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The Effect of Sodium Valproate in Cushing's Disease, Nelson's Syndrome and Addison's Disease

M. Reincke, B. Allolio, D. Kaulen, C. Jaursch-Hancke, and W. Winkelmann
II. Medizinische Universitätsklinik, Köln-Merheim

Summary. We investigated the effect of sodium valproate on plasma ACTH and serum cortisol concentrations in different pathological states of ACTH hypersecretion. Five patients with pituitary dependent Cushing's syndrome, two patients with Nelson's syndrome and five patients with Addison's disease were studied. Neither a single dose nor long term administration of sodium valproate resulted in a significant decrease of plasma ACTH levels in patients with Cushing's disease and Nelson's syndrome. Furthermore, the response of ACTH and cortisol to stimulation with lysine-vasopressin was unaffected during acute and chronic treatment. Patients with Addison's disease showed a slight attenuation of the ACTH response to lysine-vasopressin as compared to placebo but the difference was not statistically significant. In conclusion: sodium valproate does not appear to be effective in controlling ACTH hypersecretion in pituitary dependent Cushing's syndrome.

Key words: Sodium valproate cortisol ACTH – Cushing's disease – Nelson's syndrome – Addison's disease

Within the past decade selective transsphenoidal microsurgery has become well established as an effective treatment of pituitary dependent Cushing's syndrome [12]. However, if surgery fails to correct ACTH hypersecretion treatment with adrenal blocking agents or neuropharmacological agents is indicated [12]. In recent years sodium valproate, an anticonvulsant, has been shown to decrease plasma ACTH levels in Nelson's syndrome [5, 6, 9]. However, the efficacy of sodium valproate in pituitary dependent Cushing's syndrome remains controversial [1, 3, 4, 6, 10, 11, 13]. This study evaluates the effectiveness of sodium valproate in different ACTH hypersecreting states and investigates the site of its action.

Abbreviations: ACTH = Adrenocorticotrophic hormone; CRF = Corticotropin releasing factor

Patients and Methods

Five patients with pituitary dependent Cushing's syndrome, two patients with Nelson's syndrome and five patients with patients Addison's disease were studied.

Two of the patients with Cushing's disease had undergone bilateral adrenalectomy. In one of them was evidence of residual adrenal function from an adrenal remnant.

All patients received placebo on day one and 300 mg sodium valproate orally on day two at 9.00 a.m. Blood samples were collected for plasma ACTH and serum cortisol hourly between 9.00 a.m. and 1.00 p.m.

At 1.00 p.m. a lysine-vasopressin test was performed (5 IU vasopressin as a continuous infusion over 60 min). Blood samples were collected for cortisol and ACTH at 0, 15, 30, 45, 60 and 90 min after the start of the infusion.

In patients with Cushing's disease and Nelson's syndrome the effect of a long term treatment with sodium valproate was also evaluated. After day 2 the patients received 300 mg sodium valproate twice a day for four weeks. After four weeks collection of blood samples and lysine-vasopressin testing was performed as on day 1.

Plasma ACTH was measured bei RIA [2] after extraction with QUSO [16].

Serum cortisol was determined by standard RIA techniques using commercially available reagents (NEN, Dreieich, FRG). All samples from each subject were analysed in the same assay. Sta-

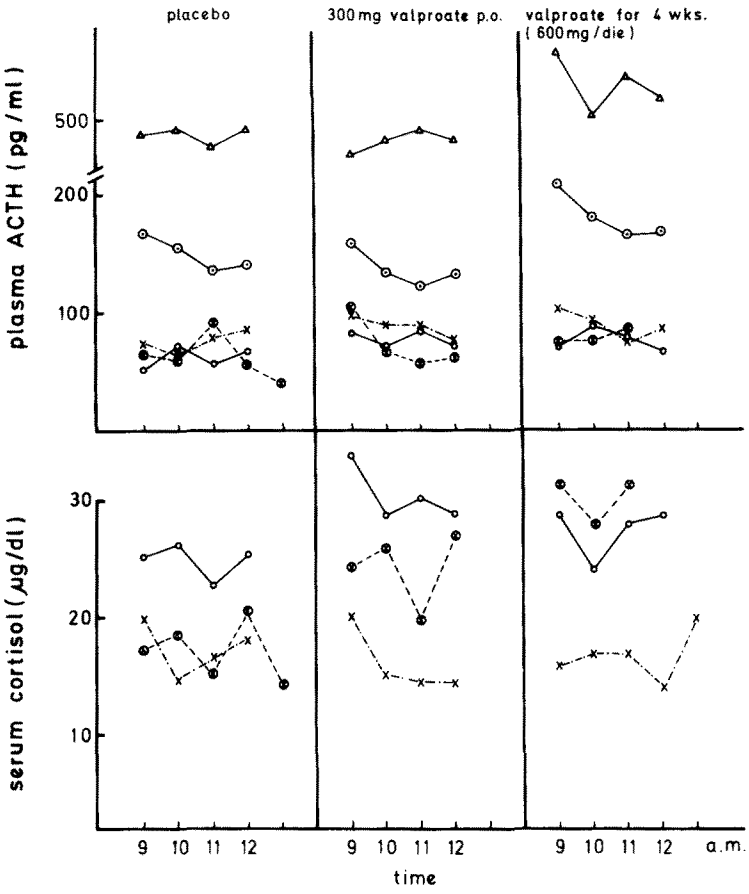

Fig. 1. Effect of sodium valproate on baseline plasma ACTH and serum cortisol concentrations in 5 patients with Cushing's disease

tistical analysis of the data was performed using Student's test for paired data.

Results

In none of the patients with Cushing's disease the ACTH and cortisol levels decreased after a single dose or after long term treatment with sodium valproate (Fig. 1).

In addition, the increase in the ACTH and cortisol concentrations in response to lysine-vasopressin administration was not attenuated by acute or chronic administration of sodium valproate as compared to placebo (Fig. 2).

In Nelson's syndrome we observed no effect on the baseline ACTH levels both during single dose and chronic sodium valproate administration. Furthermore no difference was found in the response of ACTH to lysine-vasopressin.

In Addison's disease the average rise of the plasma ACTH concentration in response to lysine-vasopressin after placebo was low (Fig. 3). After a single dose of sodium valproate an even lower response was found. However, this difference was not significant.

Discussion

Sodium valproate is a gamma-amino-butyric acid (GABA) transaminase inhibitor and raises GABA levels in the hypothalamus [14]. GABA, an inhibitory neurotransmitter, has been implicated in the control of CRF secretion from the hypothalamus [8]. Therefore it has been expected that sodium valproate may lower ACTH levels in Nelson's syndrome and Cushing's disease by increasing GABA levels in the hypothalamus and thus by inhibition of the CRF drive on the pituitary. In fact, in most patients with Nelson's syndrome sodium valproate has been reported to be effective in lowering plasma ACTH levels [5, 6, 9]. However, the results in pituitary dependent Cushing's syndrome are controversial. In our patients with active Cushing's disease plasma ACTH and serum cortisol levels did not decrease with single dose or long term treatment. This is similar to the experience of Loli et al. [13] and Ambrosi et al. [3]. However, clinical remission in Cushing's disease induced by sodium valproate has been reported occasionally [4, 10, 11] but these cases appear to be very rare. These inconsistend results may be explained by the fact

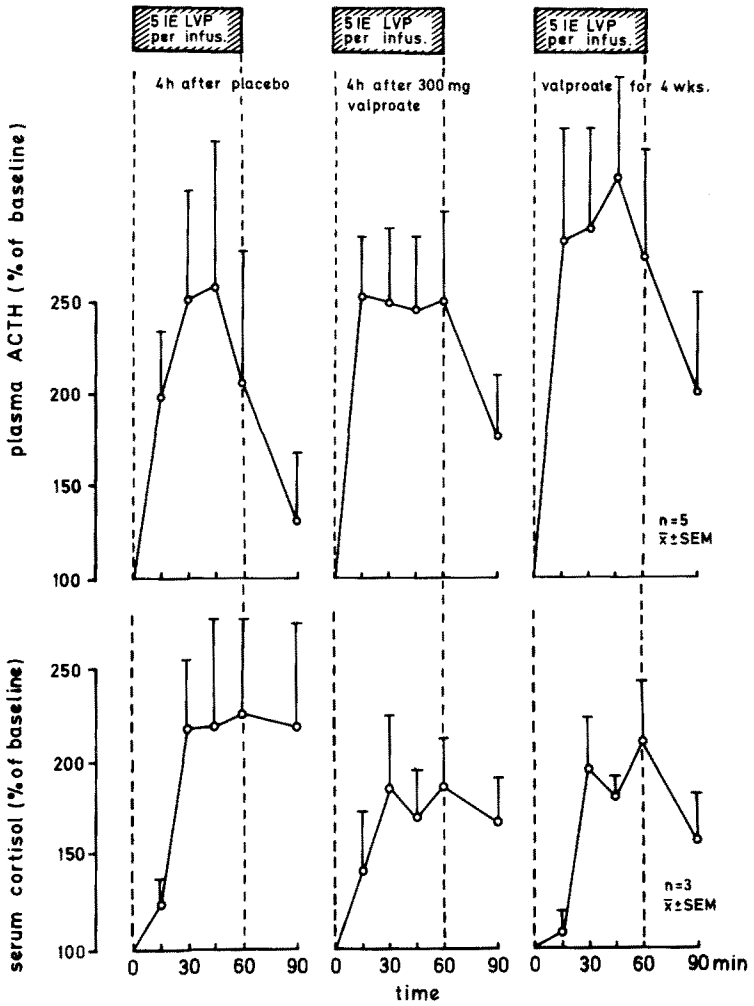

Fig. 2. Plasma ACTH and serum cortisol levels (baseline value = 100%) in response to lysine-vaspressin after placebo, after a single dose of sodium valproate and after long term treatment in 5 patients with Cushing's disease

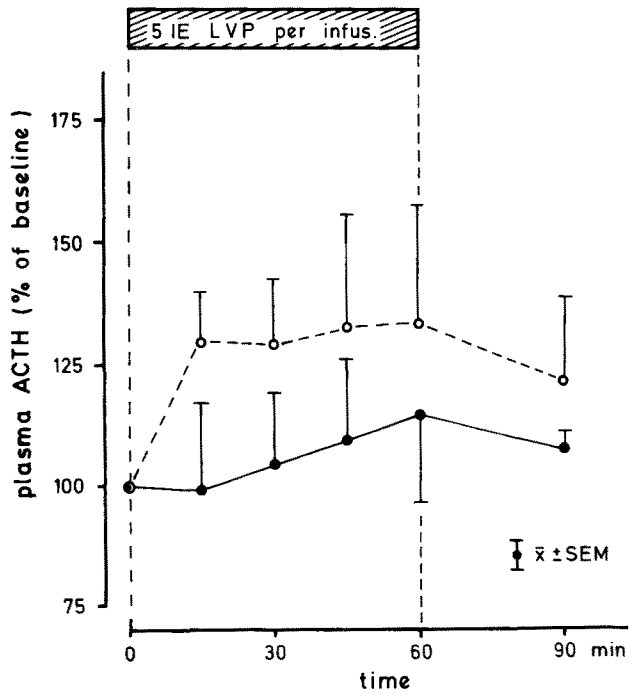

Fig. 3. Plasma ACTH levels (baseline value = 100%) in response to lysine-vasopressin after pretreatment with placebo (o——o) and with 300 mg sodium valproate (●——●) in 5 patients with Addison's disease

that in Cushing's disease the underlying disorder appears to be heterogenous. A hypothalamic origin with excessive CRF production resulting in ACTH hypersecretion has been postulated [15] but it seems to be a rare cause of Cushing's disease. The results of pituitary microsurgery are more in favour of a primary pituitary disease, since in most instances corticotropic adenomas can be removed [12]. However, even these micro- or macroadenomas seem to be heterogenous in nature [12] which might contribute to the heterogenous response pattern to sodium valproate in Cushing's disease.

Besides the hypothalamus GABA and its binding sites are also present in the human pituitary [7] indicating the possibility of a direct action of GABA on the pituitary. Nevertheless the present data, if at all, argues rather for a suprahypophyseal site of action. We found no significant inhibition of the ACTH response to lysine-vasopressin in patients with Addison's disease in whom generally the ACTH release is assumed to be sensitive to inhibitory agents. In case of a direct action on the anterior pituitary, a marked attenuation of the ACTH response to stimulation with lysine-vasopressin may be expected.

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Dr. Martin Reincke
II. Med. Universitäts-Klinik
Krankenhaus Merheim
Ostmerheimer Straße 200
D-5000 Köln 91