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Influence of Mirtazapine on Salivary Cortisol in Depressed Patients

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Key Words
Mirtazapine · Saliva · Cortisol · Depressive disorder · Treatment response

Abstract
Unlike other antidepressants, mirtazapine does not inhibit the reuptake of norepinephrine or serotonin but acts as an antagonist at presynaptic α_2-receptors, at postsynaptic 5-HT2 and 5-HT3 receptors, and at histaminergic H1 receptors. Furthermore, mirtazapine has been shown to acutely inhibit cortisol secretion in healthy subjects. In the present study, the impact of mirtazapine treatment on salivary cortisol secretion was investigated in 12 patients (4 men, 8 women) suffering from major depression according to DSM-IV criteria. Patients were treated with mirtazapine for 3 weeks, receiving 15 mg mirtazapine on day 0, 30 mg on day 1 and 45 mg per day from day 2 up to the end of the study (day 21). Response to mirtazapine treatment was defined by a reduction of at least 50% in the Hamilton Rating Scale for Depression after 3 weeks of therapy. Salivary cortisol concentrations were measured before treatment (day –1), at the beginning of treatment (day 0), after 1 week (day 7) and after 3 weeks (day 21) of treatment with mirtazapine. Saliva samples were collected hourly from 08.00 until 20.00 h. The area under the curve values served as parameter for the salivary cortisol secretion. Following analysis of variance with a repeated measures design, tests with contrasts revealed a significant reduction of cortisol concentrations already after 1 day of mirtazapine treatment that was comparable in responders and nonresponders. In addition to new pharmacological approaches such as CRH1 receptor antagonists, mirtazapine therefore appears to be an effective strategy to decrease hypercortisolism and restore HPA system dysregulation in depression. However, the importance of the acute inhibitory effects of mirtazapine on cortisol secretion for its antidepressant efficacy has to be further clarified.

Introduction

The neuroendocrine challenge paradigm is based on the involvement of monoamine pathways in the control of anterior pituitary hormone secretion [1]. Psychotropic drugs with different effects on the central neurotransmitter system have distinct effects on the anterior pituitary hormone secretion and can be characterized by certain pharmacoendocrinological profiles (table 1). Antidepressants which primarily act via noradrenaline (NA) reuptake inhibition (e.g. desimipramine, DMI) stimulate growth hormone (GH) secretion [23], whereas serotonin (5-HT) reuptake-inhibiting antidepressants (e.g. indalpine, chlorimipramine) are characterized by prolactin (PRL) stimulation [4]. Cortisol (COR) secretion can acutely be increased by antidepressants with both NA or 5-HT reuptake inhibition; the stimulatory effects of antidepressants on COR secretion are mediated via stimulation of the ACTH output of the pituitary gland [4].

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Table 1. The influence of acute administration of antidepressant agents on neurotransmitter reuptake in vitro (IC_{50} values) and GH, PRL and COR secretion in man

NA	5-HT	DA				GH	PRL	COR
0.9	210	V	DMI	25 mg	i.v.	+++	++	+++
			DMI	100 mg	p.o.	+++	+	+++
1.1	V	V	*D*-Oxa	75 mg	i.v.	+++	0	+++
V	V	V	*L*-Oxa	75 mg	p.o.	0	0	0
6.6	830	48	NF	200 mg	p.o.	++	–	n.a.
24	1.5	V	CI	25 mg	i.v.	++	+++	+++
			CI	100 mg	p.o.	++	+	+
V	2.4	V	IND	25 mg	i.v.	0	++	+++

V = IC_{50} >1,000 n*M*; NA = noradrenaline; 5-HT = serotonin; DA = dopamine; DMI = desipramine; Oxa = oxaprotiline; NF = nomifensine; CI = chlorimipramine; IND = indalpine; i.v. = intravenous; n.a. = not available; p.o. = per os; +++ = strong stimulation; ++ = moderate stimulation; + = slight stimulation; – = inhibition; 0 = no significant effect. Table modified from Hyttel [2].

Unlike other antidepressants, mirtazapine does not inhibit the reuptake of norepinephrine or serotonin but acts as an antagonist at presynaptic α_2-receptors and at postsynaptic 5-HT2 and 5-HT3 receptors [5]. Mirtazapine enhances NA release by blocking α_2-autoreceptors [5, 6]. Serotonergic neurotransmission is also increased by mirtazapine, especially in the hippocampus, via two synergistic mechanisms: an increase of 5-HT cell firing and a blockade of α_2-adrenergic heteroreceptors at the 5-HT nerve terminals [7–9]. In addition, mirtazapine is an antihistaminergic agent with a high affinity for histamine H1 receptors [10] and has only few anticholinergic side effects. Average peak plasma concentrations are achieved 2 h after oral dosing and the elimination half-life is in the range of 20–40 h [11].

In former studies of our research group mirtazapine was shown to acutely inhibit COR and ACTH secretion in healthy subjects, whereas GH and PRL secretion patterns remained unchanged [12, 13]. The endocrinological effects of mirtazapine observed in healthy volunteers strongly differ from those seen in reuptake-inhibiting antidepressants and may reflect the unique mechanism of action of mirtazapine. Whereas reuptake inhibitors acutely stimulate the COR release of the adrenal gland in healthy volunteers [4, 14–16], mirtazapine obviously acts as an acute cortisol inhibitor in normal controls.

The COR inhibition after first-time administration of mirtazapine in normal volunteers is of special interest in the light of the hypercortisolism demonstrated in depressive patients. Preclinical and clinical studies suggest that hypothalamic-pituitary-adrenal (HPA) system dysregulation is related to the occurrence of depression [17]. Significantly elevated urinary free COR excretion or 24-hour COR blood concentrations have been shown in severely depressed patients [18–23]. Furthermore, COR escape from dexamethasone suppression has been reported during major depression [24–27]. If the combined dexamethasone suppression/CRH stimulation test (DEX/CRH test) is used, the sensitivity in discriminating between depressive patients and healthy controls can be further increased [28]. These findings give reason to ask whether mirtazapine is able to rapidly restore HPA axis dysregulation in depressive disorder by acute reduction of COR secretion patterns.

Methods

Subjects

The study was carried out according to the fifth revision of the Declaration of Helsinki [29] and had been approved by an ethics committee. Twelve depressive inpatients (4 men, 8 women) gave informed written consent and were included in this study. Inclusion criteria were (a) a major depressive episode according to DSM-IV criteria [30]; (b) a score of at least 18 on the 21-item Hamilton Depression Rating Scale (21-HAMD [31]); (c) no history of substance abuse or dependency; (d) exclusion of neurological or medical disorders, and (e) no psychotropic drugs for at least 5 days prior to the study, except chloralhydrate given in case of patients experiencing difficulties sleeping. Any physical illness was ruled out by a thorough physical and psychiatric examination and routine laboratory test, including electrocardiogram and electroencephalogram. None of the female patients received hormonal contraceptives or hormone replacement therapy. Clinical characteristics are given in table 2.

Mirtazapine Treatment, Collection of Saliva Samples and Clinical Ratings

The 12 patients were treated with mirtazapine monotherapy for at least 3 weeks. They received 15 mg mirtazapine at 08.00 h on day 0; 30 mg on day 1 (15 mg at 08.00 h, 15 mg at 22.00 h), and 45 mg/

Table 2. Demographic and clinical data of 12 depressed patients treated with mirtazapine

Patient	Sex/age, years	DSM-IV diagnosis	21-HAMD				Response
			day –1	day 0	day 7	day 21	
1	M/25	296.23	28	26	10	5	R
2	F/60	296.24	36	36	33	32	NR
3	F/30	296.33	35	32	22	14	R
4	F/41	296.32	26	27	25	16	NR
5	F/48	296.32	23	23	13	9	R
6	F/34	296.32	29	28	24	19	NR
7	F/28	296.23	33	29	23	19	NR
8	F/21	296.33	28	27	25	27	NR
9	M/40	296.32	19	14	7	5	R
10	M/51	296.32	22	18	10	10	R
11	M/45	296.32	22	22	10	16	NR
12	F/56	296.32	20	18	12	10	R

21-HAMD: Hamilton Depression Rating Scale, 21-items, sum score; day –1: before mirtazapine treatment; day 0: first application of 15 mg mirtazapine; day 7 and day 21: continuation of mirtazapine treatment at a dosage of 45 mg/day; Response = ≥50% reduction in 21-HAMD sum score after 21 days of mirtazapine treatment; R = responder; NR = nonresponder.

day (15 mg at 08.00 h, 30 mg at 22.00 h) from day 2 up to the end of the study (day 21). Salivary COR concentrations were measured before treatment (day –1), at the beginning of treatment (day 0), after 1 week (day 7) and after 3 weeks (day 21) of treatment with mirtazapine. On each study day (–1, 0, 7, 21) saliva samples were collected hourly from 08.00 h up to 20.00 h. Severity of depression was assessed on the days of saliva sampling using the 21-HAMD. Response to mirtazapine treatment was defined by a reduction of at least 50% in the 21-HAMD sum score after 3 weeks of therapy. All raters were experienced psychiatrists and blind to hormonal measurements.

Measurement of Salivary COR

Saliva was obtained using special tubes containing a small cotton wool swab (Salivette, Sarstedt, Rommelsdorf, Germany). Patients were asked to take the tube, open it and put the cotton swab into the mouth. After 3 min patients had to take the swab out and put it back into the tube.

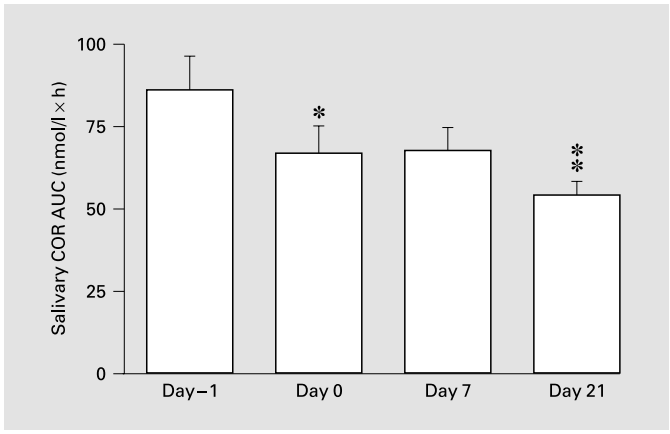
A special radioimmunoassay ('Magic COR', Ciba Corning, Fernwald, Germany) was used to determine COR concentrations in the salivary samples. As previously described by Kirschbaum et al. [32], this assay was slightly modified using diluted standards (1:10), a prolonged time of incubation (3.5 h), and a different amount of tracer as well as antibody to obtain a concentration range typical for saliva COR, which (representing the free fraction of the hormone) is about 1:10 lower in saliva than in peripheral blood.

Statistical Evaluation

The area under the curve (AUC) values between t = 0 h and t = 12 h served as parameter for the salivary COR secretion. Correlations between baseline AUC values (day –1) and both age and severity of illness at baseline (as measured by the 21-HAMD sum score at day –1) were tested for significance using Pearson's correlation coefficient. To compare the salivary COR secretion before and during mirtazapine treatment (day –1, 0, 7, and 21) and to compare the change in salivary COR levels during mirtazapine therapy between responders and nonresponders, a two-way ANOVA with a repeated measures design was carried out. 'Treatment', i.e. the salivary COR AUC values before and during mirtazapine treatment (day –1, 0, 7, and 21), was the within-subjects factor, whereas 'group' served as between-subjects factor (response versus nonresponse). As a follow-up procedure to make pairwise comparisons between the AUC values during mirtazapine treatment (day 0, 7, 21) and the baseline AUC values (day –1), respectively, tests with contrasts were performed. As a nominal level of significance, $\alpha = 0.05$ was accepted.

Results

Six patients responded to 3-week mirtazapine treatment, whereas the other 6 patients were nonresponders. At baseline (week 0), the 21-HAMD sum scores were comparable between responders and nonresponders (t = 1.410; d.f. = 10; p = n.s.). During mirtazapine treatment, responders showed a clear-cut amelioration of depressive symptoms, whereas nonresponders remained depressed. Mean 21-HAMD sum scores were (mean ± SD): responders day –1: 24.50 ± 6.02; day 0: 21.83 ± 6.52; day 7: 12.33 ± 5.16; day 21: 8.83 ± 3.43; nonresponders day –1: 29.00 ± 4.98; day 0: 28.17 ± 4.54; day 7: 23.33 ± 7.45; day 21: 21.50 ± 6.53. Male and female patients were comparable in baseline COR AUC values (t = 1.175; d.f. = 10; p = n.s.). However, there was a significant positive correlation between age and salivary COR AUC val-



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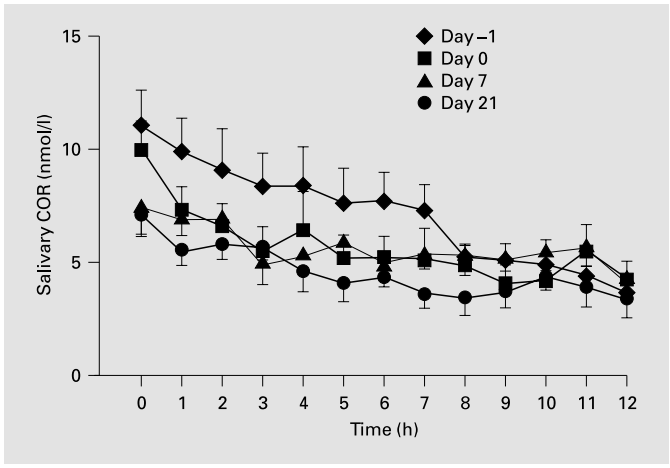

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Fig. 1. Means ± SEM of salivary COR AUC values in depressed patients (n = 12) on day –1 (before mirtazapine treatment), day 0 (first application of 15 mg mirtazapine), day 7 and day 21 (continuation of mirtazapine treatment at a dosage of 45 mg/day). * $p < 0.05$; ** $p < 0.01$. For further statistics please see Results.

Fig. 2. Means ± SEM of salivary COR concentrations in depressed patients (n = 12) on day –1 (before mirtazapine treatment), day 0 (first application of 15 mg mirtazapine), day 7 and day 21 (continuation of mirtazapine treatment at a dosage of 45 mg/day). Mean value graph represents the salivary COR concentrations from 08.00 (t = 0 h) to 20.00 h (t = 12 h).

ues on day –1 (r = 0.693; p = 0.013). Thus 'age' was considered a covariate in the repeated measures ANOVA in order to eliminate its influence on the possible effects of the factors 'treatment' and 'group'.

Before mirtazapine treatment, the mean salivary COR AUC value was 85.78 ± 37.16 nmol/l × hour. However, there was a pronounced reduction of COR AUC values after the first administration of mirtazapine (day 0) already, which lasted up to the end of the treatment period (day 0: 66.77 ± 30.24, day 7: 68.10 ± 22.99, day 21: 53.95 ± 14.79 nmol/l × hour; fig. 1, 2). Repeated measures ANOVA (Wilks' multivariate tests of significance) revealed a significant 'treatment' effect (F = 4.721; d.f. = 3, 7; sign. of F = 0.042), suggesting an significant inhibitory impact of mirtazapine on cortisol secretion. However, there was no significant 'group' effect (responders vs. nonresponders: F = 0.090; d.f. = 1, 9; sign. of F = 0.771) nor was there any significant 'treatment by group' effect (F = 0.377; d.f. = 3, 7; p = 0.773). In other words, the decline in cortisol secretion patterns (salivary COR AUC values) due to mirtazapine therapy was comparable between responders and nonresponders. In the post-hoc tests with contrasts, there was a significant decrease of COR AUC values already after the first day of mirtazapine treatment (p = 0.05). COR inhibition became also obvious on day 7; however, compared to baseline (day –1) the difference was not statistically significant (p = 0.07). On day 21, a highly significant reduction of COR secretion in comparison to day –1 could be demonstrated (p = 0.001).

Discussion

We found a positive correlation between age and COR secretion (salivary COR AUC values) at baseline (day –1). This result is in line with investigators who have found age to be positively associated with COR secretion during depression [33, 34], especially in women [35] and severely depressed patients [36].

The main finding of our investigation is that mirtazapine significantly decreases COR secretion in depressive patients. Apparently, this COR inhibition is acute and begins after the first administration of mirtazapine, since on day 0 (application of 15 mg mirtazapine at 08.00 h) the mean COR concentrations were already reduced 1 h after administration of mirtazapine compared to the drug-free condition (fig. 2). During the following 3 weeks of mirtazapine treatment, diurnal COR secretion was further reduced by mirtazapine, reaching a minimum after 3 weeks of therapy. The decline of salivary COR concentrations from morning to evening, already observed before mirtazapine treatment (day –1), can be explained best by the circadian rhythm of COR secretion (maximum of COR concentrations early in the morning followed by a physiological reduction of COR levels).

The acute COR inhibition by mirtazapine, which can be demonstrated both in healthy subjects [12, 13] and depressed patients [the present study], can hardly be explained by the α_2-blocking properties of mirtazapine because yohimbine, an α_2-blocker, increases the DMI-induced COR stimulation in humans [14]. Given alone,

COR release from the adrenal gland is not influenced by yohimbine [37]. However, there is evidence from the literature that antagonism of central 5-HT2 and histamine H1 receptors may be responsible for the acute inhibitory effects of mirtazapine on COR secretion.

Different reports have demonstrated that both the synthesis and release of CRH by hypothalamic tissues in vitro [38, 39] and in vivo [40–42] are stimulated by 5-HT, and that the antiserotonergic drug cyproheptadine inhibits these effects [39]. It seems that 5-HT is one of the physiological factors involved in CRH stimulation at the hypothalamic level [43]. The inhibitory effect of cyproheptadine on ACTH secretion via CRH is thought to be responsible for the positive results observed in some patients with Cushing disease treated with cyproheptadine [44, 45]. Furthermore, it has been shown that activation of 5-HT1A, 5-HT2A and 5-HT2C, but not of 5-HT3 receptors results in elevated levels of plasma corticosterone; according to Berendsen et al. [46], serotonergic modulation of ACTH release via CRH plays an important role in this context. In the face of the presumed serotonergic modulation of CRH, ACTH and COR secretion, it seems to be likely that the COR inhibition seen after application of mirtazapine is, at least in parts, caused by its 5-HT2A and 5-HT2C receptor-blocking properties.

Besides serotonergic transmission, the neurotransmitter histamine also has to be taken into account. Histamine stimulates the release of ACTH via activation of central postsynaptic H1 or H2 receptors; the effect of histamine is indirect and may involve the hypothalamic-regulating factors CRH and arginine vasopressin [47]. In normal human volunteers, the selective H1 receptor antagonist meclastine is able to inhibit the ACTH and COR stimulation in the insulin hypoglycemia test, whereas GH and PRL concentrations are unaffected [48]. In rats, antidepressants which display an H1 antihistaminergic activity (such as imipramine, doxepin, mianserin, desipramine, and amitriptyline) significantly suppress the histamine-induced ACTH release [49]. Regarding these human and animal studies, the H1-blocking effects of mirtazapine may also play a role in the COR inhibition demonstrated in our investigation.

There is evidence that antidepressants with reuptake-inhibiting properties may act in part through gradual normalization of HPA system hyperactivity [17, 50]. Furthermore, in patients who respond clinically to antidepressant therapy but still have a substantially increased COR response in the combined DEX/CRH test at discharge, a higher risk for relapse within the following 6 months has been demonstrated [51]. In contrast to mirtazapine, reuptake-inhibiting antidepressants acutely stimulate COR and ACTH secretion [4, 14–16] and may normalize HPA axis hyperactivity in depressed patients via upregulation of glucocorticoid receptor mRNA levels and enhancement of glucocorticoid receptor function [52]. Apparently, the acute COR inhibition in healthy subjects and depressed patients after administration of mirtazapine is due to a direct pharmacoendocrinological effect of this antidepressant (presumably acute reduction of hypothalamic CRH release by blockade of central 5-HT2 and/or H1 receptors), which seems to be different from the gradual normalization of COR and ACTH hypersecretion observed during treatment with reuptake inhibitors such as amitriptyline [50].

Future studies will have to investigate the long-term effects of mirtazapine on COR secretion and its influence on HPA axis activity in depressed patients as measured by the combined DEX/CRH test. Since the COR inhibition was comparable in responders and nonresponders, the importance of the acute inhibitory effects of mirtazapine on COR secretion for its antidepressant efficacy has to be further clarified. In addition to new pharmacological approaches such as CRH1 receptor antagonists [17], mirtazapine may be an effective strategy to restore HPA system dysregulation in depression.

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