LETTER TO THE EDITOR

Activities of 21-hydroxylase, 17 α -hydroxylase and 17,20-lyase

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We read with great interest the article by Sadoul *et al.* (1) in the *European Journal of Endocrinology* entitled 'Apparent activities of 21-hydroxylase, 17 α -hydroxylase and 17,20-lyase are impaired in adrenal incidentalomas'.

The authors investigated the activities of 21-hydroxylase, 17 α -hydroxylase and 17,20-lyase activities and concluded that a combination of enzymatic deficiencies are often present in patients with adrenal incidentalomas. We agree with their statement and, on the basis of our experience, we would like to add some comments about this interesting issue.

Out of 115 patients with adrenal incidentalomas referred to our Institute, the deficiency of 21-hydroxylase was found in 66% of cases. Moreover, in a group of 35 patients who were more recently observed, the activities of 21-hydroxylase and 11 β -hydroxylase were studied. The patients (19 women, 16 men; age range 35–74 years) were diagnosed by MR or CT scans of the abdomen: bilateral lesions were present in 9 cases (26%), a figure in accordance with most published series. While 26 cases were classified as bearing 'non-functioning' lesions, we had the opportunity to study 9 patients with a 'subclinical' Cushing's syndrome, as previously defined (2–4). All patients underwent an adrenocorticotropin (ACTH) test (250 μ g i.v.) and serum 17-hydroxyprogesterone (17-OHP), 11-deoxycortisol (S) and cortisol (F) levels were measured at 0, 30 and 60 min. The stimulated 17-OHP/S, 17-OHP/F and S/F ratios were also calculated.

In agreement with the data by Sadoul *et al.* (1), who reported a reduced 21-hydroxylase activity in 65% of their cases and a high 17-OHP/S ratio in 2 patients, we found an exaggerated 17-OHP response after ACTH stimulation (i.e. 17-OHP rate increase_{(30–0)/30 min} >0.19 nmol/l/min) in a similar percentage (69%) of the 26 patients with non-functioning lesions. An elevation of 17-OHP/F ratio was present in 11 patients and of 17-OHP/S in only 2 cases. Ten of these eighteen patients (55%) also showed an 11-deoxycortisol net increase greater than that obtained in our control subjects (i.e. >13.3 nmol/l) and a high S/F ratio. This is in agreement with previous observations (5) and with the recent findings by Sadoul *et al.* (1). By contrast, in our experience no difference in the diameter of the adrenal lesion was found between patients with

normal and those with exaggerated peak S or 17-OHP levels.

One further comment is related to the results we obtained in the 9 patients with subclinical Cushing's syndrome: in all cases exaggerated responses of 17-OHP to ACTH were present, a figure that is markedly higher than previously reported (3). Interestingly, 8 of 9 patients also showed an increased 11-deoxycortisol rise after stimulation and an augmented S/F ratio was found in 7 cases. As far as the possible coexistence of an apparent impairment of 17,20 lyase activity, the 17-OHP/ Δ 4-androstenedione ratio was found to be elevated not only in the 21% of patients with non functioning incidentaloma, but also in one patient with subclinical hypercortisolism who also displayed an impairment of both 21-hydroxylase and 11 β -hydroxylase activities.

Thus, our findings are consistent with the deficiency of enzyme activities also in patients with subclinical Cushing's syndrome, in whom, besides the existence of autonomous cortisol secretion, an impairment of 21-hydroxylase and 11 β -hydroxylase (and occasionally of 17,20 lyase) may exist. Moreover, it is reasonable to argue for an intra-tumoral dysfunction of the steroidogenic pathways, as indicated by either the normalization of responses in operated patients or their persistence in patients with bilateral lesions (2).

In conclusion, we agree with the statement by Sadoul *et al.* (1) on the frequent combination of different enzyme dysfunction in adrenal incidentalomas; moreover, we believe that a complex dysregulation of steroid biosynthesis is a general phenomenon which can also be present in the presence of glucocorticoid autonomy. Further studies using molecular approaches are required in order to clarify such alterations of steroidogenesis.

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