

## CONCENTRATIONS OF HOMOVANILLIC ACID AND GONADAL HORMONES IN THE SERUM OF MALE SCHIZOPHRENIC PATIENTS

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### SUMMARY

*The concentrations of serum homovanillic acid (HVA), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone (T) were examined in 20 male schizophrenic patients not taking neuroleptic drugs, 44 treated with neuroleptic drugs, and 15 male healthy control subjects. Kurskal-Wallis analysis of variance showed no significant difference among the three groups in serum HVA, FSH, LH or testosterone although high concentrations were found in the patients not taking neuroleptic drugs. There was a significant positive correlation between serum HVA and FSH in the patients not taking neuroleptics. The present results suggest that the change of gonadal hormones may be related to the pathogenesis of schizophrenia.*

### INTRODUCTION

Schizophrenia usually starts in adolescence (Hemmings, 1986) and the clinical manifestations differ somewhat between male and female patients (Goldstein & Link, 1988), so that an abnormal activity of the gonadal system may be involved in the pathogenesis of schizophrenia. The concentrations of testosterone (T), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the circulation have been reported in schizophrenic patients as compared with healthy control subjects, but the conclusions seem to be inconsistent. Several authors have reported that there are low levels of serum testosterone, LH and FSH in schizophrenic patients (Brambilla et al, 1975; Johnstone et al, 1977). Ferrier (1982) reported that there was no overall abnormality in testosterone secretion but that there was a mean reduction in both FSH and LH in male chronic schizophrenic patients compared with those suffering from manic-depressive illness and with aged-matched control subjects. These data suggest the possibility of decreased gonadal activity in schizophrenia.

However, Tournay & Hatfield (1972) reported that the concentrations of serum testosterone were within the normal range in schizophrenia. Several investigators have reported high concentrations of gonadal hormones in the serum of schizophrenic patients (Brophy et al, 1983; Mason et al, 1988). The different findings may be related to neurochemical instability or heterogeneity in schizophrenia due to the regulation of the hypothalamic-pituitary-gonadal activity by the neurotransmitters, especially dopamine, in the central nervous system (Hashimoto & Kimura, 1987; Davison & Kuenzel, 1991).

In this study, we have simultaneously examined HVA, FSH, LH and testosterone in the serum of schizophrenic patients both on and off neuroleptic drugs, and healthy control subjects. The primary purpose was to explore the relationship between the activity of the pituitary-gonadal system and dopamine turnover, and between the levels of gonadal hormones in the circulation and the clinical state of the schizophrenic patients.

### METHODS

**Subjects:** Twenty male schizophrenic patients who had not taken neuroleptic drugs for at least three months, aged  $38.2 \pm 13.0$  years, 44 male schizophrenic patients who were taking neuroleptic drugs, aged  $35.0 \pm 10.3$  years, and 15 male healthy control subjects aged  $43.4 \pm 11.7$  years, came to the Schizophrenia Association of Great Britain, Bangor, North Wales, from all parts of the United Kingdom. These patients had been ill for 1.5 to 41 years since the onset of the illness or first admission to hospital. Their diagnoses were made by the psychiatrists who treated them initially, and confirmed when they came for interview and blood collection. They were divided into two groups, fairly well and actively ill, according to their clinical state at the time of the interviews (Wei et al, 1992). The fairly well patients included those who were in remission, or capable of full time work, or who were slightly psychotic; the actively ill patients included those who were not capable of work, or with visibly psychotic symptoms. No patients who were severely ill were included in this study. The neuroleptic drugs that these patients were taking included chlorpromazine, clozapine, flupenthixol, fluphenazine, haloperidol, pimozide, sulphide, thioridazine, trifluoperazine and zuclopenthixol, and the dose ranges were similar to those mentioned earlier (Wei et al, 1992). Some patients were taking more than one of these drugs.

**Blood sample collection and measurements:** All the volunteers travelled the day before blood collection and they did not eat from 22.00 hours of that day until the blood samples were taken the next morning. They were asked about their health and medical histories, including mental and physical illnesses, infectious diseases, as well as any drugs they were taking. They all signed the consent forms and remained sitting for 15 to 20 minutes prior to blood collection. Venous blood was drawn from the ante-cubital vein between 8:00 and 9:00 a.m. and cooled to  $2-4^{\circ}\text{C}$  immediately. The serum was separated by centrifugation at a speed of 2000 rpm at  $4^{\circ}\text{C}$  for 15 minutes, and aliquots of 0.5 to 1.0 ml were stored in a deep freezer at  $-45^{\circ}\text{C}$ ,

until they were assayed within 10 weeks after the blood samples were taken.

Serum HVA was measured by a high performance liquid chromatography (HPLC) with electrochemical detection, which has been described in a previous study (Wei et al, 1992). Serum testosterone, LH and FSH were determined by radioimmunoassay ( $^{125}\text{I}$ -RIA systems, Pharmacia Ltd, U.K.).

All samples were measured in duplicate and blindly. The Kruskal-Wallis one-way analysis of variance, a two-tailed t-test, and Pearson correlation were used for the analysis of the data.

## RESULTS

Kruskal-Wallis analysis of variance showed no significant differences among the three groups in serum HVA ( $H=3.54$ ,  $df=2$ ,  $p>0.1$ ), FSH ( $H=4.75$ ,  $df=2$ ,  $p>0.05$ ), LH ( $H=4.19$ ,  $df=2$ ,  $p>0.1$ ) and testosterone ( $H=4.03$ ,  $df=2$ ,  $p>0.1$ ).

Table 1  
Concentrations of serum HVA, FSH, LH and T in schizophrenic patients and control subjects.

Measurements	Drug-free		Drug-treated		Control	
	Mean	$\pm$ SD n	Mean	$\pm$ SD n	Mean	$\pm$ SD n
HVA (g/L)	10.4	$\pm$ 5.5 18	8.4	$\pm$ 3.4 44	8.6	$\pm$ 3.6 15
FSH (IU/L)	5.2	$\pm$ 2.1 19	4.6	$\pm$ 3.6 41	4.9	$\pm$ 2.0 15
LH (IU/L)	7.5	$\pm$ 3.3 18	6.0	$\pm$ 3.6 40	5.2	$\pm$ 2.2 14
T (nmol/L)	35.8	$\pm$ 14.3 20	29.2	$\pm$ 10.9 43	26.3	$\pm$ 14.3 14

A trend towards a higher concentration of serum HVA, FSH, LH and testosterone was found in patients not taking neuroleptic drugs than in those treated with neuroleptic drugs or in normal control subjects, but this was not significant (Table 1).

## DISCUSSION

The present results demonstrate that there appears to be an increased activity of the pituitary-gonadal system in patients not taking neuroleptic drugs. This may be related to dopaminergic activity, as serum HVA also increases (Table 1). Circulating HVA, as a major metabolite of dopamine, may partly reflect dopamine turnover in the brain, since about half of the HVA in circulation is thought to derive from this source (Sternberg et al, 1983), particularly under conditions of controlled diet and physical activity, which minimize exogenous or peripheral contributions to circulating HVA (Kendler et al, 1983).

There is evidence that dopamine stimulates the pituitary-gonadal system through a central pathway (Markaryan, 1983; Hashimoto & Kimura, 1987). Recently, Davison and Kuenzel (1991) reported that the increased dopamine in the median eminence showed an excitatory role in gonadotropin release at puberty. The present study indicates that the concentrations of serum FSH, LH and testosterone tended to be lower in the patients taking neuroleptic drugs than in those not taking them (Table 1). Similar findings have been described by other inves-

tigators (Brown et al, 1978; Riniers et al, 1988, 1989). These data support the possibility that the increase of pituitary-gonadal activity may result from the dopaminergic overactivity in schizophrenia.

However, dopaminergic overactivity is not sufficient to explain the etiology and pathogenesis of schizophrenia, although the dopamine hypothesis has been the most popular over the past three decades (Seeman, 1987; Reynolds, 1989). This is because neuroleptic drugs are not very effective in some cases (Bowers et al, 1984; Chang et al, 1990), and because low concentrations of dopamine metabolites, such as HVA, have been found in body fluids of some patients who were not treated with neuroleptic drugs (Van Kammen et al, 1986; Davidson & Davis, 1988). This is a possible reason for the difference in changes of pituitary-gonadal hormones in Schizophrenia.

On the other hand, there was a state-dependent trait in the neurochemistry of schizophrenia (Van Kammen et al, 1985). Davis et al (1985) reported that the concentrations of plasma HVA before treatment were highly correlated with the severity of the illness. However, we did not find a significant difference in the serum HVA between patients who were fairly well and those who were actively ill, in those who were either treated or not treated with neuroleptic drugs.

There was a significant positive correlation between serum HVA and FSH only in patients not taking neuroleptic drugs ( $r=0.55$ ,  $n=16$ ,  $p<0.05$ ). This finding suggests that both HVA and FSH in the circulation could be used as an index to assess dopaminergic activity in schizophrenia. It could, perhaps, be of importance in the diagnosis and treatment of schizophrenia.

## Acknowledgements

The authors wish to thank Dr. Harold Hillman, medical adviser, for the interviews with patients and for collecting the blood samples, and all staff of the Schizophrenia Association of Great Britain for their help in this study.

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