Neuroendocrine perturbations in human obesity

Kok, P.

Chapter 8

Activation of Dopamine D2 Receptors Simultaneously Ameliorates Various Metabolic Features of Obese Women

Petra Kok, Ferdinand Roelfsema, Marijke Frölich, Johannes van Pelt, Marcel P.M. Stokkel, A Edo Meinders, Hanno Pijl

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Abstract

The metabolic syndrome comprises a cluster of metabolic anomalies, including insulin resistance, abdominal obesity, dyslipidemia and hypertension. Previous studies suggest that impaired dopamine D2 receptor (D2R) signalling is involved in its pathogenesis. We studied the acute effects of bromocriptine (a D2R agonist) on energy metabolism in obese women, while body weight and caloric intake remained constant. 18 healthy obese women (BMI 33.2 ± 0.6 kg/m^2, mean age 37.5 ± 1.7 range 22-51 years) were studied twice in the follicular phase of their menstrual cycle in a prospective, single blind, cross-over design. Subject received either bromocriptine (B) or placebo (Pl) for eight days. At each occasion blood glucose and insulin were assessed every 10 minutes during 24 hours and circadian plasma free fatty acids (FFA) and triglyceride (TG) levels were measured hourly. Fuel oxidation was determined by indirect calorimetry. Body weight and -composition were not affected by the drug. Mean 24 h blood glucose ($P < 0.01$) and insulin ($P < 0.01$) were significantly reduced by bromocriptine, whereas mean 24 h FFA levels were increased ($P < 0.01$), suggesting that lipolysis was stimulated. Bromocriptine increased oxygen consumption ($P = 0.03$) and resting energy expenditure (by 50 kCal/day, $P = 0.03$). Systolic blood pressure was significantly reduced by bromocriptine. Thus, these results imply that short term bromocriptine treatment ameliorates various components of the metabolic syndrome, while it shifts energy balance away from lipogenesis in obese humans.

Introduction

The metabolic syndrome comprises a cluster of metabolic anomalies that are well-established risk factors for type 2 diabetes and cardiovascular disease, including insulin resistance, abdominal obesity, dyslipidemia and hypertension. Their concomitant occurrence suggests that a common pathophysiological denominator underlies these distinct metabolic features. Seasonally obese birds, fish and rodents spontaneously develop virtually all components of the metabolic syndrome in preparation for winter-time. A wealth of data indicates that fluctuations of dopaminergic neurotransmission in various brain nuclei are involved in these seasonal metabolic adaptations (1). In particular, reduction of dopaminergic neurotransmission in supra chiasmatic nuclei precedes the development of obesity and insulin resistance, and treatment with the dopamine D2 receptor (D2R) agonist bromocriptine effectively redirects the obese insulin resistant state towards the lean insulin sensitive state in these rodents (2-6). Compelling evidence suggests that D2R transmitted dopaminergic tone is also diminished in the brain of various models of non-seasonal obesity (7) and D2R agonist drugs ameliorate the metabolic profile of these animals as effectively as they do in seasonal obese models (8;9). D2R binding capacity in the brain of obese humans is reduced in proportion to body mass index (10), which thus may contribute to the metabolic anomalies associated with obesity. To investigate the potential impact of diminished dopaminergic D2 receptor mediated neurotransmission per se on the regulation of energy expenditure and fuel metabolism in humans, we studied the (sub) acute effects of short-term bromocriptine treatment on various metabolic parameters in obese humans.

Subjects and Methods

Subjects

Eighteen healthy obese premenopausal women (BMI 30.1-40.5 kg/m^2, mean age 37.5 ± 1.7, range 22-51 years) were recruited through advertisements in local news papers. All subjects had medical screening, including medical history taking, physical examination, standard haematology, and blood and urine chemistry. Acute or chronic disease, depression (present or in medical history), head trauma, smoking, alcohol abuse, recent trans-meridian flights, night-shift work, weight change prior to the study (> 5 kg in 3 months), recent blood donation, participation in another clinical trial (< 3 months) and use of medication (including oral anti-conceptives) were exclusion criteria for participation. All participants were required to have regular menstrual cycles. All studies were done in the early follicular phase of the menstrual cycle.

Body composition

Body mass index (weight (kg)/(length (m))^2) was calculated according to WHO recommendations. Percentage body fat (fraction of total body weight) was quantified using dual energy X-ray absorptiometry (DEXA, Hologic QDR4500) on a separate day between the two study occasions(11).

Drugs

Subjects were assigned to bromocriptine or placebo treatment for a period of 8 days in a single blind cross-over design, with a four week time interval between each study occasion. To avoid potential cross-over effects of bromocriptine treatment, all subjects received placebo during the first intervention period. A dose of 2.5 mg of bromocriptine or placebo was prescribed at the first day. Thereafter, drug or placebo were taken twice daily (totalling 5.0 mg daily) at 0800 h and 2000 h until the end of the blood sampling period, which took place at the 8th day of treatment. All subjects tolerated the drug well, although ten participants had gastro-intestinal complaints (nausea, vomiting) at the first day of bromocriptine treatment only.

Diet

To limit confounding by nutritional factors, all subjects were prescribed a standard eucaloric diet supplied by the research center and drinks other than water were prohibited as of one day prior to admission until the end of each study occasion. The macronutrient composition and caloric content of the diet was exactly the same for each individual at both study occasions. Meals were served according to a fixed time schedule (breakfast 0930 h, lunch 1300 h, diner 1830 h) and were consumed within limited time periods (30 minutes). No dietary restrictions were imposed on the obese women between both study occasions.

Indirect calorimetry

After resting for 45 minutes, subjects (fasting) were placed under a ventilated hood, while lying on a bed, awake, in a quiet room for 30 minutes. The volume of oxygen inspired (VO_2) and the expired volume of carbon dioxide (VCO_2) were measured every minute. Subsequently, resting energy expenditure (REE), glucose and lipid oxidation were calculated with the following equations:

Glucose oxidation	=	4.57 VCO_2-3.23VO_2-2.6N
Lipid oxidation	=	1.69 VO_2-1.69VCO_2-2.03N
REE	=	3.91 VO_2 + 1.10 VCO_2-1.93 N

in which protein disappearance is ignored (N = Nitrogen) since the error thus introduced in the calculation of energy expenditure is negligible(12).

Clinical Protocol

The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center and was performed according the Helsinki declaration. All subjects gave written acknowledgement of informed consent for participation and were admitted to the Clinical Research Unit of the Department of General Internal Medicine. Obese subjects were studied

twice with an interval of four weeks, wherein body weight remained stable and subjects were instructed to keep their physical activity level constant. The clinical set-up was the same during both occasions apart from the subject receiving the alternative treatment (bromocriptine or placebo). Subjects were admitted to the research center at 0700 h am, after an overnight fast. After resting for 45 minutes, indirect calorimetry was performed using a ventilated hood for 30 minutes. Thereafter a cannula for blood sampling was inserted into an antecubital vein, which was attached to a 3-way stopcock and kept patent by a continuous 0.9% NaCl and heparin (1 U/ml) infusion (500ml/24 h). Blood samples for basal parameters were withdrawn and twenty four hour blood sampling started. Blood was collected with S-monovetten (Sarstedt, Etten-Leur, The Netherlands) at 10-minute intervals for determination of plasma insulin and glucose concentrations. Blood samples for the measurements of plasma free fatty acid (FFA) and triglyceride (TG) levels were taken hourly. The total amount of blood withdrawn during each occasion was 246 ml. All subjects remained recumbent during the blood-sampling period except for bathroom visits (24 h urine was collected). No daytime naps were allowed. Well being and vital signs were recorded at regular time intervals (hourly). Meals were served according to a fixed time schedule (0930 h breakfast, 1300 h lunch, 1830 h diner) and consumed within limited time periods. Lights were switched off at 2300 h and great care was taken not to disturb and touch subjects during withdrawal of blood samples while they were sleeping. Periods of wakefulness and toilet visits during the night were recorded by the personnel performing nocturnal blood sampling. Polygraphic sleep monitoring by EEG was not performed. Lights were switched on and subjects were awakened at 0730 h am. All data were recorded on standard data collection forms and was entered after validation in a computer system for subsequent tabulation and statistical analysis.

Assays

Samples of each subject were determined in the same assay run. Serum insulin was measured with IRMA (Biosource Europe, Nivelles, Belgium) with a detection limit of 2 µU/L.The intra and inter-assay coefficients of variation were 4.4% and 5.9%, respectively. Plasma FFA levels were determined using a NEFA-C Free Fatty acid kit (Wako Chemicals GmbH, Neuss, Germany) with a detection limit of 30 µmol/L and the inter and intra-assay coefficients of variation of 2.6% and,1.1% respectively. Plasma TG concentrations were measured using an enzymatic colorimetric kit (Roche Diagnostics GmbH, Mannheim, Germany) with a detection limit of 50 µmol/L and intra- and inter-assay coefficients of variation 1.5% and 1.8%, respectively. Progesterone concentrations were measured using a solid-phase RIA (Diagnostic Products, Los Angeles, CA, USA).

Estradiol concentrations were determined by RIA (Diagnostic Systems Laboratory, Webster, TX, USA). The detection limit was 10 pmol/L and inter and intra-assay coefficients of variation were 15.8% and 6.8% respectively. Plasma PRL concentrations were measured with a sensitive time- resolved fluoro immunoassay with a detection limit of 0.04 µg/L (Delfia, Wallac Oy, Turku, Finland). The PRL IFMA was calibrated against the 3rd WHO standard: 84/500, 1 ng/ml = 36 mU/L. The intra-assay coefficient of variation varies from 3.0-5.2% and inter-assay coefficient of variation is 3.4-6.2%. Serum glucose, cholesterol and triglyceride levels were measured using a fully automated Hitachi P800 system (Roche, Almere, The Netherlands). C-peptide concentrations were assessed by RIA (Adaltis Italia S.p.A., Casalecchio di Reno, Italy). Free thyroxine (T_4) concentrations were estimated using electro chemo luminescence immunoassay (Elecsys 2010, Roche Diagnostics Nederland BV, Almere, Netherlands).

Urine Analysis

From the moment the blood sampling period started 24 h urine was collected for the determination of catecholamine and urea nitrogen concentrations. Urinary urea concentrations were assessed by a fully automatic P 800 System (Roche, Almere, The Netherlands). Urinary epinephrine, nor-epinephrine and dopamine concentrations were assessed by high performance liquid chromatography with electron capture detection.

Calculations and statistics

Area under the Curves Metabolic Profiles
Area under the curves of insulin, glucose, FFA and TG concentration plots were calculated using the trapezoidal rule (Sigma Plot 2002 for Windows version 8.02).

HOMA model
Homeostatic model assessment (HOMA) was used to yield an estimate of longitudinal changes of insulin sensitivity before and after bromocriptine treatment in the obese subjects. The equation we used was: (fasting insulin (mU/L) x fasting glucose (mmol/l))/22.5), originating from the model firstly described by Matthews et al (13).

Statistics
Data are presented as means ± SEM, unless otherwise specified. Data was logarithmically transformed before statistical computations when appropriate and statistically analysed using a parametric test (paired samples t-test). Significance level was set at 0.05.

Results

Screening parameters obese subjects
Eighteen obese subjects were enrolled in the study. The mean age of all subjects was 37.5 ± 1.7 yrs (range 22-51 yrs). Subjects had a mean body weight of 93.9 ± 2.6 kg (range 81.2-124.1 kg), a BMI of 33.2 ± 0.6 kg/m^2 (range 30.1-40.5 kg/m^2) and total percentage body fat of 39.6 ± 0.8 % (range 32.1-44.8). Mean fasting glucose concentration was mmol/L 5.0 ± 0.1 (range 4.2-6.3 mmol/L), insulin mU/L 15.3 ± 1.7 (range 7-28 mU/L), HbA1C 4.7 ± 0.1 % (range 3.9-5.3 %), total cholesterol 4.7 ± 0.2 mmol/L (range 3.7-5.8 mmol/L), LDL cholesterol 2.99 ± 1.57 mmol/L (range 2.03-4.00 mmol/L) and HDL cholesterol 1.54 ± 0.08 mmol/L (range 1.03-2.32 mmol/L).

Baseline measurements at start study occasions
Body weight was similar at both study occasions. All subjects were studied in the early follicular phase of their menstrual cycle, as confirmed by plasma estradiol and progesterone. All subjects were clinically euthyroid. Bromocriptine significantly decreased systolic blood pressure and parameters of glucose metabolism in fasting conditions (glucose, insulin, C-peptide) at the beginning of each study occasion. Cholesterol concentrations were not affected by bromocriptine. PRL concentrations were significantly reduced by bromocriptine. An overview of body composition parameters and baseline serum measurements obtained at the start of both study occasions is given in Table 1.

Effect of bromocriptine on indirect calorimetry
Indirect calorimetry was performed in 12 subjects only (for technical reasons). Oxygen consumption (VO_2) was significantly increased by bromocriptine, whereas the drug did not affect VCO_2. Resting energy expenditure was significantly higher during bromocriptine treatment. Glucose oxidation was slightly decreased, while lipid oxidation was enhanced during bromocriptine treatment, although these differences were not statistically significant. An overview of the results is presented in table 2.

Effect of bromocriptine on circadian glucose profiles
Diurnal blood glucose concentrations as well as the AUC of the 24 h glucose concentrations were significantly reduced after bromocriptine treatment compared with placebo (Table 3 and Figure 1A). Both the maximum concentration and the AUC of the glucose peak in response to dinner was significantly decreased by bromocriptine (maximal concentration Pl 9.0 ± 0.4 vs. B 7.5 ± 0.4 mmol/L, $P < 0.01$ and AUC Pl 131 ± 5 vs. B 112 ± 4 mmol/L/3.5 h, $P < 0.01$, Figure 1A). Also, nocturnal glucose concentrations (0000 h-0700 h clock time) and the AUC of the nocturnal glucose curves were significantly lower

during bromocriptine treatment. Mean nocturnal glucose concentration Pl 4.8 ± 0.1 vs. B 4.5 ± 0.1 mmol/L, P < 0.01 and AUC P 198 ± 3 vs. B 184 ± 4 mmol/L/7h, P < 0.01, Figure 1A. Periods of wakefulness during the night were not different at both study occasions.

Effect of bromocriptine on circadian insulin profiles

Mean 24 h insulin concentrations and the AUC of 24 h insulin profiles were significantly reduced during bromocriptine treatment (Table 3 and Figure 1B). The maximum concentration of the insulin peak in response to dinner was significantly decreased (Pl 185 ± 19 vs. B 132 ± 19 mU/L, P < 0.01) and the AUC of the postprandial insulin peak was significantly lowered by bromocriptine (AUC Pl 1846 ± 209 vs. B 1216 ± 178 mU/L/3.5 h, P < 0.01). Both nocturnal insulin concentrations (0000 h-0700 h clock time) and the AUC of the nocturnal insulin curves were similar during bromocriptine and placebo treatment (Mean nocturnal insulin concentration Pl 14.0 ± 1.2 vs. B 13.1 ± 1.1 mU/L, P = 0.31 and AUC Pl 557 ± 47 vs. B 521 ± 42 mU/L/7h, P = 0.32)

Effect of bromocriptine on circadian lipid profiles

Circadian circulating plasma FFA concentrations as well as the AUC of the 24 h FFA concentration curves were significantly increased during bromocriptine treatment. TG concentrations and AUC of the 24 h TG curves showed the same (non significant) trend (Table 3 and Figure 2A and B).

Urine Analysis

Twenty four hour urea nitrogen excretion did not differ during placebo and bromocriptine treatment (Pl 357 ± 21 vs. B 362 ± 20 mmol/24 h, P = 0.64). Urine norepinephrine was significantly reduced during bromocriptine treatment (Pl 0.18 ± 0.02 vs. B 0.12 ± 0.01 umol/24 h, P < 0.01), whereas epinephrine (Pl 0.015 ± 0.005 vs. B 0.012 ± 0.004 umol/24 h, P = 0.42) and dopamine (Pl 1.58 ± 0.17 vs. B 1.55 ± 0.19 umol/24 h, P = 0.83) were not affected by bromocriptine.

Discussion

This study shows that short-term treatment with the dopamine D2 receptor agonist bromocriptine favourably affects energy metabolism and blood pressure in obese women. In particular, 8 days of bromocriptine treatment reduces diurnal glucose and insulin concentrations. In addition, bromocriptine enhances oxygen consumption and basal metabolic rate and lowers (systolic) blood pressure. Plasma free fatty acid and triglyceride concentrations were elevated during bromocriptine treatment. Notably, all of these effects come about without any change of body adiposity and independent of qualitative or quantitative changes in food intake.

As far as we are aware, this is the first study to show a beneficial effect of short-term bromocriptine treatment on energy expenditure and fuel metabolism in obese humans. The data indicate that activation of dopamine D2 receptors ameliorates various features of the metabolic syndrome in obese humans, even apart from its impact on food intake and body weight. Long-term bromocriptine treatment effectively reduces fasting insulin and glucose levels in rodents (4;9;14) and improves glucose tolerance in healthy and diabetic obese humans (15-18). However, chronic bromocriptine administration consistently reduces body fat, perhaps primarily via its inhibitory effect on food intake (19-21), which might explain the metabolic corollaries of treatment. We here show that activation of D2 receptors directly acts to reduce circadian plasma glucose and insulin concentrations, where both postprandial and nocturnal glucose levels are diminished, even without any measurable effect on body weight

Bromocriptine significantly enhanced resting energy expenditure and oxygen consumption in the current experimental context. This finding is corroborated by data documenting enhanced oxygen consumption in response to bromocriptine treatment in obese rodents (2;22). Conversely, loss of function mutations of the D2R gene are associated with reduced resting energy expenditure in humans (23). Our results further support the position that D2R signalling is involved in the control of basal metabolic rate in humans. Whether bromocriptine also affects the level of physical activity requires further investigation.

Bromocriptine significantly reduced systolic blood pressure. The autonomic nervous system plays a critical role in the

control of blood pressure (24) and sympathetic hyperactivity may indeed underlie hypertension in obese humans (25). Activation of dopamine D2R has sympatholytic effects (26;27), which thus may lower blood pressure. The fact that urinary catecholamine excretion was blunted by bromocriptine in the present study supports the notion that reduction of sympathetic tone may (in part) underlie the hypotensive effect of the drug. In addition, bromocriptine blocks 1-adrenergic receptors (28), which obviously may also contribute to the hypotensive effect of the drug (29).

The rise of circulating FFA levels induced by bromocriptine may reflect inhibition of net FFA uptake in adipocytes (4). In apparent contrast, long-term bromocriptine treatment either reduces or does not affect plasma FFA concentrations in rodents and humans (4;9;17;18). However, these effects on circulating FFA levels presumably result from loss of body fat induced by chronic bromocriptine administration, which did not occur in the present study.

The mechanisms through which dopaminergic neurons control energy balance and fuel metabolism remain to be established. Although D2R are expressed in various tissues (30), intracerebroventricular injections of bromocriptine at a very low dose completely reproduce the metabolic effects of high dose intravenous administration in rats, which suggests that the central nervous system D2R is a critical target of the drug. Activation of D2R reduces neuropeptide Y (NPY) mRNA expression in the arcuate nucleus of the hypothalamus (31-33). NPY is elevated in the arcuate nucleus of obese animal models (32-34)and icv administration of this neuropeptide directly induces (hepatic) insulin resistance and suppresses basal metabolic rate in rodents (35;36). Therefore, bromocriptine may facilitate glucose homeostasis through a reduction in hypothalamic NPY. Alternatively, bromocriptine may impact metabolism by virtue of its sympatholytic properties (37). High NE levels in the ventromedial hypothalamus are another neurochemical marker of obesity in rodents and NE infusion into this brain area produces all features of the metabolic syndrome (38). D2R activation inhibits NE gene expression and release in the arcuate nucleus and peripheral nerves (26;27) and bromocriptine's ability to act as such was supported by our data indicating that 24 h norepinephrine (NE) urine concentrations were significantly lower after bromocriptine treatment. Thus, the favourable effects of bromocriptine on glucose metabolism may also be due to reduced NE release in the ventromedial hypothalamus. Finally, activation of D2R inhibits the pituitary lactotroph axis and prolactin (PRL) has been reported to exert potent lipogenic and diabetogenic effects (for review see(39)). Thus, the ability of bromocriptine to favourably affect fuel flux in obese women could also be mediated by a decrease of circulating PRL levels.

Our data lend further support to the postulate that reduced dopaminergic D2R signalling in obese humans, as reported by Wang et al (10), has adverse metabolic consequences. In particular, deficient dopaminergic D2R transmission may be involved in the pathogenesis of various components of the metabolic syndrome in humans.

In conclusion, short-term bromocriptine treatment facilitates glucose metabolism, lowers systolic blood pressure and stimulates resting energy expenditure in obese humans. Notably, these effects occur through mechanistic routes distinct from reduction of food intake or loss of body fat. These data indicate that activation of D2R dopaminergic neurotransmission ameliorates various metabolic anomalies associated with obesity and lend further support to the thesis that reduced D2R availability in the brain of obese humans directly contributes to their adverse metabolic profile.

Tables and Figures

Table 1. Basal Measurements at the start of each study occasion

Parameter	Placebo	Bromocriptine	P-value [a)]
Weight (kg)	94.1 ± 2.5	94.4 ± 2.5	0.33
BMI (kg/m2)	33.2 ± 0.6	33.3 ± 0.6	0.35
Diastolic blood pressure (mmHg)	81 ± 3	79 ± 2	0.43
Systolic blood pressure (mmHg)	122 ± 4	112 ± 3	0.04
Fasting glucose (mmol/L)	5.3 ± 0.2	4.8 ± 0.1	<0.01
Fasting insulin (mU/L)	13.3 ± 1.4	10.9 ± 0.8	0.03
HOMA_IR [b)]	3.25 ± 0.48	2.32 ± 0.19	0.01
C-peptide (nmol/L)	0.959 ± 0.108	0.724± 0.055	0.01
Cholesterol (mmol/L)	4.41 ± 0.16	4.45 ± 0.14	0.54
LDL cholesterol (mmol/L)	2.79 ± 0.16	2.83 ± 0.16	0.66
HDL cholesterol (mmol/L)	1.40 ± 0.07	1.43 ± 0.07	0.27
Ratio total cholesterol/HDL	3.26 ± 0.19	3.13 ± 0.17	0.15
Estrogen (E2) (pmol/L)	163 ± 21	209 ± 21	0.10
Progesteron (nmol/L)	2.13 ± 0.64	2.94 ± 1.13	0.56
Free thyroxine (pmol/L)	14.6 ± 0.4	14.4 ± 0.4	0.56
Prolactin (µg/L)	6.7 ± 1.1	2.3 ± 0.4	<0.01

Data are presented as mean ± SEM

a) P-values placebo vs. bromocriptine obese women, as determined by paired samples t-test

b) The homeostasis model was used to estimate insulin sensitivity from fasting insulin and glucose levels. HOMA_IR was calculated as (fasting insulin (mU/ml) x fasting glucose (mmol/l))/22.5)(13). Data was log-transformed before statistical analysis.

Table 2. Indirect Calorimetry in 12 obese women

Parameter	Placebo	Bromocriptine	P-value [a)]
RQ	0.79 ± 0.01	0.78 ± 0.01	0.58
VO_2 (ml/min)	232.2 ± 5.7	243.6 ± 8.2	0.03
VCO_2 (ml/min)	182.8 ± 4.2	188.7 ± 6.3	0.20
Glucose oxidation (µmol/kg/min)	5.2 ± 0.9	4.6 ± 0.8	0.67
Lipid oxidation (µmol/kg/min)	3.4 ± 0.3	3.7 ± 0.3	0.38
REE (kcal/day)	1109 ± 26	1160 ± 39	0.03

Data are presented as mean ± SEM.

a) P-values placebo vs. bromocriptine obese women, as determined by paired samples t-test

Table 3. Metabolic Parameters in obese women

Parameter	Placebo	Bromocriptine	P-value [a)]
Total Mean 24 h insulin (mU/L)	38 ± 4	29 ± 3	<0.01
Total AUC insulin (mU/Lx24 h)	55 130 ± 5 188	42 029 ± 4 704	<0.01
Total Mean 24 h glucose (mmol/L)	5.4 ± 0.1	4.9 ± 0.1	<0.01
Total AUC glucose (mmol/Lx24 h)	7497 ± 165	6987 ± 158	0.02
Mean 24 h FFA (mmol/L)	0.44 ± 0.03	0.57 ± 0.05	<0.01
AUC FFA (mmol/Lx24 h)	10.45 ± 0.72	13.59 ± 1.26	<0.01
Mean 24 h triglycerides (mmol/L)	1.24 ± 0.11	1.34 ± 0.10	0.15
AUC triglycerides (mmol/Lx24 h)	29.65 ± 2.69	32.04 ± 2.38	0.14

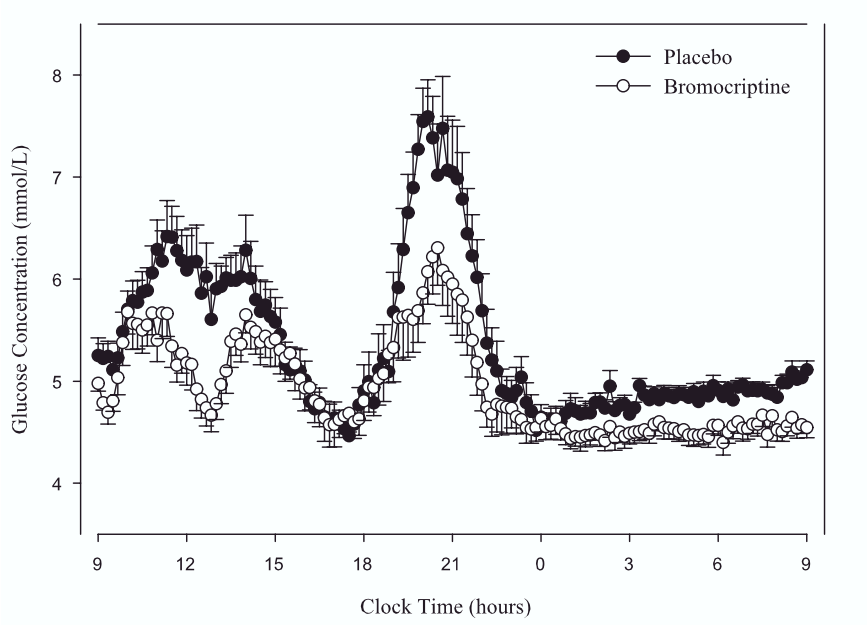
Data are presented as mean ± SEM.

a) P-values placebo vs. bromocriptine obese women, as determined by paired samples t-test

Figure 1.

Serum 24 h glucose concentration time series (A) and 24 h insulin concentrations (B) of the obese subjects (N = 18) during placebo (-•-) and bromocriptine treatment (-o-). Data reflect sampling of blood every 10 min. Error bars represent SEM. 24 h Blood sampling began at 0900 h. Lights were switched off and subjects went to sleep at 2300 h until 0730 h am, when lights were switched on (grey horizontal bar indicates dark period).

A)



B)

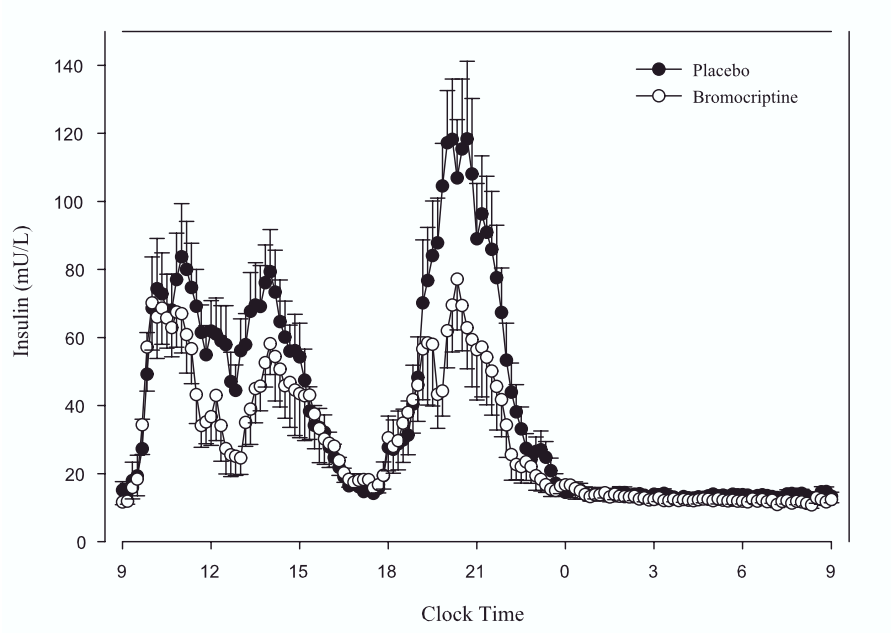
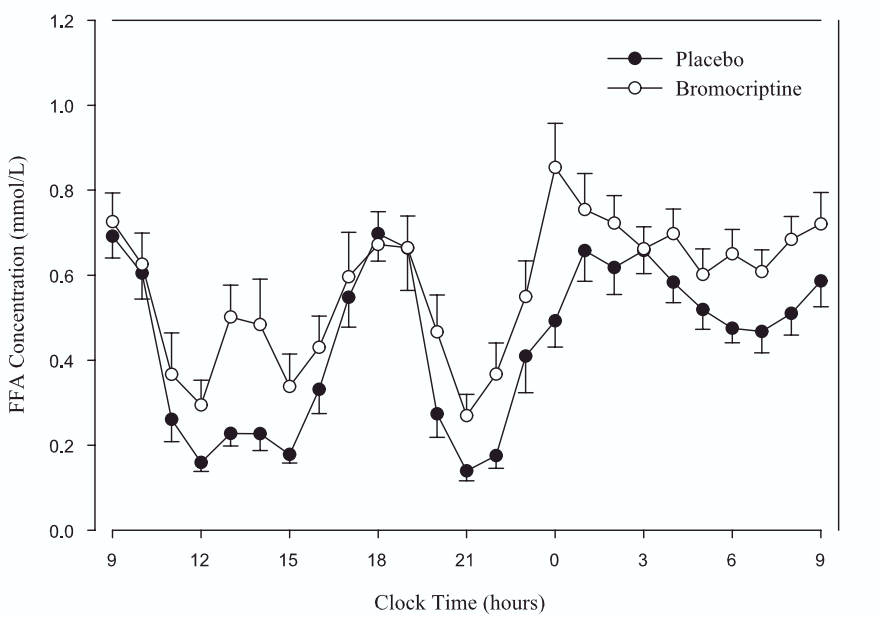


Figure 2.

Serum FFA (A) and TG (B) concentration time series of the obese subjects (N = 18) during placebo (-•-) and bromocriptine treatment (-○-). Data reflect sampling of blood every hour for 24 h. Error bars represent SEM. Blood sampling starts at 0900 h. Lights were switched off and subjects went to sleep at 2300 h until 0730 h next morning, when lights were switched on (grey horizontal bar indicates dark period).

A)



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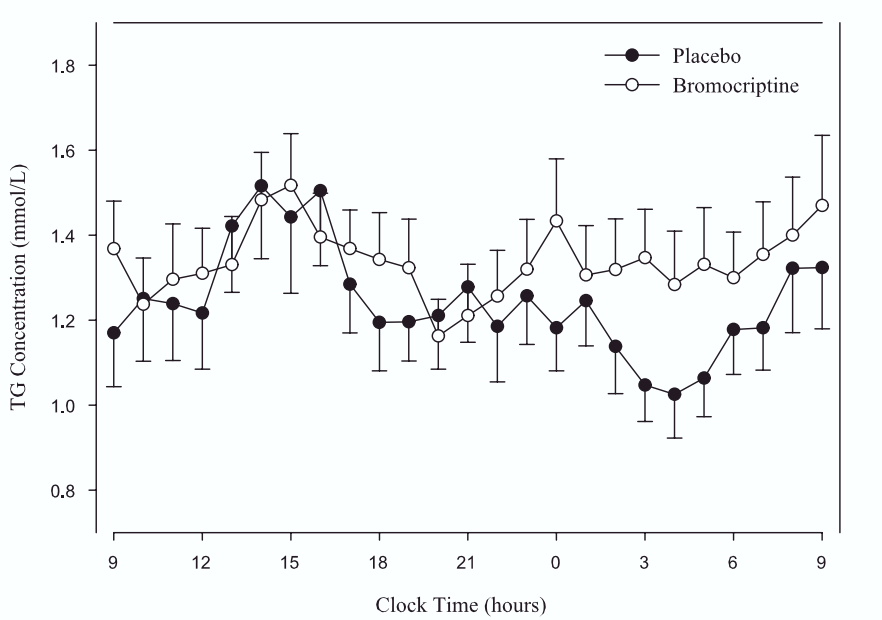

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