Testing the Hypothalamic-Pituitary-Adrenal Axis

Control of the secretion of adrenal corticosteroids by the hypothalamic-pituitary system is effected by alteration in the release of corticotrophin (A.C.T.H.). Secretion of corticotrophin is normally subject to three variables, a person's nyctohemeral* rhythm, a feedback mechanism, and the response to stress. The nyctohemeral rhythm depends on the individual's sleeping habits and his exposure to light.[1] It results in cyclical changes of corticotrophin and therefore corticosteriod secretion, usually producing the highest circulating blood levels at about the time of waking and the lowest during the early sleep period. The feedback mechanism reduces secretion of corticotrophin when the level of circulating corticosteroids is inappropriately high and increases it when the corticosteroids fall. In response to physical or psychological stress the secretion of corticotrophin and corticosteroids increases greatly and can obliterate the influences of the 24-hourly rhythm and the feedback mechanism.[2,3] Available evidence suggests that these three variables act predominantly through the hypothalamus, which controls production of corticotrophin from the pituitary by secreting corticotrophin-releasing factor. It is on this physiological basis that the interpretation of tests of hypothalamic-pituitary-adrenal function depends.

Four main dynamic tests are available for investigation of a patient with suspected adrenal insufficiency secondary to pituitary or hypothalamic disease. They are the insulin-hypoglycaemia,[4] pyrogen,[5] lysine-vasopressin,[6,7] and metyrapone tests.[8] H. S. Jacobs and J. D. N. Nabarro[9] have recently compared their clinical value in a careful study of 102 patients with suspected hypothalamic-pituitary disease. Hypoglycaemia and the response to bacterial pyrogen stimulate secretion of corticotrophin only when the hypothalamic-pituitary system is functioning normally. Lysine-vasopressin appears to act both directly on the anterior pituitary, causing release of corticotrophin, and also non-specifically via the hypothalamus as a stressor, while metyrapone inhibits synthesis of cortisol and operates the feedback mechanism. Changes in circulating levels of corticotrophin can be measured directly by biossay[10] or radioimmunoassay,[11-13] or more conveniently indirectly by measuring circulating corticosteroid levels, provided the adrenal cortex has been shown to be normally responsive to corticotrophin. The response to metyrapone is monitored by measuring the changes in urinary 17-oxogenic steroids.

Jacobs and Nabarro[9] conclude that the insulin test is clinically the most valuable procedure, being safe, sensitive, and reliable, and less disturbing to the patient than tests using pyrogen or lysine-vasopressin, which gives little additional information. Furthermore, it allows simultaneous assessment of the ability to secrete growth hormone, and unlike the metyrapone test it answers the most relevant question: Can the patient respond adequately to stress?

A normal hypoglycaemia test indicates that the patient will respond adequately to stress and therefore does not require corticosteroid replacement, whereas an impaired response implies the need for replacement. This test is also valuable in corticosteroid-treated patients, since it indicates whether corticosteroid cover for surgery will be required.[14,15] The metyrapone test is being performed less often, because it merely tests the feedback system rather than the stress mechanism. It is both unreliable owing to its variable absorption[16] and inconvenient because it necessitates accurate 24-hour collections of urine, taking days rather than hours to perform. Jacobs and Nabarro found, as have others,[7] that some patients with clinical hypopituitarism showed an inadequate corticosteroid response to hypoglycaemia but a normal response to lysine-vasopressin, suggesting that the corticotrophin could be synthesized by the anterior pituitary cells but not released normally. This is of academic interest but of little practical importance. While the hypoglycaemia test may make the patient uncomfortable for a short while and should not be done in patients with epilepsy or ischaemic heart disease, it is at present the most acceptable diagnostic tool for assessing the adequacy of the hypothalamic-pituitary-adrenal axis.

The establishment of the differential diagnosis in a patient with Cushing's syndrome has been simplified since the introduction of radioimmunoassays for corticotrophin, for the detection of circulating corticotrophin suggests the presence of corticotrophin-dependent adrenal hyperplasia rather than an adenoma or carcinoma of the adrenal.[17] In such a patient resistance to adrenocortical suppression with high doses of dexamethasone (8 mg. per day or more), together with the absence of the classical "Cushingoid" clinical features, suggests that the source of the excessive corticotrophin is an ectopic tumour rather than the pituitary gland.[18] However, it must be remembered that the same features may occur in severe depressive illness.[3] It is of interest to note that three out of seven patients with untreated pituitary-dependent adrenocortical hyperplasia in the series of Jacobs and Nabarro had normal corticosteroid responses to hypoglycaemia, since it has been suggested that hypoglycaemia unresponsiveness may be a diagnostic feature of Cushing's disease.[19,20] This concept requires further study.

* Nyctohemeral, from Greek, pertaining to 24 hours, consisting of a day and a night.

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