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Longitudinal neuroendocrine changes assessed by dexamethasone/CRH and growth hormone releasing hormone tests in psychotic depression

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Growth hormone releasing hormone (GHRH) test;
Psychotic depression

Summary

Although psychotic depression has been reported to exhibit a greater degree of dysregulation of hypothalamic–pituitary–adrenocortical (HPA) function than non-psychotic depression, little is known concerning hypothalamic–pituitary–somatotrophic (HPS) function in psychotic depression and how neuroendocrine function changes after treatment. To investigate the longitudinal changes in HPA and HPS system function in psychotic depression, we performed repeated dexamethasone/corticotropin releasing hormone (DEX/CRH) tests and growth hormone (GH) releasing hormone (GHRH) tests in inpatients with major depressive disorder. The psychotic depression group exhibited greater elevation of ACTH responses to the DEX/CRH test and stronger decreases in GH responses to the GHRH test than the non-psychotic depression group at admission. At discharge, the neuroendocrine responses to the DEX/CRH test of the psychotic depression group were still stronger than those of the non-psychotic depression group, though there were no significant differences in severity of depression between the groups. There were significant longitudinal changes in neuroendocrine responses to the DEX/CRH test between admission and discharge. The psychotic depression group exhibited increased GH responses to GHRH

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at discharge compared with those at admission, whereas no significant longitudinal change in GH response was found in the non-psychotic depression group. Consequently, there were no significant differences in GH responses to GHRH between the psychotic and non-psychotic depression groups at discharge. The results of GHRH test showed no significant relationships with severity of depression except psychotic features and the results of the DEX/CRH test. Our findings suggest that the HPS axis may be associated with psychotic features rather than general severity of depression. Further longitudinal studies are needed to clarify the role of HPS function in psychotic depression and whether sustained dysregulation of HPA function in psychotic depression is associated with a poor outcome after discharge.

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1. Introduction

Psychotic depression is a common subtype of major depression. The prevalence of major depression with psychotic features among depressive patients has been reported to be 14–19% in community surveys (Johnson et al., 1991; Thakur et al., 1999; Ohayon and Schatzberg, 2002) and 15–45% in clinical settings (Coryell et al., 1984; Schoevers et al., 2000). Psychotic depression has also been reported to have a greater risk of mortality than non-psychotic depression (Vythilingam et al., 2003).

The clinical characteristics of psychosis are known to be related to function of the dopaminergic system. Schatzberg et al. (1985) have hypothesized that enhancement by glucocorticoids of dopaminergic activity can explain the development of psychotic features in the context of a depressive episode. Indeed, patients with psychotic depression have been found to have distinct biological abnormalities in studies of the hypothalamic–pituitary–adrenal (HPA) axis. Many studies have demonstrated abnormality of the HPA system in major depression (Plotsky et al., 1998; Holsboer, 2000). A meta-analysis of 12 different studies, with a combined sample size of approximately 1000 depressed patients, indicated that psychosis was associated with elevated rates of non-suppression on the dexamethasone suppression test (DST) (Nelson and Davis, 1997). Psychotic major depression has also been reported to be associated with increased cortisol level during the quiescent hours (Keller et al., 2006). On the other hand, the DST was criticized by its low specificity and sensitivity for depression. Indeed, substantial rates of non-suppression of DST were reported in patients with various other Axis I diagnoses (Krishnan et al., 1987). Corticotropin releasing hormone (CRH), which is produced by neuroendocrine cells in the paraventricular nucleus and stimulates corticotropes in the anterior pituitary to secrete ACTH, was discovered in 1981 (Vale et al., 1981) and accelerated research on the HPA axis and depression. The combined dexamethasone (DEX)/CRH test was developed by Holsboer et al. (Holsboer et al., 1987; Holsboer-Trachsler, 1991) and the results of the dexamethasone/corticotropin releasing hormone (DEX/CRH) test are known to be more closely related to the activity of the HPA system than those of the DST (Heuser et al., 1994a; Oshima et al., 2000). Heuser et al. (1994a) reported that the sensitivity of the DEX/CRH test for major depression (about 80%) exceeds that of the DST (25–44%), and Watson et al. (2006) reported that diagnostic specificity was 71% in the

DEX/CRH test and was 48% in the DST. Furthermore, the results of the DEX/CRH test appear to be a state-dependent marker of major depressive episode (Kunugi et al., 2006). However, few studies have reported results of the DEX/CRH test in psychotic depression. Although Frieboes et al. (2003) performed a 4-week open trial in 15 inpatients with delusional depression, and reported a significant decrease in the DEX/CRH test values pre- to and post-treatment, there were no control depression subjects without delusion in their study. Dopaminergic function, on the other hand, can be evaluated by other neuroendocrine measurements. For example, neuroendocrine responses to dopamine receptor agonists such as apomorphine are useful in assessing central dopaminergic function (Meltzer et al., 1984; Lal, 1988; Pitchot et al., 1992). Apomorphine stimulates growth hormone (GH) secretion, and decreased (Pitchot et al., 1990–1991) or unchanged (Lal, 1988) GH responses to apomorphine in depression have been reported. The blunted GH responses to apomorphine might be the result of depression-related alteration at hypothalamic–pituitary level. Moreover, the GH releasing hormone (GHRH) test has been used to assess the hypothalamic–pituitary–somatotrophic (HPS) axis, and some interactions between GHRH and dopaminergic function have been reported (Crespi et al., 1985; Vance et al., 1987). Although some previous studies have reported decreased GH secretion to GHRH in depressive patients compared with healthy controls (Eriksson et al., 1988; Lesch et al., 1989; Peabody et al., 1990; Dahl et al., 2000), little is known concerning the GH responses to GHRH in psychotic depression. Contreras et al. (1996) reported that a delusional group exhibited delayed appearance of the maximum response peak and a more prolonged response, although almost no significant differences in basal GH were observed between the control and either the non-delusional or the delusional groups. GH responses to clonidine indicated a tendency toward decreased secretion in psychotic depression compared with non-psychotic depression (Lykouras et al., 1988).

To investigate the longitudinal differences of HPA and HPS function between the patients with psychotic and non-psychotic depression, we performed two neuroendocrine challenge tests of the DEX/CRH and GHRH tests, and compared the results between the groups. We hypothesized that psychotic depression would be associated with much stronger dysregulation of the HPA and HPS systems than non-psychotic depression, and that the abnormal neuroendocrine responses in psychotic depression would remain even

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