Effects of a Quick-Release Form of Bromocriptine (Ergoset) on Fasting and Postprandial Plasma Glucose, Insulin, Lipid, and Lipoprotein Concentrations in Obese Nondiabetic Hyperinsulinemic Women

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OBJECTIVE — To assess the effect on various aspects of carbohydrate and lipid metabolism of administering a quick-release formulation of bromocriptine (Ergoset) to obese, nondiabetic, hyperinsulinemic women.

RESEARCH DESIGN AND METHODS — Hourly concentrations of prolactin, glucose, insulin, free fatty acid (FFA), and triglyceride were measured for 24 h before and after approximately 8 weeks of treatment with Ergoset. In addition, fasting lipid and lipoprotein concentrations and the steady-state plasma glucose (SSPG) concentration in response to a continuous infusion of somatostatin, insulin, and glucose were determined before and after Ergoset administration.

RESULTS — Circulating prolactin concentrations were dramatically decreased ($P < 0.001$) following treatment, associated with a significant fall ($P < 0.05$) in 24-h–long plasma glucose, FFA, and triglyceride concentrations. Neither circulating plasma insulin concentrations nor the ability of insulin to mediate glucose disposal changed with treatment. Finally, fasting total cholesterol fell ($P < 0.05$) and the ratio of total to HDL cholesterol decreased ($P = 0.06$) in association with Ergoset treatment.

CONCLUSIONS — The fact that significant metabolic improvement was seen in the obese nondiabetic hyperinsulinemic women studied suggests that Ergoset could be of therapeutic benefit in clinical conditions of hyperglycemia and/or dyslipidemia.

Enhanced adipose lipolysis during months of scarce food availability not only provides an increased supply of free fatty acids (FFAs) as a vital source of energy for seasonally obese animals (1,2), but by decreasing insulin-mediated glucose uptake by muscle (3), it serves to divert glucose to the central nervous system. Studies of species living in the wild that undergo annual cycles of body-fat store levels, associated with or independent of cycles of food abundance and scarcity, suggest that this adaptation is mediated by changes in the phase relation of circadian dopaminergic and serotonergic activities (4–6). Based on this information, the metabolic effect of timed daily administration of bromocriptine, a sympatholytic dopamine D_2 agonist with serotonin antagonist activities, was examined in seasonally obese animals (7,8). The results of these studies showed that bromocriptine treatment was associated with an inhibition of hepatic lipogenesis and glucose output and adipose tissue lipolysis, leading to a decrease in body-fat stores and in plasma FFA, insulin, and triglyceride (TG) concentrations. More recently, evidence has been presented that treatment of obese patients with a hypocaloric diet plus a quick-release formulation of bromocriptine (Ergoset) was associated with improved glucose tolerance and reduced body weight when compared with individuals treated with diet alone (9). Given this background, we thought it useful to evaluate the metabolic response of obese patients to administration of Ergoset while subjects were on a weight-maintaining diet. The results to be presented demonstrate that concentrations of plasma glucose, FFA, TG, and cholesterol were decreased in association with Ergoset administration, in the absence of any change in weight.

RESEARCH DESIGN AND METHODS

— Thirteen obese, hyperinsulinemic women were recruited into an open-label study to test the effect of Ergoset on various aspects of glucose, insulin, and lipoprotein metabolism, as well as on body composition. Hyperinsulinemia was defined as a fasting plasma insulin concentration >150 pmol/l, an insulin concentration >600 pmol/l 2 h after a 75-g oral glucose load, or both. All subjects were judged to be in good general health on the basis of history, physical examination, complete blood count, routine biochemical screening, and electrocardiogram, and were judged nondiabetic on the basis of National Diabetes

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Abbreviations: FFA, free fatty acid; GCRC, General Clinical Research Center; SSPG, steady-state plasma glucose; SSPI, steady-state plasma insulin; TG, triglyceride.

Table 1—*Baseline characteristics*

Age (years)	51 ± 3 (34–68)
BMI (kg/m²)	33.2 ± 0.8 (29.8–39.9)
Fasting insulin (pmol/l)	129 ± 12 (72–208)
120-min insulin (pmol/l)	920 ± 182 (395–2,762)

Data are means ± SE (range).

Data Group criteria (10). Individuals on thyroid replacement were excluded, and all participants had normal thyroid function. Finally, they all had normal sleep patterns (no shift workers), were not taking any psychoactive or sedating drugs, and were either postmenopausal or using an effective method of contraception. This project was approved by the Stanford University Human Subjects Committee, and all women gave informed consent. Baseline characteristics of the study population are shown in Table 1.

The experimental protocol involved a 2-week run-in period, followed by 8 weeks treatment with Ergoset. At the beginning of the run-in period, subjects received a nutritional assessment and were instructed to follow a weight-maintaining diet, containing the following nutrients as a percentage of total calories: 20% protein, 30% fat, and 50% carbohydrate. Meals were consumed at 8:00 A.M., noon, and 5:00 P.M., and contained 20, 40, and 40%, respectively, of the day's total calorie intake. This dietary prescription was followed throughout the entire study.

All subjects were admitted to the General Clinical Research Center (GCRC) at the end of the 2-week run-in period for a series of baseline measurements, performed at least a day apart and in random order. After an overnight fast of 14 h, blood samples were drawn at 8:00 A.M., before breakfast, at hourly intervals thereafter until 10:00 P.M., and then at 2-h intervals throughout the night until 8:00 A.M. the next morning. Plasma was separated immediately and stored frozen for future analysis of glucose (11), insulin (12), TG (13), FFA (14), and prolactin (15). In addition to the postprandial measurements, fasting blood samples were obtained on 2 separate days for determination (16) of plasma and VLDL, LDL, and HDL cholesterol concentrations.

Resistance to insulin-mediated glucose disposal was estimated by a modification (17) of the insulin suppression test originally described by our research group (18). After an overnight fast, intravenous catheters were placed in a superficial antecubital vein in each arm. One arm was used for a continuous 180-min infusion of glucose (240 mg · m^{-2} · min^{-1}), sandostatin (octreotide acetate) (27 μg · m^{-2} · min^{-1}), and insulin (30 mU · m^{-2} · min^{-1}). Venous blood samples for glucose and insulin determinations were obtained from the contralateral arm every 30 min (to 150 min) and then every 10 min for the last half-hour of the infusion. The mean of these last four values was used to calculate the steady-state plasma glucose and insulin concentrations. Under these experimental conditions, endogenous insulin secretion is suppressed and the steady-state plasma insulin (SSPI) concentration achieved is comparable in all individuals. The steady-state plasma glucose (SSPG) concentration provides a measure of insulin-stimulated glucose disposal; the higher the SSPG, the more insulin-resistant the individual.

Following baseline metabolic testing, volunteers were discharged from the GCRC and started on Ergoset; one tablet daily (0.8 mg bromocriptine), which was taken within 2 h of awakening in the morning (~8:00 A.M.). The dose was increased by one tablet a week until a maximum of 4.8 mg was reached or side effects occurred. The major symptoms preventing attaining the maximum dose were stuffy nose, fatigue, and weakness after taking the medication. At each weekly visit, drug compliance was assessed by tablet count, and subjects were asked about adverse events. Dietary compliance was also assessed every 2 weeks, at which time subjects were weighed and their daily food consumption diary records for the previous 3 days were reviewed. At these visits, any dietary adjustments required to maintain weight were initiated. Finally, level of physical activity was estimated by determining the hours spent exercising, and patients were instructed to attempt to keep this variable constant. Consequently, body weight was similar at the beginning (74.2 ± 1.3 kg) and end (73.9 ± 1.3 kg) of the study.

Subjects were re-admitted to the GCRC 8 weeks later, and all of the baseline measurements were repeated. To minimize assay variability, samples from the before and after treatment were determined in the same assay.

Values for continuous variables are expressed as a mean ± standard error (SE). Fasting lipoprotein, SSPG, and SSPI measurements before and after the treatment were compared using paired Student's *t* tests. Differences between the day-long response to the test meals were compared by doubly repeated measures ANOVA, using SAS software.

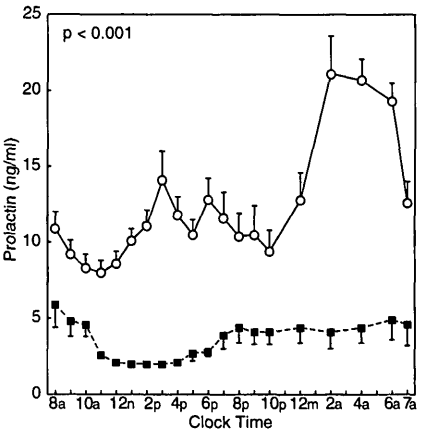

Figure 1—*Plasma prolactin concentrations throughout the 24-h period of study before* (○) *and after* (■) *administration of Ergoset.*

RESULTS — The mean maximum daily dose of Ergoset was 3.2 ± 0.4 mg/day. Of the 13 subjects studied, 9 were able to reach the maximum dose (4.8 mg/day), 2 could tolerate no more than 3.2 mg/day, and 2 could tolerate a maximum of 2.4 mg/day. Symptoms that prevented attainment of the target dose included complaints of stuffy nose, fatigue, and a feeling of weakness after taking the drug. Despite this, plasma prolactin levels fell in response to treatment in all subjects. Mean (± SE) prolactin levels before and after treatment are shown in Fig. 1. These data clearly show that prolactin concentrations decreased dramatically following Ergoset treatment.

Measurements of plasma glucose and insulin concentrations during the 24-h period of study are shown in Fig. 2. These results indicate that plasma glucose concentrations (*A*) were lower on the average throughout the period of observation ($P < 0.05$). Although of statistical significance, the magnitude of this fall was modest and most evident after lunch. On the other hand, it should be remembered that these subjects were glucose tolerant. The results in Fig. 2*B* show that the decrease of plasma insulin concentrations was not statistically significant in response to treatment with Ergoset.

In Fig. 3, plasma FFA (*A*) and TG (*B*) concentrations throughout the day and night are shown. It can be seen that there were significant decreases ($P < 0.05$) in

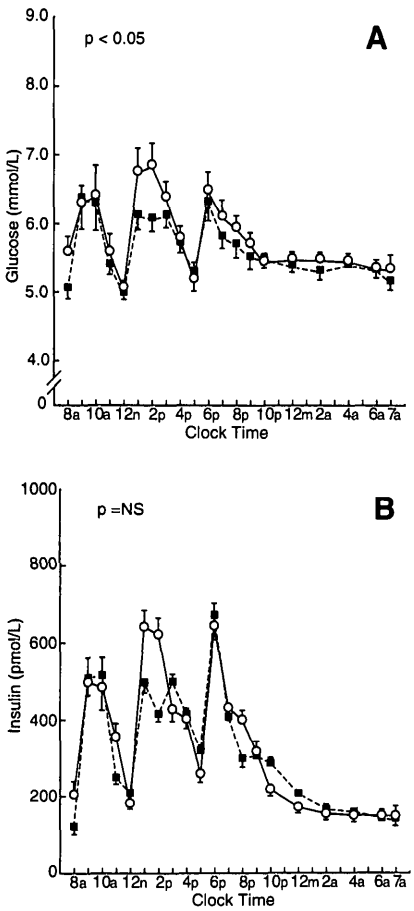

Figure 2—*Plasma glucose (A) and insulin (B) concentrations throughout the 24-h period of study before (○) and after (■) administration of Ergoset (bromocriptine mesylate).*

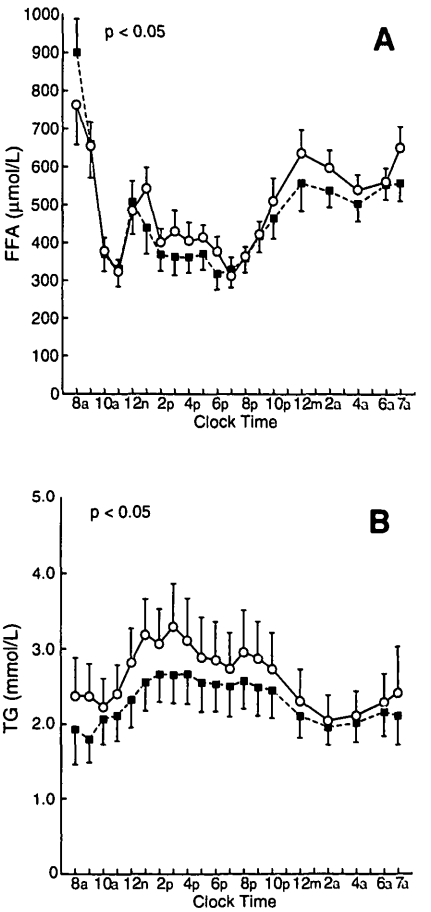

Figure 3—*Plasma FFA (A) and TG (B) concentrations throughout the 24-h period of study before (○) and after (●) administration of Ergoset (bromocriptine mesylate).*

both of these variables following Ergoset treatment.

SSPI concentrations were similar before (529 ± 36 pmol/l) and after (531 ± 29 pmol/l) treatment. Baseline SSPG concentration was high before treatment, a predictable finding in these obese, hyperinsulinemic women, and did not change in response to Ergoset (233 ± 17 vs. 238 ± 15 mg/dl).

Fasting plasma and lipoprotein cholesterol concentrations are listed in Table 2. The only statistically significant change was a 7% decrease in total cholesterol, due primarily to a fall in LDL cholesterol. In addition, a decrease in the ratio of total to HDL cholesterol approached, but did not reach, the conventional level of statistical significance ($P = 0.06$).

CONCLUSIONS — The goal of this study was to evaluate the hypothesis that a quick-release formulation of bromocriptine (Ergoset) would increase diurnal central (hypothalamic) dopaminergic activities believed to be low in these obese, hyperinsulinemic subjects, as indicated by elevated prolactin concentrations, and that this change would be associated with beneficial effects on carbohydrate and lipoprotein metabolism. To focus our discussion of the results, we will address each of these issues separately.

The results in Fig. 1 dramatically illustrate the decrease in prolactin concentrations measured over a 24-h period following approximately 8 weeks of treatment with Ergoset. It can also be seen from these data that early morning administration of Ergoset was particularly effective in lowering the grossly elevated prolactin concentrations observed during the late night and early morning hours in these obese, hyperinsulinemic women. Presumably, the ability of Ergoset to lower nocturnal prolactin concentration was due to its high affinity for the D_2 receptor on lactotroph cells (19).

Circulating plasma glucose concentrations were significantly lower ($P < 0.05$) following Ergoset treatment, but it is clear from the results in Fig. 2 that the change was modest in magnitude. However, since none of the women studied were hyperglycemic at baseline and were nondiabetic by oral glucose tolerance testing, the fact that we saw any improvement in glycemic excursions was somewhat unexpected, perhaps of physiological significance.

Given the fact that the study population was selected because they were hyperinsulinemic and presumably insulin resistant, our initial thought on seeing the changes in circulating glucose concentration was that muscle insulin sensitivity may have improved in association with Ergoset administration. Unfortunately, as appealing as this hypothesis was, it could not be supported by the experimental results. Thus, although the subjects had grossly elevated SSPG values at baseline (our assessment of muscle insulin resistance), SSPG concentrations did not decrease after the therapeutic intervention. The view that Ergoset treatment did not enhance insulin-mediated glucose disposal is also supported by the fact that circulating insulin concentrations did not change significantly before and after administration of Ergoset. It should be noted that both glucose and insulin responses to an oral glucose challenge were lower following Ergoset administration in a previously published study of long (18 weeks) treatment duration (9), which could be interpreted to mean that insulin sensitivity had improved. On the

Table 2—*Effect of Ergoset on cholesterol concentrations (mmol/l)*

Variable	Before	After	*P*
Cholesterol	5.2 ± 0.3	4.8 ± 0.2	<0.05
VLDL cholesterol	1.0 ± 0.2	1.0 ± 0.2	0.29
LDL cholesterol	3.2 ± 0.2	2.9 ± 0.2	0.10
HDL cholesterol	1.0 ± 0.1	1.0 ± 0.1	0.35
Cholesterol/HDL cholesterol	5.9 ± 0.6	5.1 ± 0.5	0.06

other hand, in contrast to the weight-loss protocol of Cincotta and Meier (9), weight was maintained throughout in the present study. Thus, in this study we did not and would not detect any improvement in insulin sensitivity in association with Ergoset that was dependent on concomitant weight loss or longer duration of treatment. We can only speculate as to other possible explanations for the decrease in ambient glucose concentrations, but the observation that the differences in glycemic level before and after treatment were most evident after meals might offer a clue. Thus, it could be argued that postprandial inhibition of hepatic glucose production is accentuated following treatment with Ergoset, a possibility consistent with the evidence that hepatic glucose production was inhibited by bromocriptine administration to Syrian hamsters (8). Fortunately, there are methods available to evaluate this hypothesis, and we are currently planning such experiments.

The fact that circulating FFA concentrations were lower following Ergoset, in the absence of any change in insulin concentration, is consistent with the possibility that adipose tissue had become more sensitive to the ability of insulin to inhibit lipolysis and/or enhance reesterification. If this were the case, it would imply that insulin sensitivity in adipose tissue, but not muscle, is enhanced in response to Ergoset. A simpler explanation, and perhaps more likely, is that adipose tissue lipolysis is decreased in Ergoset-treated patients, either directly or secondarily by attenuating the effect of other lipolytic factors. All of these possibilities are consistent with results showing that lipolysis is reduced following administration of bromocriptine to Syrian hamsters (7,8). Similar to the situation concerning the putative effect of Ergoset on lowering glucose concentrations, experimental techniques are available to discriminate between the various possible explanations for the decrease in circulating FFA concentrations shown in Fig. 3.

Irrespective of the mechanism responsible for the fall in plasma FFA concentrations, the fact that they were lower offers obvious reasons for the associated decrease in plasma TG concentrations also shown in Fig. 3. Specifically, it has been shown that day-long plasma FFA concentration is an independent predictor of postprandial TG concentration (20). There are at least two explanations for this relationship. Most simply, FFA is an essential substrate for the synthesis of hepatic VLDL TG, and a decrease in FFA flux to the liver would predictably lead to a fall in hepatic VLDL TG synthesis and secretion. In addition, elevated FFA concentrations have been shown to increase hepatic apolipoprotein B secretion (21,22), and the decrease in circulating FFA concentration seen following Ergoset administration could lead to a fall in hepatic apolipoprotein B synthesis. Finally, it is possible that Ergoset could directly inhibit hepatic VLDL TG secretion, thereby lowering plasma TG concentration (23).

In conclusion, the results presented have shown that administration of a quick-release form of bromocriptine profoundly decreased the elevated prolactin levels seen throughout the 24-h period in obese, hyperinsulinemic women. In association with the change in prolactin, we observed beneficial effects on glucose, FFA, lipid, and lipoprotein metabolism. The fact that significant metabolic improvement could be seen in these women who were in good general health, with the exception of their obesity and insulin resistance, raises the possibility that Ergoset could be of substantial benefit in various clinical conditions of hyperglycemia and/or dyslipidemia. On the other hand, certain caveats should be made explicit at this time. In the first place, the study was not placebo-controlled. Second, we cannot tell if the findings were due to the decrease in prolactin concentration, to an unknown mediator associated with the change in dopaminergic activity, or to a direct effect of bromocriptine itself. Indeed, we cannot be sure if the changes noted were dependent on the specific form of bromocriptine used. Obviously, none of these issues can be resolved at this time, and additional studies will be necessary to evaluate the therapeutic benefit of bromocriptine modulation of prolactin metabolism in various abnormal conditions, as well as defining the mechanisms responsible for the metabolic changes observed. On the other hand, the results presented suggest that these additional efforts are worth pursuing, and this notion is supported by preliminary evidence that glycemic control was improved following Ergoset treatment in patients with NIDDM (24).

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