NOTE

Extra-Adrenal Action of Metyrapone upon Human Growth Hormone Secretion in Man

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Synopsis

Extra-adrenal action of metyrapone (Metopiron, SU-4885, CIBA) upon HGH and ACTH secretion was investigated in four control subjects and three patients with hypoadrenalism. The administration of metyrapone caused the increase in plasma HGH not only in control subjects but also in three patients with hypoadrenalism. Plasma ACTH levels following the administration of metyrapone increased in a patient with Addison’s disease and in an adrenalectomized patient due to Cushing’s syndrome. Metyrapone did not cause the significant change in blood sugar levels during the test period. Plasma cortisol levels fell rapidly for 2 hr and reached a plateau and then increased at 4 hr after metyrapone administration in control subjects. In three patients with hypoadrenalism, plasma cortisol levels were low at resting time and became lower to an undetectable level after the administration. All subjects complained of side effects, such as gastric pain, fatigue etc.

These findings demonstrate that there is an extra-adrenal action of metyrapone upon HGH secretion and suggest that metyrapone may stimulate directly the release of ACTH by the pituitary. Its action may not be mediated by glucose metabolism and cortisol metabolism, but may be a direct action on the central nervous system. Our experiment does not make clear whether a direct action of metyrapone on the central nervous system is a specific effect or not.

There is general agreement that metyrapone stimulates ACTH secretion through the mechanism of 11β-hydroxylase inhibition in the adrenals; namely, negative feedback mechanism.

On the other hand, Ganong and Gold (1960) suggested that metyrapone might stimulate ACTH secretion not only by the negative feedback mechanism but also by a direct action on the central nervous system.

Recently, several investigators (Hunter and Greenwood, 1964; Kunita et al., 1970; Bruno et al., 1971.) reported that a marked increase in HGH was observed following the oral administration of a high dose of metyrapone.

The present study shows that metyrapone has an extra-adrenal action as well as the inhibition of 11β-hydroxylase in the adrenals on HGH secretion.

Materials and Methods

Four control subjects (three normal healthy volunteers and a patient with diabetes mellitus), two total-adrenalectomized patients due to bilateral adrenal hyperplasia type of Cushing’s syndrome (a female adrenalectomized patient had been radiated to the pituitary area with 60Co ray) and a patient with hypoadrenalism were treated with 37.5 mg of cortisone acetate or 20 mg of hydrocortisone.

Two of the three patients with hypoadrenalism took the last administration of corticoid on the previous night of the test day and another (T.S.) took it at 6 a.m. on the test day.
They were given 1.0g or 1.5g of metyrapone (Metopiron, SU-4885, CIBA) orally at 9 a.m. on the test day.

Blood samples for the estimation of blood sugar, plasma ACTH, plasma HGH were obtained before the administration of metyrapone and at 30 min intervals for 4 hr following the metyrapone administration.

Plasma HGH was determined by radioimmunoassay using $^{125}$I-HGH and a double antibody precipitation technique (Schalch and Parker, 1964).

Plasma ACTH was kindly measured by Dr. Ichikawa, Keio University, Tokyo, using radioimmunoassay with a seleite absorption method (Gomi et al., 1969).

Plasma cortisol was determined by Rudd’s method (Rudd et al., 1963).

Blood sugar was determined with autoanalyser.

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![Graph showing responses of plasma HGH, cortisol, and blood sugar to metyrapone administration in 4 control subjects.](image-url)

Fig. 1. Plasma HGH, cortisol and blood sugar response to the metyrapone administration in 4 control subjects.
Results

1. Effects of metyrapone administration on plasma HGH, plasma cortisol and blood sugar in control subjects

In four control subjects, plasma HGH increases markedly following the oral metyrapone administration (Fig. 1). The peaks of plasma HGH levels were observed at 60, 90 or 120 min after the administration of metyrapone. A net increment range of plasma HGH were from 6.4 to 27.2 μg/ml.

Plasma cortisol levels decreased during the first 2 hr and increased at 4 hr following the metyrapone administration.

Blood sugar levels in a normal healthy subject and a patient with diabetes mellitus showed no significant change during the test period.

2. Effects of metyrapone administration on plasma HGH, ACTH, cortisol and blood sugar in two bilateral adrenalectomized patients due to Cushing's syndrome and a patient with Addison's disease treated with cortisone acetate

In a female adrenalectomized patient who had been radiated to the pituitary area with 60Co ray (5,600 R) and had been treated with 37.5 mg of cortisone acetate daily, plasma HGH response to the administration of 1.5g of metyrapone was observed slightly at 90 min (Fig. 2), although the increment of HGH in this patient was lower than that in two other patients with hypoadrenalism and control subjects.

In a male bilateral adrenalectomized patient who had been treated with 37.5 mg of cortisone acetate daily, plasma HGH level increased from 0 min to 90 min and reached 51.4 μg/ml and then returned to normal level at 3 hr following the metyrapone administration. His skin was very dark before treatment and this pigmentation became strong after adrenalectomy.

In this respect, it was expected that his plasma ACTH levels were very high, but his plasma ACTH levels determined by radioimmunoassay were very low and could not be detected at resting time. However, plasma ACTH level increased from 0 to 50 pg/ml 90 min after the metyrapone administration. It is suggested that the discrepancy between his skin pigmentation and his plasma ACTH level measured by radioimmunoassay might be caused by the secretion of short chain ACTH that had not immunoreactive property for the anti-ACTH serum used with ACTH radioimmunoassay at resting time.

Plasma cortisol levels were very low and plasma cortisol decrement to metyrapone was not clear, blood sugar levels did not change till 120 min following the metyrapone administration.

In a patient with Addison's disease who
had been treated with 20 mg of hydrocortisone daily, plasma HGH levels increased gradually from 30 min to 120 min and reached 40 mμg/ml. Plasma ACTH level was high at 30 min following the metyrapone administration and it increased about two-fold from 30 min to 60 min. Unfortunately we could not determine plasma ACTH level before metyrapone administration because of sample loss. Plasma cortisol levels were very low and no significant change of them was observed.

All subjects complained of side effects 60 min after the administration of metyrapone, such as gastric pain, fatigue etc.

**Discussion**

It is well known that ACTH and HGH secretions occur by various types of stresses, such as insulin induced hypoglycemia, lysine-8-vasopressin and bacterial pyrogen.

Recently, there are a few reports that metyrapone brings about HGH secretion. Since Chart et al. (1958), the action of metyrapone on the adrenals has been studied and its specific inhibition of 11β-hydroxylase in the adrenals has been elucidated. However, little is known about extraadrenal effect of metyrapone upon ACTH secretion. In the present study, an extraadrenal action of metyrapone has been demonstrated upon HGH secretion. In three patients with adrenal insufficiency, increased response of HGH was made following the oral administration of a high dose of metyrapone and in two of them plasma ACTH response to metyrapone occurred simultaneously with HGH increment.

These findings clearly demonstrate that there
is an extraadrenal action of metyrapone upon HGH secretion and that metyrapone may stimulate directly the release of ACTH by the pituitary.

Ganong et al. (1960) suggested that metyrapone might cause the release of ACTH by the pituitary in the experimental animals, but yet there is no proof of this finding in man.

Hunter and Greenwood (1964) reported an increment of HGH in plasma following a large dose of oral metyrapone, they found a rise of plasma HGH in only one subject after metyrapone administration and they suggested that it was related to a decrement of blood sugar.

On the other hand, an increment of blood sugar to metyrapone has been described by several authors. Kunita et al. (1970) suggested a possibility that metyrapone might affect glucose metabolism and/or transport, because the side effects of metyrapone were moderated by intravenous glucose infusion.

In our experiment, there was a slight change of blood sugar during a single dose of oral metyrapone test in control subjects and there were no increment of blood sugar in an adrenalectomized patient. We presumed that HGH and ACTH secretion to metyrapone might not be mediated by the change of blood sugar.

Burno et al. (1971) suggested that no significant response of HGH following the metyrapone administration could be caused by a nonspecific stress, because the only one out of nine investigated subjects presented intolerance symptoms. They emphasized that there was a negative correlation between the cortisol disappearance half-time and maximal HGH increment and thus they suggested that HGH secretion might be mediated through the plasma cortisol fall.

Our experiment showed that there was no significant change of plasma cortisol levels which were very low following the administration of metyrapone in two of three patients with hypoadrenalism, but in a patient to whom 12.5 mg of cortisone acetate was administered every 8 hours, plasma cortisol decreased rapidly after metyrapone. We suggested that the low concentration of cortisol in plasma might come to make HGH secreted easily under stresses and that the decrement of cortisol level in plasma might not cause the release of HGH at resting time itself.

Our present experiment does not clarify whether HGH and ACTH secretion after metyrapone administration is caused by nonspecific stress to the central nervous system or not, but it makes clear that HGH secretion is brought about by an extra-adrenal action by metyrapone and suggests that metyrapone may stimulate the release of ACTH by the pituitary directly.

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References