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Psychoneuroendocrine research in depression

I. Hormone levels of different neuroendocrine axes and the dexamethasone suppression test

Review Article

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Summary. Psychoneuroendocrinology is of major importance in the biological research of depression. Most studies have focussed on the regulation of the hypothalamic-pituitary-adrenal (HPA) axis but other endocrine systems such as the hypothalamic-pituitary-thyroid (HPT), hypothalamic-pituitary-somatotropic (HPS), and the hypothalamic-pituitary-gonadal (HPG) axis have also been shown to be involved in the psychobiology of depression. There are close interrelations between various endocrine axes which possibly are affected during depressive illness.

A variety of neuroendocrine abnormalities has been detected in depressive disorder but the pathophysiology of these derangements remains still unclear. Although the currently used neuroendocrine tests are not of diagnostic validity they may help to clarify the pathophysiological significance of the complex regulatory mechanisms of different neuroendocrine axes in affective disorders. Neuroendocrine regulation is determined both by peripheral and central mechanisms which both have to be adequately considered as well as potent interactions between various endocrine systems in further neuroendocrine depression research.

Keywords: Hormones; neuroendocrinology; dexamethasone; depression.

Introduction

Psychoneuroendocrine research holds an important place in biological psychiatry. The knowledge on this topic has expanded widely in recent years particulary concerning biological aspects of affective disorders. Moreover other diagnostic

entities such as schizophrenia, anorectic syndroms, alcoholism, Alzheimer's disease, etc. have been object to psychoneuroendocrine research. The present review aims to give an overview of some important neuroendocrine findings in the psychobiology of depression and to focus on some questions whose implications are currently discussed among psychoneuroendocrinologists.

The dexamethasone suppression test (DST) in depression

The dexamethasone suppression test (DST) represents one of the most extensively studied biological phenomena in affective disorders. About twenty years ago it has been noted that pretreatment with an oral dose of 1 or 2 mg dexamethasone leads to an inadequate suppressibility of plasma cortisol the day after dexamethasone administration in endogenous depression (Carroll et al., 1968).

Initially the DST has been reported to be highly specific for endogenous depression and to represent a "specific laboratory test for the diagnosis of melancholia" (Carroll, 1982). However, recent studies failed to reproduce the diagnostic utility of the DST (Berger and Klein, 1984), a review comprising the results from various research groups revealed a "mean sensitivity" of 40% and a "mean specificity" of 76% for the diagnosis of endogenous depression (Berger and Klein, 1984).

It should be noted that after two decades of experience the DST cannot be considered as a specific marker for (endogenous) depression, however, cortisol nonsuppression following dexamethasone administration occurs significantly more frequently in depressed patients (Stokes et al., 1985). Cortisol nonsuppression mostly is defined as a failure to suppress postdexamethasone cortisol to below 5 µg/dl.

Positive DST results have also been reported in schizophrenia (Myers et al., 1984; Munro et al., 1984), in mania (Graham et al., 1982), schizoaffective psychosis (Greden et al., 1981), alcoholism (Kroll et al., 1983), dementia (Spar and Gerner, 1982), Parkinson's disease (Frochtengarten et al., 1987), psychosexual dysfunction (Rupprecht et al., 1988), etc. Moreover, cortisol nonsuppression may also occur in healthy controls (Stokes et al., 1985). In addition, an abnormal resistance of cortisol to dexamethasone may be induced by multiple interference factors either of somatical or psychical nature such as weight loss (Berger and Klein, 1984), stress (Domisse et al., 1985), and acute hospitalization (Berger and Klein, 1984), etc.

However, it has been suggested that a normalization of the DST may antecipate clinical improvement (Greden et al., 1983) whereas a reversal to inadequate cortisol suppression may indicate a clinical relapse (Greden et al., 1983; Yerevanian et al., 1983). Investigations on the influence of severity of depression on the DST have produced conflicting results: Stokes et al. (1975), Sangal et al. (1984), and Klein et al. (1984) noted a positive correlation between postdexamethasone cortisol levels and the HRS-D score (Hamilton, 1960) but

others were unable to confirm these findings (Brown and Shuey, 1979; Saleem, 1984).

Various attempts have also been made to demonstrate associations between psychopathological symptoms and DST results. While "psychotic features" have been reported to be associated with cortisol nonsuppression (Carroll et al., 1980), no connections between anxiety, length of the present depressive episode and familiar history of depression (Klein et al., 1984) could be established. Moreover, the DST has been reported to predict the clinical response to choliniolytic and non-choliniolytic antidepressants (Beckmann et al., 1984).

Assessments not only of cortisol but also of multiple corticosteroids during the DST have yielded an improvement in detection of adrenal hyperactivity reflected by a positive DST (Holsboer et al., 1982).

In conclusion the DST failed either to be a specific marker for a depressive subtype or to be of diagnostic validity. Furthermore, there are no consistent associations between the DST results and psychopathological symptoms, although cortisol nonsuppression may represent a "state marker" in certain cases of depression.

Cortisol levels in depression

Hypersecretion of cortisol as noted in Cushing's syndrome is likely to be associated with depression (Haskett, 1985). Typical affective syndroms meeting stringent psychopathological criteria may occur in patients with adrenocortical tumors as well as in those with ACTH dependent Cushing's syndrome (Haskett, 1985). Some years ago hyersecretion of cortisol in depression has been described by several investigators (Gibbons, 1964; Sachar et al., 1970). Sachar et al. (1973) noted elevated 24 hour mean plasma cortisol levels as well as an enhanced number of secretory peaks during depressive episodes. Mendlewicz et al. (1982) found elevated morning baseline levels of cortisol in "primary depression" when compared with "secondary depression" which Carr et al. (1984) were unable to confirm. Elevated baseline cortisol in DST nonsuppressors has been observed by Fang et al. (1981) and by Kalin et al. (1982). An evaluation of the 24 hour profile of cortisol in major depressive illness by Linkowski et al. (1985) revealed a higher 24 hour mean cortisol level in patients when compared with normal controls and an advance of the nocturnal cortisol nadir of almost 3 hours. The hypercortisolism observed in this study was due to an enhanced magnitude of secretory peaks but not to an increased number of secretory episodes as suggested by Sachar et al. (1973).

ACTH and β-endorphin levels in depression

In connection with discussions on the utility of the DST ACTH levels in depressive disorder have become an interesting object of research. However, the results reported by various authors differ quite considerably. A number of research groups have reported an increase in ACTH levels associated with

nonsuppression of cortisol (Reus et al., 1982; Nasr et al., 1983; Holsboer et al., 1984), while others were unable to reproduce these findings (Yerevanian et al., 1983). Pfohl et al. (1985) and Roy et al. (1986) observed elevated concentrations of ACTH in depressive disorder, which were not found by Fang et al. (1981) and Linkowski et al. (1985).

Studies on β-endorphin in depression are even more inconsistent. Rish et al. (1982) and Norman et al. (1987) reported elevated, Nagel et al. (1981) decreased β-endorphin values in depressive disorder, while Naber et al. (1982) found no differences in comparison with normal controls. Kärkkäinen et al. (1987) described an elevated endogenous opioid activity (β-endorphin plus β-lipotropin) in depressed patients. A reduction in β-endorphin concentrations after mianserin treatment (Drago et al., 1982) and in ACTH levels after recovery from depression (Yerevanian et al., 1983) has been noted.

It has been suggested that ACTH and β-endorphin might be secreted equimolarly (Imura, 1985). Therefore a positive correlation between these two peptides and cortisol would be probable. Such a positive correlation as well as a diurnal variation was discussed by Govoni et al. (1984) but not by Fang et al. (1981) who found no correlation between ACTH and cortisol values.

Investigations of the important question whether ACTH and β-endorphin are sufficiently suppressed by dexamethasone during the DST have produced conflicting results owing to laboratory difficulties in ACTH and β-endorphin measurement. Fang et al. (1981) and Roy et al. (1986) reported a pronounced reduction in ACTH after dexamethasone administration, Beck-Friis et al. (1985) only in cortisol nonsuppressors, while Lypka et al. (1985) found no effect of dexamethasone on ACTH levels. A suppressive effect of dexamethasone on β-endorphin was noted by Krantz and Brown (1985) but Lypka et al. (1985) were unable to confirm these findings.

Recent studies revealed an attenuated suppressibility also of β-endorphin by dexamethasone in depressed patients (Norman et al., 1987; Meador-Woodruff et al., 1987) as well as a simultaneous inadequate suppression of ACTH and β-endorphin following 1 mg dexamethasone in endogenous depressives when compared with non-endogenous depressive patients (Rupprecht et al., 1988) suggesting a suprapituitary dysfunction of the HPA axis in depression.

Evaluations of the 24 hour profiles of ACTH in major depressive illness revealed an increased 24 hour mean secretory pattern between depressed patients and normal controls (Linkowski et al., 1987) and an advance of the ACTH nadir similar to the cortisol nadir in patients suffering from depression (Linkowski et al., 1985). Moreover, ACTH and cortisol were secreted concomitantly in most of the subjects. After recovery from depression the timings of the circadian rhythms of the ACTH and cortisol were normalized (Linkowski et al., 1987).

Together with reports of an increase in CRH immunoreactivity in the CSF of depressed patients (Nemeroff et al., 1984; Banki et al., 1987) it may be assumed that alterations of the HPA axis found in depression are most likely

to be localized at a suprapituitary site (Lesch et al., 1988; Lesch and Rupprecht, 1989) though a functional hyperplasia of the adrenal gland may also play a role in this context (Kalin et al., 1987).

Pituitary-gonadal axis in depression

Only few data on the hypothalamic-pituitary-gonadal axis in depression are available owing to difficulties in evaluating the role of gonadotropins and gonadosteroids in female depressed patients in relation to their menstrual or postmenopausal state. LH levels were found to be lowered in postmenopausal women, while estradiol and FSH values showed no difference (Amsterdam et al., 1983). Moreover, an enhanced psychical vulnerability related to a decrease in gonadal steroids during the menstrual cycle has been described (Abramowitz et al., 1982). Although substitution of estrogens in depressed women may have an antidepressive property comparable to usually employed antidepressants in certain cases (Holsboer et al., 1983), affective disorders in female patients certainly do not represent only a kind of estrogen deficiency syndrome.

Several studies in depressed men revealed a reduction of testosterone levels (Vogel et al., 1978; Rubin et al., 1981; Yesavage et al., 1985), however Sachar et al. (1973) found no difference in plasma testosterone before and after recovery. Investigations on gonadotropins in male depressive patients have provided conflicting results.

Moreover, findings on gonadotropins after challenge with GnRH in affective illness have been contradictory. Some authors noted a blunted gonadotropin response to GnRH in depression (Brambilla et al. 1978; Linnoila et al., 1979) which others were unable to confirm (Amsterdam et al., 1981; Winokur et al., 1982; Amsterdam et al., 1983). Also an exaggerated response of LH to GnRH has been observed (Ettigi et al., 1979).

Recent investigations on the gonadotropin and gonadosteroid response to dexamethasone during the 1 mg DST revealed an increase in testosterone and LH after dexamethasone administration in patients with psychosexual dysfunction suffering from dysthymic disorder in contrast to normal controls (Rupprecht et al., 1988).

Further research seems to be necessary to clarify the implications of the hypothalamic-pituitary-gonadal axis in depression.

Prolactin levels in depression

In comparison with the HPA axis which has been studied thoroughly in the last two decades, prolactin has found only little interest in the biological research of depression. Reasons therefore might be the influence of age and sex, the great interindividual variability of prolactin levels as well as a certain intraindividual inconsistence which may be induced by multiple interference factors either of somatical or psychical nature (Cohen, 1983).

Judd et al. (1982) reported a small reduction of prolactin levels whereas Meltzer et al. (1982) found no significant difference in comparison with normal controls. Even a small elevation of prolactin has been described (Halbreich et al., 1979). Lisanski et al. (1984) noted a certain rise in prolactin concentrations after recovery from major depressive disorder.

An evaluation of the 24 hour profile of prolactin in depression detected striking differences between unipolar and bipolar patients (Mendlewicz et al., 1980). While an increased secretion during wakefulness was observed in unipolars, bipolars showed a lack of sleep associated elevation resulting in lower baseline levels.

Joyce et al. (1985) noted a significant correlation between postdexamethasone cortisol and prolactin levels. Moreover, studies on the influence of dexamethasone on prolactin in depression revealed a suppressive effect of dexamethasone (Meltzer et al., 1982; Klein et al., 1984) with an attenuated suppressibility of prolactin in endogenous depression when compared with non-endogenous depression or healthy controls (Rupprecht et al., 1987).

Triiodothyronine (T 3), thyroxine (T 4), and TSH levels in depression

Investigations on thyroid function in depression have become an interesting object of research. Spratt et al. (1982) observed slightly lowered levels of T 3 in psychiatric patients, while reverse T 3 concentrations were reported to be elevated both in serum and in CSF in depressive subgroups (Linnoila et al., 1983). Recent studies revealed lower TSH but normal T 3 and T 4 concentrations during depression (Unden et al., 1986). Decreased levels of free T 3 but not of free T 4 in unipolar depression in comparison with normal controls were described by Orsulak et al. (1985).

The clinical relevance of low T 3 levels during depressive episodes is supported by reports of a better response of depressed patients to tricyclic antidepressants applicating T 3 simultaneously (Earle et al., 1970; Feighner et al., 1972; Prange et al., 1984). Moreover, it has been suggested that the peripheral conversion of T 4 to T 3 might be disturbed (Orsulak et al., 1985) as noted in low T 3 syndromes (Hershman et al., 1983). Recent investigations on T 3, T 4, and TSH levels during the DST in depression revealed a marked suppressibility of T 3 and TSH by dexamethasone in healthy controls and recovered subjects in contrast to the depressive episode indicating that the low T 3 syndrome in depression might be related to the effect of glucocorticoids (Rupprecht et al., 1988).

Dexamethasone bioavailability in depression

Since the DST has found considerable interest in psychoneuroendocrine depression research, studies on dexamethasone pharmacokinetics seem to be important in this context.

Early investigations on the dexamethasone bioavailability were not able to detect an association between dexamethasone levels and the DST results in

depression (Carroll et al., 1980; Rubin et al., 1980). However, more recently several studies have reported lower circulating dexamethasone levels in non-suppressors compared with suppressors (Berger et al., 1984; Morris et al., 1986).

"Mean dexamethasone levels" comprising several studies were significantly lower in cortisol nonsuppressors than in suppressors both at 7 p.m. and at 4 a.m. after dexamethasone administration (Arana et al., 1985) indicating that dexamethasone bioavailability may actually represent a pathogenetic mechanism for inadequate cortisol suppression. Moreover, a shortened half-life for dexamethasone has been observed in nonsuppressors pointing to an enhanced elimination of dexamethasone in depression rather than to an impaired gastrointestinal absorption (Holsboer et al., 1986). A detailed review on this topic has recently appeared (Lowy and Meltzer, 1987).

Glucocorticoid receptors in depression

Not only peripheral, pituitary and hypothalamic hormone levels but also glucocorticoid receptor density and affinity might be an important factor in the regulation of the HPA axis in depression. Excess of glucocorticoid secretion has been shown to decrease the number of glucocorticoid receptors both in the hippocampus (Tornello et al., 1982) and the pituitary (Svec et al., 1981).

For reasons of the hypercortisolism reported in depressive disorder, recent investigations on glucocorticoid receptor density on lymphocytes revealed a lower number of receptor sites in depressed patients (Schlechte et al., 1985; Gormley et al., 1985; Whalley et al., 1986). Moreover, dexamethasone has been demonstrated to decrease the lymphocyte cytoplasmatic receptor number in cortisol suppressors only, whereas no such change occurred in cortisol non-suppressors (Gormley et al., 1985). These results may be important for the attenuated response not only of the HPA axis but also of other endocrine systems to dexamethasone in affective illness.

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