



Bromocriptine and insulin sensitivity in lean and obese subjects

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Abstract

Bromocriptine is a glucose-lowering drug, which was shown to be effective in obese subjects with insulin resistance. It is usually administered in the morning. The exact working mechanism of bromocriptine still has to be elucidated. Therefore, in this open-label randomized prospective cross-over mechanistic study, we assessed whether the timing of bromocriptine administration (morning vs evening) results in different effects and whether these effects differ between lean and obese subjects. We studied the effect of bromocriptine on insulin sensitivity in 8 lean and 8 overweight subjects using an oral glucose tolerance test. The subjects used bromocriptine in randomized cross-over order for 2 weeks in the morning and 2 weeks in the evening. We found that in lean subjects, bromocriptine administration in the evening resulted in a significantly higher post-prandial insulin sensitivity as compared with the pre-exposure visit (glucose area under the curve (AUC) 742 mmol/L * 120 min (695–818) vs 641 (504–750), $P=0.036$, AUC for insulin did not change, $P=0.575$). In obese subjects, both morning and evening administration of bromocriptine resulted in a significantly higher insulin sensitivity: morning administration in obese: insulin AUC (55,900 mmol/L * 120 min (43,236–96,831) vs 36,448 (25,213–57,711), $P=0.012$) and glucose AUC $P=0.069$; evening administration in obese: glucose AUC (735 mmol/L * 120 min (614–988) vs 644 (568–829), $P=0.017$) and insulin AUC, $P=0.208$. In conclusion, bromocriptine increases insulin sensitivity in both lean and obese subjects. In lean subjects, this effect only occurred when bromocriptine was administered in the evening, whereas in the obese, insulin sensitivity increased independent of the timing of bromocriptine administration.

Key Words

- ▶ dopamine
- ▶ bromocriptine
- ▶ insulin sensitivity
- ▶ obesity
- ▶ circadian rhythm

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Introduction

In 30–50% of the patients with type 2 diabetes mellitus, current pharmaceutical options to reach an adequate glucose control are insufficient (1). Therefore, the search for new and better treatment options is still ongoing. Recently, a quick release variant of bromocriptine has emerged as a new glucose-lowering treatment in obese patients with type 2 diabetes mellitus. Bromocriptine is

a centrally acting dopamine D₂-receptor agonist, but it also weakly stimulates the dopamine D₁-receptor (2). Treatment with bromocriptine was shown to improve several metabolic parameters such as glucose levels in obese patients with and without diabetes mellitus compared with placebo (3, 4, 5, 6, 7, 8, 9, 10). However, we recently performed a trial in which we administered



bromocriptine, for 2 weeks, in the evening in 8 lean, healthy subjects. Unexpectedly, these lean healthy subjects became less insulin sensitive after using bromocriptine (11). This adverse effect of bromocriptine in lean healthy males might have been caused by two factors. First, bromocriptine might exert different effects in lean compared with obese subjects. In other words, bromocriptine may correct a pathological condition in obese patients with diabetes mellitus type 2, whereas in lean subjects, there is no pathological condition. Secondly, the timing of the bromocriptine may have interfered with the normal circadian dopamine rhythm (12, 13, 14).

The aim of this clinical study was to gain a better understanding of the mechanism of action of bromocriptine on insulin sensitivity. First, we aimed to investigate whether bromocriptine administration for 2 weeks had a different effect on insulin sensitivity in lean compared with overweight subjects. Second, we aimed to investigate whether the timing of bromocriptine administration had an effect on insulin sensitivity (i.e. whether administration in the morning has a different effect on insulin sensitivity compared with administration in the evening).

Methods

Study population

Sixteen subjects were recruited by public advertisements in the Academic Medical Center (AMC) in Amsterdam and on websites for trial subjects, between October 2014 and August 2015.

Eligible for the study were healthy, Caucasian males between ages 18 and 35 years, with a stable weight for at least 3 months before inclusion. The subjects were either lean (BMI 19–23 kg/m²) or overweight (BMI >27 kg/m²). The included subjects were age matched (lean vs overweight). None of the subjects had contraindications to the use of bromocriptine (e.g. known hypersensitivity to bromocriptine, uncontrolled hypertension, a known history of coronary artery diseases or valvulopathy, a history of severe psychiatric disorders, prolactinomas), as determined by history, physical examination and blood screening. Other exclusion criteria were use of prescription medication or drugs or a foreseen aberrant lifestyle (e.g. excessive physical exercise, night shifts, excessive alcohol intake) during the study period that would potentially influence the outcome. All subjects gave written signed voluntary informed consent before

participation. The protocol was approved by the Medical Ethics Committee of the AMC. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Power analysis

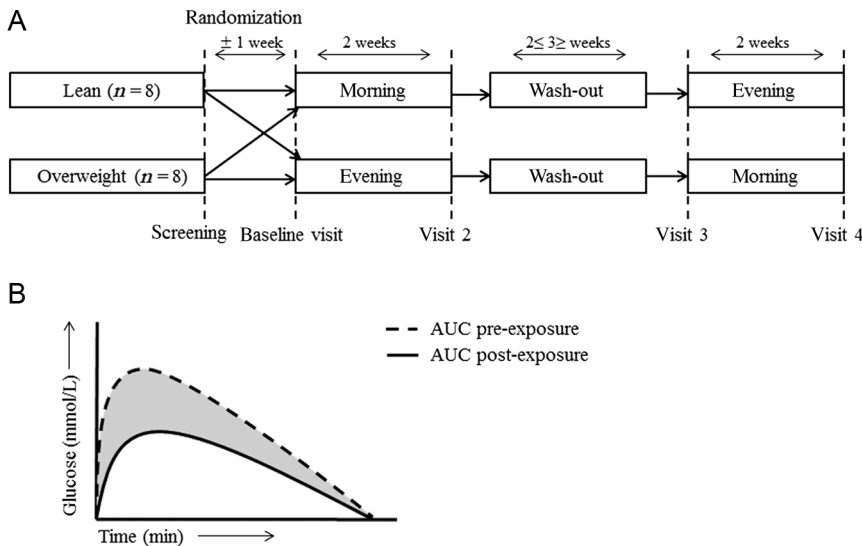
Power calculation was performed using nQuery Advisor and was based on a previous study (11). Assuming an alpha of 5%, 6 subjects were needed in each group to reach a power of 80%. To enlarge power and to allow for unexpected findings, two extra subjects per group have been included. This led to a total of 16.

Study design

This open-label randomized prospective cross-over mechanistic study consisted of 8 lean and 8 overweight subjects. All participants used bromocriptine for a period of two weeks in the morning and a period of two weeks in the evening according to a software-driven randomization order (Castor Electronic Data Capture (EDC), Amsterdam, The Netherlands). The periods were separated by a wash-out of at least two weeks (Fig. 1). The daily bromocriptine dose administered was 1.25 mg (orally) during each first week and 2.50 mg during each second week. So, the study consisted of two separate investigation periods with two pre-exposure measurements (visits 1 and 3), after which bromocriptine was used according to the randomization (i.e. bromocriptine in the evening or morning), which was followed by an investigation day (visits 2 and 4).

Study visits

For all study visits, subjects arrived in the morning at the clinical diabetology department after an overnight fast. Each of the four visits consisted of the same measurements. Subject's weight, wearing underwear only, was measured to the nearest 100g on a calibrated mechanical scale (SECA, Hamburg, Germany). Energy expenditure (EE) was measured, and a cannula was inserted into an antecubital vein to obtain blood samples during the oral glucose tolerance test (OGTT). Subjects were instructed to keep their diet as constant as possible during study participation. To check for possible changes in eating behavior between visits, the subjects were asked to record

**Figure 1**

Visual explanation of methods. (A) Overview of the visits of the subjects. Subjects came for a screening visit after which they were randomized to the timing of bromocriptine administration. Visits 1 (baseline visit) and 3 were pre-exposure visits. Visits 2 and 4 were post-bromocriptine exposure visits (in randomized order morning and evening administration) for 2 weeks. (B) Graph of the effect of bromocriptine. The effect of bromocriptine administration is the gray area.

their diet of the 3 days before each visit. On visits 2 and 4, subjects were asked whether they experienced any side effects; furthermore, adequate use of the bromocriptine was controlled by pill count.

Oral glucose tolerance test and laboratory measurements

Fasting plasma glucose and insulin values were measured within 2 min before t_0 . At t_0 , subjects ingested a standardized solution of 75 g glucose dissolved in 300 mL water (Added pharma, Oss, The Netherlands). Subsequent measurements took place at t_{10} , t_{20} , t_{30} , t_{60} , t_{90} and t_{120} with t in minutes. Plasma glucose measurements were performed using the HemoCue B-Glucose Analyzer (HemoCue AB, Ängelholm, Sweden). Insulin was measured by chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostic Products).

EE measurement

Energy expenditure (EE) was measured using a ventilated hood system (Quark RMR Canopy). Subjects were instructed to minimize physical activity (e.g. avoid walking stairs) in the morning before the visit. Before the EE, subjects had to rest for thirty minutes on a bed. During the EE, subjects were not allowed to sleep, talk or move. The EE was performed in a thermoneutral room of approximately 21°C (69.8°F). Respiratory quotient (RQ) and EE values (kcal/day) were measured by indirect calorimetry at 1-min intervals during 20 min after a stable phase had been reached.

Outcome measures

The outcome – differences in effect on insulin sensitivity – was expressed by means of various glucose and insulin parameters: areas under the curve (AUCs) for both glucose and insulin, peak values for glucose and insulin during the OGTT and homeostatic model assessment for insulin resistance (HOMA-IR type 1) (fasting insulin ($\mu\text{U/L}$) \times fasting glucose (nmol/L)/22.5) (15). Secondary outcomes were the differences in effect of bromocriptine on EE (kcal/day) and weight (kg).

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 22. Data were continuous and not normally distributed; to test for possible statistically significant differences between groups, the Mann–Whitney U test was used for unpaired data and the Wilcoxon signed-rank test for paired data. Values are presented as median and full range. $P < 0.05$ was considered statistically significant.

The relative differences ($100 \times \text{absolute value after exposure} / (\text{absolute value pre-exposure})$) were used to compare the effect of bromocriptine between the lean and obese subjects.

Results

We included 8 lean (BMI 21.5 (20.4–21.9) kg/m², age 22.5 (20.3–25.0) years) and 8 obese (BMI 32.1 (29.0–42.0) kg/m², age 22.5 (20.3–25.0) years) healthy Caucasian males (Table 1). All subjects tolerated the drug well.

Table 1 Baseline table.

	Lean	Obese	P value
N	8	8	
Age (years)	22.5 (20.3–25.0)	23.5 (18.5–30.3)	0.88
Body mass index (kg/m ²)	21.5 (20.4–21.9)	32.1 (29.0–42.0)	<0.001
Waist circumference (cm)	79.1 (77.3–83.1)	104.0 (99.6–135.2)	<0.001
Fasting plasma glucose (mmol/L)	4.2 (3.9–4.4)	4.3 (4.0–4.6)	0.645
Fasting plasma insulin (pmol/L)	13.8 (7.5–26.0)	67.0 (32.5–204.5)	0.001
HOMA-IR	0.35 (0.20–0.69)	1.9 (1.04–5.70)	0.001

Characteristics of subjects. Data presented as median (interquartile range). BMI, body mass index. Differences between the groups were calculated with the Mann–Whitney *U* test. HOMA-IR, homeostatic model assessment – insulin resistance, calculated as (glucose (mmol/L) × insulin (U/L))/(22.5).

Effect of bromocriptine on insulin and glucose levels during the OGTT

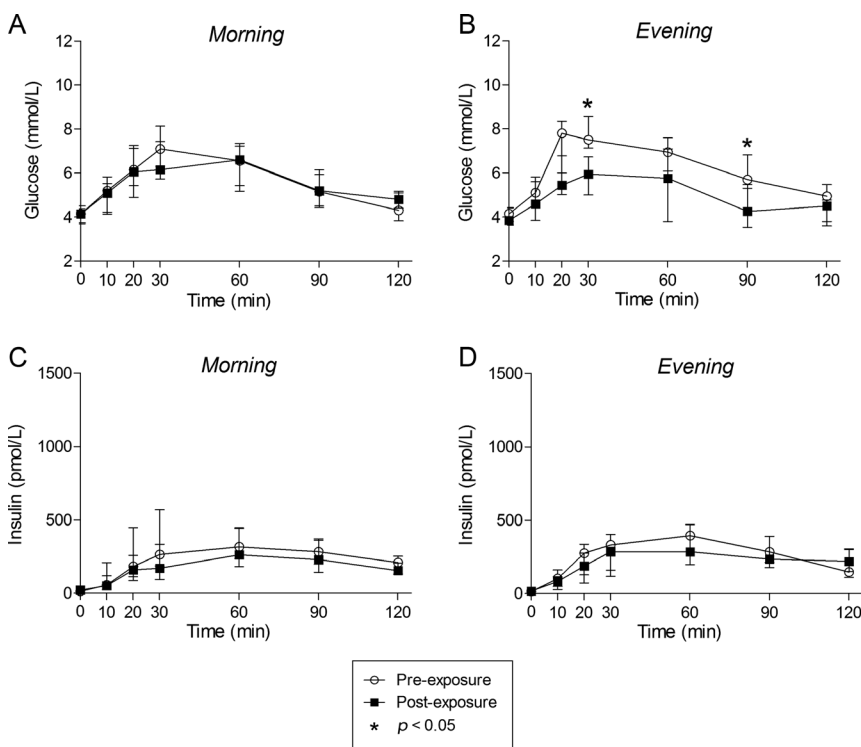
In lean subjects, there was no effect of bromocriptine administration in the morning on either glucose or insulin values during the OGTT. Bromocriptine administration in the evening resulted in significantly lower glucose values at t_{30} and t_{90} minutes (Fig. 2), but we observed no significant effect on insulin levels.

During the OGTT in obese subjects, bromocriptine administration in the morning resulted in significantly lower glucose values at t_{20} and t_{30} minutes and insulin values at t_{30} , t_{60} and t_{90} minutes. Bromocriptine administration in the evening resulted in significantly lower glucose values at t_{60} minutes (Fig. 3), but no significant effect on insulin was observed.

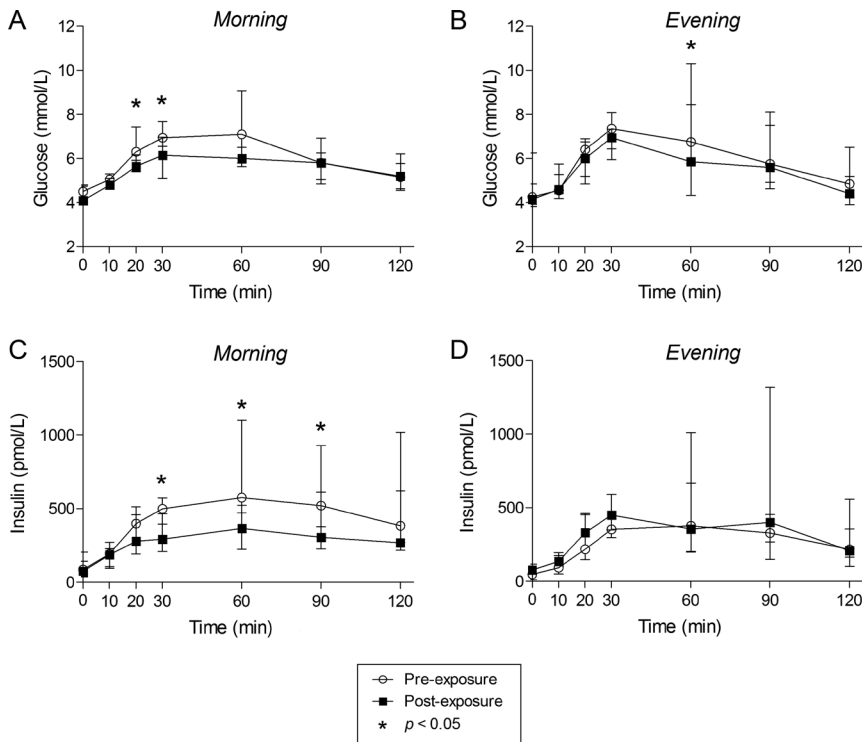
Effect of bromocriptine on insulin sensitivity

Lean subjects In lean subjects, only administration of bromocriptine in the evening had a significant effect on fasting insulin sensitivity (fasting HOMA-IR 0.35 (0.20–0.65) vs 0.42 (0.18–0.79), $P=0.036$).

Bromocriptine administration in the morning had no significant effect on the AUC for both glucose and insulin. Administration of bromocriptine in the evening led to a significant decrease in the AUC for glucose (742 mmol/L*120 min (695–818) vs 641 (504–750), $P=0.036$) but not in the AUC for insulin (32,836 pmol/L*120 min (18,823–42,053) vs 25,698 (24,244–42,143), $P=0.575$) compared with the pre-exposure visit.

**Figure 2**

Glucose and insulin values (median + IQR) obtained during the OGTT in lean subjects before the administration of bromocriptine (round icons) and after the administration of bromocriptine (square icons). (A) Glucose values obtained before and after the administration of bromocriptine in the morning. (B) Glucose values obtained before and after the administration of bromocriptine in the evening. (C) Insulin values obtained before and after the administration of bromocriptine in the morning. (D) Insulin values obtained before and after the administration of bromocriptine in the evening.

**Figure 3**

Glucose and insulin values (median + IQR) obtained during the OGTT in obese subjects before the administration of bromocriptine (round icons) and after the administration of bromocriptine (square icons). (A) Glucose values obtained before and after the administration of bromocriptine in the morning. (B) Glucose values obtained before and after the administration of bromocriptine in the evening. (C) Insulin values obtained before and after the administration of bromocriptine in the morning. (D) Insulin values obtained before and after the administration of bromocriptine in the evening.

Bromocriptine in the morning or evening had no significant effect on the AUC for HOMA-IR in lean subjects (Table 2).

Obese subjects In obese subjects, variation in the administration of bromocriptine (i.e. morning vs evening) had no significant effect on fasting insulin sensitivity compared with the pre-exposure visits.

Bromocriptine administration in the morning led to a significant decrease in the AUC for insulin ($55,900 \text{ mmol/L} \cdot 120 \text{ min}$ (43,236–96,831) vs $36,448$ (25,213–57,711), $P=0.012$) without a significant change in the AUC for glucose ($748 \text{ pmol/L} \cdot 120 \text{ min}$ (674–868) vs 669 (620–734), $P=0.069$) compared with the pre-exposure visit. The reverse was observed for bromocriptine administration in the evening: a significant decrease in AUC for glucose ($735 \text{ mmol/L} \cdot 120 \text{ min}$ (614–988) vs 644 (568–829), $P=0.017$) without a significant change of the AUC for insulin ($35,446 \text{ mmol/L} \cdot 120 \text{ min}$ (23,694–52,771) vs $38,390$ (25,664–10,4861), $P=0.208$).

The AUC for the HOMA-IRs was significantly lower after bromocriptine administration in the morning ($2405 \text{ HOMA-IR} \cdot 120 \text{ min}$ (1649–4655) vs 1229 (896–2348), $P=0.012$), but not in the evening ($1296 \text{ HOMA-IR} \cdot 120 \text{ min}$ (828–2666) vs 1356 (931–5359), $P=0.401$) (Table 2).

Difference in effect of bromocriptine between lean and obese subjects

To compare the differences in effect of bromocriptine between lean and obese subjects, we calculated the relative effect compared with the pre-exposure visit.

Fasting HOMA-IR values improved significantly more in obese subjects compared with those in the lean subjects when bromocriptine was administered in the morning (100% (73–119) vs 69% (53–81), $P=0.050$) but not in the evening (90% (39–115) vs 104% (90–162), $P=0.083$).

There was no difference in effect of bromocriptine administration between lean and obese subjects on glucose AUC. The insulin AUC values decreased significantly more in obese subjects than those in the lean subjects when bromocriptine was administered in the morning (114% (77–133) vs 58% (47–71), $P=0.015$) but not in the evening (90% (65–131) vs 111% (95–177), $P=0.401$).

The AUC for the HOMA-IRs decreased significantly more in obese subjects than that in the lean subjects when bromocriptine was administered in the evening (114% (87–256) vs 82% (59–99), $P=0.050$) but not in the morning (88% (75–131) vs 174% (104–243), $P=0.401$) (Table 3).

Table 2 Effect of bromocriptine.

	Lean subjects			Obese subjects		
	Pre-exposure	Post-exposure	P value	Pre-exposure	Post-exposure	P value
Glucose AUC _m (mmol/L * 120 min)	664 (584–767)	670 (595–784)	0.484	748 (674–868)	669 (620–734)	0.069
Insulin AUC _m (pmol/L * 120 min)	29,029 (22,069–38,126)	24,879 (15,893–38,851)	0.779	55,900 (43,236–96,831)	36,448 (25,213–57,711)	0.012
HOMA-IR _m	0.36 (0.18–0.68)	0.59 (0.18–1.1)	0.161	2.46 (1.19–5.77)	2.10 (0.92–4.25)	0.263
HOMA-IR AUC _m	1181 (797–1449)	1076 (578–1560)	0.674	2405 (1649–4655)	1229 (896–2348)	0.012
Glucose AUC _e (mmol/L * 120 min)	742 (695–818)	641 (504–750)	0.036	735 (614–988)	644 (568–829)	0.017
Insulin AUC _e (pmol/L * 120 min)	32,836 (18,823–42,053)	25,698 (24,144–42,143)	0.575	35,446 (23,694–52,771)	38,390 (25,664–104,861)	0.208
HOMA-IR _e	0.35 (0.20–0.65)	0.42 (0.18–0.79)	0.036	1.43 (0.29–3.78)	2.24 (1.20–3.25)	0.093
HOMA-IR AUC _e	1198 (799–1731)	975 (714–1290)	0.263	1296 (828–2666)	1356 (931–5359)	0.401
EE _m (kcal/day)	1673 (1441–1893)	1539 (1431–1925)	0.889	2047 (1890–2214)	2011 (1814–2305)	0.327
EE _e (kcal/day)	1694 (1542–2009)	1666 (1473–1784)	0.208	1996 (1940–2304)	2211 (1887–2356)	0.575
RQ _m	0.78 (0.76–0.81)	0.79 (0.76–0.85)	0.401	0.81 (0.76–0.90)	0.80 (0.79–0.85)	0.889
RQ _e	0.80 (0.79–0.84)	0.78 (0.75–0.80)	0.161	0.83 (0.80–0.85)	0.82 (0.79–0.91)	0.833
Weight _m (kg)	71.4 (6301–79.3)	70.7 (63.3–80.0)	0.399	103.6 (95.9–131.4)	104.3 (96.6–133.5)	0.176
Weight _e (kg)	70.1 (64.3–80.2)	70.7 (64.5–80.8)	0.176	104.3 (97.9–133.3)	105.4 (96.4–134.1)	0.865

Absolute effect of administration of bromocriptine compared with its prior pre-exposure visit. Data presented as *n* or as median (interquartile ranges). Differences between visits were calculated with the Wilcoxon signed-rank test. HOMA-IR, homeostatic model assessment – insulin resistance, calculated as (glucose (mmol/L) × insulin (U/L))/(22.5). *m*: outcome after treatment with bromocriptine in the morning. *e*: outcome after treatment with bromocriptine in the evening. AUC, area under the curve; EE, energy expenditure; RQ, respiratory quotient. Bold indicated statistical significance ($P < 0.05$).

Effect of bromocriptine on energy expenditure, weight and diet

Bromocriptine administration in the morning or evening had no effect on EE, RQ or weight in both obese and lean subjects (Table 2). There were no changes in diet, which could explain for the differences found in insulin sensitivity.

Discussion

In this study, we assessed the effect of bromocriptine administration on insulin sensitivity. We compared the effect between lean and obese subjects and between drug administration in the morning and evening. We confirm that bromocriptine administration improved insulin sensitivity in obese subjects, independent of the time of administration. The results found in lean subjects were ambiguous, there was a positive effect on insulin sensitivity of administration in the evening (i.e. lowered glucose AUC without significant changes of the AUC for insulin). However, fasting insulin sensitivity worsened in lean subjects when the bromocriptine was administered in the evening.

In lean subjects, bromocriptine administration in the evening resulted in a better overall insulin sensitivity, compared with the pre-exposure visit. Remarkably, fasting insulin sensitivity was significantly lower after bromocriptine administration in the evening. So, fasting insulin sensitivity diminished, whereas post-prandial insulin sensitivity increased. Indeed, bromocriptine is thought to promote post-prandial glucose disposal after a glucose load (e.g. a meal or an oral glucose tolerance test) (3, 16), which could explain the improvements seen in insulin sensitivity during the OGTT. Furthermore, healthy individuals show diurnal changes in insulin sensitivity and glucose metabolism (17). Glucose tolerance deteriorates in the evening with a decrease in insulin sensitivity and a reduced β -cell responsiveness to glucose (18). Circadian neuroendocrine rhythms of both dopamine and noradrenaline play a pivotal role in insulin sensitivity (12, 13) and are considered to be still intact in lean subjects. In lean subjects, dopamine physiologically peaks in the morning (14, 19).

Bromocriptine stimulates D₂-receptors, both presynaptically and postsynaptically. The presynaptic D₂ receptor is located on the cell body of dopaminergic cells, and stimulation of this receptor reduces dopamine release (feedback mechanism). The postsynaptic receptor is located at the nerve terminal level, on non-dopaminergic

Table 3 Bromocriptine effect in lean vs obese.

	Lean	Obese	P value
Glucose AUC _m (mmol/L * 120 min)	106 (91–115)	86 (81–106)	0.382
Insulin AUC _m (pmol/L * 120 min)	100 (73–119)	69 (53–81)	0.050
HOMA-IR _m	114 (77–133)	58 (47–71)	0.015
HOMA-IR AUC _m	88 (75–131)	174 (104–243)	0.083
Glucose AUC _e (mmol/L * 120 min)	93 (62–100)	91 (81–97)	1.000
Insulin AUC _e (pmol/L * 120 min)	90 (65–131)	111 (95–177)	0.401
HOMA-IR _e	90 (39–115)	104 (90–162)	0.083
HOMA-IR AUC _e	114 (87–256)	82 (59–99)	0.050

Data presented as median (interquartile range). This table shows the relative differences as compared with the pre-exposure visit (e.g. pre-exposure visit = 100%). Differences between the groups were calculated with the Mann–Whitney *U* test. HOMA-IR, homeostatic model assessment – insulin resistance, calculated as (glucose (mmol/L) × insulin (U/L))/(22.5). Bold indicated statistical significance ($P < 0.05$).

neurons or tissues, and plays a major role in dopamine signaling. Because bromocriptine directly stimulates dopamine D₂-receptors, the overall clinical effect of bromocriptine administration is mainly related to the effects on the postsynaptic receptor (20), and to a lesser extent to discrete lowering of dopamine concentration via stimulation of D₂-autoreceptors.

So, in healthy controls small changes in dopamine concentration and/or occupancy of the dopamine D₂-receptor postsynaptically, most likely will not have a large effect. However, in the evening, when the dopamine levels are lower, relatively small changes in both dopamine concentration and/or occupancy of the dopamine D₂-receptor postsynaptically may result in a larger (measurable) effect.

The effects of the D₂ agonist bromocriptine were more pronounced in obese compared with healthy controls. Bromocriptine administration in obese subjects led to an increased insulin sensitivity independent of the timing of the administration.

Interestingly, imaging studies showed quite consistently lower striatal dopamine D_{2/3}-receptor binding in obese compared with non-obese subjects, which supports the hypothesis of a hypo-dopaminergic state in obese subjects (21). This lower D_{2/3}-receptor binding can be explained by a lower expression and/or lower binding capacity for dopamine due to obesity-related conformational changes of the receptor (e.g., increased sensitivity of the receptor for dopamine). Because the insulin sensitivity is most likely related to an altered dopaminergic state, the effects of bromocriptine were expected to be more pronounced in obese compared with non-obese subjects. This is also illustrated when directly comparing the effects of bromocriptine between the lean and obese subjects in our study, showing that the effect of bromocriptine administration in obese subjects was more pronounced than in lean subjects.

The diurnal changes in insulin sensitivity and glucose metabolism, which are apparent in healthy individuals, are diminished or lost in obese patients with persistent insulin resistance (22).

Despite the fact that our obese subjects were normoglycemic, they were significantly less insulin sensitive than the lean control group. So, their circadian dopamine rhythm might be disturbed, and the timed administration of bromocriptine in the morning might have restored the diminished circadian dopamine peak and thereby improved insulin sensitivity (3, 16). Indeed, administering bromocriptine within 2 h after waking up, has been shown to prevent or even reverse insulin resistance in humans (23), because it mimics the physiological peak of dopamine in the morning.

In this study, we were unable to confirm the results found in our previous study, in which bromocriptine administration led to a decreased insulin sensitivity in young, healthy and lean subjects (11). A reason for this might be the difference in time when the OGTT was performed. In our previous study, the OGTT was performed at the end of the testing day in the afternoon, whereas in this study the OGTTs were performed in the morning. Both duration of fasting preceding the OGTT and the time of the day might affect the results of the OGTT (24). Furthermore, carbohydrate intake preceding the OGTT might also influence the results of the OGTT (25).

This study has several limitations. Due to the relative small sample size, external influences have a relatively large impact. Nonetheless, there were no significant changes in diet, which could explain for the differences found, subjects did not alter their lifestyle during the trial (e.g. physical activity, alcohol consumption, sleeping habits), and none of the subjects became ill during the trial.

Furthermore, we used an open-label randomization; this might have influenced the behavior of the subjects

and in such way that it may have influenced the results. However, the randomized order of bromocriptine administration has helped to prevent this possible effect, and there were no changes in diet during the trial.

We used a standard bromocriptine preparation instead of a quick-release variant. Standard bromocriptine preparations differ from the quick-release variant in its pharmacokinetics (e.g. bioavailability, peak levels) (16). The tablets were taken unsupervised at home, which may have resulted in inadequate use of the bromocriptine. However, the pill count was correct for all subjects and therefore the chance of inadequate use seems to be small. The daily bromocriptine dose administered was 1.25 mg (orally) during each first week and 2.50 mg during each second week. Both the treatment period as well as the used dosages may not have brought out full therapeutic effects, leading to an underestimation of the effect because the recommended dose used to treat diabetes mellitus type 2 is 4.8 mg of the quick-release formulation. Furthermore, we used standard dosing of bromocriptine, so there was no difference in dosing between the lean and obese subjects; the bromocriptine dosage was not corrected for BMI or bodyweight. However, a correction of the bromocriptine dosage according to BMI or bodyweight would have resulted in higher dosages for the obese subjects and would most likely have resulted in larger effects compared with the lean subjects. So, if anything, our results most likely underestimate the effect of bromocriptine in obese subjects. Nonetheless, future studies are needed to determine whether BMI or bodyweight influences the effect of bromocriptine and whether this has consequences for the administration of bromocriptine in clinical practice.

Lastly, the results we found apply to Caucasian, young, male subjects. It is unknown whether they can be translated to the general population. Nonetheless, our results are in line with the effect of bromocriptine on insulin sensitivity found in other trials.

Conclusion

Bromocriptine increases insulin sensitivity in both lean and obese subjects. In lean subjects, this effect was only apparent when bromocriptine was administered in the evening, whereas in obese subjects, insulin sensitivity increased, independent of the timing of bromocriptine administration.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Authors' contribution statement

L B contributed to conception, design, analysis and interpretation of data and drafting of the article. H J V contributed to conception, design, analysis and interpretation of data and critically revised the manuscript for important intellectual content. R T contributed to design, analysis of data and critical revision for important intellectual content. J B contributed to design, analysis and interpretation of data and critical revision for important intellectual content. J B H contributed to conception, analysis and interpretation of data and critical revision for important intellectual content. F H contributed to conception, design, analysis and interpretation of data and critical revision for important intellectual content.

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