NEUROENDOCRINE INVOLVEMENT IN THERAPEUTIC MECHANISMS OF NEUROLEPTIC 
AND ANTIDEPRESSANT DRUGS: STUDIES OF THYROID AXIS

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SUMMARY

Sixty-five depressed and 33 paranoid hallucinatory patients were investigated longitudinally for one year to assess short- and long term therapeutic outcome with antidepressant and neuroleptic drugs, respectively. The patients' thyrotropin (TSH) response to thyrotropin releasing hormone (TRH) was studied at admission, during inpatient treatment and at discharge. Decreased TSH responses at outcome, and normalisation of these pathological responses during treatment were associated with the highest chance for recovery. TSH responses which persisted blunted at discharge were associated with a higher relapse rate during the one year following. It is hypothesized that the blunted TSH response may reflect a nonspecific cerebral malactivation, which is disactivated by the therapeutic effects of neuroleptic and antidepressant drugs.

INTRODUCTION

It is widely recognised that modern psychotherapeutic drugs have revolutionised concepts and treatments in psychiatry. However, little is known about the biochemical mechanisms underlying the clinical response to antidepressant and neuroleptic drugs.

The study of the hypothalamic-pituitary-thyroid axis has, over the last decade, emerged as a major neuroendocrine strategy for the investigation of the biological basis of various psychiatric disorders and of the mechanisms of their therapy. In particular, much attention has been directed towards the thyrotropin (TSH) response to thyrotropin releasing hormone (TRH), first observed in
1972 to be diminished ("blunted") in a considerable portion of depressed patients before treatment (1) and widely replicated thereafter (2). Subsequent studies have revealed that this finding may be seen in quite different illnesses such as schizophrenia, alcoholism, chronic diseases and anorexia nervosa (2), suggesting that the possible clinical value of this neuroendocrine parameter may not be utilised to support the traditional diagnostic habits. Only a few studies have raised questions of concern for therapy, e.g. to examine the TRH-test for treatment outcome. It has been observed that the "disblunting" of a blunted TSH-response during therapy may predict successful outcome with antidepressants (3,4), neuroleptics (5) and ECT (3). The biological "meaning" and the mechanisms underlying this transient abnormality in the thyroid axis remain unclear. The blunted TSH-response has been thought to reflect a dysregulation on the hypothalamic level, possibly based on a serotonergic dysfunction (6). While this may be in line with other findings in depressive illness, the fact of its occurrence in a variety of neuropsychiatric illness and its similar alteration by psychotherapeutic drugs of different chemical classes points to a more general interpretation of the findings. In this paper, we report the results of our longitudinal studies in depressed and paranoid hallucinatory patients aimed at investigating the following questions: 1. Can the blunted TSH-response to TRH at admission predict outcome with antidepressant and/or neuroleptic drugs? 2. Is the blunted TSH-response to TRH also a good predictor of prophylaxis (long term outcome)? 3. Can various TSH-responses during therapy, with different associations with outcome, be identified? 4. How can the observation of the possible involvement of the thyroid axis in both, the pathogenesis and therapy of psychiatric syndromes, be formulated in a unified hypothesis?

MATERIAL AND METHODS

Patient population

The patient population consisted of 98 female patients who were evaluated on the psychobiological research ward of the department of psychiatry, University of Vienna. Sixty-five of them presented with a depressive and 33 with a paranoid-hallucinatory syndrome; by diagnostic criteria (ROC, 7) the former group was classified as major depressive disorder, whereas the latter was a mixed group of schizophrenic, schizoaffective and manic disorders. Patients with manifest cerebral-organic and medical illnesses were excluded from the study.

Study design

After admission, previous medication was withdrawn and oral diazepam (20-40mg/d) was given until the first TRH-test was done within one week. Thereafter depressed patients were treated with