Interaction between serotonin 5-HT1A receptors and β-endorphins modulates antidepressant response

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A B S T R A C T
Interactions between serotonergic and the endogenous opioid systems have been suggested to be involved in the etiopathogenesis of depression and in the mechanism of action of antidepressants. Activation of serotonin 5-HT1A receptors has been shown to increase plasma β-endorphin (β-END) levels in animal studies and in healthy humans. Objectives: To assess interaction abnormalities between 5-HT1A receptors and the endogenous opioid system in patients with major depression and the possible modulating effect of citalopram. Methods: The β-END response to the 5-HT1A receptor agonist, buspirone (30 mg), was measured in 30 patients with major depression and in 30 age- and sex-matched healthy controls before and after an 8-week treatment with citalopram. Pre-treatment score of the Hamilton Rating Scale for Depression (HRSD) was ≥17. Antidepressant response was defined by a 50% decrease in the HRSD. Pre- and post-treatment maximum peak response (Δmax) and the area under the curve (AUC) of β-END response were compared. Three time points were measured (60, 90 and 120 min). We also examined the correlations between the β-END response and the antidepressant response. Buspirone plasma levels were not measured. Results: At baseline, β-END response was similar in patients and controls. After 8 weeks of citalopram treatment depressed patients showed a significant decrease in the β-END response (Δmax: p < .001; AUC: p < .001). A significant correlation between the β-END reduction in the response and the reduction in the HRSD score (r = .656; p < .001) was observed. Conclusions: Changes in interaction between 5-HT1A receptor system and the endogenous opioid system may play a role both in the mechanism of action and response to antidepressant drugs.

1. Introduction

The serotonergic and the endogenous opioid systems appear to be involved in the pathophysiology of depression and in the mechanism of action of antidepressant drugs but the exact mechanisms are unclear (Zangen et al., 2002; Kennedy et al., 2006). The endogenous opioid β-endorphin (β-END) acts as both a neuromodulator and a neurotransmitter in the central nervous system (Bodnar and Klein, 2005). Neurones that synthesize and release β-END are predomi-

nantly located in the hypothalamic arcuate nucleus (ArN) (Zangen et al., 2002). β-END and adrenocorticotropic hormone (ACTH) are derived from the same precursor, proopiomelanocortin (POMC), and are synthesized and co-secreted (Young et al., 2000). During stress, the synthesis of central corticotropin-releasing hormone (CRF) in the paraventricular (PVN) increases and CRF is released from terminals in the median eminence into the hypothalamic–hypophysial portal vascular system (Pintor et al., 2007). When the peptide reaches the anterior pituitary gland, it binds to CRF receptors and through a cascade of intracellular steps ultimately increases POMC gene expression and the release of POMC-derived peptides such as ACTH and β-END (Arborelius et al., 1999). The opioid receptors implicated in the β-END neurotransmission are mainly the µ-opioid receptors (Bodnar and Klein, 2005). µ-Opioid receptor-mediated neurotransmission is typically activated in response to sustained or unpredictable stressful and noxious stimuli. In animal models, endogenous opioid peptides activating µ-opioid receptors are centrally involved in the induction of stress-induced analgesia and the reduction of anxiety-like responses to environmental adversity (Kennedy et al., 2006).
There is evidence that the serotonergic system exerts a stimulatory control over pituitary release of ACTH and β-END in rodents and human subjects (Majeed et al., 1985; Maes et al., 1996a,b; Kitamura et al., 1997). Serotonin (5-HT) mediates the activation of the pituitary-adrenal function, at least in part, via the 5-HT₁A receptors (Maes et al., 1996a,b; Kitamura et al., 2007). Decreased ACTH/cortisol response to the 5-HT₁A receptor agonist ipsapirone found in some studies suggests a down-regulation of 5-HT₁A receptors in depression (Lesch et al., 1990; Meltzer and Maes, 1995; Shapiro et al., 2000; Riedel et al., 2002). Nevertheless, this finding has not been confirmed in other investigations using ipsapirone (Shin Shiah et al., 1998) or buspirone (Cowen et al., 1994; Meltzer and Maes 1994; Navinés et al., 2007a). Although it might be expected that the reduced serotonin responses seen in major depression would return to normal levels after treatment with antidepressant drugs, such an effect has not been observed in the case of the 5-HT₁A receptor (Shapira et al., 2000; Navinés et al., 2007b).

There is also some evidence that in rodent and human subjects 5-HT exerts a stimulatory control over the pituitary release of β-END (Maes et al., 1996a; Jørgensen et al., 2002) and that activation of 5-HT₁A receptors results in β-END secretion. Thus, acute administration of 5-HT₁A agonists, such as 8-hydroxy-2-di-n-propylamino tetralin (8-OH-DPAT), ipsapirone or gepirone, increases plasma β-END in normal volunteers or in the rodent (Majeed et al., 1985; Koening et al., 1987; Anderson et al., 1990; Bagdy et al., 1990). The 8-OH-DPAT-stimulated β-END secretion is antagonized by pindolol (Koening et al., 1987). From the above it appears that 5-HT-acting drugs are able to stimulate β-END secretion through stimulation of 5-HT₁A receptors and that the control of serotonergic pathway on the release of POMC-derived peptides, such as ACTH and β-END, is quite similar. However, no research has investigated the β-END response to the 5-HT₁A agonists in depressed patients compared with normal controls, nor the possible modulating effects of antidepressant treatment in the response.

Buspirone is a complete agonist of the 5-HT₁A autoreceptors and a partial post-synaptic 5-HT₁A receptors agonist, but also exerts a dopamine receptor antagonism (Cowen et al., 1994; Maes et al., 1996b). 8-OH-DPAT-stimulated β-END secretion is antagonized by pindolol (Koening et al., 1987). From the above it appears that 5-HT-acting drugs are able to stimulate β-END secretion through stimulation of 5-HT₁A receptors and that the control of serotonergic pathway on the release of POMC-derived peptides, such as ACTH and β-END, is quite similar. However, no research has investigated the β-END response to the 5-HT₁A agonists in depressed patients compared with normal controls, nor the possible modulating effects of antidepressant treatment in the response.

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2. Method

2.1. Data collection and clinical assessment

The study was conducted in outpatient clinics of the service of psychiatry in a tertiary care teaching hospital, in Barcelona, Spain. The study population included 30 consecutive patients, 10 men and 20 women, with a mean (SD) age of 32.6 (7.5) years (range 18–45 years), fulfilling DSM-IV criteria for current unipolar major depression. All cases were assessed using the Spanish version of the Structured Clinical Interview for DSM-IV Axis-I Disorders (First et al., 1995) and had a baseline score of ≥ 17 on the 21-items Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). A score ≥ 7 in the Newcastle Scale (Carney et al., 1985) was used to define endogenous depression. After 8 weeks of treatment with citalopram patients were re-assessed with the HRSD. All patients underwent physical examination and laboratory test for routine screening of haematological, biochemical and hormonal blood parameters including serum electrolytes, renal, liver and thyroidal function, and standard ECG. Exclusion criteria were as follows: any associated psychiatric disorder, such as anxiety disorder or bipolar disorder; any major medical, endocrine or neurological disease; pregnancy or breastfeeding; alcohol or drug abuse in the past 6 months; and hypertension (SBP ≥ 160 mm Hg, DBP ≥ 100 mm Hg). Participants had not received hormonal or psychotrophic medication including antidepressant drugs, for at least 30 days prior to neuroendocrine challenge, except for low-dose benzodiazepines as anxiolytic or hypnotic agents. None of the participants was overweight.

The control group consisted of 30 age- and sex-matched healthy subjects who were recruited from health care personnel or local advertisements at the university. They were screened for apparent medical or psychiatric illness by a clinical interview. None of them was taking drugs, was overweight or had family history of mental disorders. Those in the control group had a score ≤ 3 in the HRSD.

Women in the study were in fertile age and the test challenge was performed in the first phase of the hormonal cycle. The study was approved by the institutional review board. Written informed consent was obtained from all subjects before enrolment in the study.

2.2. Buspirone protocol

All subjects were admitted to a psychiatric nursing unit at 08:30 a.m. after an overnight fast. Subjects were tested reclining, and indwelling catheter was inserted into a peripheral vein. After a 30-min rest period to minimize stress factors, a blood sample of 5 mL was taken for baseline determinations of plasma β-END. Cortisol baseline levels were also examined to test the possible effects of cortisol in the 5-HT₁A receptors sensitivity. Following this an oral dose of 30 mg buspirone was administered. Further blood samples were taken 60, 90 and 120 min after buspirone administration for β-END determinations. Every 30 min, the subject completed 100 mm visual analogue scales for nausea, light-headedness, cephalgia and dizziness. After 8 weeks of citalopram treatment, challenge with buspirone was repeated. Venous sample for cortisol was taken into tubes and were stored at −20 °C until thawed for cortisol assays. Venous sample for β-END was collected into tubes containing EDTA, stored on ice and centrifuged within 60 min after sampling. Serum was separated and stored at −80 °C for assay at a later time.

2.3. Citalopram treatment

Following the completion of the buspirone protocol, all patients started treatment with 15 mg/day of citalopram increasing to 30 mg/day on day 7. The daily dose of 30 mg/day was maintained for the next 7 weeks. Patients were assessed by a psychiatrist at 2-week intervals. Compliance was monitored by pill counts on every return visit.

2.4. Hormone assays

All samples were assayed at the endocrine and hormonal department of the hospital. Cortisol was determined by standard radioimmunoassay using a commercially available kit (Immunotech, Marseille, France), β-END was determined by means of an immunoradiometric (IRMA) assay (Nichols Institute, USA). Inter- and intra-assay coefficients of variation over the range encompassed by the standard curves were 4% and 8% for cortisol, and 5% and 11% for β-END, respectively.

2.5. Data analysis

Statistical analysis was carried out using the statistical software SPSS (version 12.0) including its module for exact tests. In the case of
The β-END response to buspirone was calculated as the maximum peak response (Δmax) and the area under the curve (AUC) from baseline. The Mann–Whitney U test was used to determine whether β-END response in subjects with major depression and healthy controls was significantly different. The differences in the maximal β-END response to buspirone before and after 8 weeks of citalopram treatment were calculated by the non-parametric Wilcoxon test. Time course of changes from baseline plasma levels of β-END was compared using two-way repeated-measures ANOVA with treatment condition (patients vs. controls and before vs. after treatment, respectively) and time (0, 60, 90, and 120 min) as well as their interaction as factors. If time × treatment interaction was statistically significant, one-way repeated-measures ANOVA was applied to study the time course in each group separately. All tests were two-tailed, with significance set at p < .05. The Spearman’s correlation coefficient was calculated to quantify the association of continuous variables.

3. Results
3.1. Patients vs. controls

At baseline, the only socio-demographic difference between cases and controls was in the level of education (χ² = 13.6; df = 3; p = .03) and working status (χ² = 30.179; df = 4; p = .00). Depressed patients had a mean (SD) HDRS score of 21.6 (4.82) vs. 17.3 (4.3) in controls. Forty per cent of patients (N = 12) had melancholic depression, with 9 recurrent episodes and 21 first episodes. The mean (SD) HDRS score of melancholic was 24.5 (6.4) compared with 21.67 (4.82) in nonmelancholic (see Table 1). Side effects related to buspirone administration included dizziness in 6 subjects and slight sedation in 4, which occurred about 15 min after drug ingestion. Symptoms disappeared in about 30–45 min and none of the subjects had to discontinue buspirone challenge test.

The results of the time course of changes from baseline β-END levels compared with treatment condition (patients vs. controls) using 2-way repeated-measures ANOVA showed that there were significant changes over time (F = 6.828149; p = .0098). In addition, the time × treatment condition (patients vs. controls) was borderline significant (F = 2.988617; p = .0542). This was due to the fact that among patients a significant change (p = .004) from baseline was observed after 90 min. On the other hand, among controls changes after 90 and 120 min were non-significant (p = .34 and p = .65, respectively), but borderline significant after 1 h (p = .06).

Table 2 shows data of baseline plasma β-END levels and β-END response after buspirone challenge (Δmax and AUC) in depressed patients and healthy controls. There were no significant differences in baseline plasma β-END levels (median [25th–75th Interquartile range] 24.5 [20.0–36.0] pg/mL vs. 26.5 [20.0–35.2] pg/mL) or in baseline plasma cortisol levels (median [25th–75th interquartile range] 11.7 [9.1–16.1] µg/dL vs. 13.6 [10.9–15.9] µg/dL) between patients and controls. The Δmax and AUC for β-END response did not differ between both groups. There were no significant differences in the peak β-END response between patients with or without melancholia, nor between melancholic patients and controls. The peak β-END response of male patients did not differ from male controls and the response of the female patients and controls did not show significant differences either. The peak β-END response of patients with recurrent depressive episodes compared with patients with the first depressive episode was similar. A possible correlation between the Hamilton scale or the Newcastle scale and the β-END response was not observed.

![Fig. 1. Time concentration curves with the beta-endorphin responses (mean ± SEM)](0, 60, 90, and 120 min) in both depressed patients and normal controls and before and after citalopram treatment patients.)
Pharmacologic challenge test with 5-HT\textsubscript{1A} receptor agonists have been used by several authors to investigate the sensitivity of 5-HT\textsubscript{1A} receptors in depressed patients. However, to our knowledge, there are no published studies of the \(\beta\)-END response to the 5-HT\textsubscript{1A} receptor agonists in depressed patients. The modulating effects of the antidepressant treatment on this response have not been investigated in normal subjects neither in depressed patients.

The finding of no differences in the \(\beta\)-END response to buspirone between patients and controls is in agreement with our previous study (Navinés et al., 2007a), the study of Cowen et al. (1994) and Meltzer and Maes (1994) using buspirone as well as with the study of Shin Shiah et al. (1998) using ipsapirone regarding the ACTH/cortisol response. In contrast, other authors reported decreased ACTH/cortisol responses to the 5-HT\textsubscript{1A} agonist ipsapirone (Lesch et al., 1999; Meltzer and Maes, 1995; Shapira et al., 2000; Riedel et al., 2002) in depressed patients compared with healthy controls.

Our results suggest that there is no consistent alteration in the \(\beta\)-END response to the 5-HT\textsubscript{1A} receptor agonist buspirone in drug-free depressed patients. It is possible that some of the differences between buspirone- and ipsapirone-induced responses may be due to the weaker 5-HT\textsubscript{1A} properties of buspirone compared to ipsapirone (Maes et al., 1996a). An additional potential explanation could be that the method applied was unable to detect alterations in the functional 5-HT\textsubscript{1A} receptors. The \(\beta\)-END response was not mediated by the 5-HT\textsubscript{1A} receptor via a direct mechanism on the level of the pituitary and did not parallel to the ACTH secretion. Nevertheless a number of authors have shown that stimulation of 5-HT\textsubscript{1A} receptors enhances the \(\beta\)-END response in animals and healthy humans (Koening et al., 1987; Anderson et al., 1990) and that the control of serotonergic pathway on the release of ACTH and \(\beta\)-END, is quite similar (Maes et al., 1996a).

Studies in which hormonal response decreased generally include inpatients or melancholic patients (Lesch et al., 1990; Cowen et al., 1994). In our study all patients were outpatients and only some of them were melancholic. This may explain in part differences in the results obtained. In addition, studies in which depressed patients showed an attenuated hormonal response also indicated an increased secretion of cortisol (Lesch et al., 1990; Meltzer and Maes, 1995) but this association was not observed by others (Shapira et al., 2000; Riedel et al., 2002). In our study, no differences in baseline cortisol concentrations between patients and controls were observed, and this may partly account for a nonattenuated \(\beta\)-END response. Further studies with larger samples including different subtype of depression are necessary for assessing the relationship between severity of depression and 5-HT\textsubscript{1A} induced-hormonal or opioid responses.

On the other hand, the investigation of the 5-HT-\(\beta\)-END interaction in specific brain regions may provide an avenue to better understand the associated abnormalities between serotonergic and the endogenous opioid system in the etiological mechanism in depression. In this respect, there are studies in the rat model of depression suggesting that depressive behaviour may relate to an impaired effect of 5-HT on 5-HT\textsubscript{1A} receptor function (Zangen et al., 1996a). An additional potential explanation could be that the method applied was unable to detect alterations in the functional 5-HT\textsubscript{1A} receptors. The \(\beta\)-END response was not mediated by the 5-HT\textsubscript{1A} receptor via a direct mechanism on the level of the pituitary and did not parallel to the ACTH secretion. Nevertheless a number of authors have shown that stimulation of 5-HT\textsubscript{1A} receptors enhances the \(\beta\)-END response in animals and healthy humans (Koening et al., 1987; Anderson et al., 1990) and that the control of serotonergic pathway on the release of ACTH and \(\beta\)-END, is quite similar (Maes et al., 1996a). Studies in which hormonal response decreased generally include inpatients or melancholic patients (Lesch et al., 1990; Cowen et al., 1994).

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3.2. Patients before and after citalopram treatment

Five depressed patients refused buspirone challenge test after 8-week treatment with citalopram. Therefore, post-treatment data presented refer to 25 patients who completed both buspirone challenge tests before and after antidepressant treatment. On the other hand, citalopram was well tolerated. Only 3 patients presented nausea in the first days of treatment and 2 patient increased anxiety symptoms. All subjects continued the study without reduction or withdrawal of the antidepressant drug.

Baseline plasma \(\beta\)-END levels of depressed patients after 8 weeks of citalopram treatment were significantly lower than before treatment (median [25th–75th Interquartile range] 24.5 [20.0–36.0] pg/mL vs. 21.8 [18.5–29.0] pg/mL; \(p=.046\)). Baseline plasma cortisol levels did not show significant differences before and after treatment.

The results of the time course changes from baseline \(\beta\)-END levels compared between treatment condition (before and after citalopram) using 2-way repeated measures showed no statistical difference (\(F=1.018364; p=.8924\)). Since changes were in an opposite direction, neither the factor time \((F=11.690973; p=.5593)\) nor its interaction with treatment condition \((F=1.944074; p=.1244)\) were statistically significant.

On respect to the buspirone challenge depressed patients showed a significant decrease in the \(\Delta\text{max} (p<.001)\) and AUC \((p<.001)\) for \(\beta\)-END response after 8 weeks of citalopram (Fig. 1). The mean (SD) of total score of HRSD at baseline was 22.20 (5.06) [range 32–17] and at 8 weeks of citalopram treatment was 11.48 (4.55) [range 20–6] (paired-\(t\) test = 14.79; \(p<.001\)). At the end of the study, 18 subjects (60%) showed a 50% of reduction in the HRSD score. Moreover, a significant correlation between the decrease in the \(\beta\)-END response \((r=.656)\) and clinical improvement after treatment with citalopram was found (Fig. 2).

4. Discussion

In our study, at baseline buspirone stimulated plasma secretion of \(\beta\)-END was evident in both depressed patients and controls, although significant differences in the \(\beta\)-END response were not found. After 8 weeks of citalopram treatment in depressed patients we observed a reduction in the \(\beta\)-END response to buspirone. Moreover, the reduction in the response was significantly related to the improvement in the severity of illness as measured by the HDRS score.
patients compared with normal subjects have been found to be higher in some studies (Goodwin et al., 1993), lower in others (Darko et al., 1992; Djurovic et al., 1999) or similar (Alexopoulos et al., 1983). Our results suggest that the levels of cortisol of β-END in these patients are not transcendental to the symptoms of depression.

The decrease in the β-END response after 8 weeks of citalopram treatment in depressed patients could implicate a desensitization of post-synaptic 5-HT1A receptors. This finding confirms with data of neuroendocrine studies in both in rats and humans (Anderson et al., 1996; Sargent et al., 1997; Lerer et al., 1999; Navinés et al., 2007b), but does not support the hypothesis that selective serotonin reuptake inhibitors (SSRI) and other antidepressants cause an enhancement of 5-HT1A function responsible for antidepressant effects (Blizer and de Montigny, 1994). However, neuroendocrine testing procedures reflect 5-HT1A receptor function in the raphe hypothalamic area, which may be different than antidepressant effects on 5-HT1A receptors in the hippocampus and other cortical regions. The decrease in the β-END response could be explained also by an effect on the endogenous opioid system activity. It was hypothesized that the effect of antidepressants on chronic pain might be due to an interaction of the serotonergic system with the endogenous opioid system, i.e., to a 5-HT-mediated activation of the endogenous opioid system (Micó et al., 2005; Zubieta et al., 2001). Furthermore, the correlation between the decrease in the β-END response and the reduction in the HRSD after citalopram treatment suggests that the decrease in the endogenous opioid system activity may be one factor associated with the therapeutic response of citalopram. This agrees with a recent positron emission tomography (PET) study in patients with major depression who did not respond to a 10-week course of an SSRI antidepressant demonstrated an increases in µ-opioid system activation during a sadness challenge. In contrast, responders displayed responses more closely related with deactivation of opioid neurotransmission (Kennedy et al., 2006). The mechanism by which changes in endogenous opioid system function could produce a reduced β-END response may arise from an increase in µ-opioid receptors sensitivity and enhancing the µ-opioid receptors-mediated feedback inhibition, which leads to a decrease in the β-END response (Kennedy et al., 2006). This reduction in the endogenous opioid system activity may run in parallel to deactivation of the HPA axis after antidepressant treatment seen in some studies and also correlated with a satisfactory antidepressant response (Heuser et al., 1996; Holsboer and Barden, 1996; Young et al., 2004; Navinés et al., 2007b). Indeed, ACTH and β-END are derived from the same precursor, the POMC, and either hormone serves as an index of CRF secretion (Young et al., 2000). Therefore, potential therapies that selectively block CRF secretion or act in the β-END neurotransmission may prove useful as novel antidepressant treatments.

The study has some limitations. Buspirone affects dopamine transmission (Cownen et al., 1994) and is not an ideal drug to challenge the serotonergic system. We used buspirone for its availability and the extensive data attesting its clinical safety (Cownen et al., 1994). However, we cannot exclude that altered responses to the challenge in treatment in depressed patients are due to a test–test phenomenon explained for a time effect instead of a specific action of citalopram on the 5-HT1A receptor–β-END interaction. The administration of citalopram leads to a statistically significant decrease in serum β-END level in depressed patients. This could account for decreased β-END response after treatment. On the other hand, citalopram could increase plasma buspirone levels and the results may correspond to changes in plasma pharmacokinetics of buspirone (Anderson et al., 1996). Plasma buspirone levels were not measured in our study. Finally, the placebo and the citalopram conditions were excluded in depressed patients and healthy subjects, respectively, for ethical reasons.

Despite the absence of a controlled experimental design, repeat assessment of control subjects or a direct in vivo measurement of 5-HT1A receptor availability, the present findings seem to suggest an association between the modulating 5-HT1A receptor–β-END interaction by citalopram treatment and the therapeutic response. Moreover, the study may suggest that functionality of post-synaptic 5-HT1A receptor that putatively mediates the β-END response is unchanged in depressed patients compared with healthy controls, but are rendered subsensitive by chronic citalopram administration in patients with major depression. The interaction between 5-HT1A receptor system and β-END may be considered when assessing mood circuits and the action of antidepressant drugs.

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