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MURTHY RAO ORATION

DOPAMINE RELATED HORMONE LEVELS IN ACUTE SCHIZOPHRENIA
(A STUDY OF 84 PATIENTS)*

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SUMMARY

The functional significance of hypothalamo-pituitary axis as a neurohormonal link between endocrine glands and target organs is well established. It has also been demonstrated that three hormones of anterior pituitary viz. Prolactin (PRL), Lutenising hormone (LH) and Growth hormone (GH) have definite link with Dopamine (DA), the latter being implicated in the pathogenesis of schizophrenia. Radio immune assay technique was employed in estimation. Significantly low PRL level was found in majority of cases. However there was no significant correlation with effects of therapy or with L-DOPA administration. Similarly LH level was also found low indicating increased DA activity but the low level persisted even after therapy. GH level did not show any alteration in the patients, even when compared to different blood sugar levels and L-DOPA administration.

Introduction

The relationship between endocrine functions and psychiatric illnesses had attracted interest of both endocrinologists and psychiatrists for a long time. In the past, a number of psychiatric conditions were attributed empirically to endocrine abnormalities. The functional significance of hypothalmo-pituitary axis as a neurohormonal link between hypothalamus, anterior pituitary gland and target organs was demonstrated long back (Green et al. 1947). Recent advances in endocrine research techniques have helped substantially in gaining insight into possible biological etiology of so called functional psychiatric illnesses. It is known that endocrine functions are primarily controlled by the hypothalamus which is an integral part of the limbic system. The latter is implicated today as the prime seat for mental functioning and any abnormality in it is likely to produce psychiatric abnormalities. Neuro-endocrine evaluation is thus a rational probe into the functions of the limbic system.

It has been demonstrated by animal experiments as well as human studies that out of the six hormones of the anterior pituitary, at least three of them have definite link with dopamine (DA). They are: Prolactin (PRL), Lutenising hormone (LH), and Growth hormone (GH). Prolactin has inverse relation with dopaminergic activity as evidenced by its rise with DA block by antipsychotic drugs. DA is the release inhibiting factor for LH and the DA agonists stimulate the release of GH (Shaw et al. 82). Dopamine hypothesis still holds the pride of place in the possible etiological hypothesis of schizophrenia. The increased dopaminergic activity ought to reflect in the circulating levels of the hormones with which it is lined. Thus finding the levels of these hormones viz. prolactin, LH and GH would indicate the degree of dopaminergic activity in a schizophrenic. With this assumption the present project was planned.

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Material and Methods

The work was carried out in two large service hospitals, during 1982-84. Fresh patients of schizophrenia who met with the criteria (as below) of selection were entered into the study sample. Criteria were: (a) General: 1. They must be free from any drug for at least two weeks. 2. No evidence of any physical illness, particularly pointing to endocrinopathy. 3. They must be willing and cooperative enough to undergo various tests.

(b) Diagnosis: 1. Patients showing a number of Schneider's first order of symptoms or a combination with other characteristic symptoms were only included. 2. Two senior psychiatrists (one of whom being the author) must agree on the diagnosis. 3. Psychological tests viz. Rorschach's test and MMPI also corroborated the diagnosis. In all, eighty four patients satisfied the above criteria and constituted the study sample. Forty age matched healthy individuals, screened thoroughly to exclude any physical illness, were picked up from staff of the hospitals. Age range of the patient sample was 22 to 46 years, mean being 32.45 while that of control the mean was 30, range being 21 to 45 years.

All the subjects were in-patients, admitted fresh. Seven days passed before the study started and during this period, diagnostic and routine investigations were carried out. The schedule for the endocrine analysis was as follows:

Day 8: (i) Fasting blood was collected for estimation of GH, LH, PRL and blood sugar. (ii) Glucose tolerance Test (GTT) was performed using 100 gms glucose load. Blood samples were taken after 30, 60, 90, and 120 minutes for estimation of sugar as well as GH. Blood sugar and GTT were done as they are known to influence GH, hypoglycaemia being a stimulating factor.

Day 11: 2 tablets of L-DOPA were given to each patient and their blood was collected at 0.90 and 120 minutes. This was done to see further the effects of enhanced DA activity.

Antipsychotic drugs or convulsive therapy was not given before twelfth day of admission. The schedule of the endocrine tests was repeated again after (i) three weeks of starting therapy (ii) when clinical recovery was apparent at about twelve to sixteen weeks. For the control sample, the tests were not repeated.

Radio Immune Assay Technique (RIA) was employed for the analysis of hormones. Estimation of PRL, GH and LH were done by the method of Berson and Yalow (1964). Standards for all the hormones were made available by the courtesy of the National Institute of Health, USA. The labelled hormones for RIA were prepared in our own laboratory by the method of Greenwood and Hunter (1963).

Results

Table 1
(Levels of PRL, LH and HGH)

| Subjects          | Mean & SE PRL ng/ml | Mean & SE LH IU/L | Mean & SE HGH ng/ml |
|-------------------|---------------------|-------------------|---------------------|
| Control           | 13.09 ± 0.95        | 12.10 ± 0.92      | 5.83 ± 0.59         |
| Patients Before therapy | 11.88 ± 0.69       | 6.05** ± 0.60     | 5.90 ± 0.60         |
| During therapy    | 12.61 ± 0.91        | 5.86** ± 0.53     | 5.75 ± 0.58         |
| After recovery    | 12.80 ± 0.16        | 5.69** ± 0.42     | 6.04 ± 0.61         |

* Indicate significance at 5.0% (p < 0.05)
** Indicate significance at 1.0% (p < 0.01)
### Table 2
*(GTT and simultaneous HGH Level)*

| Subject | Mean & SEM ± | F | 30 | 60 | 90 | 120 |
|---------|--------------|---|----|----|----|-----|
| **GTT** |              |   |    |    |    |     |
| Control | 82.80        | 95.70 | 101.05 | 90.60 | 77.00 |
| Patients | 73.33        | 108.33 | 105.55 | 96.11 | 90.00 |
| Before | 2.68         | 2.70 | 3.07 | 6.94 | 2.21 |
| During therapy | 79.33 | 104.89 | 102.33 | 85.22 | 78.50 |
| Mean & SEM ± | 3.33 | 12.43 | 6.70 | 7.89 | 12.40 |
| After | 82.22         | 105.00 | 105.90 | 92.78 | 80.00 |
| recovery | 3.16 | 5.83 | 6.03 | 6.23 | 5.66 |

| **HGH** |              |   |    |    |    |     |
|---------|--------------|---|----|----|----|-----|
| Control | 5.83         | 4.81 | 4.31 | 4.89 | 5.66 |
| Patients | 5.90         | 6.63 | 5.45 | 5.82 | 6.61 |
| before therapy | 0.59 | 0.32 | 0.29 | 0.32 | 0.29 |
| During therapy | 5.75 | 5.81 | 5.40 | 6.05 | 6.73 |
| Mean & SEM ± | 0.60 | 0.29 | 0.27 | 0.15 | 0.17 |
| After | 6.04         | 5.44 | 4.80 | 5.33 | 6.16 |
| recovery | 0.61 | 0.24 | 0.20 | 0.20 | 0.18 |

### Table 3
*(L-DOPA Effects on HGH and PRL)*

| Subject | Mean & SEM ± | HGH ng/ml | PRL ng/ml |
|---------|--------------|-----------|-----------|
| Control | 6.08         | 5.87      | 13.09     | 13.16    | 12.49 |
| SEM ± | 0.35 | 0.27 | 0.95 | 1.07 | 0.91 |
| Patients | 5.90         | 5.68      | 11.88*    | 9.45*    | 9.56* |
| before therapy | 0.60 | 0.14 | 0.57 | 0.69 | 0.68 |
| During therapy | 5.75 | 5.63 | 12.61 | 9.32* | 10.11* |
| Mean & SEM ± | 0.58 | 0.56 | 0.61 | 0.60 | 0.72 |
| After | 5.66         | 5.91 | 12.80 | 9.80* | 10.80* |
| recovery | 0.61 | 0.94 | 0.57 | 0.16 | 0.63 |
| SEM ± | 0.73 | 0.32 | 0.29 | 0.29 | 0.29 |

* Indicate significance at 5.0% level p < 0.05

### Discussion

Dopamine hypothesis is mainly dependent on two observations viz. (a) effect of DA agonists, mainly amphetamine, in producing and/or aggravating psychotic picture (b) antipsychotic drugs produce their effect by DA blockade. However, estimation of DA level of serum in vivo is not a certain method and hence estimation of prolactin (PRL) is utilised to indicate DA activity by virtue of its inverse relationship with DA. Today it is universally acknowledged that PRL response reliably reflects the DA blocking properties of neuroleptics (Kolkowska et al. 1975 and Wilson et al. 1975). For the last two decades, PRL is being used as a DA marker, rise of PRL level indicating positive response to therapy. While quite a few workers have found low level of PRL in schizophrenics, Gruen et al. (1978) did not find so; on the contrary they found either normal or slightly elevated PRL level in unmedicated patients. Our finding of significant low level of PRL in a large number of patients before therapy support the findings of majority of workers. Strangely, the mean PRL level did not show any significant rise with therapy, for which we do not find any ready explanation. It could be that dosage of neuroleptics was much lower than what is prescribed in the western countries. We normally do not have to go beyond 300 mg of Chlorpromazine or its equivalent, unless the condition of a particular patient demands so. However about the fourth of the patients did show significant rise though this is not reflected in the mean reading because three fourth of them did not show any significant rise. Another observation was the effect of L-DOPA administration, when reduction of PRL level became significantly more than control.
This would perhaps indicate the DA sensitivity of schizophrenics. Attempts to correlate PRL response with the activity of antipsychotic drugs and the clinical response remain still controversial. Meltzer and Fang (1976) had reported significant correlation while Gruen et al. (1978) were unable to find any such. In our study too there was no correlation because though clinical recovery was apparent in all the patients, PRL rise was not significant.

Of the three principal subgroups of DA distribution, viz. substantia nigra, nucleus accumbens and the arcuate nucleus of hypothalamus, the last group is believed to be responsible for the production of LH releasing factor (LHRF), which is a peptide, while LH release inhibiting factor has been identified as Dopamine. Serotonin stimulates production of PRL which in turn depresses LH level either directly or by suppressing LHRH secretion (Pilotte and Porter 1981). Recently it has been shown that LH is also under control of a dopaminergic pathway and will be influenced by DA blocking drugs (Shaw et al. 1982). It has also been shown experimentally that LH does influence animal's behaviour also. If simple overactivity of DA system is the cause of schizophrenia, then we would expect a diminution of LH level in plasma. Our observations point out to this fact (table 1), where low level of LH was highly significant. However, the low level persisted even after therapy and also after apparent clinical recovery, when sufficient DA block presumably could have been achieved. This cannot be explained so simply. Possibly the same reason as in the case of PRL, viz. inadequate dosage of neuroleptics could have made the difference.

Growth hormone (GH) like other hormones of anterior pituitary, is under influence of many stimulatory and inhibitory mechanisms. As per present knowledge, it is stimulated by 5HT, dopamine and catechol receptors while inhibited by somatostatin and catechol receptors (Shaw et al. 1982). Hypoglycaemia is also known to stimulate its production and aberrations of GH production has been noted in a number of conditions like anorexia nervosa, post menopausal women etc. There are quite a few studies linking GH with schizophrenia; unfortunately the results are confusing. Syvalahti and Pekkarinen (1977) studied GH response to sleep in ten chronic schizophrenics and compared them with five epileptics. They did not find any difference. Day time agonist study by 0.75 mg apomorphine administration was done by Ettigi et al. (1976) in seventeen chronic schizophrenic and they compared them with twelve controls. Schizophrenics showed significantly low GH response. Tamminga et al. (1977), used L-DOPA as agonist in nine chronic schizophrenics and compared with twelve controls. They also noticed blunted peak GH response. However, Retrosen et al. (1979) found a bimodal distribution (some having high and some of them low) in GH response to apomorphine while Meltzer et al. (1981) found GH response higher in schizophrenics. In our patients GH level did not show any significant increase from normal control (table 1); thus influence of DA overactivity if any in them, did not materially affect the GH production. With varying glucose levels during GTT, GH did not show any significant variation either and L-DOPA also similarly did not affect its plasma level (tables 2 & 3). Patient population of present study were all acute cases in contrast to chronic cases studied by others.

The results of this study of the three dopamine related hormones do not give a clear picture of a simple increased dopaminergic activity. Some areas (prolactin and LH) are positive while GH is not. It appears that in the light of the recent
thinking of dividing the schizophrenics into larger and normal ventricular size groups and the positive/negative symptoms, a hormone study needs to be supplemented with clinical scrutiny as well as CT scan.

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