

ACTH AND THE DEXAMETHASONE SUPPRESSION TEST IN DEPRESSION

ASHOK KUMAR JAINER¹, MUKUL SHARMA², J.K. TRIVEDI³,
C.G. AGARWAL⁴ AND S.C. TIWARI⁵

Hypercortisolemia, as measured by baseline serum cortisol levels (Carroll and Mendels, 1976) and abnormal response to dexamethasone suppression test (DST) (Carroll et al., 1981) is thought to characterize abnormal hypothalamic-pituitary-adrenal (HPA) axis functions in patients of depression. Whether adrenocorticotrophic hormone (ACTH) shows similar abnormalities is a matter of controversy. Whereas Nasr et al. (1983) and Roy et al. (1986) reported higher plasma ACTH levels in depressed patients as compared to controls. Fang et al. (1981) and Yerevanian and Woolf (1983) did not find such difference.

Reus et al. (1982), Kalin et al. (1982) and Holsboer et al. (1984) found that DST non-suppressor depressives had higher ACTH values as compared to DST-suppressor group. Nasr et al. (1983) have reported the opposite with DST-suppressors having a higher ACTH levels than controls. Recently Galard et al. (1991) found a trend toward greater baseline plasma ACTH levels in patients with endogenous depression than in those with non-endogenous depression and healthy controls. As pointed out by Pfohl et al. (1985) difference in study design could account for these disparate findings. To overcome some of these methodological shortcomings we carried out ACTH measurements both at baseline and post-DST time points in group of depressives and healthy controls.

MATERIAL AND METHODS

The study consisted of 20 admitted patients of Major Depression (DSM III-R criteria) (13 men, 7 women, mean age 32.3 years, range 20-50 years) and 5 medical controls (3 men, 2 women, mean age 32 years, range 22-50 years). The depressed patients had a mean total score of 26.8 (range 22-33) on Hamilton Psychiatric Rating Scale for Depression (Murphy et al. 1982), were medication free for atleast 7 days prior to inclusion in the study and were physically healthy. The controls were medical inpatients who did not have an illness which could have affected their cortisol or ACTH levels. They were medication free and had no evidence of current or past psychiatric illness.

Five ml blood was collected in all subjects at 8.00 A.M. on the first day in chilled EDTA tubes which were then immediately placed on ice and centrifuged within 30 minutes. The plasma thus separated was stored at -80°C until analysis. Subsequently the subjects were given 1 mg of dexamethasone at 11.00 p.m. and the next day 5 ml blood samples were drawn at 8.00 A.M. and 4.00 P.M. plasma was separated and stored according to the procedure described above.

The plasma ACTH was estimated by using RIA kit (ACTHK-PR) from Compagnie ORIS Industrie, S.A., France and serum cortisol by Amerlex RIA kit (code I.M. 2021) from Amersham International Plc., Amersham, U.K.

RESULTS AND DISCUSSION

We found that the basal values of both plasma cortisol and plasma ACTH were significantly higher in the depressed group as compared to controls. The values of the two hormones were however not different to significant extent when depressed patients were divided according to their DST-suppressor or non-suppressor status. Our observations are in conformity with the findings of (Asnis et al., 1981) for cortisol and Kalin et al. (1982), Sherman et al. (1982) for ACTH. Using 5 µg/dl criterion of Carroll (1981) as a cut off point we found that 8 depressed patients were dexamethasone suppressors and 12 dexamethasone non-suppressors. In both these groups however the ACTH post DX values were significantly higher ($p < .005$) than that of controls. The levels of post DX-ACTH was not significantly different in the DST-suppressor & non-suppressor group.

Our results which indicate abnormalities in plasma ACTH both before and after DST are in agreement with studies by Fang et al. (1981) and Yerevanian & Woolf (1983). It has been pointed out by Pfohl et al. (1985) that even in case of negative studies the findings indicate a trend in the predicted direction. These authors emphasize that since some depressed patients continue to show abnormally high level of ACTH despite abnormally high level of cortisol (a failure of normal feedback inhibition) it indicates abnormality in the HPA axis at or proximal to the level of pituitary.

Table- Pre and post DST plasma cortisol and ACTH levels in Depressed patients & Controls.

Subjects	N	Cortisol Base line	($\mu\text{g/dl}$) Post-DX	ACTH (Pg/Ml) Base line	Post-DX
Controls	5	6.9 \pm 2.8	3.3 \pm 1.2	46.6 \pm 4.9	24.2 \pm 3.2
Depressed patients					
Suppressors	8	10.2 \pm 2.8 ^c	3.25 \pm 2.9	76.5 \pm 7.3 ^b	73.2 \pm 6.9 ^b
Non-suppressors	12	15.2 \pm 3.4 ^b	12.5 \pm 3.9 ^d	79.6 \pm 5.6 ^b	75.25 \pm 6.3 ^b

a- Baseline & post DX plasma samples of controls.

b- Significantly different from value for controls ($p < 0.05$)

c- Significantly different from value for controls ($p < 0.05$)

d- Significantly different from value for controls and suppressors ($p < 0.05$)

Other explanations have been forwarded from time to time which could clarify the lack of correlation between ACTH & cortisol, or sometimes even negative correlation as reported by Fang *et al.* (1981) and Yerevanian and Woolf (1983). It has been suggested that cortisol differences between depressed patients and normal controls are mediated by other factors in addition to ACTH (Pfohl *et al.*, 1985). Saito *et al.* (1979) has suggested that dexamethasone may have direct inhibitory effect on the adrenal gland that is not mediated by ACTH. Furthermore animal based studies have shown that substances besides ACTH may stimulate or modulate cortico-steroidogenesis (Cunningham and Hobzwarth, 1988).

Since the exclusive role of ACTH in the regulation of cortisol secretion in human beings has been questioned the possibility exists that the biochemical alterations in depressed patients at the brain or pituitary could influence cortisol secretion through a peripheral site of action or through the autonomic innervation of the adrenal cortex.

REFERENCES

Annis, G.M.; Sachar, E.J. and Halbech, (1981). Cortisol secretion and dexamethasone response in depression. *Int. J. Psychiatry*, 150, 459-462.

Carroll, B.J. and Mendels, J. (1976). Neuroendocrine regulation in affective disorders. In: Sachar, E.J. (ed.), *Hormones, behaviour and psychopathology* New York: Raven Press, 193-223.

Carroll, B.J.; Feinberg, M.; Greden, S.F. (1981). A specific laboratory test for the diagnosis of melancholia. *Arch Gen Psychiatry*, 38, 15-22.

Cunningham, L.A. and Holzwarth, M.A. (1988). Vasopressin intestinal peptide stimulates adrenal aldosterone and corticosterone secretion. *Endocrinology*, 122, 2090-2097

Fang, V.S.; Tricou, B.J.; Robertson, A. and Metzger, H.Y. (1981). Plasma ACTH and cortisol levels in depressed patients: Relation to dexamethasone suppression test. *Life Sci.*, 29, 931-938.

Galar, R.; Gallart, J.; Catalan, R.; Schwartz, S.; Jose, M.; Arguello and Castellanos, J. (1991). Salivary Cortisol levels and their correlation with plasma ACTH levels in depressed patients before and after the DST. *Am. J. Psychiatry*, 148, 505-508.

Hobzwarth, F.; Doerr, H.G.; Gerken, A.; Muller, O.A. and Sippell, W.G. (1984). Cortisol, 11-deoxycortisol, and ACTH concentrations after dexamethasone in depressed patients and healthy volunteers. *Psychiatry Res.*, 11, 15-23.

Kalin, N.H.; Weller, S.J. and Shelton, S.E. (1982). Plasma ACTH and cortisol concentrations before and after dexamethasone. *Psychiatry Res.*, 7, 87-92.

Murphy, D.L.; Pickar, D. and Alterman, I.S. (1982). In: *Experimental and clinical Psychiatry* (Eds.) Burdick, E.L.; Sudilowski, A. and Gershon, S. N.Y.: M. Dekkar Inc., vol 7, 355-393.

Nasr, S.J.; Rodgers, C.; Pandey, G.; Altman, E.G.; Moises, F.; Gavista, F.N. and Davis, J.M. (1983). ACTH and the Dexamethasone Suppression Test in Depression. *Biological Psychiatry*, 18, 1069-73.

Pfohl, B.; Sherman, B.; Schlechte, J. and Winokur, G. (1985). Differences in plasma ACTH and Cortisol between depressed patients and normal controls. *Biol. Psychiatry*, 20, 1055-1072.

Reus, V.I.; Joseph, M.S. and Dallman, M.F. (1982). ACTH levels after the dexamethasone test in depression. *New Engl. J. Med.*, 306, 238-239.

Roy, A.; Gold, P.; Pickar, D.; Waknitz, O.M.; Chrousos, G. and Paul, S.M. (1986). Pre and post dexamethasone plasma ACTH levels in depressed patients and normal controls. *Journal of Affective Disorder*, 10, 95-99.

Saito, E.; Ichikawa, Y.; Mitsuo, H. (1979). Direct inhibitory effect of dexamethasone on steroidogenesis of human adrenal *in vivo*. *J. Clin. Endocrinol. Metab.*, 48, 861-863.

Sherman, B.; Pfohl, B. and Winokur, G. (1982). Dissociation of plasma cortisol and ACTH responses to dexamethasone in healthy subjects and depressed patients. *Clin. Res.*, 30, 722.

Yerevanian, B.I.; Woolf, P.D. (1983). Plasma ACTH levels in primary depression, relationship to the 24 hour dexamethasone suppression test. *Psychiatry. Res.*, 9, 45-51.