Activation of dopamine D2 receptors simultaneously ameliorates various metabolic features of obese women

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Activation of dopamine D2 receptors simultaneously ameliorates various metabolic features of obese women. Am J Physiol Endocrinol Metab 291: E1038–E1043, 2006. First published June 27, 2006; doi:10.1152/ajpendo.00567.2005.—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) signaling is involved in its pathogenesis. We studied the acute effects of bromocriptine (a D2R agonist) on energy metabolism in obese women; body weight and caloric intake remained constant. Eighteen healthy, obese premenopausal women (BMI 33.2 ± 0.6 kg/m², mean age 37.5 ± 1.7, range 22–51 yr) were studied twice in the follicular phase of their menstrual cycle in a prospective, single-blind, crossover design. Subjects received both placebo (P; always first occasion) and bromocriptine (B; always second occasion) on separate occasions for 8 days. At each occasion blood glucose and insulin were assessed every 10 min for 24 h, and circadian plasma free fatty acid (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.

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 wintertime. A wealth of data indicate that fluctuations of dopaminergic neurotransmission in various brain nuclei are involved in these seasonal metabolic adaptations (24). In particular, reduction of dopaminergic neurotransmission in suprachiasmatic 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 (6, 8, 10, 21, 22). Compelling evidence suggests that D2R-transmitted dopaminergic tone is also diminished in the brain of various models of nonseasonal obesity (30), and D2R agonist drugs ameliorate the metabolic profile of these animals as effectively as they do in seasonal obese models (7, 11). D2R binding capacity in the brain of obese humans is reduced in proportion to body mass index (BMI) (38), which may therefore contribute to the metabolic anomalies associated with obesity. To investigate the potential impact of diminished dopaminergic D2R-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/m², mean age 37.5 ± 1.7, range 22–51 yr) were recruited through advertisements in local newspapers. All subjects had medical screening including medical history, physical examination, standard haematology, blood, and urine chemistry. Acute or chronic disease, depression (present or in medical history), head trauma, smoking, alcohol abuse, recent transmeridian flights, nightshift work, weight change prior to the study (>5 kg in 3 mo), recent blood donation, participation in another clinical trial (<3 mo), and use of medication (including oral contraceptives) 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

BMI [weight (kg)/length (m²)] was calculated according to World Health Organization recommendations. Percentage of body fat (fraction of total body weight) was quantified using dual energy X-ray absorptiometry (Hologic QDR 4500) on a separate day between the two study occasions (2).

Drugs

Subjects were assigned to bromocriptine and placebo treatment for periods of 8 days each in a single-blind crossover design, with a 4-wk time interval between each study occasion. To avoid potential crossover 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 on the first day. Thereafter, drug or placebo

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was taken twice daily (totaling 5.0 mg/day) at 0800 and 2000 until the end of the blood sampling period, which took place on the 8th day of treatment. All subjects tolerated the drug well, although 10 participants had gastrointestinal complaints (nausea, vomiting) on the first day of bromocriptine treatment only.

**Diet**

To limit confounding by nutritional factors, all subjects were prescribed a standard isocaloric diet supplied by the research center, and drinks other than water were prohibited as of 1 day before admission until the end of each study occasion. The macronutrient composition and caloric content of the diet were exactly the same for each individual on both study occasions. Meals were served according to a fixed time schedule (breakfast 0930, lunch 1300, dinner 1830) and were consumed within limited time periods (30 min). No dietary restrictions were imposed on the obese women between both study occasions.

**Indirect Calorimetry**

After resting for 45 min, subjects (fasting) were placed under a ventilated hood while lying on a bed, awake, in a quiet room for 30 min. The volume of oxygen inspired ($V_{O_2}$) and the expired volume of carbon dioxide ($V_{CO_2}$) were measured every minute. Subsequently, resting energy expenditure (REE), glucose, and lipid oxidation were calculated with the following equations:

\[
\text{glucose oxidation} = 4.57 \, V_{CO_2} - 3.23 \, V_{O_2} - 2.6 \, N
\]

\[
\text{lipid oxidation} = 1.69 \, V_{O_2} - 1.69 \, V_{CO_2} - 2.03 \, N
\]

RE = 3.91 $V_{O_2} + 1.10 \, V_{CO_2} - 1.93 \, N$

in which protein disappearance is ignored ($N = \text{nitrogen}$), since the error thus introduced in the calculation of energy expenditure is negligible.

**Clinical Protocol**

The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center and was performed according to the Helsinki Declaration. All subjects gave written acknowledgment 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 4 wk, where body weight remained stable and subjects were instructed to keep their physical activity level constant. The clinical setup was the same during both study occasions, apart from the subject receiving the alternative treatment (bromocriptine or placebo). Subjects were admitted to the research center at 0700 after an overnight fast. After the subjects rested for 45 min, indirect calorimetry was performed using a ventilated hood for 30 min. Thereafter, a cannula for blood sampling was inserted into an antecubital vein, which was attached to a three-way stopcock and kept patent by a continuous 0.9% NaCl and heparin (1 U/ml) infusion (500 ml/24 h). Blood samples for basal parameters were withdrawn, and 24-h blood sampling was started. Blood was collected with S-monovetten (Sarstedt, Ethen-Leur, The Netherlands) at 10-min 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 breakfast, 1300 lunch, 1830 dinner) and consumed within limited time periods. Lights were switched off at 2300, and great care was taken not to disturb or touch the 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. All assays and analyses were done by coworkers who were blinded to the type of intervention. All data were recorded on standard data collection forms and were 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 immunoradiometric assay (Biosource Europe, Nivelles, Belgium) with a detection limit of 2 μIU. The intra- and interassay coefficients of variation were 4.4 and 5.9%, respectively. Plasma FFA levels were determined using a NEFA C FFA kit (Wako Chemicals, Neuss, Germany) with a detection limit of 30 μmol/l and 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, Mannheim, Germany) with a detection limit of 50 μmol/l and intra- and interassay coefficients of variation of 1.5 and 1.8%, respectively. Progesterone concentrations were measured using a solid-phase RIA (Diagnostic Products, Los Angeles, CA).

Estradiol concentrations were determined by RIA (Diagnostic Systems Laboratory, Webster, TX). The detection limit was 10 pmol/l, and inter- and intra-assay coefficients of variation were 15.8 and 6.8%, respectively. Plasma prolactin (PRL) concentrations were measured with a sensitive time-resolved fluoroimmunoassay with a detection limit of 0.04 μg/l (Delfia; Wallac Oy, Turku, Finland). The PRL immunofluorometric assay was calibrated against the third World Health Organization standard: 84/500, 1 ng/ml = 36 μIU/l. The intra-assay coefficient of variation varies from 3.0 to 5.2%, and the interassay coefficient of variation is 3.4 to 6.2%. Serum glucose, cholesterol, and TG levels were measured using a fully automated Hitachi P800 system (Roche, Almere, The Netherlands). C-peptide concentrations were assessed by RIA (Adaltis Italia, Casalecchio di Reno, Italy). Free thyroxine concentrations were estimated using electrochemiluminescence immunoassay (Elecys 2010; Roche Diagnostics Nederland, Almere, The Netherlands).

**Urine Analysis**

From the moment the blood sampling period started, 24-h urine was collected for the determination of catecholamine and uroa nitrogen concentrations. Urinary urea concentrations were assessed by a fully automatic P800 System (Roche). Urinary epinephrine, norepinephrine (NE), and dopamine concentrations were assessed by high-performance liquid chromatography with electron capture detection.

**Calculations and Statistics**

*Area under the curve metabolic profiles. Area under the curves (AUCs) of insulin, glucose, FFA, and TG concentration plots were calculated using the trapezoidal rule (Sigma Plot 2002 for Windows, version 8.02).*

**Homeostatic model assessment.** Homeostatic model assessment (HOMA) was used to yield an estimate of longitudinal changes in insulin sensitivity before and after bromocriptine treatment in the obese subjects. The equation we used was: [fasting insulin (μU/l) × fasting glucose (mmol/l)/22.5], originating from the model first described by Matthews et al. (23).

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

**RESULTS**

**Screening Parameters**

Eighteen obese subjects were enrolled in the study. The mean age of all subjects was 37.5 ± 1.7 yr (range 22–51 yr).
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/m² (range 30.1–40.5 kg/m²), and total percentage body fat of 39.6 ± 0.8% (range 32.1–44.8). Mean fasting glucose concentration was 5.0 ± 0.1 mmol/l (range 4.2–6.3 mmol/l), insulin 15.3 ± 1.7 mU/l (range 7–28 mU/l), glycosylated hemoglobin (Hb A1c) 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). Metabolic parameters (including fasting blood glucose, insulin, Hb A1c) and blood pressure (systolic and diastolic) were not significantly different during the medical screening compared with the values obtained during placebo treatment.

Effect of Bromocriptine on Basal Measurements, at the End of Each Treatment, Immediately Before the Blood Sampling Period

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, at the end of each treatment, immediately before the blood sampling period, is given in Table 1.

Effect of Bromocriptine on Indirect Calorimetry

Indirect calorimetry was performed in only 12 subjects (for technical reasons). VO2 was significantly increased by bromocriptine, whereas the drug did not affect VCO2. REE was significantly higher during bromocriptine treatment. Glucose oxidation was slightly decreased, whereas 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 Fig. 1A). Both the maximum concentration and the AUC of the glucose peak in response to dinner was significantly decreased by bromocriptine [maximal concentration placebo (P) 9.0 ± 0.4 vs. bromocriptine (B) 7.5 ± 0.4 mmol/l, P < 0.01, and AUC P 131 ± 5 vs. B 112 ± 4 mmol·l⁻¹·3.5 h⁻¹, P < 0.01; Fig. 1A]. Also, nocturnal glucose concentrations (0000–0700 clock time) and the AUC of the nocturnal glucose curves were significantly lower during bromocriptine treatment (mean nocturnal glucose concentration P 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⁻¹·7 h⁻¹, P < 0.01; Fig. 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 concentrations were significantly reduced during bromocriptine treatment (Table 3 and Fig. 1B). The maximum concentration of the insulin peak in response to dinner was significantly decreased (P 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 P 1,846 ± 209 vs. B 1,216 ± 178 mU·l⁻¹·3.5 h⁻¹, P < 0.01). Both nocturnal insulin concentrations (0000–0700 clock time) and the AUC of the nocturnal insulin curves were similar during bromocriptine and placebo treatment (mean nocturnal insulin concentration P 14.0 ± 1.2 vs. B 13.1 ± 1.1 mU/l, P = 0.31, and AUC P 557 ± 47 vs. B 521 ± 42 mU·l⁻¹·7 h⁻¹, 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 (nonsignificant) trend (Table 3 and Fig. 2, A and B).

Table 1. Basal measurements after each treatment at the start of each blood sampling period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Bromocriptine</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>94.1 ± 2.5</td>
<td>94.4 ± 2.5</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.2 ± 0.6</td>
<td>33.3 ± 0.6</td>
<td>0.35</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>81 ± 3</td>
<td>79 ± 2</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122 ± 4</td>
<td>112 ± 3</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.3 ± 0.2</td>
<td>4.8 ± 0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fasting insulin, mU/l</td>
<td>13.2 ± 1.4</td>
<td>10.9 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>HOMA-IR†</td>
<td>3.25 ± 0.48</td>
<td>2.32 ± 0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>C-peptide, nmol/l</td>
<td>0.959 ± 0.108</td>
<td>0.724 ± 0.055</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.41 ± 0.16</td>
<td>4.45 ± 0.14</td>
<td>0.54</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>2.79 ± 0.16</td>
<td>2.83 ± 0.16</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.40 ± 0.07</td>
<td>1.43 ± 0.07</td>
<td>0.27</td>
</tr>
<tr>
<td>Ratio total cholesterol/HDL</td>
<td>3.26 ± 0.19</td>
<td>3.13 ± 0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>Estrogen (E₂), pmol/l</td>
<td>163 ± 21</td>
<td>209 ± 21</td>
<td>0.10</td>
</tr>
<tr>
<td>Progesterone, nmol/l</td>
<td>2.13 ± 0.64</td>
<td>2.94 ± 1.13</td>
<td>0.56</td>
</tr>
<tr>
<td>Free thyroxine, pmol/l</td>
<td>14.6 ± 0.4</td>
<td>14.8 ± 0.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Prolactin, μg/l</td>
<td>6.7 ± 1.1</td>
<td>2.3 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; E₂, estradiol. *P values, placebo vs. bromocriptine obese women, as determined by paired-samples t-test. HOMA-IR model was used to estimate insulin sensitivity from fasting insulin and glucose levels. HOMA-IR was calculated as [(fasting insulin (mU/ml) × fasting glucose (mmol/l))/22.5] (23). Data were log transformed before statistical analysis.

Table 2. Indirect calorimetry in 12 obese women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Bromocriptine</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, ml/min</td>
<td>232.2 ± 5.7</td>
<td>243.6 ± 8.2</td>
<td>0.03</td>
</tr>
<tr>
<td>VCO₂, ml/min</td>
<td>182.8 ± 4.2</td>
<td>188.7 ± 6.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Glucose oxidation, μmol·kg⁻¹·min⁻¹</td>
<td>5.2 ± 0.9</td>
<td>4.6 ± 0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Lipid oxidation, μmol·kg⁻¹·min⁻¹</td>
<td>3.4 ± 0.3</td>
<td>3.7 ± 0.3</td>
<td>0.38</td>
</tr>
<tr>
<td>REE, kcal/day</td>
<td>1109 ± 26</td>
<td>1160 ± 39</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. REE, respiratory quotient; VO₂, volume of oxygen inspired; VCO₂, expired volume of carbon dioxide; REE, resting energy expenditure. *P values, placebo vs. bromocriptine obese women, as determined by paired-samples t-test.
Twenty-four-hour urea nitrogen excretion did not differ during placebo and bromocriptine treatment (P 0.64). Urine NE was significantly reduced during bromocriptine treatment (P 0.01), whereas epinephrine (P 0.015 vs. B 0.004 umol/24 h, P = 0.42) and dopamine (P 1.58 vs. B 1.55 umol/24 h, P = 0.83) were not affected by bromocriptine.

DISCUSSION

This study shows that short-term treatment with the dopamine D2R agonist bromocriptine favorably 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 FFA and triglyceride concentrations were elevated during bromocriptine treatment. Notably, all of these effects came about without any change in 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 D2Rs 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 (10, 11, 20) and improves glucose tolerance in healthy and diabetic obese humans (9, 16, 25, 31). However, chronic bromocriptine administration consistently reduces body fat, perhaps primarily via its inhibitory effect on food intake (19, 28, 39), which might explain the metabolic corollaries of treatment. Here, we show that activation of D2Rs 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 present experimental context. This finding is corroborated by data documenting enhanced oxygen consumption in response to bromocriptine treatment in obese rodents (6, 32). Conversely, loss of function mutations of the D2R gene are associated with reduced resting energy expenditure in humans (36). Our results further support the position that D2R signaling 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 (27), and sympathetic hyperactivity may indeed underlie hypertension in obese humans (14). Activation of dopamine D2R has sympatholytic effects (4, 29), which may therefore 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 α1-adrenergic receptors (12), which obviously may also contribute to the hypotensive effect of the drug (33).

The rise of circulating FFA levels induced by bromocriptine may reflect inhibition of net FFA uptake in adipocytes (10). In apparent contrast, long-term bromocriptine treatment either reduces or does not affect plasma FFA concentrations in rodents and humans (10, 11, 16, 31). 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 D2Rs are expressed in various tissues (26), intracerebroventricular injections of bromocriptine at very low doses 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 (1, 18, 35). NPY is elevated in the arcuate nucleus of obese animal models (15, 18, 35), and intracerebroventricular administration of this neuropeptide directly induces (hepatic) insulin resistance and suppresses basal metabolic rate in rodents (17, 37).

Therefore, bromocriptine may facilitate glucose homeostasis through a reduction in hypothalamic NPY. Alternatively, bromocriptine may impact metabolism by virtue of its sympatholytic properties (13). 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 (5). D2R activation inhibits NE release in the arcuate nucleus and peripheral nerves (4, 29), and bromocriptine’s ability to act as such was supported by our data indicating that 24-h 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 PRL has been reported to exert potent lipogenic and diabetogenic effects (for review, see Ref. 3). Thus the ability of bromocriptine to favorably affect fuel flux in obese women could also be mediated by a decrease of circulating PRL levels.

We chose to administer placebo first and then bromocriptine in all subjects to avoid potential crossover effects of bromocriptine on metabolic parameters. Bromocriptine treatment has been shown to impact on metabolism by resetting circadian rhythms of various hormones in rodents (24). This neuroendocrine correlate of bromocriptine treatment may persist for long periods of time (24). However, we cannot exclude the (remote) possibility that the mere fact that the subjects were tested a second time somehow affected their metabolic status.

Our data lend further support to the postulate that reduced dopaminergic D2R signaling in obese humans, as reported by Wang et al. (38), 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 brains of obese humans directly contributes to their adverse metabolic profile.

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REFERENCES

Bromocriptine inhibits the seasonally occurring obesity, hyperinsulinemia, insulin resistance, and impaired glucose tolerance in the Syrian hamster, Mesocricetus auratus. 

"Regulatory" dopamine receptors by bromocriptine (CB-154).


Di Chiara G, Brotto GL, and Gessa GL.


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