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Impact on cortisol and antidepressant efficacy of quetiapine and escitalopram in depression☆

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Summary
Background: In this study, the impact of quetiapine fumarate extended release (QXR) and escitalopram (ESC) on HPA axis activity was investigated in depressed patients in relationship to antidepressant efficacy.
Methods: In a randomized, open-label 5-week trial 60 inpatients suffering from major depression (DSM-IV criteria) were treated for 5 weeks with either QXR (300 mg/day) or ESC (10 mg/day). The dexamethasone/CRH (DEX/CRH) test was performed before treatment, after 1, and after 5 weeks of treatment. Cortisol (COR) AUC values were used to assess HPA axis function. The Hamilton Depression Rating Scale was used weekly to estimate antidepressant efficacy.
Results: QXR and ESC showed comparable antidepressant effects but strongly differed in their impact on HPA axis activity. In the QXR group, a marked inhibition of COR AUC levels was observed which was most pronounced after one week of treatment but showed a partial re-increase after 5 weeks of treatment. In contrast, ESC transiently stimulated COR AUC values (week 1) whereas COR AUC levels at week 0 and week 5 were comparable. COR improvement at week 1 (defined as COR peak value reduction between DEX/CRH test 1 and 2) was significantly associated with better clinical outcome.

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Conclusion: Apparently, different effects on HPA axis activity reflect distinct pharmacoendocrinological properties of psychotropic drugs.

1. Introduction

One of the most widely discussed moderating or mediating factors regarding the etiology of major depression is a dysregulation of hypothalamic-pituitary-adrenocortical (HPA) axis activity (Holsboer, 2000, 2001). Proponents of the corticosteroid receptor hypothesis (neuroendocrinological hypothesis) of depression argue that a gradual normalization of HPA system dysregulation, as measured by serial dexamethasone/CRH (DEX/CRH) tests, precedes or coincides with the response to antidepressant treatment (Holsboer, 2000, 2001; Ising et al., 2007). The reduction of HPA axis activity is a necessary prerequisite for clinical remission to become manifest and also assert that all antidepressants developed so far may have a dampening impact on HPA axis function, irrespective of their type of action within monoaminergic systems (Ising et al., 2007; Schule et al., 2009).

However, the rate of non-suppression in the DEX/CRH test in acutely depressed patients is inconsistent in more recent studies and lies within the range between 20 and 30 percent (Ising et al., 2005; Schule et al., 2009). A considerable part of acutely depressed patients shows normally regulated HPA axis activity in the DEX/CRH test already before antidepressant treatment and may nevertheless benefit from these drugs. Some researchers even found an enhanced HPA system activity at discharge in a certain proportion of depressed patients in spite of clinical recovery (Zobel et al., 2001; Schule et al., 2009). On the other hand, down-regulation of HPA axis activity in depressed patients is not necessarily followed by a favorable response (Schule et al., 2009). These apparently contradictory findings suggest that down-regulation of an increased HPA axis activity may be partly involved in the pathophysiology of depression and its treatment but is a neither necessary nor sufficient condition for a beneficial treatment outcome (Schule et al., 2009).

Moreover, the assumption of a uniform normalizing influence of different types of antidepressants on HPA axis hyperactivity — irrespective of their mode of action — is challenged by the finding that various antidepressants show different effects on cortisol (COR) and acetylcholine (ACTH) release after acute administration in healthy volunteers (Laakmann, 1988). Whereas inhibitors of noradrenaline and/or serotonin reuptake acutely stimulate COR and ACTH secretion (Laakmann, 1988), other antidepressants with different pharmacodynamic properties, such as mirtazapine, do not (Schule, 2007). Mirtazapine is not a reuptake inhibitor but acts as an antagonist at presynaptic α_2-receptors and at postsynaptic 5-HT_2, 5-HT_3, and histamine H_1 receptors (De Boer, 1995). In several investigations, our research group could demonstrate that single administration of 15 mg mirtazapine acutely inhibits ACTH and COR release in healthy male controls, presumably due to central antagonism at H_1 and 5-HT_2 receptors thereby reducing the hypothalamic CRH output (Schule et al., 2002). Whereas reuptake inhibitors of serotonin (Bschor et al., 2012) or noradrenaline (Schule et al., 2006) show a delayed and gradual down-regulation of HPA axis activity in depressed patients, mirtazapine markedly inhibits HPA system function already after 1 week of treatment, followed by a partial re-increase of COR levels in the DEX/CRH test after 5 weeks of therapy (Schule et al., 2006).

In the present study, the influence of 5-week treatment with the atypical antipsychotic drug quetiapine fumarate extended release (QXR) and of the selective serotonin-reuptake inhibitor escitalopram (ESC) on the time course of HPA axis activity was investigated in depressed inpatients. Quetiapine is an atypical antipsychotic which acts as an antagonist with high affinity at histaminergic H_1 receptors; with moderate affinity at serotonergic 5-HT_{1A} and 5-HT_2, adrenergic α_1, and dopaminergic D_{1-3} receptors; and almost no affinity for D_4, α_2, and muscarinic acetylcholine (ACh) receptors or benzodiazepine binding sites (Green, 1999). The pharmacological effects of quetiapine have some similarities compared to mirtazapine: both drugs are antagonists at 5-HT_2 and H_1 receptors which may cause inhibition of hypothalamic CRH release and consecutively inhibit ACTH and COR secretion (Schule, 2007). In addition, quetiapine is an antagonist at α_1-receptors; this pharmacological property is also expected to reduce hypothalamic CRH secretion (Schule, 2007). In fact, both mirtazapine (Laakmann, 1988; Schule et al., 2002) and quetiapine (de Borja et al., 2005) have been shown to acutely inhibit ACTH and/or COR secretion after single administration in healthy male volunteers.

Quetiapine, which has primarily been developed as an atypical antipsychotic, has also been demonstrated to have antidepressant properties as monotherapy in the acute treatment of bipolar depression at dosages of 300 and 600 mg/day (Calabrese et al., 2005; McElroy et al., 2010). Moreover, extended release quetiapine fumarate (QXR) may exert significant antidepressant efficacy both in acute treatment (Cutler et al., 2009; Katila et al., 2012) and maintenance therapy (Liebowitz et al., 2010) of unipolar depression, when given as monotherapy at dosages of 150 or 300 mg/day. In addition, the onset of antidepressant action during treatment with QXR appears to be earlier than that of conventional antidepressant drugs such as duloxetine (Cutler et al., 2009). The efficacy of quetiapine or QXR as an augmentation strategy in the treatment of major depressive episodes has also been shown in several controlled (McIntyre et al., 2007; Bauer et al., 2010; El-Khalili et al., 2010) or open-label (Devarajan et al., 2006; Sagud et al., 2006; Anderson et al., 2009) trials.

The aim of the study was to investigate the influence of 5-week treatment with QXR monotherapy on HPA axis activity in depressed inpatients and to answer the question whether putative changes in HPA system function are related to the antidepressant effects of QXR. Moreover, ESC which is the S-enantiomer of citalopram and is one of the most potent SSRIs due to its special affinity for the allosteric and orthosteric binding sites of the serotonin-transporter (Plenge et al., 2007) served as an active comparator drug.