Application of the Metopirone Test to Tumors in the Region of the Sella Turcica

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There have been a number of studies concerning the regulation of cortisol by the secretion of ACTH. In the tuber cinereum of the ventral hypothalamus there seem to be structures which respond to the concentration of cortisol in the blood. These are able to produce an increase in ACTH secretion when the cortisol level is reduced, and a decrease when it rises. This feed-back mechanism is, however, only one of the factors which regulate the secretion of ACTH. Everything that, in the endocrinological sense, is usually summarized by the word “stress” increases ACTH secretion. Painful stimuli activate the hypothalamus by purely neural mechanisms via peripheral nerves and the spinal cord. Immobilization stress activates the hypothalamus probably via the amygdala and stria terminalis. On the other hand, humoral substances liberated by tissue damage probably stimulate the hypothalamic secretion of ACTH directly.

In the central nervous system there are other mechanisms which inhibit the secretion of ACTH. The hippocampus-fornix system seems to be important in this connection and possibly also regulates the endogenous diurnal rhythm of cortisol production. It is now generally agreed that the link between the hypothalamus and the hypophysis is vascular and consists of the portal vessels. In the neurons of certain hypothalamic nuclei whose neurites connect with the first capillary network of the portal vessels in the median eminence, a substance, CRF (corticotropin releasing factor), is produced. This is probably a polypeptide closely related to vasopressin. CRF is transported via the portal vessels to the ACTH-producing cells in the anterior lobe of the hypophysis and contributes towards the production of ACTH.

The different links of this circuit provide a number of different possibilities for testing disturbances in the system, even in man. The ACTH test for increasing the activity of the adrenal cortex is well-known. On the other hand, if a cortisol-like preparation (e.g. dexamethasone) is administered exogenously, the cortisol production is suppressed. No such response is obtained when a lesion is present somewhere in the system represented by the hypothalamus, hypophysis, and adrenal cortex. However, this test is not suitable in hypo-function of the adrenal cortex. This is partly because the resultant suppression reduces the already low values, and analyses become difficult since low steroid concentrations cannot be determined with accuracy.

Liddle et al. suggested another method for studying the feed-back mechanism. By administering Metopirone® (methypyraron, SU-4885) the final stage in the cortisol synthesis in the adrenal cortex is blocked. The blood cortisol level then decreases, causing a stimulation of ACTH production and thereby an increase in steroid synthesis in the adrenal cortex up to the cortisol stage. If the feed-back mechanism is intact, a large increase in the urinary excretion of total 17-hydroxycorticosteroids is observed. If any part of the chain is damaged, no such increase occurs. The Metopirone test has now become a routine endocrinological method.

This method has been used in cases of tumors of the hypophysis by several authors, where it has been shown that a pathological result is sometimes obtained, but usually the response is normal. Some findings seem to indicate that the result obtained depends on the suprasellar distribution of the tumor. Other results have been confused by the fact that at the time of the test the patients had already undergone operation or roentgen therapy, or were taking anticonvulsive drugs.

There has been no systematic investigation of sellar tumors, whose size may influence different structures in the hypothalamic-hypophysial region. Neither is it known whether the hypothalamus is also essential for

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Material and Method

The original series drawn from the Neurological and Neurosurgical Clinics in Uppsala included 70 patients with tumors in the region of the sella turcica. For different reasons, 22 of these patients were excluded from the series, some because of difficulty in demarcating the tumor anatomically, or because the Metopirone test was unsatisfactory. In other cases current medication with corticoids or drugs acting on the central nervous system, such as anti-convulsants, phenothiazine derivatives or barbiturates, made the results difficult to evaluate, and these were also excluded from the series. A few of the patients were too ill or required immediate operation, and in these cases it was not possible to carry out the Metopirone test preoperatively.

Forty-eight patients thus remained and were used in the study; 40 of these were operated upon after the test. The diagnoses included chromophobe adenoma, meningioma, glioma, acromegaly, craniopharyngioma and metastatic cancer. The anatomical extension of the tumors and their influence especially on the hypophysis, hypophysial stalk and hypothalamus were ascertained by inspection of the skull x-rays and air-encephalograms (in most cases with tomography) and by the operative reports on those patients who had undergone surgery.

The Metopirone test was performed preoperatively according to the method described by Liddle et al. The urine was collected for 1 to 3 days, during which period no medication was given, and 4.5 gm. Metopirone were then given by mouth in six 4-hourly doses. The urine was collected during this period and the following 24 hours. The urinary 17-ketosteroids (17-O) were determined according to Vestergaard's modification of the Zimmermann and Callow procedure, and total 17-hydroxycorticosteroids (17-OH) according to the method of Birke et al. The normal lower limit for 17-OH was placed at 7 mg. per 24 hours, according to values we obtained from a large standard series.

If the 17-OH values did not rise by at least 10 mg. during the 24 hours in which the Metopirone was given, or the following 24 hours, the test result was regarded as abnormal. The 17-O-steroid excretion is not greatly affected by Metopirone, and no definite conclusions could therefore be drawn from these determinations.

Results

The results of the Metopirone tests are given in Table 1. On the basis of the test results, the cases have been divided into three groups, A, B, and C.

Group A. In 6 patients the initial 17-OH values were remarkably low (less than 5.1 mg./24 hours) and there was no response to the Metopirone. Two of these patients had suprasellar meningiomas, and the other 4 had chromophobe adenomas, all verified surgically (Fig. 1).

Group B. In 17 cases some increase in the 17-OH excretion was observed, but the increase was less than 10 mg./24 hours and was therefore regarded as abnormally low. However, the initial values lay above the lower normal limit (i.e. higher than 7 mg./24 hours) in no fewer than 10 of these cases. Eight of these 17 patients had chromophobe adenoma, 2 craniopharyngioma, 3 acromegaly, 3 suprasellar meningioma and 2 subfrontal glioma.

Group C. In 25 of the patients both the initial values and the response lay within the normal limits. Of these patients, 2 had suprasellar meningioma, 2 optic glioma, 2 thalamic glioma, 2 acromegaly, 1 metastatic cancer and 10 chromophobe adenoma. In addition this group included 6 patients with adenoma that had not been verified surgically (Fig. 2).

It is evident from Table 1 that the site of the tumor is of great importance in the response to the Metopirone test. Groups A and B, which showed no response or abnormally low response, included all 8 patients in whom the tumor exerted pressure on the anterior...