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Different Endocrine Effects of an Evening Dose of Amitriptyline, Escitalopram, and Placebo in Healthy Participants

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Objective: The primary aim of this study was to further characterize the acute effects of amitriptyline (AMI) and escitalopram (ESC) on serum levels of ghrelin, leptin, cortisol and prolactin in healthy humans.
Methods: Eleven healthy male participants received a single dose of AMI 75 mg, ESC 10 mg, or placebo (PLA) at 9:00 PM in a double blind, randomized, controlled, repeated measures study separated by one week. Fasting morning serum levels (7:00 AM) of ghrelin, leptin, cortisol and prolactin were assessed.
Results: A repeated measures multivariate analysis of variance revealed a significant main effect for the factor condition (AMI, ESC, PLA). Subsequent univariate analyses demonstrated significant condition effects for ghrelin and cortisol. *Post-hoc* analyses demonstrated a significant reduction of ghrelin levels after AMI in comparison to PLA, and a significant reduction of cortisol levels after AMI in comparison to both ESC and PLA. Other contrasts did not reach statistical significance.
Conclusion: Administration of a single dose of AMI, but not of ESC, leads to a significant reduction in morning serum ghrelin and cortisol levels. No effects on leptin and prolactin levels were observed. The differential impact of AMI and ESC on hormones might contribute to different adverse effect profiles of both substances.

KEY WORDS: Ghrelin; Leptin; Prolactin; Cortisol; Weight gain; Adverse effects.

INTRODUCTION

Right now, up to 121 million people worldwide suffer from major depressive disorder (MDD; World Health Organization, 2005). The prevalence is rising and by 2020 MDD is expected to represent the second most prevalent disorder in the world.[1)] In Germany, citalopram and its S-enantiomer escitalopram (ESC) are the most widely prescribed selective serotonin reuptake inhibitor (SSRI), while amitriptyline (AMI) is the most common tricyclic antidepressant.[2)] In spite of being effective and, in most cases, well-tolerated, several limiting adverse effects have been described. While tricyclic antidepressants frequently induce weight gain and daytime sleepiness, SSRI can reduce food intake by suppressing hunger and enhancing satiety in humans during the first weeks of treatment.[3)] Furthermore a disrupt in sexual functioning is often observed in patients taking SSRI.[4)] Weight gain and loss of sexual functioning have been proposed to be, at least in part, mediated by endocrine systems.

In the brain, the hypothalamus integrates various peripheral signals and sends efferences to the pituary gland. There, metabolic and sexual functions are controlled directly and release hormones regulate subsequent glands, such as the adrenal glands for peripheral stress regulation (hypothalamic-pituitary-adrenal axis, HPA). For food intake, the antagonistic hormones ghrelin and leptin have

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been identified as important hypothalamic modulators.[5] However, the exact mechanisms of the described adverse effects remain to be further investigated.

Ghrelin is a 28-amino acid peptide hormone mainly secreted by stomach cells after meals. Peripherally acylated ghrelin binds at the growth hormone secretagogue receptor in the hypothalamus where it activates a second messenger pathway triggering food intake.[6] In addition, smaller amounts of ghrelin can be found directly in the hypothalamus. It is thought to act as a mediator of different pathways involving reward and motivation, stress, anxiety, MDD and possibly sleep regulation.[7,8]

Leptin, a 16-kDa protein, is released by white adipocytes and actively transported through the blood-brain barrier via a specific receptor mainly in the hippocampus and near the hypothalamic arcuate nucleus.[9] Two different neural cell groups in the hypothalamus are targeted. Here, information about energy status is integrated to this important regulatory brain region.[10] Leptin has been proposed to act as an antagonist to ghrelin and mainly suppresses food intake,[5] but might have additional effects on other regulatory systems.[11]

Cortisol, a steroid hormone produced in humans by the adrenal cortex,[12] acts as a peripheral endpoint of the HPA axis. Cortisol levels are elevated in patients with insomnia or MDD.[13]

Prolactin, also known as luteotropic hormone, is mostly noted for its influence on mammalian milk production. Symptomatic hyperprolactinemia, a common adverse effect of different antidepressive medications, can result in galactorrhea and erectile dysfunction.[14,15] In addition, prolactin has been linked to various different systems, including growth and development, brain and behavior, and immune regulation.[16]

Only few studies have centered on the effects of AMI on endocrine levels during pharmacological treatment. For ghrelin serum levels, an increase in 28 healthy volunteers has been detected following one week of administration.[17] In addition, an increase of leptin serum levels during AMI treatment was reported in patients with MDD.[18] However conflicting data exists, as unchanged leptin levels in 12 inpatients with major depression have been determined during six weeks of AMI treatment.[19] In addition, a reduction of cortisol levels has been shown in AMI responders following 25 days of treatment.[20] So far, no study has investigated the effects of AMI on prolactin serum levels.

Other studies have analyzed the effects of ESC and citalopram. Patients with MDD showed reduced ghrelin serum levels prior to treatment with citalopram, without normalization following treatment.[21] Forty-four outpatients with binge eating disorder received either ESC or placebo (PLA) in a 12-week, double-blind, flexible dose study reporting no changes in ghrelin or leptin levels.[22] No changes in leptin serum levels have been observed following 8 weeks of citalopram treatment in 14 depressed and 18 non-depressed women.[23] In contrast, forty patients with premature ejaculation, a syndrome recently linked to increased leptin serum levels, demonstrated a reduction in serum levels after eight weeks of citalopram treatment.[24] An acute increase of cortisol serum levels in healthy volunteers has been observed following oral citalopram administration.[25,26] In addition, an immediate increase of cortisol and prolactin serum levels has been reported following a 20 mg citalopram infusion.[27]

This study represents the first double-blind, randomized, repeated measures, PLA-controlled trial directly comparing the short term effects of the two antidepressants AMI and ESC on the serum levels of ghrelin, leptin, cortisol and prolactin in healthy participants.

METHODS

Participants

Fourteen healthy male volunteers were recruited via personal contact for a double-blind, randomized, repeated measures, PLA-controlled trial on the impact of AMI and ESC on polysomnographic sleep and endocrinological parameters. Polysomnographic findings from this trial have already been published.[28] Two participants were excluded after the adaptation night (atrio-ventricular block, technical recording failure). One participant was excluded due to protocol violation (shift working), leading to a total of 11 analyzed participants for the current analysis (24.7±2.4 years; age range, 20-32 years; body mass index, 22.5±1.4 kg/m^2).

The study had been approved by the local ethics committee and registered in the German Register for Clinical Studies (www.germanctr.de, DRKS00000160). Participants provided written informed consent prior to the onset of the study. All participants underwent a thorough screening process by an experienced clinician, including a phys-

ical examination, a semi-structured interview for psychiatric disorders or substance use, and tests for specific laboratory parameters (thyroid, renal and liver function, hematology, biochemistry, electroencephalography [EEG] and electrocardiogram [ECG], urine drug screening). Polysomnography was used to ensure the absence of a respiratory (apnea-hypopnea-index, <5/hour) or movement-related sleep disorder (periodic limb movements with arousal, <5/hour). Additional exclusion criteria included any clinically relevant disorder, unstable sleep patterns, participation in any other clinical trial within the last month, and intake of any medication within 2 weeks prior to and during the study. All participants received financial remuneration.

Study Design

All participants underwent a within-subject, double-blind, PLA-controlled, randomized, repeated-measures protocol comprising three blocks with polysomnographic monitoring from 11:00 PM to 7:00 AM at the sleep laboratory of the University Medical Center Freiburg (Fig. 1).

Each block consisted of one adaptation night followed by one experimental night. The blocks were separated by at least 7 days. At 9:00 PM prior to the experimental nights, a single dose of either 75 mg AMI, 10 mg ESC or PLA was orally administered. Medications were matching white capsules provided and randomized by the pharmacy of the Johannes Gutenberg-University of Mainz. Daytime sleepiness was measured by the multiple sleep latency test (MSLT). Daytime alertness and vigilance was measured by neurocognitive tasks (Testbatterie zur Aufmerksamkeitsleistung, TAP; and D2 concentration test).[29,30] Blood samples were collected at 7:15 AM following an overnight fast and immediately stored at −70°C. Immediately after completion of the study, serum ghrelin, leptin, cortisol and prolactin levels were analyzed.

Endocrine Analyses

Serum ghrelin and leptin levels were measured at the research laboratory of the Centre for Mental Disorders, University Medical Center Freiburg (ghrelin: [Human] EIA-Kit from Phoenix Pharmaceutical Cat. No. EK-031-30, intra-assay error: <5%, inter-assay error: <14%; leptin: [Human] ELISA-Kit from DRG GmbH, Marburg Cat. No. EIA-2395, intra-assay error: <7%, inter-assay error: <12%). Levels were determined twice and mean values were further analyzed. Serum levels of cortisol and prolactin were investigated at the central laboratory of the University Medical Center Freiburg (cortisol: Electrochemiluminescence Immunoassay "ECLIA", Modular Analytics E170, Elecsys 2010 and cobas e 411 and cobas e 601 as Immunoassay Analyzers; prolactin: Electrochemiluminescence Immunoassay "ECLIA", Modular Analytics E170, Elecsys 2010 and cobas e 411 and cobas e 601 as Immunoassay Analyzers).

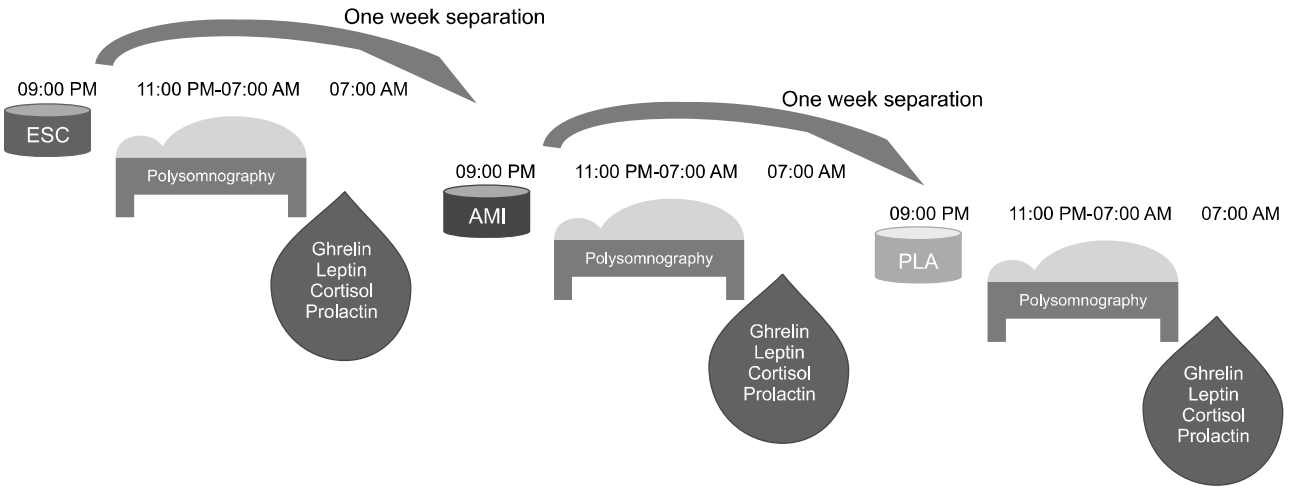

Fig. 1. Study design. Eleven healthy male participants underwent a within-subject repeated-measures protocol comprising 3 blocks with polysomnographic monitoring from 11:00 PM to 07:00 AM separated by one week. Either 10 mg escitalopram (ESC), 75 mg amitryptilin (AMI) or placebo (PLA) were orally administered at 09:00 PM. Blood samples were collected between 7:00 and 7:30 AM shortly after awakening and tested for ghrelin, leptin, prolactin and cortisol serum levels.

Statistical Analysis

Early morning serum levels of leptin, ghrelin, prolactin and cortisol were defined as primary outcome parameters. Descriptive values are given as means and standard deviations. To test for differences in endocrine responses to the medication, a repeated-measures multivariate analysis of variance (rmMANOVA) with the within-subject factor condition (ESC, AMI, PLA) was conducted. *Post-hoc* contrasts were calculated for significant main effects. For the estimation of effect sizes, partial eta square ($pETA^2$) values were calculated (low, <0.06; medium, ≥ 0.06 and <0.14; large, ≥ 0.14). The level of significance was set at $p<0.05$ (two-tailed). Assuming an a priori test power of 80%, the selected sample size of 15 participants was sufficient to detect medium to large effect sizes for the primary analysis. All analyses were con-

Table 1. Early morning serum levels of ghrelin, leptin, prolactin and cortisol after 10 mg ESC, 75 mg AMI or PLA

Variable	ESC	AMI	PLA	*F*	*p*	$pETA^2$
Ghrelin (pg/ml)	198.6±39.9	146.5±82.6	217.8±109.3	4.2	0.031*	0.294
Leptin (ng/ml)	6.4±3.3	6.7±3.5	7.6±4.6	1.2	0.323	0.107
Prolactin (mIU/L)	355.1±151.6	301.0±158.4	339.5±165.3	1.1	0.338	0.103
Cortisol (nmol/L)	636.0±120.3	515.5±128.8	608.8±124.0	5.9	0.010*,†	0.372

Values are presented as mean±standard deviation.
ESC, escitalopram; AMI, amitriptyline; PLA, placebo; ESC, escitalopram; $pETA^2$, partial eta square.
ANOVAs with the factor condition (ESCIT, AMI, PLA).
*Significant contrast AMI vs. PLC; †significant ESCIT vs. AMI.

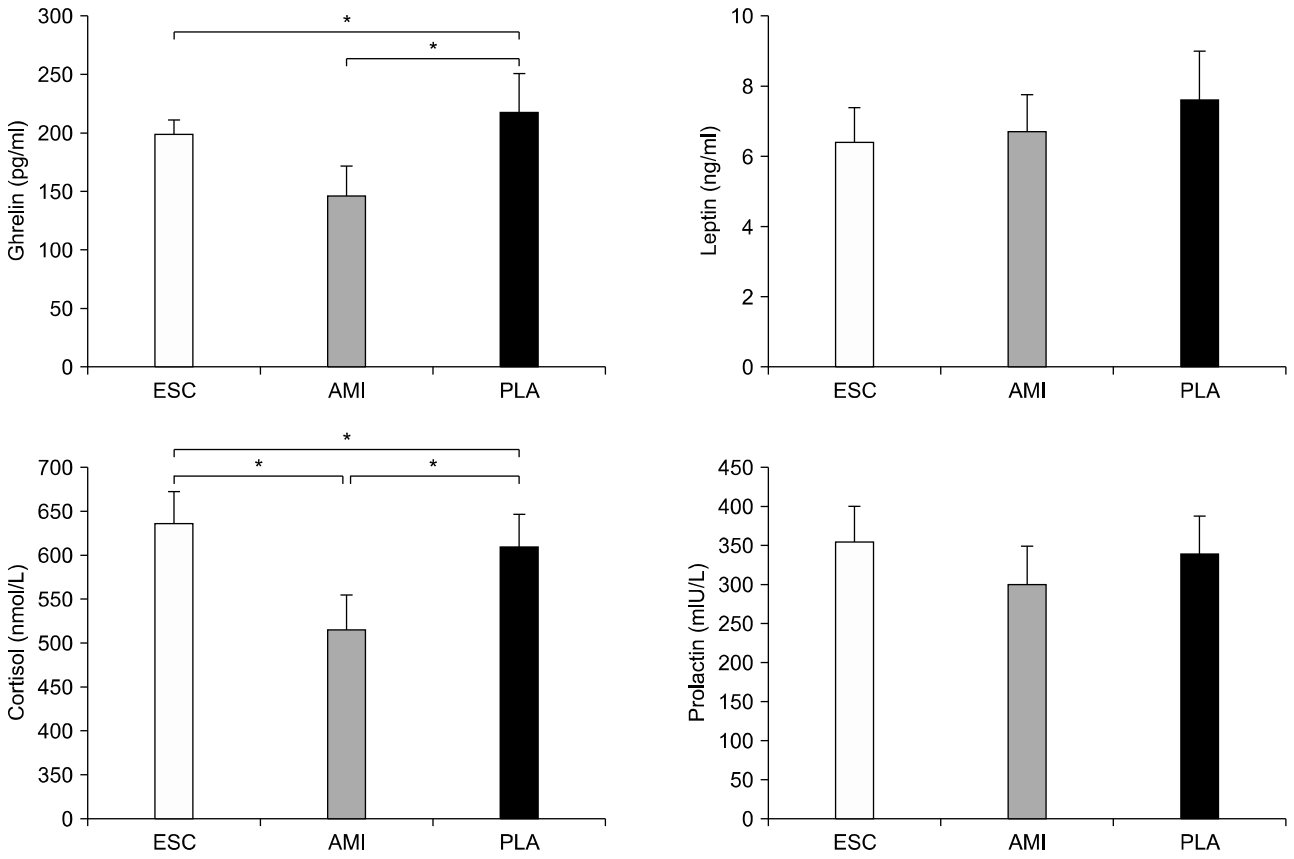

Fig. 2. Morning levels of ghrelin, leptin, prolactin and cortisol after evening administration of 10 mg escitalopram (ESC), 75 mg amitryptilin (AMI) or placebo (PLA). A significant within-subject condition effect was detected for ghrelin and cortisol levels. *Post-hoc* tests revealed significantly lower levels of ghrelin following AMI compared to PLA and of cortisol following AMI compared to PLA and ESC.
Bars indicate the standard error of the mean; *Significant main effect for condition.

ducted using the statistical software IBM SPSS Statistics, version 21 (IBM Co., Armonk, NY, USA), and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Morning Levels of Ghrelin, Leptin, Cortisol, and Prolactin

The morning levels of ghrelin, leptin, cortisol and prolactin for each condition are listed in Table 1.

The rmMANOVA indicated a highly significant main effect for the factor condition (F=3.3, p=0.006). Subsequent univariate analyses demonstrated significant condition effects for ghrelin and cortisol. *Post-hoc* tests revealed a significant reduction of ghrelin levels after administration of AMI compared to PLA, and a significant reduction of cortisol levels after administration of AMI compared to both PLA and ESC. No significant effects on leptin or prolactin were detected. The main findings are visualized in Figure 2.

Exploratory Correlation of Endocrine Changes with Sleep and Vigilance

Assuming that early morning serum concentrations correlates with hormone concentrations during the preceding night and to further explore possible relationships of endocrine changes on polysomnographic nighttime sleep, daytime sleepiness (MSLT) and attention (TAP, D2), two linear regression models were employed with these dependent variables on already published polysomnographic findings from this trial.[28] The intra- and interindividual influences on sleep and daytime performance are listed in Table 2.

The first multiple regression analysis (R module stats::lm) related ghrelin, leptin, cortisol and prolactin serum levels to the dependent variables across subjects within the PLA condition to determine the absolute individual influence of ghrelin, leptin, cortisol and prolactin serum levels on sleep and daytime performance (interindividual effects). The analyses demonstrated a significant positive relationship between morning ghrelin serum levels and wake periods in the preceding night. No other correlations were found.

The second analysis utilized a linear mixed-effects model (R module nlme::lme) with the within-subject factor condition (ESC, AMI, PLA) and ghrelin, leptin, cortisol and prolactin serum levels as covariates to disentangle direct pharmacological influences on sleep and daytime sleepiness and performance from possible, indirect effects through changes in ghrelin, leptin, cortisol or prolactin serum levels (intraindividual effects). Reported beta values of the linear model are differences, relative to PLA by the factor condition and regression coefficients for the serum levels. As already reported by Doerr *et al.*,[28] ESC led to a significantly lower total sleep time (TST) and sleep efficiency (SE) compared to AMI. Wake time after sleep onset decreased after AMI compared to PLA and ESC and increased after ESC compared to PLA and AMI. In addition, both substances significantly suppressed rapid eye movement sleep (REM) and increased REM latency (REML). Sleep stage 2 increased following AMI and was lower under ESC than PLA and AMI. During the next day, AMI decreased daytime sleep onset latency (SOL) and WE (WE) in the multiple sleep latency test (MSLT) and led to longer reaction times in an alertness task (TAP) and fewer correctly marked letters in the 'd2 concentration test' (D2) compared to PLA and ESC, while ESC increased SOL and WE and slightly improved performance tasks compared to AMI, but not PLA.[28]

The intraindividual regression model showed an increased amount of stage 2 sleep, reduced amount of REM sleep, increased REML as well as reduced MSLT SOL and WE and reduced D2 performance after AMI. ESC reduced TST and SE, increased wake periods, decreased REM sleep, increased REML and decreased REM density.

Larger ghrelin serum level were found to be related to increased SOL and number of wake periods as well as MSLT WE. Larger leptin level were only related to an increased amount of REM sleep. Prolactin and cortisol serum levels were not significantly related to sleep and daytime performance parameters.

DISCUSSION

The results of this study indicate that a single dose of AMI reduces early morning ghrelin and cortisol serum levels. More specifically, a single evening dose of 75-mg AMI decreased ghrelin serum levels in the morning compared to PLA and cortisol serum levels in the morning compared to ESC and PLA in healthy young men. Those results were not found at ESC.

Table 2. Inter- and intraindividual relationships of endocrine changes with sleep, daytime sleepiness and vigilance parameters

Parameter	Interindividual effects (placebo)								Intraindividual effects											
	Ghrelin		Leptin		Prolactin		Cortisol		ESC		AMI		Ghrelin		Leptin		Prolactin		Cortisol	
	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*	Beta	*p*
TST	−0.18	0.176	0.85	0.795	0.02	0.836	0.06	0.649	−45.76	0.005*	3.22	0.839	−0.0	0.232	0.07	0.972	−0.2	0.750	−0.03	0.571
SEI	−0.04	0.187	0.03	0.964	0.00	0.926	0.01	0.693	−9.28	0.004*	1.40	0.658	−0.02	0.192	−0.05	0.896	0.00	0.713	−0.01	0.526
SOL	0.15	0.053	0.63	0.721	0.03	0.552	−0.09	0.239	1.74	0.762	−4.69	0.484	0.08	0.047*	10.23	0.177	0.02	0.383	0.01	0.672
WASO	0.05	0.386	−0.42	0.756	−0.02	0.670	0.02	0.704	41.40	0.003*	0.17	0.990	0.04	0.516	−0.68	0.658	0.01	0.894	0.03	0.611
Wake periods	0.06	0.003*	0.11	0.756	−0.02	0.056	0.01	0.698	6.64	0.086	0.44	0.914	0.06	0.013*	−0.69	0.153	−0.02	0.055	0.00	0.850
Wake	0.01	0.315	−0.11	0.744	0.00	0.752	0.00	0.880	9.06	0.003*	−0.02	0.995	0.01	0.459	−0.12	0.714	0.00	0.836	0.01	0.600
Stage 1	0.01	0.197	0.09	0.669	0.01	0.066	−0.01	0.426	1.18	0.224	−2.11	0.103	0.01	0.203	−0.23	0.261	0.00	0.970	0.00	0.424
Stage 2	−0.01	0.556	−0.28	0.515	0.00	0.925	0.01	0.669	−3.29	0.243	1.11	0.008*	−0.01	0.479	−0.30	0.555	0.00	0.928	0.00	0.876
SWP	−0.03	0.083	−0.23	0.551	−0.02	0.136	0.00	0.983	2.74	0.139	3.43	0.164	−0.01	0.648	0.07	0.868	−0.01	0.089	0.00	0.885
REM	0.02	0.159	0.54	0.089	0.01	0.382	0.00	0.877	−9.62	0.000*	−1.94	0.000*	0.01	0.280	0.65	0.005*	0.01	0.189	0.00	0.596
REML	−0.01	0.955	3.08	0.331	0.07	0.415	0.03	0.796	157.38	0.000*	244.50	0.000*	0.17	0.403	−4.13	0.367	−0.11	0.344	−0.06	0.695
REMD	0.02	0.631	0.62	0.492	0.00	0.989	0.02	0.660	−4.45	0.033*	1.83	0.511	0.02	0.339	0.19	0.696	0.00	0.622	0.01	0.397
MSLT SOL	−0.01	0.253	0.04	0.897	0.00	0.602	0.00	0.998	2.16	0.082	−4.77	0.005*	−0.01	0.115	0.15	0.519	−0.01	0.252	0.01	0.338
MSLT WE	−0.07	0.122	0.11	0.922	−0.04	0.234	0.03	0.460	6.96	0.180	−26.21	0.001*	−0.09	0.034*	0.21	0.847	−0.03	0.254	0.04	0.169
TAP	−0.05	0.426	0.02	0.607	0.05	0.389	−1.13	0.483	−2.47	0.577	4.32	0.476	−0.02	0.522	0.01	0.729	0.00	0.887	−1.34	0.205
D2	−0.02	0.968	0.05	0.855	0.14	0.695	5.71	0.545	6.97	0.592	−43.03	0.045*	−0.15	0.100	−0.08	0.287	−0.05	0.685	−1.33	0.734

ESC, escitalopram; AMI, amitriptyline; TST, total sleep time (min); SEI, sleep efficiency; SOL, sleep onset latency; WASO, wake time after sleep onset; SWP, percentage of slow wave sleep; REM, rapid eye movement sleep; REMD, rapid eye movement density; MSLT SOL, sleep onset latency in the multiple sleep latency test; MSLT WE, wake efficiency in the multiple sleep latency test; TAP, alertness test; D2, D2 concentration test.

*Significant correlation.

The observed reduction of ghrelin serum levels after a single dose of AMI differs from the reported increase following long-term administration.[17] Thus, our finding complements the described increase after long term treatment in the literature. Increased food intake and weight-gain are common side effects of AMI. It remains to be further determined whether the acute reduction of serum ghrelin levels observed in the current study, after administration of AMI, can mediate this weight gain. With regard to potential mechanisms, anticholinergic properties of AMI might mediate the acute reduction of ghrelin, since circulating ghrelin levels in humans are reduced by cholinergic antagonists.[31] As a complementary explanation for an AMI-induced weight gain, it is to note that AMI acts antagonistically on the histamine H1 receptor in rats, another pathway with high importance for the regulation of body weight.[32,33] Yet it should be noted that the complex regulation of body weight remains to be fully delineated. Despite the acute promotion of food intake, ghrelin serum levels are, for example, inversely related to the body mass index.[34]

The current study is also the first to report reduced cortisol levels after AMI. It thereby complements reports on reduced cortisol levels after the sedating antidepressants trazodone and mirtazapine in healthy humans.[35,36] This acute reduction of daytime cortisol levels might play an independent role in the described side effects of weight gain. In contrast to AMI, a single-dose of ESC in the evening showed no significant impact on morning hormone serum levels. This observation corroborates studies describing no effect on leptin serum levels after treatment with citalopram or ESC.[22,23] It is possible that a reduction can only be observed in populations with increased leptin levels, such as described for premature ejaculation.[24] This would, at least indirectly, be in line with animal studies, in which a novel serotonin-reuptake inhibitor 3-methoxy-N-p-tolylquinoxalin-2-carboxamide (QCM-4) attenuated HPA axis hyperactivity in an obese mouse model of MDD by reversing increased plasma leptin.[37] It is of further interest that no immediate effect on prolactin levels were detected despite frequent sexual dysfunctions under treatment with ESC. The underlying mechanisms remain to be fully understood. It might be that alterations on prolactin levels emerge only after long-term treatment with ESC. Alternatively, adverse effects of ESC on sexual functioning might be mediated by non-endocrinological effects, such as neuronal nitrogen monoxide.[38]

In an exploratory approach we referred to already published data on the direct impact of AMI and ESC on polysomnographic nighttime sleep, daytime sleepiness (MSLT) and attention.[28]

As our main finding here, individually higher morning ghrelin serum levels were related to wake periods in the preceding night during the PLA condition. In addition, ghrelin was associated with the amount of wake periods and sleep onset latency as well as with WE in the MSLT independently of ESC/AMI in the experimental nights. The strong decrease in daytime WE reported for AMI could therefore be partially driven or enhanced by modulation of the ghrelin system in addition to an ongoing sedating antihistaminic effect of AMI due to its long half-value period of 10 to 28 hours. However, as the study design cannot identify causal relationships, it is also possible that an enhancement of wake periods during the night leads to changes in ghrelin serum levels. This alternative explanation would be supported by findings of reduced leptin and elevated ghrelin serum levels following short sleep duration.[39]

In addition, higher individual leptin levels were negatively related to REM sleep. This finding might represent a REM sleep suppressing effect of leptin, possibly through a direct interaction with the serotonergic system, which could enhance direct pharmacological REM suppression.[40,41] It is to note though, that these interpretations are only based on exploratory analyses.

The reported increased sleep continuity, suppressed REM sleep, and impaired daytime vigilance and performance following AMI are, according to the employed simultaneous regression model, to be regarded largely independent of the endocrine systems we considered, i.e. they are not mediated by changes in ghrelin, leptin, cortisol or prolactin. This appears to be true as well for the decreased sleep continuity, suppressed REM sleep and improved daytime sleepiness and performance following ESC.[28] The effects of AMI and ESC on REM sleep are well known and mainly induced by noradrenergic/serotoninergic and anticholinergic effects.[42-44]

It is to note, though, that at least cortisol undergoes a circadian rhythm with differing serum levels. Twenty-four hour-sampling would be needed to further delineate the time-course of serum hormone levels. It is to note that we investigated serum levels 10 hours after medication

intake. Early onset effects might have been missed as well as enduring long-time changes. Another limitation of the current analysis is sample size. However, we used a well-controlled, repeated measures design and observed large effect sizes for the impact of AMI on ghrelin and cortisol levels.

A single-dose of AMI in the evening decreased early morning levels of ghrelin and cortisol, but did not affect leptin or prolactin levels. ESC did not to have acute effects on the described endocrine systems. These findings on acute effects complement those on long-term administration and contribute to further disentangle the acute and long-term clinical effects of the described antidepressants. In addition, individually higher ghrelin serum levels were related to increased wake periods and higher leptin serum levels to reduced REM sleep periods in the preceding night. The relationship between sleep and daytime performance on one hand and early morning ghrelin and leptin serum levels on the other hand warrants further examination.

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SUPPLEMENTARY MATERIALS

Supplementary data is available at https://doi.org/10.9758/cpn.2018.16.3.253.

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