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Effect of bupropion on nocturnal urinary free cortisol and its association with antidepressant response

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Abstract

The study examined the relationship between pre-treatment nocturnal hypothalamic–pituitary–adrenal (HPA) activity, as reflected by nocturnal urinary free cortisol (NUFC) response to a single-dose of sustained-release bupropion, and the antidepressant effect of the drug. NUFC changes in response to treatment with bupropion also were assessed.

NUFC was measured in 20 patients with unipolar major depressive disorder before and after initiating treatment with sustained-release bupropion. Prior to treatment, subjects were studied on two separate sessions, one week apart. On the morning of each session, the participants received bupropion (150 mg, PO) or placebo using a randomized, double-blind procedure. Following the second session, subjects then received open-label treatment with bupropion for 8 weeks. NUFC sampling was repeated at the end of treatment.

There was a significant interaction between NUFC concentration in response to single-dose bupropion and its antidepressant effect. Treatment non-responders showed a significant increase in NUFC in response to a single-dose of bupropion, whereas responders showed no such change. In addition, the NUFC response to bupropion challenge correlated significantly with the change in depression ratings as a result of treatment. In contrast to many other antidepressants, treatment with bupropion for 8 weeks did not reduce HPA activity in either responders or non-responders.

These findings suggest that the NUFC response to a test-dose of bupropion might be helpful in predicting its antidepressant effect. One possible mechanism for the association between the NUFC response to acute bupropion challenge and antidepressant efficacy might be linked through dopaminergic and/or noradrenergic mechanisms.

Keywords: Depression; Cortisol; Antidepressant; Bupropion; HPA axis; Treatment

1. Introduction

There is considerable evidence for altered HPA activity in patients with major depressive disorder, and recent evidence suggests that the mechanism driving the HPA system might be causally related to the mechanism underling depression (for reviews, see Holsboer, 2000; Plotsky et al., 1998). Although HPA dysregulation is a prominent feature of depression, and investigation of this system has been an active endeavor of both clinical and preclinical research for numerous years, the exact nature of their association remains elusive. Possibly, genetic and experience-related factors of developmental and non-developmental origin might interact to induce manifold changes in corticosteroid receptor signaling, resulting in hypersecretion of corticotrophin-releasing hormone (CRH) and other secretagogues of corticotropin (De Kloet et al., 1998; Holsboer, 2000; Kellendonk et al., 2002; Meyer et al., 2001; Müller et al., 2000, 2001; Purba et al., 1996; Raadsheer et al., 1995; Schulkin et al., 1998). In recent years, considerable evidence has accumulated suggesting that normalization of the HPA system might be the final step necessary for stable remission

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of depressive illness (Banki et al., 1992; Brady et al., 1991; De Bellis et al., 1993; Heuser et al., 1998; Holsboer and Barden, 1996; Inder et al., 2001; Reul et al., 1994; Ribeiro et al., 1993; Veith et al., 1993; Zobel et al., 1999, 2000). Based on these findings, it has been hypothesized that antidepressant drugs might achieve their action, at least in part, through reduction in HPA activity (Dinan, 2001; Holsboer, 2001; Holsboer and Barden, 1996; Keck and Holsboer, 2001; Thase et al., 1993).

This investigation was undertaken to study the effects of bupropion on NUFC in depressed patients, and to evaluate whether NUFC changes after single-dose bupropion administration are associated with subsequent treatment response to the drug. Another goal of the study was to assess whether antidepressant response to bupropion is associated with a reduction in HPA activity. Bupropion is an atypical antidepressant agent (Preskorn and Othmer, 1984). Its mechanism of action is unclear, but it is purported to have some effects on dopamine and norepinephrine uptake, but shows little activity on serotonergic (5-HT) systems (Cooper et al., 1980, 1994; Ferris et al., 1981; Goodnick et al., 1998; Little et al., 1999). To the best of our knowledge, the effect of bupropion on the HPA axis in relation to clinical response has not been examined.

2. Materials and methods

2.1. Clinical assessments

Subjects were recruited from the outpatient clinic at Harbor-UCLA Medical Center and through advertisements in local newspapers. The study was carried out in accordance with the latest version of the Declaration of Helsinki. The protocol was approved by the Institutional Review Boards at Harbor-UCLA Research and Education Institute and at Cedars-Sinai Medical Center. Subjects signed an informed consent document prior to participation in the study. All participants were assessed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1994) for the identification of major depressive disorder and co-morbid conditions. Severity of depressive symptoms was determined by the 24-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Diagnosis of major depressive disorder and a minimum score of 15 on the first 17 items of HAM-D were required for acceptance into the study. Patients were free from antidepressant drugs and other psychotropic agents for at least 4 weeks (8 weeks for fluoxetine). All subjects were medically healthy, as determined by physical examination, full chemistry panel, thyroid function tests, electrocardiogram and urine drug screens.

Exclusion criteria included prior use of bupropion for the treatment of depression or for other conditions (e.g., smoking), history of seizure disorder or other neurological conditions, active suicidal ideation or a recent suicide attempt, and current or previous diagnosis of anorexia/bulimia nervosa, primary anxiety disorder, bipolar disorder or psychotic disorder. Also, subjects with substance use disorder diagnosis in the previous 6 months, patients with a personal history of sleep disorder(s), and pregnant women were excluded from the study.

2.2. NUFC sampling prior to treatment

At baseline, each participant was studied in two separate sessions, approximately one week apart. On the morning of each session, subjects were given placebo or sustained-release bupropion (Wellbutrin SR®; 150 mg, PO) at 7:00 a.m., in a randomized, double-blind, crossover fashion. Subjects voided at 11:00 p.m. and all urine was collected for the next eight hours including the 7:00 am sample. Urine samples were collected in our General Clinical Research Center in conjunction with sleep polysomnography measures (see Ott et al., 2002).

2.3. Treatment of depression with bupropion

After the second NUFC sampling session, subjects began standard clinical treatment with sustained-release bupropion under the care of a psychiatrist for approximately 8 weeks (mean = 55.1 days; SD = 9.4 days), with weekly monitoring of symptoms and side effects. The protocol required 8 weeks of treatment. However, due to scheduling difficulties for some subjects, the final assessment was not obtained exactly at Week 8. Thus, treatment duration ranged from 7 to 9 weeks. Dose adjustments were made throughout treatment, and were based on clinical assessment and reports of depressive symptoms and side effects. The final dosage ranged from 150 to 400 mg/day.

Subjects who showed $\geqslant 50\%$ reduction in HAM-D score in response to bupropion treatment were classified as responders. In order to determine change in HAM-D scores in response to treatment, the final HAM-D score was subtracted from the baseline (pre-treatment) value. For post-hoc analyses, remission from depression (a final HAM-D score of $\leqslant 7$) was used as a secondary outcome measure.

2.4. Post-treatment NUFC sampling

At the end of treatment, NUFC sampling was repeated, using the same procedures as performed at baseline. However, the post-treatment protocol consisted only of a single session. For this session, subjects received their usual prescribed dose of sustained-release bupropion.