

# Enhancement of stress-induced pituitary hormone release and cardiovascular activation by antidepressant treatment in healthy men

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A randomized, double-blind, placebo-controlled trial was performed to verify the suggestion that (i) in accordance with the results of animal studies, treatment with antidepressants inhibits hormone release in response to stressful stimulation in humans and (ii) drugs with opposing effects on brain serotonin (citalopram and tianeptine) exert similar modulatory effects on neuroendocrine activation during stress. Healthy male volunteers were treated with citalopram (20 mg), tianeptine (37.5 mg) or placebo for 7 days. As a stress stimulus, insulin-induced hypoglycaemia was used. Measurement of hormone concentrations revealed an enhanced release of adrenocorticotrophic hormone and growth hormone in response to stress of hypoglycaemia in subjects treated with both antidepressants used. A similar augmentation was observed in systolic blood pressure. Stress-induced prolactin release was potentiated by citalopram only. Plasma renin activity, epinephrine, norepinephrine and cortisol levels failed to be modified by antidepressants. The present study demonstrates that (i) repeated antidepressant treatment in healthy men does not inhibit, but enhances, neuroendocrine activation during stress and (ii) such effects were observed after treatment with antidepressants having opposing actions on brain serotonin, indicating involvement of nonserotonergic mechanisms.

**Key words:** antidepressants, blood pressure, healthy volunteers, hormones, serotonin, stress

## Introduction

Stress is generally considered to be one of the factors involved in the pathogenesis of affective disorders (McEwen, 2000; Holsboer, 2001). The dominant part of the stress response is neuroendocrine activation with consequent alterations in psychosomatic functions (Stratakis and Chrousos, 1995). Neuroendocrine activation includes profound changes in central neurotransmitter systems as well as increased release of stress hormones, such as cortisol, catecholamines, adrenocorticotrophic hormone (ACTH), growth hormone, prolactin or angiotensin II. Of particular importance is the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, as its disturbances have been implicated in the development of major depression and other psychiatric disorders (Arborelius *et al.*, 1999; Holsboer, 2000; Pariante and Miller, 2001).

Neuroendocrine system is a target for antidepressant drug action. It is well known that antidepressants affect monoaminergic neurotransmission and they may also modulate central neuropeptides (e.g. corticotropin releasing hormone, CRH), a peptide involved in the coordination of stress response and the control of HPA axis. CRH antagonists modulate neuroendocrine changes during stress (Deak *et al.*, 1999; Ježová *et al.*, 1999) and exert antidepressive and anxiolytic effects (Zobel *et al.*, 2000; Keck and Holsboer, 2001).

The relationship between antidepressants and stress is further substantiated by their effects on stress hormone release. Acute administration of antidepressants leads to a rise in hormone secretion, whereas prolonged treatment can be associated with inhibitory effects. Thus, decreased levels of plasma corticosterone and ACTH were observed after chronic treatment with several antidepressants (Holsboer and Barden, 1996).

The inhibitory action of antidepressants on hormone release observed under basal conditions suggests an attenuation of neuroendocrine activation during stress. Indeed, such effects were observed in preclinical studies. In experimental animals, long-term treatment with amitriptyline, moclobemide or tianeptine reduced HPA axis activation in response to stress stimuli (Delbende *et al.*, 1994; Reul *et al.*, 1994). However, other treatments were found to be ineffective (Duncan *et al.*, 1998) and two studies described a stimulatory action of fluoxetine on stress-induced rise in plasma corticosterone (Ježová *et al.*, 1984; Durand *et al.*, 1999). Surprisingly, no information is available on the effects of antidepressants on hormone release during stress exposure in humans.

The aim of the present investigation was to verify the hypothesis that (i) in accordance with the results of animal studies, treatment with antidepressants inhibits hormone release in response to stressful stimulation in humans and (ii) drugs with

opposing effects on brain serotonin (citalopram and tianeptine) exert similar modulatory effects on neuroendocrine activation during stress. As a stress stimulus, insulin-induced hypoglycaemia was selected because hypoglycaemia induces the release of a wide spectrum of hormones (Ježová *et al.*, 1998) and the insulin tolerance test is a clinically useful tool to assess pituitary function (Mahajan and Lightman, 2000)

## Subjects and methods

### Subjects

A total of 31 healthy male volunteers, aged 20–27 years, participated in the investigation. Subjects were included if they had normal body weight (body mass index between 19–26 kg/m<sup>2</sup>), were not currently taking any medication, and avoided alcohol and excessive physical activity at least 24 h before the study. Subjects were excluded from the study if they were suffering from any somatic or mental diseases (as approved by general and psychiatric examination), had a family history of psychiatric disorders or had a control blood pressure higher than 140/90 mmHg. The subjects gave their written informed consent to participate after the procedures and possible side-effects were explained to them. The study was performed in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of the Slovak Academy of Sciences, Bratislava, Slovakia.

### Drug treatments

The study was designed as a randomized, double-blind, placebo-controlled trial. All treatments were given three times daily (one of active drugs or placebo) with the main meals for 7 days. The subjects were treated with tianeptine (Coaxil, synonym Stablon, Servier, Neuilly Sur Seine, France, 37.5 mg p.o. daily divided in three doses) or citalopram (Seropram, Lundbeck, Valby, Denmark, 20 mg p.o. daily in one dose in the morning while placebo was given at noon and evening) or placebo given in the same manner as the active drugs. The subjects were asked not to take any alcoholic beverages, to be aware of any unusual signs or feelings during the treatment and to call the investigators in the case of any problem.

### Stress model

Hypoglycaemia was induced by administration of insulin (Actrapid Human, Novo, Bagsvaerd, Denmark, 0.1 IU/kg i.v.). An appropriate dose of insulin was diluted in 5 ml of isotonic saline and injected into the catheter inserted in a cubital vein within 1 min.

### Procedure and measurements

After 7 days of drug treatment, the investigations started the following morning at 07.30 h after an overnight fast. Each subject was seated and asked to take the last dose of his treatment. Subsequently, an indwelling catheter was inserted into a cubital vein and the subject remained in the sitting position. The first blood sample for measurement of basal pre-stress hormone levels was taken at least 30 min after catheter insertion and exactly 45 min after the last drug administration. Insulin was injected 60 min after the drug and blood samples were collected at 30, 45, 60 and 90 min after insulin injection. Blood pressure was recorded (Dinamap, Critikon, Stampa, FL, USA) before each blood sample. Blood was divided into two polyethylene tubes using heparin

(catecholamines, glucose) or ethylenediaminetetraacetic acid (ACTH, cortisol, growth hormone, prolactin, plasma renin activity) as anticoagulants. After centrifugation at 4 °C, aliquots of plasma were stored frozen at –30 °C until analysed. Concentrations of ACTH and cortisol were measured in unextracted plasma by radioimmunoassay (RIA) as described previously (Ježová and Vigaš, 1988). Commercial kits were used for immunoradiometric assay of growth hormone (Immunotech, Marseille, France) and prolactin (Immunotech, Prague, Czech Republic). Plasma catecholamines were analysed by the radioenzymatic method according to Peuler and Johnson (1977) and plasma renin activity by RIA (Immunotech, Prague, Czech Republic). Blood glucose was determined using the glucose-oxidase method (Boehringer Mannheim, Mannheim, Germany).

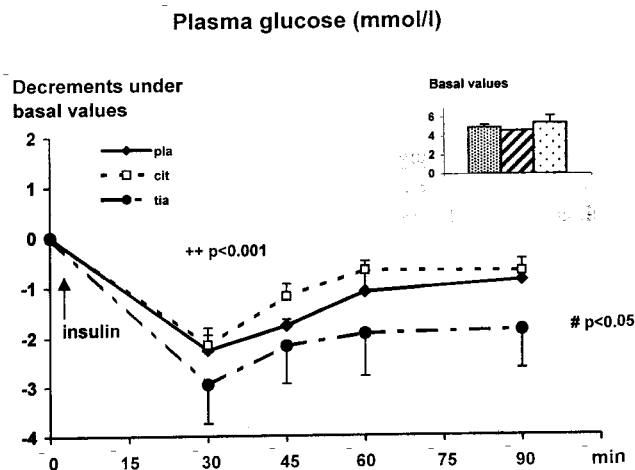
### Statistical analysis

Statistical evaluation of the results was performed using two-way analysis of variance followed by a post-hoc Tukey's test. Calculations were performed using Jandel Sigma Stat statistical software. Data are presented as means ± SEM of the increments above the basal pre-stress values. Basal levels in absolute values are shown in the upper right corner of each figure.

## Results

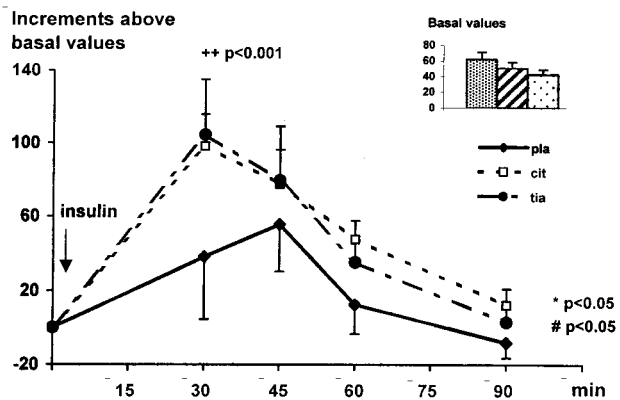
The compliance of the volunteers was very good. With the exception of one subject, who forgot to take his tablets twice (and who was finally found to be in the placebo group), all volunteers claimed to fulfil the criteria set for the trial. No serious adverse effects were reported. Transient problems (lasting less than 2 days), such as strange feelings, drowsiness or slight headache were mentioned by some volunteers in all treatment groups at the beginning of the treatment period.

As expected, insulin administration induced a decrease in blood glucose ( $F = 10.6$ ,  $p < 0.001$ ), which reached the nadir at 30 min and then returned towards the control levels (Fig. 1). No

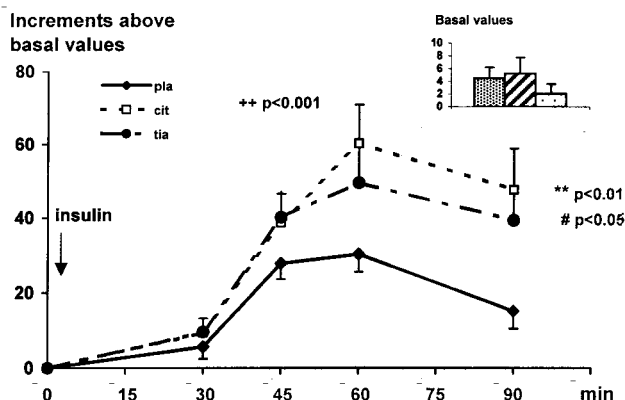


**Figure 1** Decrease in plasma glucose levels induced by insulin infusion (0.1 IU/kg i.v.) in citalopram (cit), tianeptine (tia) or placebo (pla) treated subjects. Statistical significance, two-way ANOVA: effect of time  $++p < 0.001$ ; effect of treatment  $p < 0.05$ ; post-hoc test (treatment), tia versus cit  $\#p < 0.05$

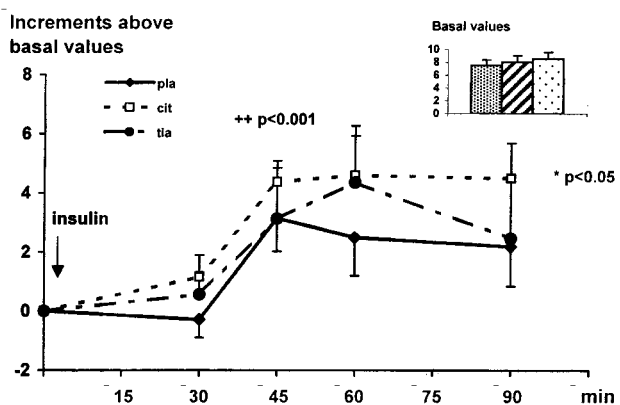
## ACTH (pg/ml)



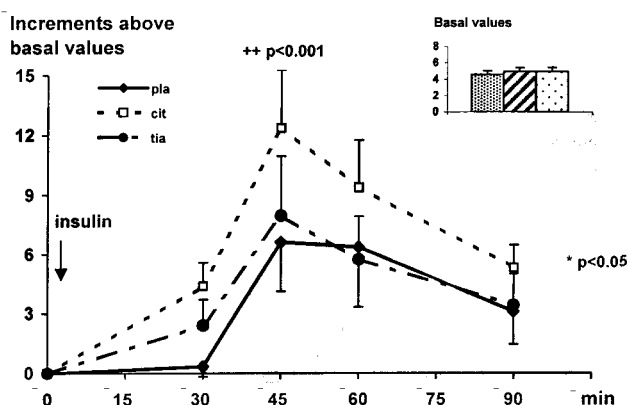
## Growth hormone (mIU/l)



## Cortisol (ug/100ml)



## Prolactin (ng/ml)



**Figure 2** Elevation of plasma ACTH and cortisol levels during stress of hypoglycaemia in subjects treated with citalopram (cit), tianeptine (tia) or placebo (pla) for 7 days. Statistical significance: effect of time ++  $p < 0.001$ ; post-hoc test (treatment), cit versus pla \*  $p < 0.01$ ; tia versus pla #  $p < 0.01$

**Figure 3** Enhancement of growth hormone response during stress of hypoglycaemia by treatment with citalopram (cit) or tianeptine (tia) in comparison to placebo (pla). The rise in plasma prolactin levels was potentiated in citalopram treated subjects only. Statistical significance: effect of time ++  $p < 0.001$ ; post-hoc test (treatment), cit versus pla \*  $p < 0.05$ , \*\*  $p < 0.01$ ; tia versus pla #  $p < 0.01$

statistically significant differences in blood glucose concentrations were found between placebo and any of the antidepressant treated groups. Insulin-induced hypoglycaemia was somewhat more prolonged in subjects treated with tianeptine ( $p < 0.05$ ) compared to the values in citalopram but not placebo treated group.

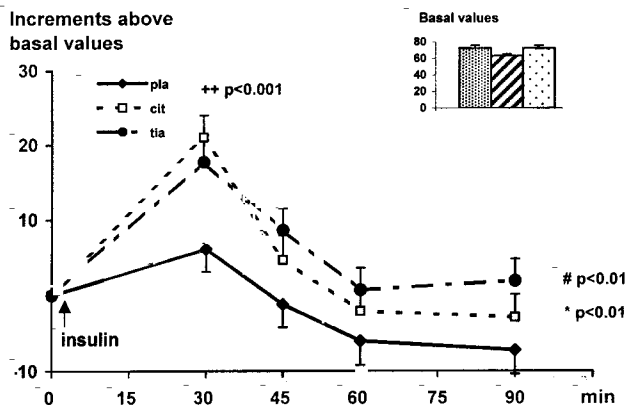
ACTH levels increased significantly in response to insulin hypoglycaemia (Fig. 2). Two-way ANOVA revealed differences for both time ( $F = 12.5$ ,  $p < 0.001$ ) and treatment ( $F = 3.3$ ,  $p < 0.05$ ). ACTH responses were enhanced in subjects treated with both antidepressants compared to those treated with placebo. The differences between the values in placebo versus citalopram, as well as placebo versus tianeptine-pretreated groups, were found to be statistically significant ( $p < 0.05$ ). The changes in cortisol levels were less pronounced. Stress of hypoglycaemia was associated with a similar rise in cortisol levels in the control and tianeptine-pretreated groups. In subjects treated with citalopram, the elevation in cortisol levels was more pronounced and prolonged compared to that in the control group (Fig. 2), but this

difference was statistically significant if evaluated by a one-way ANOVA only.

Release of growth hormone induced by insulin hypoglycaemia was significantly potentiated by both citalopram and tianeptine treatments (Fig. 3). Statistically significant differences were found for both time ( $F = 26.1$ ,  $p < 0.001$ ) and treatment ( $F = 7.0$ ,  $p < 0.001$ ). Thus, the rise in growth hormone release during stress was higher in subjects treated with citalopram ( $p < 0.01$ ) as well as with tianeptine ( $p < 0.05$ ) compared to those treated with placebo. There were no differences between the groups treated with citalopram or tianeptine. Similarly, changes in prolactin levels showed significant differences for both time ( $F = 11.0$ ,  $p < 0.001$ ) and treatment ( $F = 3.2$ ,  $p < 0.05$ ). However, a potentiation of stress-induced prolactin release was found in citalopram-pretreated volunteers ( $p < 0.05$ ), while this hormone levels were similar in tianeptine and placebo treated groups (Fig. 3).

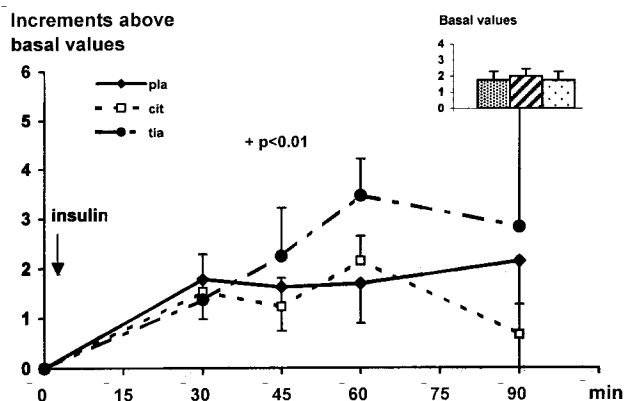
With respect to cardiovascular responses, changes in systolic

## Systolic blood pressure (Torr)

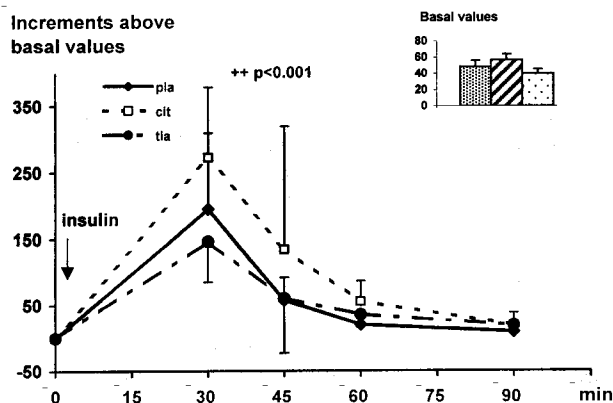


**Figure 4** Enhancement of systolic blood pressure response during stress of hypoglycaemia by treatment with citalopram (cit) or tianeptine (tia) in comparison to placebo (pla). Statistical significance: two-way ANOVA: effect of time  $++p < 0.001$ ; effect of treatment  $p < 0.001$ ; post-hoc test (treatment), cit versus pla  $*p < 0.01$ ; tia versus pla  $\#p < 0.01$

## Plasma renin activity (ng/ml)



## Epinephrine (pg/ml)



**Figure 5** Increase of plasma renin activity and epinephrine levels during stress of hypoglycaemia in subjects treated with citalopram (cit), tianeptine (tia) or placebo (pla) for 7 days. Statistical significance: effect of time  $+p < 0.01$ ,  $++p < 0.001$

blood pressure reached statistical significance for both time ( $F = 22.4$ ,  $p < 0.001$ ) and treatment ( $F = 10.5$ ,  $p < 0.001$ ). Stress-induced rise in systolic blood pressure was significantly higher in the citalopram and tianeptine groups ( $p < 0.01$ ) compared to that in subjects treated with placebo (Fig. 4). Diastolic blood pressure decreased in time ( $F = 3.6$ ,  $p < 0.01$ ), but no statistically significant differences among groups were observed (data not shown).

Plasma renin activity rose in response to insulin-induced hypoglycaemia ( $F = 5.8$ ,  $p < 0.001$ ) in all groups (Fig. 5). With respect to treatment, no significant differences were observed. Concentrations of epinephrine in plasma increased significantly ( $F = 9.4$ ,  $p < 0.001$ ) in a similar manner in all treatment groups (Fig. 5). Insulin-induced hypoglycaemia was not accompanied by significant changes in plasma norepinephrine (data not shown).

## Discussion

The present study shows that treatment with antidepressants in healthy men results in an augmentation of neuroendocrine response during stress of hypoglycaemia, manifested by increased release of ACTH, growth hormone and prolactin, as well as by enhanced rise in systolic blood pressure. A similar influence on neuroendocrine function was achieved by two antidepressants having opposing actions on brain serotonin (i.e. citalopram and tianeptine).

According to our original hypothesis based on preclinical studies, and also according to a general belief, treatment with antidepressants should have induced an attenuation of the stress response. The opposite effect observed in the present study was an unexpected finding. It was not due to altered intensity of the stress stimulus, as the degree of hypoglycaemia in antidepressant treated groups was not different from that in the control, placebo treated group. It may be argued that the observed changes are specific to the stress of hypoglycaemia. Indeed, stress-induced changes, as well as the mechanisms involved, are affected by several factors, particularly by the character of the stress stimulus (Vigaš *et al.*, 1984; Ježová and Škultétyová, 1997; Pacak *et al.*, 1998). However, our preliminary data show that a similar treatment with antidepressants results in an attenuation of cardiovascular responses to a mental stress (Dunčko *et al.*, unpublished data).

Enhanced neuroendocrine activation during acute stress induced by antidepressant treatment may be of clinical relevance. Data obtained in the limited number of human studies dealing with stress in depression indicate a reduced neuroendocrine activation in depressed patients. Patients with major depression were found to exhibit decreased responses of ACTH or prolactin to the stress of hypoglycaemia (Grof *et al.*, 1982; Lopez *et al.*, 1987; Kathol *et al.*, 1992), attenuated beta-endorphin responses in Trier's social stress test (Young *et al.*, 2000) and lower cardiovascular activation in response to a cognitive challenge (Gotthardt *et al.*, 1995). It may be that an augmentation of neuroendocrine and cardiovascular activation induced by antidepressant treatment, as observed in the present study, leads to a normalization of the stress response in patients. However, as the present study was performed in healthy subjects, a similar modulation of acute stress responses by antidepressants in depressed patients remains to be confirmed. Because only some depressive patients exhibit increased basal cortisol levels, while a higher sensitivity and specificity was observed in the dex/CRH test (Heuser *et al.*, 1994; Holsboer,

2000), an evaluation of neuroendocrine activation during stress might be of clinical value.

The mechanism of action of antidepressants is not fully understood. The main characteristic of drugs used in the treatment of depression is their ability to enhance monoaminergic neurotransmission, particularly by inhibiting reuptake of monoamines in nerve endings (Pacher *et al.*, 2001). This applies to one or more of the key neurotransmitters (i.e. norepinephrine, serotonin and dopamine) (Chaouloff, 2000). However, some drugs, such as tianeptine, cause a reduction of serotonin availability in the brain (De Simoni *et al.*, 1992; Ortiz *et al.*, 1993), which is opposite to the action of the most widely used group of antidepressants acting as specific serotonin reuptake inhibitors.

Thus, other mechanisms appear to exist, which would be common for drugs acting differently on brain monoamines. Indeed, such mechanisms may be suggested on the basis of the present findings showing the ability of both citalopram and tianeptine to enhance neuroendocrine activation during stress. The common effects of citalopram and tianeptine were observed on ACTH and growth hormone release, as well as on changes in systolic blood pressure, during stress of insulin-induced hypoglycaemia.

Single intravenous infusion of citalopram is known to increase plasma cortisol and prolactin levels in healthy individuals and the procedure was suggested as a neuroendocrine challenge test for the investigation of serotonergic function in psychiatric illness (Seifritz *et al.*, 1996; Kapitany *et al.*, 1999; Attenburrow *et al.*, 2001). The results obtained in the present study show that repeated oral treatment with citalopram has no effect on basal hormone levels (prolactin, growth hormone, ACTH, cortisol) and does not modify plasma renin activity or blood pressure in healthy males. The same was true for tianeptine treatment. On the other hand, neuroendocrine activation during stress was found to be potentiated by both treatments. The actions of citalopram and tianeptine were similar. Neuroendocrine and cardiovascular parameters studied were either unaffected (epinephrine, plasma renin activity) or augmented (growth hormone, ACTH, systolic blood pressure). The only exception was observed in stress-induced prolactin release, which was enhanced by citalopram but not tianeptine administration. This finding may be considered as additional evidence for a crucial role of serotonin in stimulating prolactin secretion during stress, which is in line with the well-documented involvement of serotonin in the control of pituitary prolactin release (Freeman *et al.*, 2000). It should be noted that prolactin levels were not modified by tianeptine treatment despite a slightly greater decrease of plasma glucose compared to that in the citalopram treated group.

The present data further indicate that cortisol is not an optimal indicator of ACTH release as the changes in ACTH levels were much more evident than those in cortisol secretion. However, the observation period of 90 min was not long enough to reveal any possible differences in the duration of the cortisol response, which might be induced by the drug treatments used. Although plasma renin activity and plasma catecholamine concentrations failed to be modified by citalopram or tianeptine, the rise in systolic blood pressure was enhanced in both treatment groups. Interestingly, increased noradrenergic function, as evaluated by excretion of a melatonin metabolite, was observed in responders to antidepressant therapy (fluvoxamine, imipramine). It was suggested that enhanced noradrenergic function might play an important role in determining the clinical response to antidepressant treatment (Miller *et al.*, 2001). Alterations in central monoamines in line with modulation

of HPA axis function can also be observed in animal models of depression (Dunčko *et al.*, 2001).

In conclusion, the present study demonstrates that repeated antidepressant treatment in healthy men does not inhibit, but enhances neuroendocrine activation during stress. Such effects were observed after treatment with antidepressants having opposing actions on brain serotonin. Stress induces both protective and damaging effects on the body (McEwen, 2000). It is suggested that an enhancement of neuroendocrine activation to acute stress stimuli may be of benefit for patients with depression, in which an attenuated stress response has been reported.

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