Concept of the Importance of Nutritional Status in the Regulation of Adrenal Androgen Secretion

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It is well known that in anorexia nervosa and during fasting the urinary excretion of adrenal androgens is decreased [1]. On the other hand obese persons frequently show increased urinary excretion, plasma levels, or production of adrenal androgens [2-4]. The cause of this relationship between nutritional status and adrenal androgen secretion is not yet fully understood [1, 2].

One main reason for this obscurity is to be seen in the fact that the mechanism of control of adrenal androgen secretion itself is also still a subject of investigation and controversial hypotheses abound. Adrenocorticotropic hormone (ACTH) is not always accepted as the only important modulator of adrenal androgen secretion [1, 2]. Pintor et al. [5] for instance argued an involvement of a yet unknown but frequently postulated cortico-adrenal-stimulating hormone in the increased adrenal androgen secretion seen in obese children. According to Adams [2] nutritional status may also play a direct role in the control of adrenal androgens, for example, by decreasing the synthesis of certain adrenal enzymes of androgen formation during severe food deprivation.

Studies in rabbits and rats clearly reveal that the capacity for adrenal androgen secretion is preferentially enhanced when the ACTH-dependent basal activity of the adrenal gland is increased due to chronic stress [6, 7]. And since increases in the ACTH-controlled adrenocortical function occur in obesity or disappear during fasting [8] an alternative explanation (summarizing hypothesis) is presented here, one which considers additional endocrine and metabolic events related to the nutritional status.

OBESITY

In human obesity elevated production rates of dehydroepiandrosterone (DHEA) [4] and dehydroepiandrosterone sulphate (DHEA-S) [4, 9], as well as increased blood levels of dehydroepiandrosterone [3, 5, 10] and its sulphate ester [9], have been demon-

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strated. These primarily adrenal androgens, dehydroepiandrosterone sulphate and dehydroepiandrosterone, are the principal contributors to urinary 17-ketosteroids [11], and renal excretion of 17-ketosteroids has frequently been found to be elevated or at the upper limits of the normal laboratory values in obese subjects [8, 12, 13]. Even a positive correlation between body weight and urinary 17-ketosteroids could be demonstrated in a group of patients with menstrual disorders [14]. However, Wild et al. [15] described an inverse relationship between plasma DHEA-S and body weight in women with hirsutism, acne, or oligomenorrhea. Also, normal DHEA-S serum concentrations have been measured in female obese subjects [11].

These latter results do not necessarily reflect a lowered or normal DHEA-S secretion, since circulating steroid levels may be more rapidly reduced by an elevated metabolic clearance rate (MCR). Indeed an increased MCR of DHEA-S has been observed occurring simultaneously with an elevated production rate of DHEA-S in obese female subjects [4]. As discussed by Grenman et al. [16] the net result of elevation of both factors (production and MCR) can be normal or even decreased serum androgen levels in obesity.

Since the MCR of cortisol is also increased in obesity [17, 18] and cortisol or 17-hydroxycorticosteroid plasma concentrations are found in the normal range [8, 16–18], the additional finding of an elevated cortisol secretion rate in obese persons [17–19] has been interpreted as an ACTH-mediated compensatory response of the adrenal gland to maintain normal concentrations of free cortisol in circulation [20]. As a consequence DHEA-S secretion should likewise be enhanced by the enlarged pituitary ACTH release [20]. This is in accordance with the above-mentioned observations of an enhanced androgen production in obesity.

So it is substantiated that obesity is associated with a kind of stress situation, which obviously is induced by an elevated catabolism of cortisol resulting in an ACTH-mediated rise in adrenal activity with consequent increased basal glucocorticoid and androgen output. The existence of an increased cortico-adrenal activity has also been suggested for obese children with elevated adrenal androgen secretion, however, the enhanced androgen output was attributed to an increased secretion of an adrenal androgen-stimulating hormone or to an enhanced adrenal sensitivity to this hypothetical hormone [5].

Adrenocortical overactivity reported in obese persons [17, 19, 21] has been reproduced in normal subjects who gained weight by overeating: the cortisol production rates were significantly increased after a weight gaining period lasting from 3 to 5 months and fell to normal values after return to the initial weight [18].

As suggested by Migeon et al. [17] an increase in the cortisol production rate may occur as a consequence of obesity or weight gain in order to adapt the adrenal gland, as well as the rest of the endocrine system, to the imbalance between energy intake and energy output. This view seems to be partly confirmed by findings revealing higher triiodothyronine (T₃) levels in patients with alimentary obesity than in normal weight controls [22–24]. First of all elevated serum levels j. clin. Biochem. Nutr.
of the metabolically active $T_3$ could induce an adaptation of the metabolism of obese persons to an increased energy input. This would explain, for instance, why subjects who gained weight by overeating [18] had to ingest more kcal/m² body surface area during the peak weight period of study than during the baseline period in order to maintain their respective weight. Secondly a rise in circulating $T_3$ concentrations is obviously the causal factor for the increase in the MCR of cortisol and thus for the nutritional stress seen in obesity, since thyroid hormones have been shown to stimulate microsomal $5\alpha$-reductase [25], an enzyme involved in the metabolism of androgens and cortisol [26]. Furthermore $T_3$ treatment has been shown to raise the MCR of cortisol [27].

It is suggested here that nutritionally induced stress (adrenocortical overactivity in obesity due to elevated $T_3$ levels) is responsible for the increased responsivity of DHEA to ACTH recently observed in obese women by Komindr et al. [3]. The responsivity of cortisol to ACTH is not altered in obesity [3].

Stress or an increase in the ACTH-controlled basal activity of the adrenal gland appears to enhance especially the androgen response to an acute trophic stimulation. This view is substantiated by findings of an increase in the capacity for DHEA-S secretion in rats with elevated adrenocortical function either, stressed by chronic food restriction [7] or by ACTH pretreatment [28]. Corticosterone or 11-desoxycorticosterone responses to ACTH or metyrapone stimulation, however, remained unchanged in these studies whether animals were submitted to preceding and/or lasting stress or not.

The importance of a chronically increased ACTH influence on the adrenal gland with respect to a preferential enhancement of the capacity to secrete adrenal androgens is also discernible in a study of Kolanowski et al. [6]. These authors found a drastically enhanced androgen production by rabbit adrenocortical cells stimulated with ACTH in vitro, when the cells were harvested from animals after a prolonged in vivo treatment with corticotropin. In vitro-stimulated androgen (DHEA-S, DHEA) to glucocorticoid (corticosterone and cortisol) ratios were markedly higher after ACTH pretreatment than without pretreatment.

While in rats an important nutritional factor (dietary restriction associated with severe hunger) has been shown to increase the ability of androgen secretion by affecting the adrenal function as a direct stressor [7], in humans nutritional influences seem to be more indirectly mediated by changes in the MCR of cortisol induced by an altered $T_3$ state. This can also be deduced from findings obtained in studies on fasting and anorexia nervosa.

### FASTING AND ANOREXIA NERVOSA

A marked decrease in DHEA serum levels without clear-cut changes in plasma cortisol was observed in obese children after weight loss [5, 10]. During short-term fasting a decrease in production and clearance of DHEA-S has been demonstrated in obese subjects as well as reduced urinary excretion of DHEA and total...
17-ketosteroids in normal and obese fasting volunteers (detailed literature references are given by Parker and Odell [1]). Urinary 17-hydroxycorticosteroid excretion is also reduced during a fast in obese persons [8, 17]. It is proposed that these changes are due to a normalization or rather a marked diminution of the metabolic clearance of cortisol under weight loss. This should result in a reduction of the ACTH-controlled adrenal state of function associated with a lowered secretion of both glucocorticoids and androgens. In such a way Anderson [29] has already explained the sharp DHEA-S fall occurring in hypothyroidism. One consequence of hypothyroidism is a drop in the clearance rate of cortisol [29]. Anderson concludes that the slowed glucocorticoid catabolism is the prime mover of the decrease in DHEA-S production. Under conditions of a subnormal MCR of cortisol the ACTH secretion and the secretory activity of the adrenals probably fall, since less ACTH is needed to maintain normal peripheral plasma cortisol levels [29].

A correspondingly reduced cortisol metabolism must likewise be assumed in fasting subjects, because during fasting, as well as in hypothyroidism, serum T₃ concentrations are clearly reduced [24, 30]. The importance of circulating T₃ levels in the metabolism of cortisol has been demonstrated in the “low T₃ syndrome” of patients with anorexia nervosa, in which T₃ administration restored the impaired glucocorticoid catabolism towards a normal cortisol half-life [27].

Taken together the lowered adrenal secretion of androgens and glucocorticoids in fasting subjects seems to be due to a T₃ drop-induced fall in the MCR of cortisol resulting in a lesser need for adrenal ACTH stimulation.

The decreased urinary excretion of DHEA, total 17-ketosteroids, and 17-hydroxycorticosteroids repeatedly but not regularly observed in anorexia nervosa (for literature references see [1, 27]) can be explained by the same mechanism as postulated for fasting, since plasma T₃ levels are likewise reduced [27, 31]. So the subnormal DHEA-S [32, 33] and DHEA [33] plasma concentrations found in anorexia nervosa patients suggest a fall in adrenal androgen production rate, which is obviously not balanced by an adequate decrease in the metabolic clearance of androgens.

The observation that women with anorexia nervosa—when studied at very low body weight—have reduced ACTH-stimulated serum responses of DHEA and androstendione [34] can be interpreted to be in harmony with our findings regarding DHEA-S secretion in rats [7] as the result of a lower basal activity of the adrenal cortex. However, one discrepancy between humans and rats concerning the effects of undernutrition becomes evident: the lower DHEA-S response to exogenously administered ACTH has been seen in the unstressed well-nourished rat; whereas increased capacity for DHEA-S secretion occurred in undernourished rats, which unequivocally reveal a parallel elevated adrenal activity. In this species stronger forms of dietary restriction are known to be associated with a marked chronic overactivity of the adrenal gland [35–37]. In human undernutrition rather the opposite is the case. Even in the impaired nutritional status due to anorexia nervosa, the ACTH-dependent adrenal activity, as reflected

by the urinary excretion of 17-hydroxycorticosteroids, has been found to be decreased [38], although this disorder is frequently connected with stress situations such as psychic tension and physical hyperactivity. Since under partial adrenal suppression (e.g., due to glucocorticoid therapy or developing hypopituitarism) the secretion of \( \Delta^2 \)-adrenal androgens is impaired to a greater degree than is the secretion of cortisol [1], circulating DHEA-S and DHEA as well as their responses to ACTH should likewise be reduced in a state of lowered adrenal activity due to undernutrition. This is in accord with the hormone measurements in anorexia nervosa mentioned above. On the other hand, if stronger forms of psychic and/or activity stress are persistently stimulating excessive ACTH release, the effect of the lowered cortisol metabolism resulting in a decreased adrenal activity should be compensated or overcompensated. Indeed, also normal [27] or even increased [39] cortisol production rates have been observed in patients with anorexia nervosa and furthermore, the elevated adrenal secretion clearly declines after only a small increase in weight when psychological and behavioural remission occurs under psychodynamically oriented psychotherapy [39].

Considering that severe stress situations may be present in anorexia nervosa it is thus intelligible why adrenal androgen (17-ketosteroid) excretion is not necessarily reduced in this disorder [27]. However, findings of decreased ACTH-stimulated adrenal androgen responses in anorexia nervosa obviously reflect a lowered level of basal activity of the adrenal cortex, which can not be markedly influenced by severe stress.

The significant increase in the ACTH-stimulated androgen reserve, found in anorexia nervosa patients after long-term weight recovery [34] appears to be the outcome of an elevation in the basal activity of the adrenal cortex. That is very likely due to an increased cortisol catabolism, which according to Boyar et al. [27] results from a rise in serum \( T_3 \) levels.

The importance of the nutritional status concerning \( T_3 \) formation becomes apparent from the finding of an increased ratio of \( T_3 \) to \( T_4 \), in response to parenteral nutrition in a group of chronically ill patients [40]. Also in the calorie deficient rat a decreased \( T_3 \) level occurs [41], however its effect on glucocorticoid metabolism seems to be overcompensated by the immediate stress that results from such a dietary regimen in this species.

CONCLUSIONS

It is evident that the nutritional status is one of the important factors indirectly involved in the regulation of adrenal androgen secretion. On the basis of the findings discussed in this review, and apart from individually varying intra-adrenal factors, which may influence the degree of adrenal androgen secretion, the following summarizing hypothesis is presented.

The magnitude of androgen responses to ACTH stimulation is determined by the existent level of the ACTH-controlled basal activity of the adrenal gland.
Changes in the latter modify the degree of the gland's capacity to secrete adrenal androgens. Even moderate increases and decreases in the basal state of adrenal activity, e.g. due to marked weight gain and undernutrition respectively, amplify or else diminish adrenal $C_{19}$-$\Delta^4$-steroid responses to an ACTH stimulus.

In human beings the nutritional status appears to exert its effect on adrenal activity and consequently on the capacity for adrenal androgen secretion via modifications of the MCR of cortisol, probably induced by an altered $T_3$ state. The $T_3$ state itself seems to be closely related to the nutritional status.

Studies in which a given basal state of adrenal activity has been altered due to obesity [3], glucocorticoid therapy [1], hypothalamic-pituitary disease [1], stress [7], or prolonged ACTH administration [6] additionally reveal that the steroidogenic response to ACTH, when expressed in relative amounts, is altered to a much greater degree with respect to androgens than it is with regard to glucocorticoids.

This difference in the secretory characteristics of androgens and glucocorticoids could also account for the impaired ACTH-stimulated DHEA-reserve occurring in combination with normal cortisol responses to ACTH in a variety of seriously ill patients, as reported by Parker et al. [42]. Since severe illnesses are frequently associated with low serum $T_3$ concentrations [30], a low $T_3$-induced slowing of cortisol metabolism can be assumed, which reduces the basal state of adrenal activity and subsequently results in a preferential decrease in the capacity to secrete adrenal androgens. The impaired adrenal androgen secretion found after medical stress or major surgery [1] may also be caused by decreased serum $T_3$ levels, since surgical stress lowers the plasma $T_3$ [43].

Taking all of the data into consideration there is obviously no necessity to propose a separate adrenal androgen-stimulating hormone, other than ACTH, in order to explain why in several physiological or pathological situations glucocorticoid secretion appears to be dissociated from adrenal androgen secretion.

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