

# The role of the hypophysis in the regulation of the daily rhythm of aldosterone secretion

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In 12 patients treated with prednisone for more than two months, the daily rhythm of aldosterone secretion was disturbed during treatment as well as in the first week after discontinuing the therapy. The secretion of aldosterone was at the lower limit of the normal range. The daily rhythm of aldosterone secretion became normal earlier than the rhythm of 17-hydrocorticosteroids, approximately at a time when ACTH secretion became normal. A shift in maximum aldosterone secretion from morning to the afternoon or evening hours was observed in eight patients as early as on the third day of dexamethasone administration.

A similar disturbance in the daily rhythm of aldosterone secretion was found in five of six patients with pituitary dwarfism.

The regulation of aldosterone secretion is of a complicated feed-back character. The role of the inhibitory factor is not played directly by the hormone level in the blood, but by changes in its biochemical composition, or by their effect on the circulation. Owing to this, some factors regulating the secretion of aldosterone have remained unclear. The renin-angiotensin system is generally considered the leading stimulating factor, while the role of ACTH and other hypophyseal trophic hormones is questionable; only the stimulating effect of ACTH during stress has been accepted together with its intensification of other stimuli [2, 5].

A study of aldosterone secretion in patients treated with prednisone showed some changes in the daily rhythm

[11]. We have therefore decided to study the importance of the hypophysis in the regulation of the rhythm of aldosterone secretion.

## MATERIALS AND METHODS

Three groups of patients were investigated.

1. Twelve children aged from 3 to 14 years were treated with prednisone for more than 2 months because of haematologic disease or idiopathic nephrosis. The initial dose was 40 mg/m<sup>2</sup> body surface or 2 mg/kg weight. These patients were examined during and 4 weeks after the therapy.

2. Eight patients who received dexamethasone in the usual dose for 3 days were examined before and on the third day of treatment.

3. Six patients with pituitary dwarfism who showed a serious disturbance of pi-

tuitary secretion. Three were operated upon to remove a tumour, and three represented a heavy form of idiopathic pituitary dwarfism with complete absence of trophic hormone secretion including ACTH.

Aldosterone was determined by gas chromatography with electron detector and an inner radioactive standard [10]. The daily rhythm of aldosterone secretion was studied in urine samples collected at 3-hour intervals, beginning at 6 a.m. The rhythm was expressed in percents of the daily secretion.

### RESULTS

Total daily aldosterone secretion decreased slightly during prednisone treatment ( $3.1 \pm 1.2 \text{ mg/m}^2/\text{day}$ ). Most values were at the lower limit of the normal range ( $6.4 \pm 3 \text{ mg/m}^2/\text{day}$ ) or closely below it. The daily rhythm was disturbed in all patients. In control children (N-16) aldosterone secretion was highest in the early morning hours, and between the 3rd and 6th, or between the 6th and 9th hour. In patients treated with prednisone (N-12) the curve was practically inverse: peak secretion was observed

in the afternoon or evening hours (Fig. 1).

The disturbance in the daily rhythm of aldosterone secretion persisted even after the therapy had come to an end, irrespective of the interruption being intermittent or sudden (N-8). Total aldosterone secretion in 24 hours also remained lower.

The daily rhythm of aldosterone secretion after prednisone therapy was investigated in 12 children. The tests were performed at 7 or 10-day intervals after the last administration of prednisone. All children showed a disturbance of the daily rhythm in the first week after termination of therapy. In 8 of 10 patients, the rhythm was disturbed even in the second week, and in 3 of 12 subjects also in the 3rd week after the end of treatment. Later examinations revealed normal aldosterone secretion.

During the 3rd or 4th week after conclusion of the treatment, daily total aldosterone secretion too became normal, with the maximum in the early morning hours. When subsequently dexamethasone administration was started, after 3 days aldo-

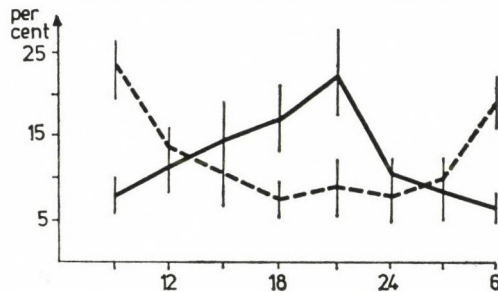


FIG. 1. Daily rhythm of aldosterone secretion in per cent of the total daily secretion: ———— control group (N = 16); ————— patients treated with prednisone (N = 12)



sterone secretion decreased from  $7.2 \pm 1.0 \mu\text{g}/\text{m}^2/\text{day}$  to  $3.7 \pm 1.3 \mu\text{g}/\text{m}^2/\text{day}$ , and the peak shifted to the afternoon hours, similarly as during prednisone therapy.

In patients with pituitary dwarfism, aldosterone secretion decreased insignificantly ( $4.5 \pm 2.7 \mu\text{g}/\text{m}^2/\text{day}$ ), but in 5 of 6 patients the daily rhythm was disturbed, with a shift of the peak to the afternoon or evening hours.

### DISCUSSION

In patients treated with prednisone or dexamethasone and in patients with pituitary dwarfism only a small decrease occurred in the daily secretion, in accordance with the literature. A more striking feature was the change in the daily rhythm of aldosterone secretion in all the three groups investigated. The change occurred as early as on the third day of dexamethasone administration. In patients treated with prednisone, the disturbance persisted for various periods from one to three weeks after the end of treatment up to a time when normal secretion of ACTH was expected according to data in the literature, although some authors observed normalization to take two months after the discontinuation of several years prednisone therapy [4, 6]. In our patients normalization occurred earlier as the treatment had been shorter.

Similar changes in the daily rhythm of aldosterone secretion were observed in most patients with pituitary dwarf-

ism. Our results thus support the view that the daily rhythm of aldosterone secretion is regulated prevalently by the action of ACTH, provided the supply of sodium is normal [7, 11].

The cause underlying the changes in the daily rhythm of aldosterone secretion is not quite clear. If we assume that the renin-angiotensin system is the directing factor, then the daily rhythm of the secretion should not change after suppressing pituitary secretion. The daily secretion rhythm of renin is almost parallel with the ACTH rhythm [3, 8]. In a previous study we have shown that an identical change in the secretion rhythm of aldosterone occurred even when renin secretion had been blocked by adrenergic beta inhibitors [11]. Therefore, the daily rhythm of aldosterone secretion seems to be regulated by a mutual interaction of two factors: renin and pituitary trophic hormones. If one of them is eliminated, the secretion of aldosterone is prevalently regulated by the salts comprised in the food.

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