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Mirtazapine Decreases Stimulatory Effects of Reboxetine on Cortisol, Adrenocorticotropin and Prolactin Secretion in Healthy Male Subjects

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Key Words

Reboxetine · Mirtazapine · Growth hormone · Prolactin · Adrenal steroids · Corticotropin · Clinical neuroendocrinology

Abstract

Reboxetine is a selective noradrenaline reuptake inhibitor, whereas mirtazapine acts as an antagonist at noradrenergic α_2, serotonin (5-HT_2), 5-HT_3 and histamine H_1 receptors. In a former study we could demonstrate an inhibitory impact of mirtazapine on cortisol secretion. In the present investigation, the influence of combined administration of 15 mg mirtazapine and 4 mg reboxetine on the cortisol (COR), adrenocorticotropin (ACTH), growth hormone (GH), and prolactin (PRL) secretion was examined in 12 healthy male subjects, compared to reboxetine alone (4 mg). In a randomized order, the subjects received reboxetine (4 mg) alone or the combination of reboxetine (4 mg) and mirtazapine (15 mg) at 8:00 a.m. on two different days. After insertion of an intravenous catheter, blood samples were drawn 1 h prior to the administration of single reboxetine or the combination (reboxetine and mirtazapine), at time of administration, and during the time of 5 h thereafter in periods of 30 min. Serum concentrations of COR, GH, and PRL as well as plasma levels of ACTH were determined in each blood sample by means of double antibody RIA, fluoroimmunoassay and chemiluminescence immunometric assay methods. The area under the curve (AUC) was used as parameter for the COR, ACTH, GH, and PRL response. For statistical evaluation, the Wilcoxon signed-ranks test was performed. There was a pronounced stimulation of COR, ACTH, GH, and PRL concentrations after single administration of reboxetine. When reboxetine was given in combination with mirtazapine, a significant reduction of the COR, ACTH, and PRL stimulation was observed whereas GH secretion patterns remained unchanged, compared to single administration of reboxetine. Apparently, the stimulatory effects of reboxetine on pituitary hormone secretion via noradrenergic mechanisms are counteracted in part by the α_2-blocking properties of mirtazapine and its inhibitory influence on cortisol secretion.

Introduction

The neuroendocrine challenge paradigm is based on the involvement of monoamine pathways in the control of anterior pituitary hormone secretion [1, 2] and has been described extensively [3–5]. 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 pharmacoendo-

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Table 1. Influence of acute administration of antidepressant agents on neurotransmitter reuptake in vitro (IC_{50} values) and GH, PRL, and COR secretion in man, modified according to Hyttel [6, 7]

NA	5-HT	DA		GH	PRL	COR
0.9	210	–*	desipramine 25 mg i.v.	+++	++	+++
			desipramine 100 mg p.o.	+++	+	+++
14	35	–*	imipramine 100 mg p.o.	++	+++	+++
0.6	0.2	2.8	venlafaxine 75 mg p.o.	+	++	+++
1.1	–*	–*	*D*-oxaprotiline 75 mg i.v.	+++	0	+++
–*	–*	–*	*L*-oxaprotiline 75 mg p.o.	0	0	0
8.0	–*	–*	maprotiline [10, 11] 50 mg p.o.	++	0	n.a.
6.6	830	48	nomifensine 200 mg p.o.	++	–	n.a.
24	1.5	–*	clomipramine 25 mg i.v.	++	+++	+++
			clomipramine 100 mg p.o.	++	+	+
–*	2.4	–*	indalpine 25 mg i.v.	0	++	+++
370	6.8	–*	fluoxetine [12, 13] 80 mg p.o.	0	0	+++
620	3.8	–*	fluvoxamine 100 mg p.o.	n.a.	n.a.	+++
–*	1.8	–*	citalopram 20 mg i.v.	0	+++	+++

IC_{50} values (n*M*) indicated; –* = $IC_{50} > 1{,}000$ n*M*; NA = noradrenaline; 5-HT = serotonin; DA = dopamine; +++ = strong stimulation; ++ = moderate stimulation; + = slight stimulation; – = inhibition; 0 = no significant effect; n.a. = not available.

crinological profiles (table 1) [4, 6–15]. Antidepressants which primarily act via noradrenaline (NA) reuptake inhibition (e.g. desipramine) stimulate growth hormone (GH) secretion [16], whereas serotonin (5-HT)-reuptake-inhibiting antidepressants (e.g. indalpine, chlomipramine) 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 adrenocorticotropin (ACTH) output of the pituitary gland [4].

Mirtazapine that does not inhibit the reuptake of NA or 5-HT but acts as an antagonist at α_2-, 5-HT_2 and 5-HT_3 receptors [17] displays a special pharmacoendocrinological profile, since it acutely inhibits COR secretion [18] and ACTH release [19], probably due to central 5-HT_2 and/or H_1 receptor antagonism and acute reduction of corticotropin-releasing hormone (CRH) and vasopressin release. Mirtazapine enhances NA release by blocking α_2-autoreceptors [17]. 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 [20, 21]. In addition, mirtazapine is an antihistaminergic agent with a high affinity for histamine H_1 receptors [22] and has only few anticholinergic side effects. Average peak plasma concentrations (C_{max}) are achieved 2 h after oral dosing and the elimination half-life is in the range between 20 and 40 h [23].

Reboxetine is a novel antidepressant drug that selectively inhibits NA reuptake (IC_{50} values: NA reuptake 8 n*M*; 5-HT reuptake 1,070 n*M*; functional selectivity 5-HT/NA 130; DA reuptake >10,000 n*M*) [24]. Unlike desipramine or imipramine, reboxetine has only weak affinity ($K_i > 1{,}000$ nmol/l) for muscarinergic, histaminergic H_1, adrenergic α_1, and dopaminergic D_2 receptors [24]. Moreover, reboxetine is rapidly absorbed in man (t_{max} about 2 h) with a terminal elimination half-life of 13 h and has linear pharmacokinetics in young, healthy males for single doses of 1–5 mg [25]. In clinical studies, reboxetine has been shown to have a favorable tolerability and safety profile with only few side effects such as dry mouth, constipation, increased sweating, insomnia, urinary hesitancy or retention, and tachycardia [26, 27]. Furthermore, in placebo-controlled and active comparator trials, the antidepressant efficacy of reboxetine has been demonstrated [28].

Studies of our research group concerning the endocrinological effects of single administration of 4 mg reboxetine in healthy volunteers revealed significantly stimulatory effects of reboxetine on COR, ACTH, GH and PRL secretion compared to placebo [29]. In the present investigation, the influence of combined oral administration of 15 mg mirtazapine and 4 mg reboxetine on the COR, ACTH, GH, and PRL secretion was examined in 12 healthy male subjects, compared to reboxetine alone (4 mg). Because reboxetine selectively inhibits the NA reuptake, we tried to elucidate the question whether mir-

tazapine is able to antagonize the endocrinological effects of reboxetine by its α_2-blocking properties and its inhibitory influence on COR secretion. In particular with respect to COR and ACTH release, the questions to be answered in the present study may be of clinical interest since it has been hypothesized that hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis contributes to the pathophysiology of depression [30] and the reduction of HPA axis hyperactivity by antidepressant drugs plays a role in their antidepressant efficacy [31]. The study was designed as a pre-study in healthy volunteers to further investigate in depressed patients the possible interrelationship between fast abolition of COR stimulatory effects of reuptake-inhibiting antidepressants and presumptive early onset of antidepressant efficacy when mirtazapine is given simultaneously for several weeks. Therefore, we decided not to use specific α_2-blockers such as yohimbine in the present study, which are usually not used in treatment of depressive disorder.

Subjects and Methods

Study Population and Study Design

12 healthy male subjects of normal weight, age 20–35 years, were included upon receipt of their informed consent, following a clinical examination (psychiatric and medical history, physical examination) and establishment of normal laboratory parameters (Hb, K^+, Na^+, glutamate oxalo-acetate transaminase (GOT), glutamate pyruvate transaminase (GPT), γ-GT, blood glucose, bilirubin, serum creatinine, heart rate, electrocardiogram and electroencephalogram). Alcohol abstinence 24 h prior to each experiment and abstinence from medication beginning 4 weeks before the study were mandatory.

Each subject took part twice in the trial; in a randomized order the volunteers received reboxetine (4 mg) alone or the combination of reboxetine (4 mg) and mirtazapine (15 mg) at 8:00 a.m. on two different days. The interval between these two conditions was at least 1 week, at most 3 weeks. Randomization was performed by an online computer randomization program (http://www.randomization.com). The volunteers received two tablets on each study day (reboxetine 4 mg and placebo ['dummy' tablet]; reboxetine 4 mg and mirtazapine 15 mg). The study drugs were dispensed as film-coated tablets, which were identical in all aspects of their appearance and were kindly supplied by the Pharmacia & Upjohn Company. On each study day, at 7:00 a.m. an intravenous catheter was inserted into the antecubital vein and kept open with physiological saline solution. The subjects rested in bed throughout the experiments (up to t = 300 min). At t = –60 min (7:00 a.m.), t = 0 min (8:00 a.m.; administration of placebo or reboxetine), and at intervals of 30 min thereafter up to t = 300 min (1:00 p.m.), blood was drawn. Moreover, blood pressure, heart rate and side effects which occurred in the course of the experiment were recorded every 30 min in the study protocol. Since food intake and leptin levels have an impact on the anterior pituitary hormone secretion [32, 33], subjects fasted from completion of the evening meal the day before until conclusion of the experiment to achieve standardized nutritional conditions on each study day.

The study was carried out according to the fifth revision of the Declaration of Helsinki [34] and had been approved by an ethics committee.

Endocrinological Measurements

Serum and plasma samples were separated by centrifugation as soon as possible, frozen at –80°C, and stored for the assay of hormone concentrations. Serum concentrations of COR, GH, and PRL and plasma concentrations of ACTH were determined in each blood sample. COR, GH, and PRL levels were determined by double-antibody radioimmunoassay (RIA) and fluoroimmunoassay methods. The sensitivity ('minimal detectable dose') of the commercially available immunoassay kits was approximately 6.1 nmol/l for the COR RIA (Diagnostic Products Corporation®); 4.5 pmol/l for the GH fluoroimmunoassay (DELFIA® hGH), and 1.74 pmol/l for the PRL fluoroimmunoassay (DELFIA® Prolactin). The specificity was very high for the immunoassays with an extremely low cross-reactivity to other natural hormones; the percental cross-reactivity to other naturally occurring steroids in quality control tests (apparent concentrations related to the amount added in the experiment) was up to 6.8% for the COR RIA (although some steroids exhibit slight cross-reactivity, their normal physiological concentrations are low compared to COR so as not significantly interfere in the double antibody cortisol procedure); 0.1% for the GH fluoroimmunoassay, and <0.01% for the PRL fluoroimmunoassay. The total variation (% CV) was 6.6% for the COR RIA; 3.9% for the GH fluoroimmunoassay, and 2.7% for the PRL fluoroimmunoassay. ACTH was measured using a chemiluminescence immunometric assay (Nichols, San Juan Capistrano, Calif., USA); the lower detection limit of this assay is 0.11 pmol/l, intra- and interassay CVs are below 4 and 7%, respectively.

Data Analysis

In addition to the descriptive and graphical evaluation of the mean curves of the hormonal concentrations, the areas under the curve (AUCs, 0–300 min) were calculated according to Simpson [35], representing the total COR, ACTH, GH, and PRL secretion following oral administration of reboxetine alone (4 mg) or the combination of reboxetine (4 mg) and mirtazapine (15 mg). For statistical comparison of the mean AUC values after single and combined administration, the Wilcoxon signed-ranks test was performed. As a nominal level of significance, alpha = 0.05 was accepted. In the 'Results' section, mean values and standard errors of mean (SEM) are indicated.

Results

COR and ACTH Secretion

After single administration of reboxetine (4 mg), a remarkable increase of serum COR and plasma ACTH concentrations occurred (fig. 1) (single administration: COR AUC_{0-300}: 127,893.20 ± 8,125.75 nmol/l × min; ACTH AUC_{0-300}: 2,385.68 ± 387.19 pmol/l × min). After combined administration of reboxetine (4 mg) and mirtazapine (15 mg), both the COR and ACTH stimulation were less pronounced (combined administration:

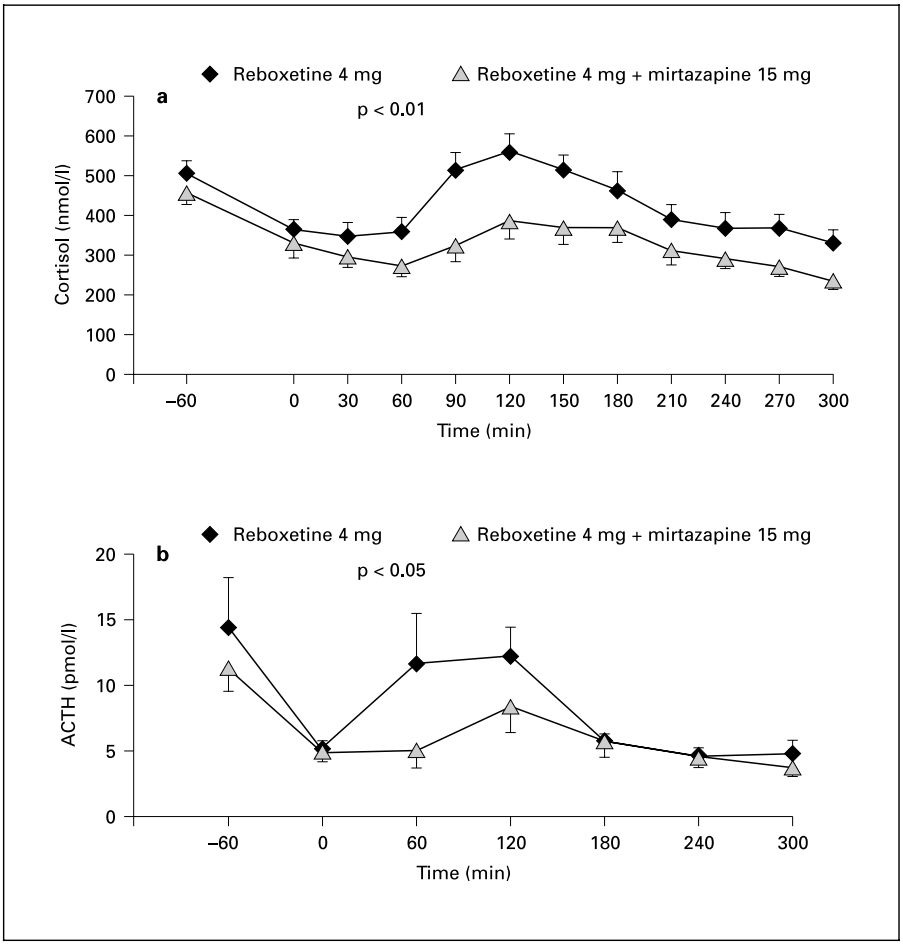

Fig. 1. Means ± SEM of cortisol (**a**) and ACTH (**b**) concentrations after single administration of 4 mg reboxetine and after combined administration of 4 mg reboxetine and 15 mg mirtazapine in 12 healthy male subjects. $p < 0.05$ and $p < 0.01$ indicate a significant or a highly significant difference, respectively.

COR $AUC_{0–300}$: 95,348.74 ± 8,141.30 nmol/l × min; ACTH $AUC_{0–300}$: 1,656.45 ± 215.26 pmol/l × min). The Wilcoxon test revealed significant differences both for COR and ACTH secretion (COR: Z = –3.059; p = 0.002; ACTH: Z = –2.510; p = 0.012).

GH Secretion

GH stimulation was comparable after both single administration of reboxetine (4 mg) and combined administration of reboxetine (4 mg) and mirtazapine (fig. 2) (single administration: GH $AUC_{0–300}$ = 56,026.59 ± 15,594.87 pmol/l × min; combined administration: GH $AUC_{0–300}$ = 48,425.84 ± 12,244.22 pmol/l × min). No statistical difference could be demonstrated (Wilcoxon test: Z = –0.549; p = 0.583).

PRL Secretion

A pronounced PRL stimulation after single administration of reboxetine (4 mg) was observed (fig. 2) (single administration: PRL $AUC_{0–300}$ = 113,961.60 ± 10,280.44 pmol/l × min). When reboxetine (4 mg) and mirtazapine (15 mg) were given simultaneously, this PRL stimulation was markedly diminished (combined administration: PRL $AUC_{0–300}$ = 81,292.30 ± 7,249.30 pmol/l × min). Using the Wilcoxon signed-ranks test, there was a highly significant difference (Z = –2.981; p = 0.003).

Side Effects

After single administration of reboxetine, 3 volunteers reported dry mouth to a moderate degree, in 4 subjects mild agitation occurred, and 3 participants complained of slightly to moderately increased sweating. When reboxetine and mirtazapine were given simultaneously, dry mouth and increased sweating happened in 2 subjects, respectively. However, all volunteers reported feeling moderately to markedly sedated after additional administration of mirtazapine. The sedation began 0.5 or 1 h after the combination of reboxetine and mirtazapine was given

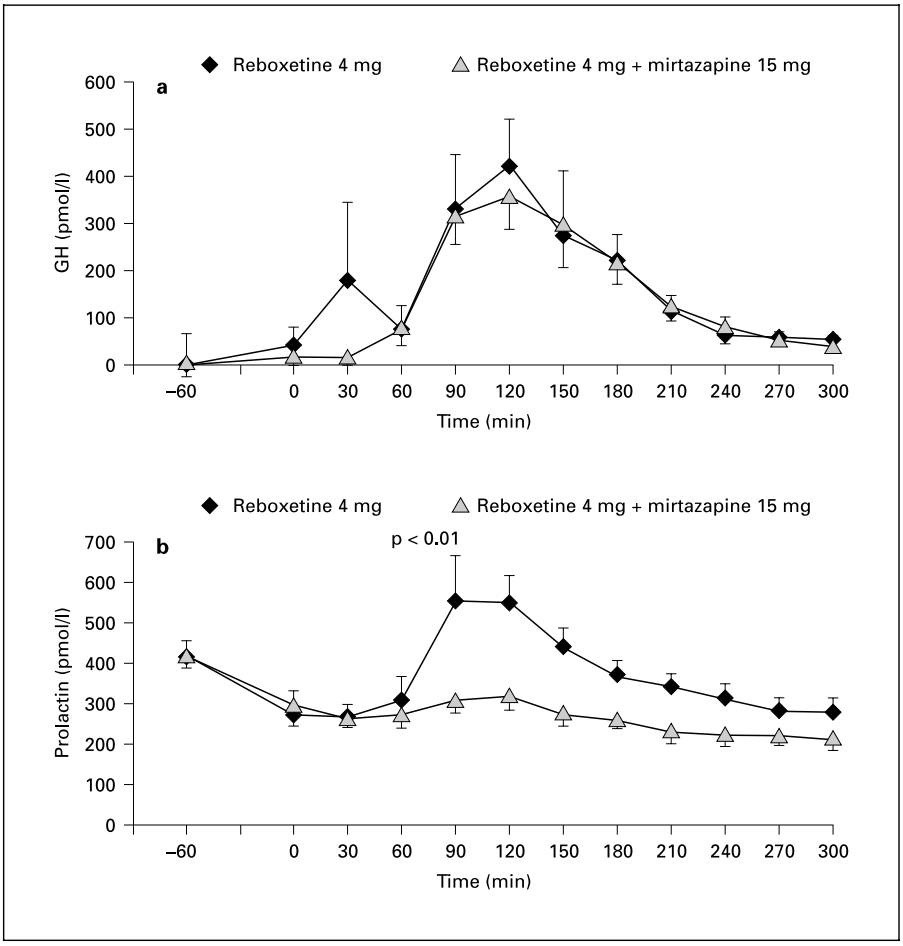

Fig. 2. Means ± SEM of GH (**a**) and PRL (**b**) concentrations after single administration of 4 mg reboxetine and after combined administration of 4 mg reboxetine and 15 mg mirtazapine in 12 healthy male subjects. $p < 0.01$ indicates a highly significant difference.

and lasted up to the end of the measurement period in most cases. No clinically relevant changes were observed in blood pressure and heart rate during both treatment conditions with the exception of one volunteer who showed increased heart rate and developed tachycardia (heart rate greater than 100 beats per minute) after a single administration of reboxetine.

Discussion

COR and ACTH Secretion

As already demonstrated by investigations of our research group concerning the endocrinological effects of single administration of 4 mg reboxetine in healthy volunteers, reboxetine significantly stimulates COR, ACTH, GH and PRL secretion compared to placebo [29]. This is in line with a study of Piacentini et al. [36] who reported significantly elevated COR, ACTH and PRL responses to physical exercises in 7 healthy well-trained male cyclists after treatment with 2 × 4 mg reboxetine in comparison to placebo and is also in accordance with an investigation of Hennig et al. [37] who found a reboxetine-induced stimulation of salivary COR in healthy male subjects, particularly in those scoring high on subclinical depression. In the present study, the stimulatory effects of single administration of reboxetine (4 mg) on COR, ACTH, and PRL secretion, but not on GH release were significantly reduced after combined administration of reboxetine (4 mg) and mirtazapine (15 mg).

Animal studies suggest that activation of α_1-adrenoceptors stimulates the secretion of CRH and vasopressin [38–42], whereas α_2-adrenergic mechanisms play rather a modulatory inhibitory role with regard to hypothalamic-pituitary-adrenocortical (HPA) axis activity [43], and have been shown to inhibit ACTH secretion during stress in dogs [44, 45]. In humans, the desipramine-induced COR stimulation is reduced by simultaneous administra-

tion of the α_1-blocker prazosin and increased if yohimbine, an α_2-adrenoceptor, is given at the same time whereas the β-adrenoceptor blocker propranolol does not have any influence [46]. Therefore one can assume that the increased ACTH and COR release after single administration of the selective NA reuptake inhibitor reboxetine observed in our study is mediated via activation of hypothalamic α_1-adrenoceptors, thereby stimulating CRH and/or vasopressin output.

In former studies we could demonstrate an acute inhibitory effect of single administration of mirtazapine on COR and ACTH secretion in healthy subjects, presumably due to blockade of central 5-HT_2 and histamine H_1 receptors [18, 19]. In our study reboxetine stimulates ACTH and COR secretion probably via activation of hypothalamic α_1-adrenoceptors. Mirtazapine does not block these receptors but seems to inhibit ACTH and COR release via central 5-HT_2 and H_1 antagonism. Therefore, mirtazapine markedly decreases the reboxetine-induced ACTH and COR stimulation when given simultaneously. However our study is methodologically limited by the fact that a cross-over design was not used, and thus did not allow to detect drug interaction effects, which are nevertheless rather unlikely since reboxetine and mirtazapine follow different kinds of mechanisms of action.

It has been suggested that antidepressants with reuptake-inhibiting properties may act in part through gradual normalization of hypothalamic-pituitary-adrenocortical (HPA) system hyperactivity [30, 31, 47]. In contrast to mirtazapine, reuptake-inhibiting antidepressants such as reboxetine or others acutely stimulate COR and ACTH secretion in both healthy subjects [4, 29] and depressed patients [48–50] and may gradually normalize HPA axis hyperactivity in depressed patients via up-regulation of glucocorticoid receptor mRNA levels and enhancement of glucocorticoid receptor function [51]. This upregulation takes several weeks and may be triggered by the acute stimulatory effects of reuptake inhibitors on COR and ACTH release. However, mirtazapine acutely tunes down HPA axis activity via direct pharmacoendocrinological effects and inhibition of hypothalamic CRH and/or vasopressin release. It has not been investigated so far whether mirtazapine treatment enhances mRNA levels of the glucocorticoid receptor in depressed patients. Nevertheless, the acute reduction of HPA axis hyperactivity by mirtazapine may contribute to its antidepressant efficacy or may at any rate accelerate the amelioration of symptoms in depressed patients. In fact, several studies suggest a notably early onset of antidepressant action in depressed patients treated with mirtazapine [52–55]. Since the reboxetine-induced COR and ACTH stimulation is reduced but not abolished when given simultaneously with mirtazapine, one may speculate whether combined administration of reuptake inhibitors such as reboxetine (enhancement of glucocorticoid receptor function for several weeks) and mirtazapine (direct inhibition of hypothalamic CRH and/or vasopressin release) effectively reduces HPA axis hyperactivity in depression via two different mechanisms and is suitable to improve or accelerate antidepressant efficacy.

GH Secretion

In the present investigation, GH release was markedly increased after single administration of reboxetine. However, a similar GH stimulation was also observed after combined administration of reboxetine and mirtazapine.

There is evidence from animal and human studies that the reboxetine-induced GH stimulation is mediated via activation of hypothalamic α_2-receptors. GH release from pituitary somatotropes is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, which are both modulated by the central adrenergic system. Activation of α_2-adrenoceptors stimulates the secretion of GHRH from rat hypothalamic slices in vitro [56, 57], and pretreatment with antiserum to GHRH abolishes the GH response to the α_2-agonist clonidine in rats [58]. It is likely that activation of postsynaptic α_2-adrenoceptors may, in addition, inhibit the secretion of somatostatin [59]. Clonidine does not stimulate GH release directly from the rat pituitary [60]. In analogy to the data obtained in rats, clonidine also stimulates GH secretion in humans [61, 62]. Moreover, there is evidence from human studies that the action of clonidine is exerted via both stimulation of GHRH [60] and inhibition of somatostatin [63, 64].

An inhibitory action of catecholamines on GH secretion appears to be exerted via β-adrenoceptors. Administration of the β-blocker propranolol has no effect on the GH output under basal conditions [65], but the β-blocker propranolol increases GH stimulation after administration of the NA reuptake inhibitor desipramine [66], indicating an inhibitory influence of β-receptors on GH release. Therefore, the most plausible explanation for the reboxetine-induced GH stimulation seen in our study is noradrenergic enhancement of GHRH release and inhibition of somatostatin output via hypothalamic α_2-adrenoceptors that overcome the inhibitory impact of β-receptors on GH secretion.

Surprisingly in our study the reboxetine-induced GH stimulation was not reduced by simultaneous administration of the α_2-blocker mirtazapine. Since the α_2-blocker yohimbine has been demonstrated to significantly reduce GH stimulation after administration of the NA reuptake inhibitor desipramine in man [66], one would rather expect similar inhibitory effects of mirtazapine on GH stimulation after reboxetine. However, it has to be taken into account that presynaptic and postsynaptic α_2-receptors exert different effects on noradrenergic neurotransmission. It has been observed that the α_2-blocker idazoxan seems to cause a modest increase of GH in man [67]. According to Schmidt and his colleagues [67], the explanation for this result is that idazoxan has a higher affinity for presynaptic α_2-receptors (leading to an increased NA release) than for postsynaptic α_2-receptors (blocking the stimulatory effects of NA on GH secretion); thus, the enhanced NA release overcomes the moderate blockade of postsynaptic α_2-receptors, thereby increasing GH secretion. This interplay between pre- and postsynaptic blockade of α_2-receptors may also be responsible for our observation that simultaneous administration of the α_2-blocker mirtazapine at a dosage of 15 mg does not have any impact on the reboxetine-induced GH stimulation. Obviously, the presumed blockade of postsynaptic α_2-receptors after 15 mg mirtazapine is compensated by the enhancement of NA release via antagonism of presynaptic α_2-receptors.

PRL Secretion

In the present investigation, reboxetine markedly enhanced PRL secretion in healthy male subjects. Since reboxetine is a highly selective NA reuptake inhibitor, this PRL stimulation can only be explained by noradrenergic mechanisms. Indeed, in several animal and human studies a possible adrenergic control of PRL release has been suggested. In rat studies, infusion of adrenaline into the preoptic hypothalamic area or into the lateral cerebral ventricle enhanced PRL output and the effect was blocked by phentolamine [68, 69]. In humans, intravenous infusion of the α_1-agonist methoxamine that can cross the blood-brain barrier stimulates PRL secretion [70]. Most human studies provide no clear evidence for an important role of α-adrenoceptors in the control of PRL secretion in man [71–73]. Moreover, in healthy human volunteers under basal conditions, secretion of PRL is unaffected in most studies by the α_2-antagonists yohimbine, idazoxan and atipremazole [74–77], or by the α_2-agonists clonidine and guanfacine [61, 78–81]. However, there are also investigations suggesting PRL stimulation by clonidine in healthy controls and depressed patients [82] and PRL stimulation by yohimbine in recently detoxified alcoholics [81].

In our study, simultaneous administration of mirtazapine significantly reduced PRL stimulation after reboxetine. Mirtazapine is thought to stimulate 5-HT_{1A}-receptors in an indirect manner by enhancement of serotonergic cell firing and by increasing 5-HT release, whereas 5-HT_2 and 5-HT_3 receptors are directly blocked [20, 21]. In contrast to direct 5-HT_{1A}-receptor agonists such as ipsapirone or buspirone [83] and 5-HT-reuptake inhibitors such as indalpine or chlorimipramine [4] that stimulate PRL release, indirect serotonergic agonists such as mirtazapine fail to cause PRL stimulation [18, 19]. The significant reduction of reboxetine-induced PRL stimulation after simultaneous administration of the α_2-blocker mirtazapine suggests a role of α_2-receptors in the enhancement of PRL release after single administration of reboxetine. However, conflicting results in the literature concerning noradrenergic regulation of PRL secretion do not allow an accurate explanation for this observation.

Side Effects

Taken together, both single administration of 4 mg reboxetine and combined dosage of 4 mg reboxetine and 15 mg mirtazapine were quite well tolerated. No medical intervention was necessary. Slight-to-moderate side effects such as dry mouth, mild agitation, increased sweating or slight tachycardia which could be observed in some but not all volunteers are in accordance with the known tolerability profile of reboxetine which is nevertheless favorable [26, 27]. The acute sedative effects after combined administration which could be demonstrated in each subject can be attributed to mirtazapine and its antagonistic impact on histamine H_1 receptors [22].

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