake in depressed patients and effect of ECT in these patients.

MATERIAL & METHOD

Subjects for the study consisted of a depressive group and a control group. All consecutive drug-naive patients of depression of both sexes between 17-60 years admitted in the Department of Psychiatry, K.G.'s Medical College, Lucknow were screened. DSM-III-R criteria (APA, 1987) was used for the diagnosis of major depression (single episode or recurrent). Hamilton Rating Scale for Depression (Hamilton, 1960) was used to rate the severity of depression and those patients scoring 17 points or more on 17-item scale were included in the study. Exclusion criteria were presence of physical illness requiring active medication, papilloedema, epilepsy, mental retardation, organic brain syndrome, pregnancy, and drug and/or alcohol dependence.

Control group comprised of normal healthy volunteers matched for age and sex with depressives. Controls were screened on Cornell Medical Index (CMI) (Brodman et al., 1949) and those who gave thirty or more "yes" responses on entire CMI and/or ten or more "yes" responses on M-R sections of CMI were excluded. Controls with past or family history of depression were also excluded. Other exclusion criteria were same as for the depressive group.

All the subjects included in the study were kept drug free except tablet lorazepam on s.o.s basis because antidepressants or antipsychotics may alter platelet 5-HT uptake (Todrick & Tait, 1969; Boullin et al., 1978). The subjects were kept on a diet free of pineapples, bananas, plums and nuts for the entire duration of study. Controls were also kept on a similar dietary restriction for a period of 7 days before taking blood sample. This specific restriction on the diet was imposed especially for tryptophan containing food items as tryptophan, a precursor of 5-hydroxytryptamine (5-HT), could have altered the levels of 5-HT and its metabolites in serum and CSF (Wurtman & Fernstrom, 1974; Sneddon, 1973; Knott & Curson, 1972), thus altering the results.

The depressives were given only modified electroconvulsive therapy, first three on alternate days and on every fourth day thereafter to a maximum of ten by the end of five weeks treatment phase. Subsequently, all depressives were kept free of ECT or drug for 7 days after last ECT. Atropine (1 mg IV) was administered two minutes before the anaesthetic medication. Thiopental (2-3 mg/kg body weight IV) was used as the anaesthetic agent and succinylcholine (0.5-1.0 mg/kg body weight IV) as muscle relaxant. Sine wave ECT was administered by "Electrocon" Model manufactured by associated electronic engineers, Bangalore, using bitemporal electrodes. 90 to 120 volt electrical stimulus for 0.5-1.0 seconds was given to induce seizures.

Severity of depression and response to ECT was assessed on Hamilton Rating Scale for depression (HRSD) which was administered on the day of hospitalization and then at weekly interval till the end of the treatment phase (day 35 or when HRSD sore fell below 5 points) and 7 days after last ECT.

Routine haemogram, SGOT, serum bilirubin, serum creatinine, serum proteins, blood urea, blood sugar, urine examination and bilateral fundus oculi examination were done in all subjects and those with abnormal test results were excluded. For platelet 5-HT uptake estimation, subjects were kept overnight fasting and in the morning (between 8 to 9 a.m.) 10 ml. venous blood was drawn by a disposable syringe rinsed with 3.8% sodium citrate and transferred into polypropylene tube containing 1 ml. of 3.8% sodium citrate as anticoagulant (Born & Cross, 1963; Mills & Robert, 1967). Blood samples were drawn in fasting condition in the morning (Meltzer et al., 1981) to control for the diurnal rhythm of platelet 5-HT uptake. The sample tubes were immediately (within one hour) sent to Industrial Toxicology Research Centre, Lucknow for assessment.

The platelet 5-HT uptake was estimated by following the principles of the method described by Scott et al. (1979). The counting was done in a liquid scintillation counter (LKB wallac). In order to assess the active uptake, the passive uptake was substracted from the total uptake. The data is represented in terms of picomoles of ^{3}H (tritiated) 5-HT uptaken/10^{8} platelets/5 minutes.

For depressives the platelet 5-HT uptake estimation was done prior to starting the treatment, at the end of ECT treatment and 7 days after last ECT. For controls only one sample was estimated.

Student's 't' test was used to find the level of significance between two mean values. Paired "t" test was used to determine the level of significance of mean of difference where the observations were paired. Pearson's product moment correlation coefficient was used to measure the degree of association between two series of observations.

RESULTS

The sample for the study consisted of 15 patients of major depression and equal number of age and sex-matched controls. Mean age of depressives and controls was 43.93 (range 25-56) and 42.60 (range 26-54) years respectively and there was no significant difference between the two. There were 8 males and 7 females in each group.

HRSD scores in depressives prior to treatment was 28.47± 4.41 which decreased significantly to 4.73±4.09 after treatment with ECT and this improvement remained nearly maintained after 7 days of last ECT (5.87±.80).

Active platelet 5-HT uptake in depressives prior to treatment was 1.32±0.40 (pmol/10^{8} platelets/5min.). There was no significant correlation between active platelet 5-HT uptake and severity of depression (r=0.13;NS). There was also no significant difference in active platelet 5HT uptake between the subject with first episode depression and recurrent depression.

Active platelet 5-HT uptake (in pmol/10^{8} platelets/5min) was significantly lower in depressives (1.32±0.42) as compared to controls (1.77±0.47) prior to treatment. After treatment with ECT, there was a significant increase in active platelet 5-HT uptake (1.97±0.38) from pretreatment levels but 7 days after last ECT the active platelet 5-HT uptake decreased to 1.35±0.38 which was nearly similar to pretreatment levels (table -1). Mean number of ECTs given to depressives was 8.87±2.45. Percentage increase in active platelet 5-HT uptake after ECT's was 47.06±34.71.

DISCUSSION

This study was undertaken with the aim to study the active platelet 5-HT uptake in depressed patients and the effect of ECT on active platelet 5-HT uptake in these patients. The major finding of our study was that platelet 5-HT uptake was lower in patients of major depression as compared to controls and ECT treatment resulted in increase in active platelet 5-HT uptake.

Pretreatment HRSD score in depressives was 28.47± 4.41. ECT successfully ameliorated the depressive symptoms with post treatment HRSD score being 4.73±4.09 and this clinical improvement was maintained after seven days of treatment free period (HRSD score 5.87±4.80). The mean duration of treatment with ECT was 3.99 weeks. The response rate was 82.77% which is in keeping with the reports that most of the depressives show good therapeutic response to ECT (Dubovsky, 1995).

The uptake of 5-HT in both brain and blood platelet requires active uptake process against a considerable concentration gradient (Blackburn et al., 1967; Chase et al., 1969). The process of passive uptake of 5-HT in both brain and blood platelets is of little or no physiological importance, only contributing to uptake at high susbtrate concentrations and not influenced by drugs such as imipramine which block the active transport process (Fuke et al., 1964). The 5-HT concentration in whole blood or platelets and the total 5-HT uptake (both active & passive) lack the specificity which the active platelet 5-HT uptake has and do not

TABLE
COMPARISON OF ACTIVE PLATELET 5-HT UPTAKE IN DEPRESSIVES AND CONTROLS

Group	Mean	S.D.
A. Controls (N=15)	1 77	0.47
B. Pre-ECT (N=15)	1.32	0.40
C. After a course of ECT (N=15)	1.97	0.38
D. 7 days after last ECT (N=15)	1.35	0.38

* Uptake values in picomoles of ^{3}H 5-HT uptake /10^{8} platelets /5min

A. vs. B t=2.82; df=28; p<01
A vs. C t=1.28; df=28; NS
A vs. D t=2.69; df=28, p,.05
B vs C t=3.87; df=14; p<.01
B vs D t=0.39; df=14; NS
C vs.D t=5.44; df=14; p<.05

parallel with the CNS parameters so closely as the active platelet 5-HT uptake does. Hence, active platelet 5-HT uptake was studied and for this the estimation was done at a low concentration of 5HT and for a short incubation period which is necessary for accurate results (Sneddon, 1973).

Active platelet 5-HT uptake was significantly lower in depressed patients as compared to controls prior to treatment (table -1). Similar findings have been reported by Hallstrom et al. (1976), Scott et al. (1979), Ehsanullah (1980) and Born et al. (1980), However, Shaw et al. (1971) found no difference in the uptake of platelet 5-HT in depressed patients, but the excessive concentration of 5-HT and the long incubation time used in that study precluded accurate determination of active 5-HT.

Lingjaerde (1983) hypothesized that there is a lowered turnover of 5-HT in at least a subgroup of depressed patients which is reflected in lowered concentration of 5-HIAA in the CSF or lowered concentration of 5-HT in blood or in platelet or lowered active 5-HT uptake in blood platelets of these patients (uptake can be taken as a reflection for turnover). Moreover, as platelet can be taken as neuronal model for 5-HT, it can be interpreted that akin to platelets, in the pre-synaptic neurons the active 5-HT uptake is lowered in depressed patients which may be a compensatory mechanism, the function of which is to "make the best" out of the reduced amount of 5-HT in the synaptic cleft.

Treatment with ECT resulted in a significant increase in the active platelet 5-HT uptake (1.9 ± 38 pmol/10^{8} platelets/5min) as compared to the pretreatment levels (1.32 ± 0.40 pmol/10^{8} platelets/5min) This increase in active platelet 5-HT uptake was higher than controls (1.77± 0.47) though statistically there was no significant difference between the two (table). This means that clinical improvement in depressive symptoms (i.e. HRSD score), after treatment with ECT corresponded with increase in active platelet 5-HT uptake.

Although ECT is highly effective as short-term treatment for depression, 50 to 70% of nonpsychotically depressed patients and upto 95% of psychotically depressed patients relapse, at least one half to four fifths of them in the first two to four months after the completion of therapy. The relapse rate is reduced to about 20% in patients maintained after ECT on antidepressants or lithium (Dubovsky, 1995). In the present study, the increase in active platelet 5-HT uptake after treatment with ECT reverted to nearly pretreatment levels after 7 days of treatment free period indicating a risk for relapse. This finding substantiates the need for maintenance treatment in depression even after clinical improvement in depressive symptoms has occurred. As stated earlier that uptake could be taken as a reflection for turnover, the findings of the present study suggest that ECT might increase the turnover of 5-HT in platelets. Gayford et al. (1973) found increased 5-HT blood levels after ECT in depressed patients. Subramanyam (1975) reported that ECT produced sustained increase in synthesis, utilization and turnover of the amines in the brain of depressives. Jori et al. (1975) reported that ECT determined significant

increase in CSF 5-HIIA at the time of recovery than at the beginning of the treatment. Costain et al. (1979) found that ECT potentiates 5-HT effects in test animals (rats). Although no firm conclusions can be drawn, it is possible that by ECT increased turnover of 5-HT in blood platelets (findings of the present study), in blood (Gayford et al., 1973) and increased turnover of CSF 5-HIIA (Subramanyam, 1975; Jori et al., 1975; Costain et al., 1979) may be relevant to the antidepressant activity of ECT.

REFERENCES

American Psychiatric Association (1987) Diagnostic and Statistical Manual of mental disorders, Edn. 3rd (revised), Washington DC : American Psychiatric Association.

Asarch, K.B., Shih, J.C. & Kulcsar, A. (1980) Decreased ^{3}H- imipramine binding in depressed males and females. *Community Psychopharmacology*, 4, 425-432.

Asberg, M., Bertilsson, L., Martensson, B., Scaliatomba, G.P., Thoren, P. & Traskman-Bendz, L. (1984) CSF monoamine metabolites in melancholia. *Acta Psychiatrica Scandinavica*, 69, 201-219.

Blackburn, K.J., French, P.G. & Merrills, R.J. (1967) 5-hydroxytryptamine uptake by ratbrain in vitro. *Life Science*, 6,1653.

Born, G.V.R. & Cross, M.J. (1963) The aggregation of blood platelets. *Journal Physiol.*, 168, 178.

Born, G.V.R., Grignani, G. & Martin, K. (1980) Long-term effect of lithium on the uptake of 5-HT by human platelets. *British Journal of Clinical Psychopharmacology*, 9, 321.

Boullin, D.J., Molynoux, D. & Roach, B. (1978) The binding of haloperidol to human platelets and interactions with 5-hydroxytryptamine and dopamine. *British Journal of Pharmacology*, 63, 561.

Briley, M.S., Langer, S.Z., Raisman, R., Sechter, D. & Zarifian, E. (1980) Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. *Science*, 209, 303-305.

Broadman, K., Erdmann, A.J. Jr., Large, I. & Wolft, H.G. (1949) The cornell medical index-an adjunct to medical interview. *Journal of American Medical Association*, 140, 530

Chase, R.N., Katz, R.I. & Kopin, R.J. (1969) Release of (^{3}H) serotonin from brain slices. *Journal of Neurochemistry*, 16, 607.

Coppen, A., Swade, C. & Wood, K. (1978) Platelet 5-hydroxytryptamine accumulation in depressive illness. *Clin. Chin., Acta.*, 87, 165-168.

Coppen, A., Turner, P., Rosewell, A.R. & Padgham, C. (1976) 5-hydroxy tryptamine (5-HT) in whole blood of patients with depressive illness. *Postgraduate Medical Journal*, 52, 156-158.

Costain, D.W., Green, A.R. & Grahame-Smith, D.G.(1979) Enhanced 5-HT mediated behavioural responses in rats following repeated electroconvulsive shock : Relevance to the mechanism of the antidepressant effect of electroconvulsive treatment. *Psychopharmacology*, 61,167.

Dubovsky, S.L. (1995) Electroconvulsive therapies. In: *Comprehensive Textbook of Psychiatry*, Edn. 6, Vol. 2, pp 2129-2139, (Eds.) Kaplan, H.I. & Sadock B.J., Baltimore: Williams & Wilkins.

Ehsanullah, R.S. (1980) Uptake of 5-HT and dopamine into platelets from depressed patients and normal subjects. *Postgraduate Medical Journal*, 56 (Suppl 1), 31

Fusk, Z., Lanman, R.C. & Shanker, L.S.(1964) On the membrane effects of Chlorpromazine : Uptake of biologic amines by blood platelets and cell. *International Journal of Neuropharmacology*, 3, 623.

Gayford, J.J, Parker, A.L., Phillips, E.M. & Rowsell, A.R. (1973) Whole blood 5-hydroxytryptamine during treatment of endogenous depressive illness. *British Journal of Psychiatry*, 122, 597.

Hallstrom, C.U.S., Rees, U.L. & Pare, C.M.B. (1976) Platelet uptake of 5-hydroxytryptamine and dopamine in depression. *Postgraduate Medical Journal*, 52, 44.

Hamilton, M. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, 23, 56

Jeffery, R.L., Nand Kumar, S.S., Burck, E.A. & Donald, A.G. (1982) Platelet serotonin uptake in depressed patients circadian effect. *Biological Psychiatry*, 17, 121.

Jori, A., Dolfini, E., Casati, C. & Argenta, G. (1975) Effect of ECT and imipramine treatment on the concentration of 5-HIAA and HVA in the cerebrospinal fluid of depressed patients. *Psychopharmacoligia*, 44, 287.

Knott, P.J. & Curson, G. (1972) Free tryptophan in plasma and brain tryptophan metabolism. *Nature*, 239, 452.

LeGuan-Bui, K.H., Plaisant, U., Leboyer, M. (1984) Reduced platelet serotonin in depression. *Psychiatry Research*, 13, 129-139.

Lingjaerde, O. (1983) The biochemistry of depression: A survey of monoaminergic, neuroendocrinological and biorhythmic disturbances in endogenous depression. *Acta Psychiatrica Scandinavica*, 67 (Suppl. 302), 36.

Malmgren, R., Arora, R.C., Olsson, P., Tornling, G. & Vnge, G. (1981) Defective serotonin transport mechanism in platelets from endogenously depressed patients. *Life Science*, 29, 2649-2658.

Meltzer, H.Y., Arora, R.C., Baber, R. & Tricou, B.J. (1981) Serotonin uptake in blood platelets of Psychiatric patients. *Archives of General Psychiatry*, 38, 1322-1326.

Mills, D.C.B. & Roberts, G.C.K. (1967) Effects of adrenaline on human blood platelets. *Journal of Physiology*, 193, 443.

Paul, S.M., Rehavi, M., Skdnik, P., Ballenger, J.C. & Goodwin, F.K. (1981) Depressed patients have decreased binding of tritriated imipramine to platelet serotonin transporter. *Archives of General Psychiatry*, 38, 1315-1317.

Sarrias, M.J., Arigas, F., Martinez, E. et al (1987) Decreased plasma serotonin in depression. *Biological Psychiatry*, 22, 1429-1438.

Scott, M., Reading, H.W. & Loudon, J.B. (1979) Studies on human platelets in affective disorders. *Psychopharmacology*, 60, 131.

Shapira, B., Lerer, B., Kindler, S., Lichtenberg, P., Gropp, C., Cooper, T. & Clev, A. (1992) Enhanced serotonergic responsivity following electroconvulsive therapy in patients with major depression. *British Journal of Psychiatry*, 160, 223-229.

Shaw, D.M., McSweency, D.A, Woolock, N. & Bevan Jones, A.B. (1971) Uptake and release of ^{14}C 5-hydroxytryptamine by platelets in affective illness. *Journal of Neurology Neurosurgery and Neuropsychiatry*, 34, 224.

Sheline, Y.I., Bardgett, M.E., Jackson, J.L., New comer, J.W. & Csernansky, J.G. (1995) Platelet serotonin markers and depressive symptomatology. *Biological Psychiatry*, 37 (7), 442-447.

Sneddon, J.M. (1973) Blood platelet as a model for monoamine containing neurons. *Progressive Neurobiology*, 1, 151.

Stecker,T., Ruggeberg-Schmidt,K. & Muller-Overlinghausen,B. (1993) Human platelet 5-HT2 receptor binding sites re-evaluated. J. Neural. Transm. Gen. Sect., 92(1), 11-24.

Subramanyam, S. (1975) Role of biogenic amines in certain pathological conditions. *Brain Research*, 87, 355.

Todrick, A. & Tait, A.C. (1969) The inhibition of human platelet 5-hydroxy tryptamine uptake by tricyclic antidepressive drugs : the relation between structure and potency. *Journal of Pharmacy & Pharmacology*, 21, 751.

Tuomisto, J. & Tukiainen, E. (1976) Decreased uptake of 5-hydroxytryptamine in blood platelets from depressed patients. *Nature*, 262, 596-598.

Wagner, A., Aberg-Wistedt, A., Asberg, M., Ekqvist, B., Martensson, B. & Montero, D. (1985) Lower ^{3}H-imipramine binding in platelets from untreated depressed patients compared to healthy controls. *Psychiatry Research*, 16, 131-139.

Wurtman, R.J. & Fernstrom, J.D. (1974) Effects of the diet on brain neurotransnitters. *Nutr., Rev.*, 32, 193.

P.K DALAL, MD, Associate Professor. NAROTTAM LAL, MD., Professor, J.K. TRIVEDI, MD, Professor, P.K. SÈTH, MSc., Ph.D, Director, A.K. AGARWAL, MSc., Ph.D, Scientist, ABDUL KHALID, MD, Senior Resident, Department of Psychiatry. K.G.'S Medical College, Lucknow-226003.*

Correspondence