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Serum cortisol concentration in patients with major depression after treatment with clomipramine

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Abstract:
Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and elevated cortisol (CORT) levels are characteristics of the pathophysiology of major depressive disorder.
The aim of this study was to determine whether increased plasma CORT levels appear in patients with major depression and if effective antidepressant treatment by clomipramine (CLO) leads to regulation of CORT level. Plasma CORT levels were measured using high performance liquid chromatography (HPLC) methods in patients with major depression at time zero (before therapy) and after 3 h, 24 h, 4, 6 and 8 weeks of CLO administration. The study included 17 patients (12 women, 5 men; mean age 54.5 years, SD =12.3) and 21 healthy comparison subjects. The patients had a mean score on the 21-item Hamilton Depression Rating Scale (HDRS) of 26.8 (range 22–35). Eight of the patients with major depression recruited for the study showed a 46% increase in CORT concentration compared to the established standard. In 13 patients treated with CLO, serum CLO levels reached a therapeutic range. In recovered depressed patients, antidepressant treatment significantly reduced HDRS scores from the 6th week of treatment. A drop in plasma CORT levels in recovered depressed subjects occurred 0 to 6 weeks after CLO treatment ($n = 5$, $p < 0.046$). However, neither subject group exhibited any definitive markers of CORT secretion. In the population studied, patients had distinct profiles of HPA axis dysregulation. Finding a linear correlation between lower CORT secretion and therapeutic plasma CLO levels is the first aim of monitored therapy and may be important for understanding the pathophysiology of major depressive disorder.

Key words:
cortisol, clomipramine, depression, hypothalamic-pituitary-adrenal axis

Introduction

Major depression is a serious medical illness accompanied by symptoms such as the inability to experience pleasure, sadness, loss of interest, low energy, weight gain or loss, feelings of worthlessness, and hypersomnia or insomnia [17, 18]. A number of studies have shown that major depression is often accompanied by dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and cortisol (CORT) hypersecretion [8, 9, 12, 13, 23]. CORT, a glucocorticoid released from the adrenal cortex, is the end product of the HPA axis. During periods of physical and psycho-

logical stress, the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the circulatory system of the pituitary. This causes the release of adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary. In response to ACTH, CORT is released from the adrenal cortex, which interacts with receptors in tissues. In humans, there are at least two glucocorticoid receptors (GR): MR (high-affinity receptor) and GR (low-affinity receptor). The activated receptors translocate to the nucleus, bind to specific hormone response elements (HREs) and regulate the expression of certain genes [10, 12, 13, 19, 20]. Although glucocorticoids are essential for survival, their overproduction is associated with impaired HPA negative feedback.

Numerous studies [3, 4, 17, 18, 23] have shown that patients with major depression have increased CORT secretion, although several studies did not find the same result [15, 26]. These divergent results may indicate differences in methodologies and statistical analyses. For example, the levels of ApEn may reveal endocrine dysregulation in circumstances in which hormone levels provide no information [16, 27].

Bhagwagar et al. [3] suggested that acutely depressed, medication-free subjects have increased CORT levels. They studied the pattern of waking salivary CORT in 20 depressed subjects and 40 healthy controls. Patients with acute depression secreted approximately 25% more CORT than controls, though 60 min after waking, their CORT levels were similar [3]. In addition, they previously found similar greater levels of waking salivary CORT in recovered depressed patients [4]. It is known that CORT and ACTH are secreted in pulses and have circadian and ultradian rhythms, although measurements at the moment of waking show a consistent single "pulse" of CORT, even if total CORT secretion is not increased. Therefore, the present study attempted to assay serum CORT levels in the morning.

Various studies by Stokes [23] on the role of dysfunction in the endocrine system and the pathogenesis of mood disorders have shown. The reports have shown that high CORT can affect mood, behavior and cognition and consequently can induce enlargement of the pituitary and adrenal glands. The autoregulation of the HPA axis is related to the concentration of CORT in the hippocampus. As the hippocampus is an important structure for memory and learning, the role of CORT in relation to depression and the integrity of the hippocampus has received considerable attention. Several studies have shown reduced hippocampal volumes in depressed patients compared to normal subjects [2, 7], and another study investigating hippocampal topography using high-dimensional brain mapping demonstrated the deformation of the hippocampal surface in 27 patients with major depressive disorder [16]. Moreover, the function of the GR is diminished in depressed patients, which may contribute to increased HPA activity [5, 12]. Animal data suggest that mice with reduced GR expression or function have some behavioral changes. For example, Boyle and coworkers [5] observed that the transgenic mice (mice with time-dependent, forebrain – specific disruption of GR) consumed significantly less of a sucrose solution than controls. This sucrose preference test is a commonly used measure of anhedonia in rodents. Furthermore, mice showed depression-like behaviors and despair, based on decreased activity in forced swim tests.

Together, the data suggest that elevated levels of glucocorticoids in depression is associated with damage to the hippocampus and may be neurotoxic for a brain area involved in learning and memory, resulting in cognitive decline or dementia [2, 21].

High CORT is associated with altered neurotransmitter function, diminished brain serotonin synthesis and increased noradrenergic activity [23]. The vast majority of studies using triacyclic antidepressants have shown that antidepressants increase expression GR, enhance negative feedback by endogenous glucocorticoids and stimulate HPA axis activity [5, 11–13]. Studies in depressed patients have demonstrated that antidepressants modulate GR function by inhibiting membrane steroid transporters (MDR PGP), which regulate the intracellular concentration of glucocorticoids [14]. Moreover, clomipramine (CLO) regulates several neurotransmitter receptors and enhances serotonergic activity by inhibiting 5-hydroxytryptamine (5-HT) reuptake [22]. Therefore, the present study attempts to examine whether serum CLO levels and its metabolite demethylclomipramine (DCLO) correlate with the therapeutic effects measured by the Hamilton Depression Rating Scale (HDRS). Thus, we assessed CORT levels to test the hypothesis that antidepressant treatment leads to normalization of the HPA axis in depressed patients.

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