THE HYPOTHALAMUS OF DEPRESSED PATIENTS

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Several systems in the human hypothalamus and its afferents (e.g. the locus coeruleus) appear to be involved in the pathophysiology of mood disorders. Abnormalities of biological rhythms and the effectiveness of light therapy in depression suggest that the suprachiasmatic nucleus (SCN), the clock of the brain, may be involved in the pathophysiology of depression. Increased activity of corticotropin releasing hormone (CRH) neurons has not only been implicated in the non-suppression of the dexamethasone suppression test, but also in symptoms of depression.

We recently determined the activity state of these peptidergic systems in the hypothalamus of patients with a mood disorder and found no differences in the number of vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) neurons in the SCN, only the nuclear diameter of the VIP neurons was smaller in depressed patients, suggesting a possible disorder of the entrainment system.

An increase was found in AVP-, oxytocin- and CRH neuron numbers in the paraventricular nucleus (PVN) as compared to matched control subjects. Also an increase was found in CRH-mRNA and AVP colocalization in CRH neurons in the PVN. These data are interpreted as activation of the oxytocin, AVP and CRH neurons in the PVN, that may, because of their central effects, be related to symptoms of mood disorders.

At present we are testing the involvement of the hypothalamus and the locus coeruleus, that innervates the PVN, in the pathophysiology of mood disorders by comparing Alzheimer's disease patients with and without depression. No differences were observed in the number of pigmented noradrenergic neurons in the locus coeruleus.

Brain material was provided by the Netherlands Brain Bank (coordinator Dr. R. Ravid).

THE DISRUPTION OF CORTICOSTEROID FEEDBACK IN CHRONIC STRESS

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Exogenous administration of corticosteroids results in a reduction in adrenal corticosterone secretion, pituitary ACTH release and pituitary POMC mRNA and hypothalamic CRH and AVP mRNAs. Chronic stress also results in increased plasma corticosteroids — but despite this, there is activation rather than suppression of the HPA axis. There is therefore a relative insensitivity to corticosteroid feedback. Further investigation of the hypothalamic response to chronic stressors suggests that the chronic activation of pituitary ACTH secretion is achieved by increased synthesis and release of arginine vasopressin rather than CRH from the hypothalamus. Indeed CRH is actually suppressed in the three models of chronic stress which we have studied

ALTERED HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL REGULATION IN INDIVIDUALS AT HIGH FAMILIAL RISK FOR AFFECTIVE DISORDERS

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A frequent sign of major depression is a disturbance of the hypothalamic-pituitary-adrenocortical (HPA) system. It is reflected by an increase in the secretion of cortisol and adrenocorticotropin (ACTH), a relative refractoriness of ACTH and cortisol to the suppressive effect of dexamethasone (DEX) and a blunted ACTH response to corticotropin-releasing hormone (CRH).

The dexamethasone suppression test is one of the most frequently used neuroendocrine tests to assess HPA-system function in depression, but its sensitivity is low. It has therefore been refined by combining it with a human CRH challenge. After pretreatment with 1.5 mg DEX (2300 h) followed by stimulation with 100 μg CRH at 1500 h the next day depressed patients show an increased ACTH and cortisol release. The level of this effect is dependent on the DEX dose in both patients and controls. In a recent dosage study with the DEX-CRH test (DEX pretreatment 0.75 mg; 1.5 mg; 3.0 mg) we found a linear dose-dependent ACTH and cortisol response, with higher ACTH and cortisol levels in depressed patients than in control subjects in comparable dosage groups. This suggests that the pathological DEX-CRH-test reflects a decreased central glucocorticoid receptor capacity in depression. The mechanism underlying is long-lasting disturbance of the HPA-system remains still unclear. Either early stressful life events or a genetically transmitted risk factor could play a major role. If the latter is the case this HPA disturbance could possibly be observed in healthy individuals with a high genetic risk for psychiatric disorders. Such genetic risk is likely among people with a first-degree relative who has a mood disorder.

Using rigid psychodiagnostic techniques, we screened 431 consecutively admitted inpatients with depression and identified 35 families with one or more high-risk probands. The results of the DEX-CRH test showed that the group of DEX-pretreated (1.5 mg; 2300 h) high-risk probands released more cortisol after stimulation with human CRH (100 μg; 1500 h the next day) than a control group, but less than a group of patients with an acute major depressive episode. A linear discriminant analysis identified 32% of the high-risk probands as showing cortisol response patterns indistinguishable from those of the depressed patients.

These findings support our hypothesis that a genetically transmitted risk factor reflected by a decreased corticosteroid receptor capacity leads to an HPA feedback disturbance that renders the at-risk individuals susceptible to developing an affective disorder.

S4. WHO ICD-10: Evaluation and evolution

Chairmen: JE Cooper, N Sartorius

VALIDITY STUDIES

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A classic paper, written by late Eli Robins and Sam Guze in 1970 — "Establishment of Diagnostic Validity in Psychiatric Illness: its Application to Schizophrenia" — cuts the Gordian knot of semantic wrangles about "disease entities" in psychiatry, by demanding that diagnostic concepts have construct validity. This required validators external to the defining criteria. The St. Louis pioneers grouped all the possible validators under three headings:

Concurrent validators (clinical features and biological measurements made during the episode)

Antecedent validators (demographic and genetic factors, personality and precipitating events)

Predictive validators (diagnostic consistency over time, deterioration, recurrences and response to treatment).

In this paper, the success of their strategy is reviewed, 25 years

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