Eur Arch Psychiatr Neurol Sci (1984) 234 : 8-12

European Archives of Psychiatry and Neurological Sciences

Altered Interrelationship of Dopamine, Prolactin, Thyrotropin and Thyroid Hormone in Schizophrenic Patients

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Summary. Increased dopaminergic activity has been postulated to be one of the main causes of schizophrenia. To evaluate this hypothesis further, the interrelation between dopamine, prolactin, thyrotropin (TSH) and L-thyroxine was studied by determining their concentrations in the serum of ten acutely ill schizophrenic patients exhibiting distinct stages of process activity and ten healthy subjects. The level of dopamine was elevated in the sera of schizophrenic patients, whereas the levels of prolactin, TSH and L-thyroxine were decreased. On the basis of these results we hypothesize that 1. increased dopaminergic activity affects pituitary secretory function, and 2. decreased β-adrenergic activity may be a consequence of decreased thyroid hormone concentration in plasma.

Key words: Schizophrenia - Serum - Dopamine - Prolactin - Thyrotropin - L-Thyroxine

Introduction

The biological factors underlying the mechanisms of the etiology of schizophrenias are poorly understood. However, scrutiny of a number of hypotheses, based on experimental data, permit reasonable predictions toward understanding some aspects of this malady. The dopamine-related hypotheses (for a discussion of different hypotheses related to dopamine, see Wyatt et al. 1979) of the schizophrenias were founded on indirect pharmacological evidence in the thirties. They were based initially on the observation that psychosis occurred in non-schizophrenics after administration of the dopamine agonist amphetamine (Huber 1972; Haracz 1982). Some 25 years later these hypotheses were further supported by the development of drugs that blocked central dopaminergic transmission. These drugs possess antipsychotic properties that parallel their affinities to the dopamine receptors in the striatum. It is therefore not surprising that an intense search was launched to measure direct changes in dopaminergic activities at the cellular and molecular level.

Direct and indirect evidence for altered dopaminergic activity in schizophrenic patients has been obtained from estimations of dopamine and its metabolites as well as dopamine receptors in post-mortem brain specimens from schizophrenics. Farley et al. found increased concentrations of dopamine in the ventral septum of post-mortem brain specimens from schizophrenics (for review see Haracz 1982). Crow et al. (1979) detected a significant increase in the concentration of dopamine in some areas of corpus striatum, and Bird et al. (for review see Crow et al. 1979) in the nucleus accumbens of post-mortem brain specimens from schizophrenics. Of special interest are the findings of Mackay et al. (1982) who reported significant differences in the concentration of dopamine in the nucleus caudatus and nucleus accumbens of young schizophrenic patients compared to a control group of the same age and sex; however, differences were not observed between groups comprising a wide range of ages. Thus significant differences became apparent when age-matched controls were selected.

For obvious reasons direct estimates of dopaminergic activity in the brain are not possible. Indirect evidence for changes in transmitter activity in the brain may be obtained by the measurement of pituitary hormones in serum. It is known that the secretion of hormones from neurosecretory neurons is regulated by neurotransmitters, e.g. dopamine (for review see Reichlin 1981). Thus changes in dopaminergic activity may be expressed as changes in the output and/or concentrations of hypothalamic releasing factors/hormones and/or pituitary hormones with concomitant changes in the concentrations of hormones in serum.

Dopamine exerts a tonic inhibition on the release of hypothalamic thyrotropin releasing hormone (TRH), thyrotropin (TSH) (Martin et al. 1977; Quijada et al. 1973) and prolactin from the pituitary (Massara et al. 1976; Leblanc et al. 1976; Langer et al. 1978). In conformity with the dopamine hypothesis of schizophrenia some investigators found decreased concentrations of prolactin in the serum and plasma of chronically ill schizophrenic patients (Kleinman et al. 1982). Meltzer et al. (1980a) found higher prolactin levels in the serum of acute schizophrenic patients than in that of normal controls; serum prolactin tended to be lower in chronic schizophrenic patients. However, other investigators (Johnstone et al. 1977) failed to confirm these differences between chronic patients and controls. This apparent discrepancy may be due to differences in methodology especially in classifying subgroups of schizophrenia.

Very few investigators have concerned themselves with the hypothalamic-pituitary-thyroid axis in schizophrenia (Prange et al. 1979), although it is known that TRH occurs ubiquitously in the brain (Reichlin 1981) and may have mood altering properties (Loosen et al. 1980; Prange and Wilson 1972). TRH has pronounced influences on the brain; it modifies the release of catecholamines in the CNS (Bennet et al. 1983). On the other hand thyroid hormones increase the sensitivity of noradrenergic receptors (Whybrow and Prange 1981).

On the basis of these considerations the purpose of our paper is to propose a working hypothesis for explaining altered dopaminergic activity as evidenced by alterations in the con-

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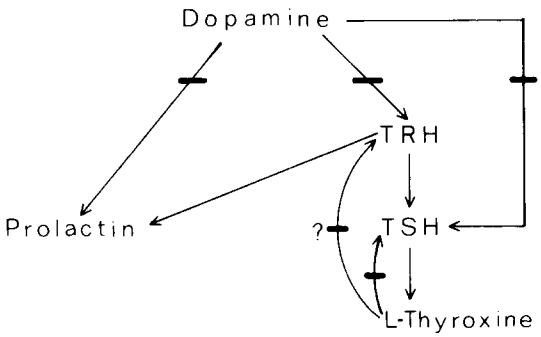

Fig. 1. Interrelationship between dopamine, prolactin, and the hypothalamic-pituitary-thyroid axis

centrations of hormones which in turn could play a causative role in the changes of receptor activity speculated to occur in schizophrenia. Thus we set out from the observations of pharmacological evidence (for review see Haracz 1982) that one of the causes for schizophrenia or a certain subtype of schizophrenia may be excess of brain dopaminergic activity. Increased dopaminergic activity inhibits the secretion of prolactin, TRH and TSH (Reichlin 1981) (Fig. 1). TRH is known to stimulate the release of TSH from the thyrotroph as well as that of prolactin from the lactotroph; thus decreases in the output of TRH will also cause a decrease in the release of TSH and prolactin. On the other hand, a reduction in the secretion of TSH will eventually lead to reduced concentrations of thyroid hormones.

The experiments were designed to test the possibility of altered concentrations of dopamine in schizophrenic patients using a highly sensitive method. The data were compared with those of age and sex-matched healthy subjects; furthermore prolactin, TSH and thyroid hormone were determined in order to investigate the existence of a possible interrelationship regarding the postulated increase in dopaminergic activity and decrease in the secretion of hormones.

Material and Methods

The patients were diagnosed independently for the purpose of the study by two psychiatrists. The diagnosis of schizophrenia was made according to the criteria of Schneider (1980). Ten acute schizophrenic patients (males) with different degrees of "process activity" took part in the study. The stages of "process activity" were differentiated according to the four different degrees described by Huber and Penin (1968; Penin et al. 1982). The main criteria underlying this classification are the substrate-close basic symptoms (Huber 1966, 1976, and 1983a) primarily present only during those brief episodes of schizophrenia in which a high degree of process activity prevails. Changes of biochemical and other somatic disturbances, e.g. in EEG, can be expected to reveal themselves only during these fluctuating and transitional stages of process activity, with more or less marked basic symptoms (Huber 1983a, and b). The mean age of the patients was 36 ± 14 years, all patients were drug free and gave consent to participate in this study. The control group comprised of ten males with a mean age of 24 ± 4 years.

The patients and subjects in the control group received a normal hospital diet which consisted of 80 ± 5 g of protein, 100 ± 5 g of fat, 220 ± 20 g of carbohydrate per day; 50% of the caloric intake was at noon. Neither the control group nor their families had a history of psychiatric illness; both groups were German males. They did not show clinical signs of endocrinopathies or other diseases, and their weight was in the normal range. During the study the patients and the control subjects pursued their normal activities. Blood was taken at 13:00, 16:00, 19:00, 23:00, 3:00, 7:00, 10:00 and 13:00 h from the antecubital vein after a resting period of 30 min. The blood samples were transferred to the laboratory and centrifuged for 10 min at 3000 g. One part of the serum was stabilized by the addition of EGTA (ethyleneglycol-bis (2-aminoethylether)−N, N, N'−tetraacetic acid) and glutathione (final concentration 6.1 and 4.8 mmol/l, respectively) and frozen at −82° C for the radioenzymatic determination of dopamine. Separate aliquots were stored at −28° C for the determination of hormones.

Determination of Dopamine

Dopamine was determined by radioenzymatic assay according to Peuler and Johnson (1977) using ^{3}H-S-adenosylmethionine and catechol-o-methyl-transferase. Rat liver catechol-o-methyl-transferase was partially purified according to Axelrod and Tomchick (1958). The animals were pretreated according to Brown and Jenner (1981) in order to reduce endogenous catecholamines and to improve the sensitivity of the assay. Standard curves of dopamine were carried out using buffer or steroid- and transmitter-free serum. The regression lines of both sets of curves passed through the origin and the two curves were superimposable; 10 pg of dopamine/ml could be differentiated from blank values ($P<0.05$). The intra-assay coefficient of variation was 24% ($n = 12$) and the inter-assay coefficient of variation 24% ($n = 7$). Each series included an internal quality control sample the assay of which indicated good reproducibility of the method.

Determination of Hormones

Prolactin was determined by radioimmunoassay using anti-prolactin rabbit antibody which was precipitated with anti-γ-globulin rabbit antibody. The intra-assay coefficient of variation was 5%, and the inter-assay coefficient of variation 8%.

TSH was determined by double antibody radioimmunoassay. The antibody was obtained by immunization of sheep and contained HCG (Marschner et al. 1983). The kit was calibrated according to WHO-standard 68/38, and the sensitivity of the assay was 0.19 μU/ml. The intra-assay coefficient of variation was 2.0%, the inter-assay coefficient (from 5 day to day determinations) was 8.5%.

L-thyroxine was determined using a specific anti-thyroxine rabbit antiserum which was produced against an L-thyroxine-BSA conjugate. Cross reactivity with L-triiodo-thyronine was <1%. The intra-assay coefficient of variation was 1.5%, the inter-assay coefficient of variation 4.5%.

Statistical Analysis

The results were evaluated using the Student's *t*-test for comparing the results obtained in sera of patients with those of the control group. Regression analysis was performed on relevant data.

Results

In an attempt to study the interrelationship of neurotransmitters and hormones in schizophrenic patients and healthy

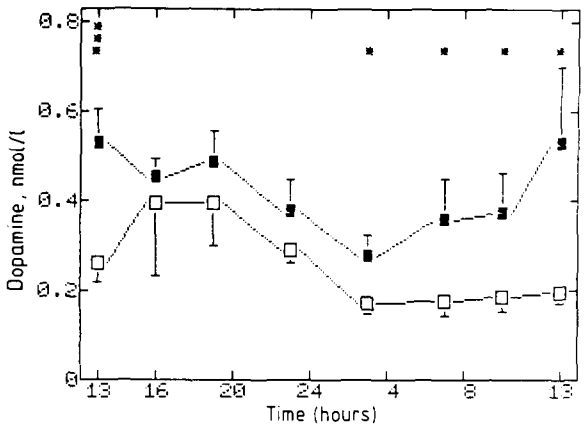

Fig. 2. Temporal pattern of the concentrations of dopamine in schizophrenic patients (males; ■) and healthy male subjects (□). Each value is averaged from ten subjects. The symbols represent the mean, and the vertical bars the standard error of the mean; *** denotes $P<0.01$; ** $P<0.05$, and * $P<0.1$

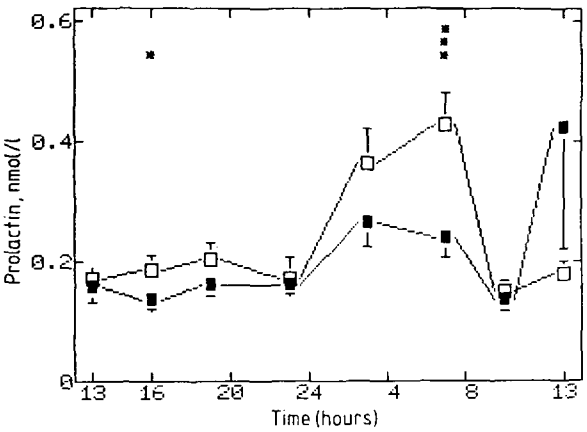

Fig. 3. Temporal pattern of the concentration of prolactin in schizophrenic patients (males; ■) and healthy male subjects (□). For details of this and the following Figs. refer to legend of Fig. 2

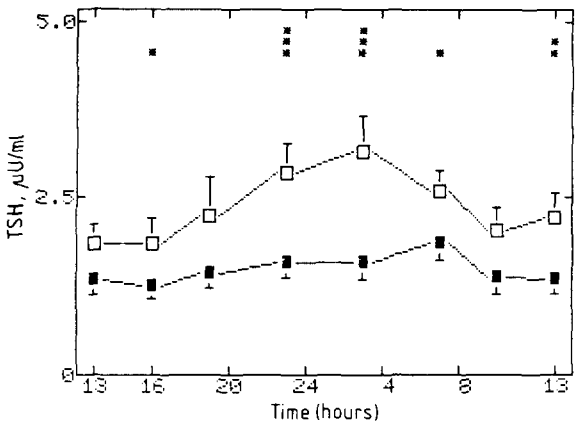

Fig. 4. Temporal pattern of the concentration of TSH in schizoprenic patients (males; ■) and healthy male subjects (□)

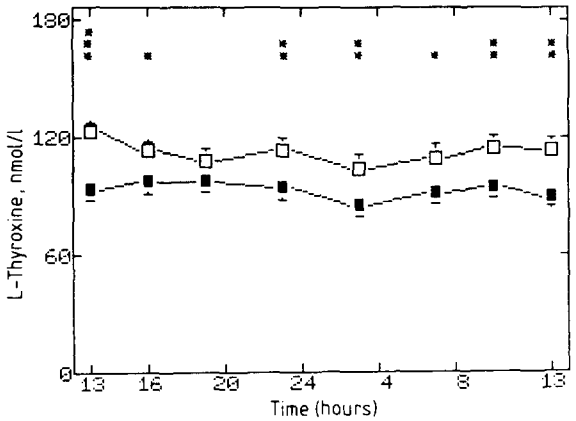

Fig. 5. Temporal pattern of the concentration of L-thyroxine in schizophrenic patients (males; ■) and healthy male subjects (□)

controls, dopamine, prolactin, TSH and L-thyroxine were determined in serum of these subjects. To account for the periodicity of these agents blood was taken eight times during a period of 24 h as indicated in Figs. 2–5.

The concentrations of dopamine in the control group remained generally low between 3:00 and 13:00 h (Fig. 2). They showed a tendency to rise in the afternoon; peak values were observed between 16:00 and 19:00 h. The profile of dopamine of the patients began to rise after 3:00 and reached maximum values between 13:00 and 19:00 h. The concentrations of dopamine showed a tendency to be elevated between 3:00 and 13:00 h ($P<0.1$; $P<0.01$ at the first 13:00 h blood sample) compared to those of the controls.

Concomitant with low concentrations of dopamine during the night, in the serum of the control group (Fig. 2) a rise in prolactin was observed between 3:00 and 7:00 h (Fig. 3). The schizophrenic patients exhibited similar baseline values of prolactin between 13:00 and 23:00 h as those of the control group. However, the rise of prolactin early in the morning between 3:00 and 7:00 h was less pronounced in patients compared to that of the control subjects ($P<0.01$ at 7:00 h). The steep increase of prolactin in patients observed at the second 13:00 h point was not significant ($P>0.05$). It was attributed to the surge in the concentration of the hormone of one patient and may be due to stress; it has been pointed out before (Kleinman et al. 1982) that collection of blood could be a source of stress which may cause increases in prolactin levels in approximately 3% of the patients.

The concentration of TSH in control subjects remained generally low during daytime (between 10:00 and 16:00 h; Fig. 4). At 19:00 h a tendency to rise was noted; peak values were attained at 23:00 and 3:00 h. Similar results have been obtained by Patel et al. (1972). The values in patients remained lower throughout the entire 24 h than those of the controls ($P<0.01$ at 23:00 and 3.00 h) with only a slight increase toward 7:00. Peak values were not detected.

The 24-h profile of L-thyroxine in control subjects was without marked elevations (Fig. 5). It has been shown before that serum L-thyroxine does not exhibit a circadian rhythm. Similar results were obtained from serum of patients examined for the existence of circadian variations. The concentrations of L-thyroxine in patients also indicated generally lower hormone concentrations during the entire day ($P<0.05$) as compared to controls.

Discussion

There is only direct evidence supporting increased dopaminergic activity in schizophrenic patients. We felt that increased

dopaminergic activity may be expressed as a change in the concentrations of pituitary hormones in the periphery. Using a sensitive assay method to measure dopamine in serum, it was also found that concentrations of dopamine were elevated in schizophrenic patients. These findings agree with earlier results of Fujita et al. (1978) and Meltzer et al. (1980b) who proposed that the elevation of dopamine was due to a decrease in the activity of dopamine-β-hydroxylase, an enzyme that catalyzes the conversion of dopamine to noradrenaline. Both research groups based their diagnosis of schizophrenia on Schneider's criteria and on the Research Diagnostic Criteria (RDC) which also rely to a major extent on that of Schneider. Our classification system (Huber 1981; Huber et al. 1979) is also based on the criteria of Schneider.

It is known that increases in the concentration of dopamine have an inhibitory influence on the secretion of TSH and prolactin (Reichlin 1981). During the period of low basal concentrations of dopamine a rise in the concentration of prolactin was observed in the control group. One may speculate that high concentrations of dopamine in patients might be the cause of lowered concentrations of prolactin during the same time. Differences between patients and controls were found in blood samples taken early in the morning ($P<0.01$); this may account for the discrepancy with other studies that do not show differences between patients and the control group (Johnstone et al. 1977) when sampling was carried out during the daytime.

The postulated inhibitory influence of dopamine on the secretion of pituitary hormones (Reichlin 1981) is seen in this study, and the secretion of TSH appears to be strongly affected in schizophrenics. The rise in the concentration of TSH in the control group during the night is practically absent in the patients. On the other hand the low concentrations of TSH in schizophrenic patients might also have been due to increased concentrations of serum L-thyroxine, since thyroid hormones mediate the feedback regulation of TSH secretion (Ingbar 1981). However, a close inspection of the data (Fig. 5) reveals lower levels of L-thyroxine ($P<0.05$) in schizophrenic patients as compared to controls, which is an obvious discrepancy considering the feedback regulation mechanism.

Low levels of thyroid hormone have been shown to lead to a down regulation of the number of β-adrenergic receptors (Banerjee and Kung 1977; Ciaraldi and Marinetti 1977; Hoffman and Lefkowitz 1980). In this connection Whybrow and Prange (1981) and Smith et al. (1972) have speculated that modulation of the β-adrenergic receptor response to catecholamines by thyroid hormones may be the cause for lowering the threshold for depression in hypothyroidism. Since thyroid hormone binds to numerous structures in the brain (Thierry et al. 1973; Berger et al. 1974) and modulates noradrenergic neurons in the cortex, decreased levels of the hormone may lead to a deficiency in the function of the brain noradrenergic system (Hartmann 1976) which may account for some of the improper functioning of the feedback processes in schizophrenic patients.

Acknowledgments. We gratefully acknowledge Henning Berlin for providing the RIA testkits for the determination of TSH and thyroid hormone.

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Received September 16, 1983