bution of co-administered drugs that bind to HSA in blood. They also point to the utility of bilirubin as a sensitive three-dimensional chiroptical probe.

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Editorial note

A. H. Meier and his group are among the few biologists working to understand the implications of the periodicity evident in many physiological systems, such as the circadian changes of blood hormone levels, neuronal activities, and state of energy metabolism. It is known today, due to his and a few others' work, that from teleosts to mammals the daily rhythms of prolactin and corticosteroid secretion seem critically involved in the control of body lipid stores. To manipulate prolactin serum levels, either a prolactin preparation can be injected which in most instances will be heterologous with the consequence of possible differing in the profile of activities from the homologous hormone. Or, endogenous prolactin secretion may be temporarily suppressed by giving a D_2 dopamine receptor agonist, e.g. bromocriptine, accepting the possible complication that after the systemic application such drug's action is possibly not restricted to the inhibitory D_2 receptors of the anterior pituitary prolactin cells, but may affect other dopaminergically controlled systems as well, such as the hypothalamus. Despite these possible complications in the interpretation of experimental findings the results will be of interest to internal medicine.

E. Flückiger

Timed bromocriptine administration reduces body fat stores in obese subjects and hyperglycemia in type II diabetics*

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Abstract. Obese postmenopausal female volunteers were given timed daily oral dosages of bromocriptine, and tested for reduction of body fat stores. This dopamine agonist has been shown to reset circadian rhythms that are altered in obese animals and to reduce body fat levels in several animal models. The participants were instructed not to alter

their existing exercise and eating behavior during treatment. Skinfold measurements were taken on 33 subjects as indices of body fat. The measurements (e.g., suprailiac) were reduced after six weeks by about 25%, which represents a reduction of 11.7% of the total body fat. These dramatic decreases in body fat, which are equivalent to that produced by severe caloric restriction, were accompanied by more modest reductions of body weight (2.5%), indicating a possible conservation of protein that is usually lost as a consequence of such caloric restriction.
The effects of bromocriptine treatment on body fat and hyperglycemia were also examined in non-insulin dependent diabetics being treated with oral hypoglycemics (7 subjects) or insulin (7 subjects). Total body fat was reduced by 10.7% and 5.1% in diabetics on oral hypoglycemics and insulin, respectively, without any significant reductions in body weight.
Hyperglycemia was reduced in most of the 15 diabetic subjects treated leading to euglycemia and even cessation of hypoglycemic drugs in 3 of the 7 subjects during 4–8 weeks of bromocriptine treatment. These findings support the hypothesis that obesity and type II diabetes may be treated effectively with bromocriptine when administered at the proper times and dosages.

Recent studies by our laboratory [1–3] and others [4–6] indicate that bromocriptine, a dopamine agonist, can dramatically decrease body fat stores in mammals with little or no reduction in body weight and food intake. Accordingly, a preliminary study was carried out with postmenopausal women volunteers to test whether bromocriptine might be used to reduce body fat in humans. Because obesity is often associated with type II diabetes, a second study tested effects of bromocriptine treatment on fat stores and blood glucose levels in male and female non-insulin dependent diabetics.

Methods

Study 1. The non-diabetic volunteers used in this study were postmenopausal women recruited from the Baton Rouge metropolitan area. They gave written consent to participate in a study to examine the effects of bromocriptine on body fat. There were 33 participants who completed a six-week trial period of bromocriptine treatment during winter and early spring. Twenty-six of these individuals were receiving estradiol implants. The percentage of body fat calculated from skinfold measurements (see below) ranged between 32–40.

Study 2. A second group of 15 participants from the Baton Rouge metropolitan area were diagnosed with non-insulin dependent (type II) diabetes mellitus and gave written consent to participate in a study to examine the effects of bromocriptine on body fat and hyperglycemia. Seven diabetics (2 males and 5 females) were being treated orally with stimulants for endogenous insulin secretion (hypoglycemic drugs: diabenase and micronase) and seven diabetics (2 males and 5 females) were receiving daily injections (morning and evening administrations) of insulin. Only those who were found to be very hyperglycemic (i.e., fasting plasma glucose > 160 mg/dl) in the morning after a night of fasting and before insulin injection or taking other medications were accepted for the study. One obese man with severe hyperglycemia who refused conventional treatment for diabetes was permitted to participate in this bromocriptine study and is included with the group receiving hypoglycemic drugs (table). Skinfold measurements were made before and after 6 weeks of treatment and plasma glucose determinations were made before and after 4–8 weeks.

Bromocriptine was taken orally daily at times calculated to reset circadian hormone rhythms to phase relationships that cause loss of body fat [1,4]. Eight subjects in Study 1 received 1.25 mg daily and the other participants received 2.5 mg daily. The calculations for determining the dosing and timing of bromocriptine to maximize reduction of body fat are beyond the scope of this article and will be addressed separately in another publication. Generally, however, bromocriptine was administered in the morning within 7 h after awakening. Nausea was usually avoided by starting with the lower dosage

Reductions of plasma glucose concentration and body fat in Type II diabetics after 4–8 weeks of timed bromocriptine treatment

Parameter examined	Subjects on hypoglycemic drugs (8)		Subjects receiving insulin (7)	
	Initial	Final	Initial	Final
Plasma glucose (mg/dl)	231 ± 19	166 ± 19 [1]	283 ± 14	184 ± 22 [1]
Plasma glucose (% initial)		72 ± 6 [1]		65 ± 8 [1]
Total body weight (pounds)	255 ± 21	253 ± 20	182 ± 9	182 ± 10
Loss of body weight (pounds)		−2.4 ± 2.0		−0.4 ± 2.0
Skinfold measurements (% initial) [2]		79 [1]		84 [1]
Body fat (% body weight)	36.5 ± 2.3	32.9 ± 2.0 [1]	33.4 ± 2.2	31.7 ± 1.7 [1]
Body fat loss (pounds)		−10.0 ± 2.2 [1]		−3.1 ± 0.9 [1]

[1] Plasma glucose, skinfold thickness and total body fat were reduced in every individual in the groups taking hypoglycemic drugs (8 subjects) or insulin (7 subjects). The mean reductions are significant ($p < 0.05$). [2] Initial skinfold measurements (mm) for the subscapular, triceps, biceps, and suprailiac regions were 26 ± 3, 14 ± 2, 9 ± 0 and 19 ± 2 in those taking hypoglycemic drugs and 26 ± 2, 15 ± 2, 12 ± 2 and 19 ± 1 in those taking insulin. Final skinfold measurements were taken after 6 weeks of treatment.

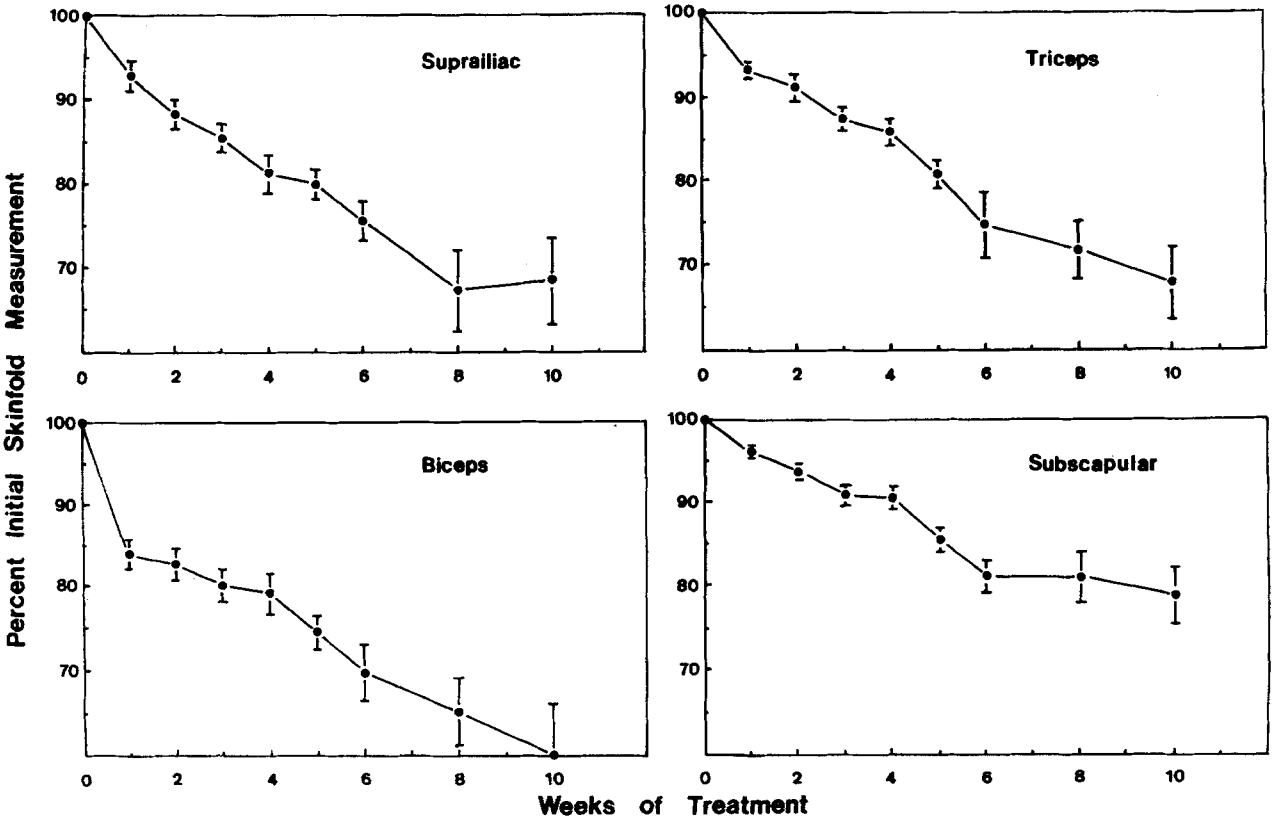
(1.25 mg) for the first 2–3 days. Only mild nausea was observed by less than 10% of the participants and was transient, lasting only for the first few days. The participants were carefully instructed not to alter their daily activity or eating habits during the course of treatment. Patient compliance was excellent as indicated by weekly interviews of subjects who monitored their food intake (see also 'Discussion'), and the transient anorexic effects sometimes produced by higher doses of bromocriptine did not occur in this study.

Skinfold thickness was measured on the left side of the body by a trained anthropometrist in four regions: biceps, triceps, subscapular, and suprailiac, following the recommendations of the International Biological Program [7]. Because of its frequent use, percent body fat was estimated from the common logarithm of the sum of the four skinfolds, using the equations of Durnin and Rahman [8] and of Siri [9]. A recent study indicates very similar estimations of body fat by hydrodensitometry and skinfold thickness measurement methods [10]. Skinfold measurements were taken initially and at weekly intervals by the same individual. Blood pressure was also determined at these times. Morning fasting plasma glucose in the diabetic group was determined initially and after 4–8 weeks. P values based on two-tailed, matched pair t tests were calculated for the comparisons between the pre- and post-treatment values in Study 1 (obese postmenopausal women) and in Study 2 (NIDDM subjects on oral hypoglycemics and NIDDM subjects on insulin).

The experimental design was reviewed and approved by The Institutional Review Board at Our Lady of the Lake Hospital in Baton Rouge, LA. It is an unblinded and uncontrolled preliminary investigation.

Results

Study 1. Skinfold measurements of the non-diabetic group underwent dramatic decreases during the course of bromocriptine treatment (fig.). Reductions after six weeks approximated 25% for all skinfold measurements: suprailiac (SI), 25%; triceps (TC) 26%; biceps (BC), 31%; subscapular (SS), 20%. There were evidences of further declines with continued treatment. After 10 weeks in the 6 subjects examined, there was a 32% reduction in mean skinfold measurements at the four sites. Two individuals who began treatment earlier than the others were treated for 20 weeks. The mean of their skinfold measurements was reduced by 45%. The percentage body fat calculated from the skinfold measurements of all participants was 37.3 ± 0.8 at the beginning of treatment and 33.8 ± 0.7 after 6 weeks. The skinfold measurements and percentages of body fat indicate a mean of 73.1 lbs of fat for each individual (mean body weight, 196 lbs), initially, and 64.5 lbs of fat (191 lbs body weight) after 6 weeks, a loss of 8.6 lbs of fat result-



Reductions of skinfold measurements in normal subjects receiving daily oral doses of bromocriptine. The number of subjects measured was 33 for the first 6 weeks. Six participants were measured on weeks 8 and 10 of treatment. See results for statistical analysis.

ing in a decline in total body fat of 11.7%. The skinfold measurements and percentages of body fat at 6 and 10 weeks differ significantly ($p < 0.02$; Student's t) from the initial values. Measurements were reduced in every participant.

Study 2. Both blood glucose concentrations and skinfold measurements were reduced in every diabetic subject after 4–8 weeks of bromocriptine treatment (table). The initial fasting blood glucose concentrations before morning medications for diabetes were 283 ± 14 mg/dl and 231 ± 19 mg/dl for those taking insulin and hypoglycemic drugs, respectively. After 4–8 weeks, mean glucose concentrations were reduced ($p < 0.05$; student's t) to 184 ± 22 mg/dl (insulin) and 166 ± 19 mg/dl (hypoglycemic drugs). Oral hypoglycemic medication was completely discontinued during bromocriptine treatment in three individuals and blood glucose levels remained near normal (< 120 mg/dl) for at least two months after bromocriptine treatment was terminated. Doses of hypoglycemic drugs and insulin were reduced in three other subjects during bromocriptine treatment.

Body fat stores were substantially reduced by timed bromocriptine treatment in NIDDM subjects taking hypoglycemic drugs as evidenced by a mean reduction of 21% in the skinfold measurements at the four regions examined (table). This reduction amounts to a mean loss of 10 lbs for each individual and a decline in total body fat of 10.7% within 4 to 8 weeks. The reductions in skinfold (16%), body fat (3.1 lbs) and % body fat (3.1) were significant ($p < 0.05$) but less in those subjects taking insulin. Body weights were perhaps slightly reduced (2.4 lbs per subject, not statistically significant) in subjects taking hypoglycemic drugs and not at all reduced in those taking insulin.

Blood pressure was reduced in many of the subjects during bromocriptine treatment. The initial mean systolic pressure of the non-diabetics was 133 ± 3 mm Hg and the initial diastolic pressure was 83 ± 2. The systolic pressure was reduced ($p < 0.05$) to 118 ± 2 mm Hg at 6 weeks and the diastolic pressure was reduced ($p < 0.05$) to 76 ± 1 mm Hg. Medication to reduce blood pressure was discontinued during bromocriptine treatment in several participants.

Discussion

These results demonstrate that bromocriptine treatment can dramatically reduce body fat stores in postmenopausal women. Bromocriptine treatment also substantially reduced body fat and hyperglycemia within two months in non-insulin dependent (type II) diabetics. These results were achieved without changing individual existing diets and exercise regimens.

It may seem incredible that the reductions in body fat (4.4% of the body weight) achieved in the present study after 6 weeks without food restriction are equivalent to those obtained utilizing a very low calorie diet (420 kcal/day) for a similar period of time[11]. Amatruda and coworkers[11] reported an 8% reduction of body weight in obese NIDDM subjects of which less than 50% can be assumed to be fat under these conditions[12]. Furthermore, Kanders et al.[13] reported an average body weight loss of 2.3 lbs per week in non-diabetic obese females subjected to similar very low calorie diets. This also amounts to a reduction of about one pound of fat per week under these restricted calorie conditions[12], which is less than the fat loss of 1.4 lbs per week average achieved with bromocriptine treatment in the present study (Study 1).

The reduction of body fat produced by bromocriptine treatment differs in a significant way from reduction of fat achieved by caloric restriction. With very low calorie diets only about 45% if the weight loss is lipid; the remainder includes protein, carbohydrate and water[12]. In the present bromocriptine study with humans (Study 1), as in numerous animal studies[1–6], more fat is lost (8.6 lbs or 4.3 of body weight) after 6 weeks than can be accounted for by the reduction in body weight (5 lbs or 2.5% of body weight). Recent studies with Syrian hamsters investigating whole body protein turnover employing ^{15}N-lysine and ^{15}N-urea indicate that such bromocriptine treatment enhances protein synthesis, redirecting anabolic activities from lipid to protein (Cincotta, unpublished data).

In this regard, the results of this bromocriptine study are very much like those obtained in a similar (unblinded, non-placebo-controlled) investigation on the effects of growth hormone on body composition of elderly men (greater than 60 years of age). Six months of growth hormone treatment reduced body fat by 7.8 lbs (14.4% decrease in total body fat) but increased lean body mass so that body weight remained constant[14]. However, it seems unlikely that similar results produced by bromocriptine treatment in 6 weeks are ascribable to a stimulation of growth hormone secretion. Growth hormone is widely recognized as a diabetogenic hormone whereas bromocriptine substantially improved NIDDM hyperglycemia (Study 2) and prediabetic features in animals[3]. Accordingly, the relatively modest loss of body weight relative to fat loss in the present study argues stongly that the fat loss was not a consequence of decreased food consumption. In fact, a large body of evidence strongly indicates that daily lipogenic/lipolytic cycles in rodents and humans regulate feeding patterns (via hypothalamic centers) and not vice versa[15]. Our own studies also indicate that a cause-effect relationship between overfeeding and obesity is oversimplistic and that food intake and lipid synthesis may be regulated in a concerted fashion by circadian neuroendocrine activities[16,17].

Total body fat was also substantially reduced by bromocriptine treatment in NIDDM subjects treated with hypoglycemic drugs, from 36.5% body weight initially to 32.9% after 4–8 weeks (table). That is, the mean loss of body fat was 10 lbs whereas body weight was reduced by

only 2.4 lbs during that interval. Accordingly, a loss in fat but probably not of body weight may be directly correlated with the hypoglycemic activities of timed bromocriptine treatment. Fat loss (3.1 lbs) was less in subjects treated with insulin, perhaps due to the lipogenic activities of the exogenous hormone. Moreover, there was no reduction in body weight. The reduction of plasma glucose level does not appear to be a consequence of loss in body weight.

It has been proposed on the basis of animal studies that body fat stores are set by a lipostat with circadian neuroendocrine components[18,19]. Changes in the phase relations of two circadian systems are thought to control metabolic activities and conditions. At the target tissue level, temporal interaction is expressed by circadian stimuli (e.g., hormones) and circadian responses to the stimuli. The greatest net effect occurs when the daily stimulus peak coincides with the daily interval of greatest responsiveness. All other relations produce a gradation of lesser effects. For example, the daily peak of plasma insulin concentration occurs during the daily interval of lipogenic responsiveness to insulin in fat hamsters and at another time of day in lean animals[20]. A parallel finding applies to prolactin, a hormone that greatly increases hepatic insulin receptor number[21] and the lipogenic response to insulin[22] when it is injected during a specific daily interval. The phase of the prolactin rhythm differs in lean and fat sparrows[23], fish[24], hamsters (Wilson and Meier, unpublished data), rats (Cincotta, unpublished data) and humans[25]. Daily injections of prolactin in animals at times when the daily peaks occur in the plasma of lean and fat animals produce the appropriate decrease or increase in fat stores within two weeks[18,26]. Elevated prolactin levels at all times of day do not have comparable stimulatory influences on fattening[5] and hepatic lipogenesis[27] as higher levels occurring only during a discreet sensitive interval.

The circadian lipostat can apparently be reset by timed daily injections of hormones (i.e., corticosteroid and prolactin[18,19,26]) and neurotransmitter affecting drugs (i.e., 5-hydroxytryptophan and L-dihydroxyphenylalanine[26,28]). Although both hormones also have direct effects on lipid metabolism, it is hypothesized that the corticosteroid and prolactin rhythms are expressions of two neural oscillations that have many other circadian neural and hormonal expressions. The injections of these hormones or neurotransmitter precursors are thought to reset phase-relations of the two neural oscillations as well as their multiple circadian expressions and thereby alter metabolism[18,26,28]. A recent study of Syrian hamsters is especially germane. The female hamster becomes obese during winter and has other characteristics often associated with type II diabetes, i.e., hyperinsulinemia and high insulin resistance[3,20,29]. Daily injections of prolactin given for 10 days at the same time as daily cortisol injections reduce fat stores, plasma insulin levels and insulin resistance, which remain markedly reduced for at least 10 weeks after the termination of injections. Other temporal relations of hormone injections are ineffectual[29]. It was proposed that development of type II diabetes may be the result of altered circadian neuroendocrine relations and that resetting biological clocks may be an efficacious treatment.

Although speculative at this time, the bromocriptine effects on lipid and glucose metabolism may be explained in terms of its dopamimetic activities. Prolactin, L-DOPA and bromocriptine all have marked influences on hypothalamic tuberoinfundibular dopamine turnover[30,31] which in turn influences the ventromedial (VMH), lateral (LH) and suprachiasmatic (SCN) nuclei of the hypothalamus[32]. These centers, particularly the VMH, have primary regulatory roles in energy balance and lipid metabolism and exhibit circadian organization[15]. Interestingly, the tuberoinfundibular area also has a circadian component[33] and its activation by prolactin and dopamine antagonists is strictly temporally dependent[31,34]. Accordingly, appropriately timed bromocriptine treatment may reset the phases of circadian hormone rhythms[35] by shifting circadian dopaminergic activities within the tuberoinfundibular area. These associations do not preclude other dopaminergic centers (e.g., nigrostriatal[36]) from involvement with bromocriptine's effects.

A possible causal role for hyperprolactinemia in glucose intolerance[37,38], hyperglycemia[39] and hyperinsulinemia[40], all hallmarks of type II diabetes, has been studied previously, but the results are contradictory. Impaired glucose tolerance was improved in diabetic subjects after lowering plasma prolactin levels[41,42]. However, other studies indicate no such correlations of diabetes with hyperprolactinemia and no alleviation of diabetic symptoms by inhibitors of prolactin secretion[43,44]. In light of conclusive evidence that prolactin and drugs can have variable effects on fat stores and diabetic symptoms as a function of time of day when they are present or provided, it seems possible that such variable results reported by others may also be the consequences of individual differences in circadian neuroendocrine profile among the subjects examined and differences in the times of day when the drug treatments were administered. Basal levels of prolactin are probably of lesser consequence than the circadian rhythms of and responses to prolactin. In this respect as well, additional studies are underway to determine the best possible times and dosages for bromocriptine administration. Inappropriate timing has the demonstrated potential for worsening obesity and diabetic conditions. 'Fine tuning' may well produce better results than those observed in this initial study. The primary purpose of this initial report is to generate interest in a new approach for investigating the causes of obesity and diabetes. Double-blinded, placebo-controlled studies with bromocriptine and other drugs capable of resetting circadian systems involved in regulating metabolism are underway.

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* This is a process patented by Louisiana State University and licensed to Ergo, Inc., Newport, Rhode Island. A. H. Meier and A. H. Cincotta have financial interest in the process.

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Effect of dipyridamole and adenosine monophosphate on cell proliferation in the hemopoietic tissue of normal and gamma-irradiated mice

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Abstract. Combined treatment with dipyridamole and adenosine monophosphate enhances cell proliferation in the hemopoietic tissue of normal and gamma-irradiated mice. This effect can be explained by the elevation of extracellular adenosine, and the receptor-mediated activation of the cell adenylate cyclase system.
Key words. Dipyridamole; adenosine monophosphate; cell proliferation; hemopoiesis; gamma-irradiation.

Adenosine, an endogenous purine nucleoside, is an important regulatory metabolite which exerts modulating effects on various physiological processes [1]. Some in vitro studies indicate that adenosine could stimulate the proliferative activity of cells of the hemopoietic tissue. An increased spontaneous incorporation of ^{3}H-thymidine into thymocytes after incubation with high doses of adenosine was reported [2], and the addition of adenosine or adenosine monophosphate to long-term bone marrow cultures resulted in an increased granulocyte produc-