Bromocriptine Inhibits In Vivo Free Fatty Acid Oxidation and Hepatic Glucose Output in Seasonally Obese Hamsters (*Mesocricetus auratus*)

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Seasonally obese hyperinsulinemic hamsters were treated for 5 weeks with bromocriptine (500 to 600 μg per animal) and tested for drug effects on energy balance, body fat stores, nocturnal whole-body free fatty acid (FFA) metabolism and hepatic glucose output, and diurnal glucose tolerance. After 5 weeks, bromocriptine treatment reduced retroperitoneal fat pad weight by 45% without altering either daily food consumption or end-treatment total daily energy expenditure. Also, 5 weeks of treatment improved the diurnal glucose tolerance, resulting in a 47% and 33% decrease in the area under glucose and insulin curves, respectively. After 4 weeks, bromocriptine treatment reduced nocturnal lipolysis by 28%, palmitate rate of appearance into plasma by 30%, palmitate oxidation by 33%, and hepatic glucose output by 28%. Moreover, these reductions were accompanied by a 75% reduction in plasma insulin concentration. The data suggest that bromocriptine may improve diurnal glucose tolerance in part by inhibiting the preceding nocturnal lipolysis and FFA oxidation. Reductions in nocturnal FFA oxidation and hepatic glucose production may result from bromocriptine's influences on circadian organization of hypothalamic centers known to regulate these activities. Available evidence suggests that bromocriptine may impact this neuroendocrine organization of metabolism by increasing the dopamine to noradrenaline activity ratio in central (hypothalamic) and peripheral (eg, liver and adipose) target tissues.

ECOLOGICAL AND PHYSIOLOGICAL research on animals under natural conditions has demonstrated that most vertebrate species undergo dramatic seasonal changes in metabolism resulting in the development of an obese, insulin-resistant, hyperinsulinemic condition.[1-5] Moreover, it has been observed that development of this seasonal condition cannot be entirely accounted for by either increased food consumption or decreased energy expenditure.[5-10] Our laboratory has demonstrated that changes in the phase relations of circadian neuroendocrine rhythms have primary roles in the expression and regulation of the annual cycle of metabolism in vertebrates.[5,11,12] Although seasonal metabolic conditions are consequences of temporal synergisms among many circadian neuroendocrine activities, the interactions of prolactin and insulin are of particular interest. For example, in the Syrian hamster seasonal lipid production and body fat stores are regulated by interactions between circadian rhythms of plasma insulin[13] and liver lipogenic responsiveness to insulin.[14,15] During the fattening season, the daily peak of plasma insulin coincides with the daily interval of lipogenic responsiveness to insulin. In contrast, during the other seasons when the animals are lean, the peak in plasma insulin rhythm is out of phase with the peak in lipogenic response rhythm to insulin so that much less (90%) insulin is available during this sensitive daily interval.[13] The amplitude of the peak in daily lipogenic response rhythm to insulin is regulated by a circadian hepatic responsiveness to prolactin.[15,16] Both increased levels of plasma prolactin in vivo and addition of prolactin in vitro to primary cultured hepatocytes during the appropriate daily interval function to increase the daily peak in hepatic lipogenic responsiveness to insulin.[15-17] Timed daily treatment with the prolactin-inhibiting D_2-dopamine agonist, bromocriptine, to reset circadian neuroendocrine activities was found to substantially reduce body fat stores and 24-hour hyperinsulinemia and improved diurnal insulin-stimulated glucose disposal[18,19] in seasonally obese hamsters. A central mechanism by which bromocriptine reduces body fat relates to its inhibition of basal and insulin-stimulated hepatic lipogenesis and triglyceride secretion.[15,18] However, the mechanisms by which bromocriptine alleviates insulin resistance and hyperinsulinemia are less clear. Several studies have shown that interactions between lipid and carbohydrate substrates may be important in the development of insulin resistance.[20] In obese insulin-resistant states, increased rates of free fatty acid (FFA) oxidation are negatively correlated with rates of basal and insulin-stimulated glucose disposal and positively correlated with the rate of basal hepatic glucose production.[21,22] Furthermore, in obese insulin-resistant states, increases in FFA plasma levels and oxidation may increase hepatic glucose production.[21-23] A time dependence appears to be critical to this lipid-carbohydrate interaction in that increases in FFA oxidation must precede initiation of a euglycemic insulin clamp to inhibit insulin-stimulated oxidative and nonoxidative glucose metabolism 2 hours later.[24] Recently, it was demonstrated that an intravenous infusion of elevated physiologic levels of FFA was necessary for 4 to 6 hours to inhibit both insulin-stimulated glucose uptake and insulin suppression of hepatic glucose output.[25] We therefore investigated the possibility that bromocriptine may reduce diurnal insulin resistance in the hamster by reducing the preceding nocturnal peak in FFA mobilization and oxidation. Because of the association between FFA oxidation and hepatic glucose production, we also studied bromocriptine effects on hepatic glucose output during this nocturnal interval.

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MATERIALS AND METHODS

Animal Model

In common with most vertebrate species in the wild, the annual cycle of metabolic activity of the female Syrian hamster (*Mesocricetus auratus*) is the result of an interaction of daily photoperiod with an endogenous seasonal timing mechanism.[9,10,13,18,26] Transfer of adult female Syrian hamsters from 14-hour daily photoperiods (14 hours of light:10 hours of dark; ie, summer condition) to 10-hour daily photoperiods (ie, winter condition) results in development of obesity, insulin resistance, and hyperinsulinemia.[13,18] However, after approximately 20 weeks on 10-hour daily photoperiods, the animals "spontaneously" become lean, insulin-sensitive, and euinsulinemic.[18] Transfer of animals back to 14-hour daily photoperiods for approximately 10 weeks is necessary to re-establish the fattening response to 10-hour daily photoperiods.

Experimental Design

Adult (~150 g) female Syrian hamsters were purchased from Simonson (Gilroy, CA) and raised on 14-hour daily photoperiods from birth for 10 weeks. After adaptation to 10-hour daily photoperiods (light to dark ratio, 10:14) for 7 days, animals were injected intraperitoneally daily at light onset with bromocriptine 600 μg per animal ($n = 6$) or vehicle ($n = 6$) for 5 weeks. Following 4 weeks of treatment, animals were fasted for 4 hours from 8 to 12 hours after light onset and then anesthetized (sodium pentobarbital; 65 mg/kg body weight [BW]) and infused via the right jugular vein with stable isotopes for analyses of whole-body FFA oxidation and hepatic glucose output as described later. Therefore, these metabolic analyses were conducted during the middle of the nocturnal phase of the day. Plasma from blood samples taken before initiation of infusions was analyzed for insulin and glucose concentrations. One week following recovery from infusions, total daily energy expenditure was assayed as described later. The Syrian hamster eats intermittently throughout the day and stores food in its oral pouches.[13] Food consumption of animals (fed Ralston Purina Chow no. 5001, Indianapolis, IN, ad libitum) was monitored daily by weighing the food in the cage at light onset. Another group of animals was similarly treated with bromocriptine 500 μg per animal) ($n = 6$) or vehicle ($n = 6$) for 5 weeks and then subjected to a glucose tolerance test (2.0 g glucose/kg) as previously described[18] at light onset.

Humoral Assays

Plasma insulin level was assayed with a commercially available and previously validated[13] radioimmunoassay kit (Binex, S Portland, ME). Plasma glucose concentration was determined by a colorimetric/enzymatic assay system using glucose oxidase coupled to peroxidase (procedure no. 315; Sigma Diagnostics, St Louis, MO).

Determination of In Vivo Lipolysis Rate and FFA Flux

The rate of appearance (Ra) of glycerol into the plasma was used to estimate lipolysis using the stable-isotope dilution technique essentially as previously described,[19] except that the bolus prime injection of ($^2H_5$)glycerol was 60 μg/100 g BW and steady-state values for ($^2H_5$)glycerol were obtained by averaging plasma values at 90 and 120 minutes after initiation of infusion. Lipolysis was calculated as three times the rate of glycerol turnover. Similarly, Ra of palmitate and blood $^{13}CO_2$ enrichment from (1-^{13}C)sodium palmitate were used to determine whole-body FFA oxidation. A primed (400 μg/100 g BW) dose of ^{13}C-sodium bicarbonate was followed by a constant infusion (3 μg/100 g BW/min) of (1-^{13}C)sodium palmitate in phosphate-buffered saline–2.5% fatty acid–free bovine serum albumin, pH 7.4, for 120 minutes. Steady-state values for $^{13}CO_2$ and (1-^{13}C)sodium palmitate were obtained by averaging plasma values at 90 and 120 minutes after initiation of the infusion. Plasma (1-^{13}C)palmitate and blood $^{13}CO_2$ were analyzed by mass spectroscopy as previously described.[27] The Ra of palmitate into plasma and palmitate oxidation were calculated according to methods reported by Royle et al.[28]

Determination of Hepatic Glucose Output

The Ra of glucose into the plasma using the isotope dilution technique as previously described[29] was used to determine hepatic glucose output. A primed (500 μg/100 g BW) constant infusion (6 μg/100 g BW/min) of (6,6-D_2)glucose in phosphate-buffered saline–2.5% bovine serum albumin, pH 7.4, was used for this purpose, and the Ra of glucose was determined as previously described.[30] Steady-state values for (6,6-D_2)glucose were obtained by averaging plasma values at 90 and 120 minutes after initiation of infusion. Samples of (6,6-D_2)glucose were analyzed using a Hewlett Packard 5971 gas chromatograph/mass spectrometer (Palo Alto, CA).

Total Energy Expenditure

Total daily energy expenditure was measured using doubly labeled water (D_2 ^{18}O) following the method reported by Lifson et al.[31] The two-point method was used to calculate isotopic disappearance rate constants from the beginning (25 hours postdose) and end (72 hours postdate) sample periods. Isotope abundance was corrected for isotopic backgrounds. Energy expenditure was calculated from carbon dioxide production, assuming 127 kcal/mol carbon dioxide (respiratory quotient, 0.85 with 15% of energy from protein oxidation) and 0.85 g urinary nitrogen excretion per day. Daily bromocriptine treatment was continued over this 72-hour period. Blood samples for deuterium and ^{18}O analyses were obtained by orbital sinus puncture. At the end of this 72-hour period, animals were killed by sodium pentobarbital overdose, and retroperitoneal fat pads were removed and weighed as an index of body fat.[9,18]

Statistical Analyses

Differences in metabolic parameters or plasma constituents between bromocriptine and control animals were examined by Student's *t* test. Statistically significant differences were accepted at the P less than .05 level.

RESULTS

Bromocriptine treatment reduced retroperitoneal fat pad weight by 45% (from 9.3 ± 0.8 to 5.1 ± 0.7 g, $P < .01$) and BW increase (from 64 ± 9 to 25 ± 3 g) relative to controls ($P < .01$). However, bromocriptine treatment did not alter daily food consumption during treatment (12.0 ± 0.7 *v* control value 13.2 ± 0.4 g/d) or total daily energy expenditure measured at the end of treatment (22.6 ± 0.7 *v* control value 22.4 ± 1.8 kcal/d; Table 1).

Bromocriptine treatment reduced the nocturnal lipolysis rate by 28% (from 109 ± 7 to 79 ± 4 μmol/kg/min, $P < .01$), Ra of palmitate by 30% (from 28.8 ± 2.8 to 20.3 ± 1.8 μmol/kg/min, $P < .01$), and palmitate oxidation by 33% (from 8.9 ± 0.7 to 5.9 ± 0.4 μmol/kg/min, $P < .01$). We have found that palmitate comprises approximately 30% of the total plasma FFA concentration in these hamsters. Nocturnal hepatic glucose output was also reduced by bromocriptine treatment by 28% (from 42.6 ± 3.1 to 30.6 ± 3.1 μmol/kg/min, $P < .01$). Although nocturnal

Table 1. Effect of 5 Weeks of Bromocriptine Treatment on Body Fat and Energy Balance of Female Syrian Hamsters Held on 10-Hour Daily Photoperiods for 6 weeks

Group	Final BW (g)	BW Increase		Retroperitoneal Fat Pad Weight (g)	Food Consumption (g/d)	End-Treatment Total Energy Expenditure (kcal/d)
		% Initial BW	g			
Control (n = 6)	214 ± 9	37 ± 4	64 ± 9	9.3 ± 0.8	13.2 ± 0.4	22.4 ± 1.8
Bromocriptine (n = 6)	175 ± 3*	17 ± 2*	25 ± 3*	5.1 ± 0.7*	12.0 ± 0.7	22.6 ± 0.7

NOTE: Values are the mean ± SE.
*$P < .01$ compared with vehicle-injected controls.

plasma glucose levels were unaffected by bromocriptine, the drug treatment did decrease plasma insulin concentration at this time by 75% (from 269 ± 79 to 66 ± 14 μU/mL, $P < .05$; Table 2).

In a second group of animals used to investigate the bromocriptine effect on diurnal glucose tolerance, bromocriptine treatment reduced diurnal (light onset) basal glucose and insulin levels from 154 ± 9 to 129 ± 4 mg/dL and 443 ± 33 to 284 ± 26 μU/mL, respectively ($P < .01$). Bromocriptine also reduced the area under the glucose tolerance curve (from 544 ± 62 to 291 ± 30 mg · h/dL, $P < .01$) and the area under the insulin curve (from 884 ± 57 to 590 ± 50 μU · h/mL, $P < .01$; Fig 1) when assayed at light onset.

DISCUSSION

This study is the first to demonstrate an inhibitory effect of bromocriptine on basal FFA oxidation and hepatic glucose output in vivo in a naturally occurring animal model of the obese insulin-resistant syndrome. Moreover, this inhibition of these metabolic activities was accompanied by a concurrent substantial (75%) reduction in hyperinsulinemia. This suggests that resistance to insulin suppression of both adipose FFA mobilization and hepatic glucose output has been reduced by bromocriptine. Within the context of analysis, it should be emphasized that absolute quantitative measures of FFA oxidation using the isotope dilution technique used here cannot be made without knowing the intracellular substrate specific activity, which in the case of FFA is complex.[32] However, qualitative (relative) differences between treatment groups determined by this method are valid.[32] Moreover, states of relative hyperinsulinemia and increased lipogenesis (such as in our control group relative to bromocriptine group) tend to result in an underestimation of total FFA oxidation with this method.[32] Therefore, the magnitude of bromocriptine's inhibitory effect on FFA oxidation determined by this method may well be an underestimation.

In agreement with previous studies,[18,19] bromocriptine reduced nocturnal and diurnal plasma insulin levels; however, these data further demonstrate that insulin levels during the glucose tolerance test were also reduced by bromocriptine. As such, the observed improvement in glucose tolerance cannot be attributable to increased insulin secretion, and affirms other data[19] that bromocriptine is increasing insulin-stimulated glucose disposal.

Table 2. Effect of 4 Weeks of Bromocriptine Treatment on Nocturnal Whole-Body Lipolysis, Palmitate Oxidation, and Hepatic Glucose Output Rates and Nocturnal Plasma Insulin and Glucose Concentrations in Female Syrian Hamsters Held on 10-Hour Daily Photoperiods for 5 Weeks

Parameter	Control		Bromocriptine	
	μmol/kg/min	μmol/whole BW/min	μmol/kg/min	μmol/whole BW/min
Ra glucose	42.6 ± 3.1	9.0 ± 0.5	30.6 ± 3.1*	5.3 ± 0.5*
Lipolysis (3× Ra glycerol)	109 ± 7	23.1 ± 1.1	79 ± 4*	13.7 ± 0.6*
Ra palmitate	28.8 ± 2.3	6.1 ± 0.5	20.3 ± 1.8*	3.6 ± 0.3*
Palmitate oxidation	8.9 ± 0.7	1.9 ± 0.2	5.9 ± 0.4*	1.0 ± 0.1*
Plasma insulin (μU/mL)	269 ± 79		66 ± 14†	
Plasma glucose (mg/dL)	97 ± 6		100 ± 7	

NOTE. Values are the mean ± SE.
*$P < .01$, †$P < .05$, compared with vehicle-injected controls.

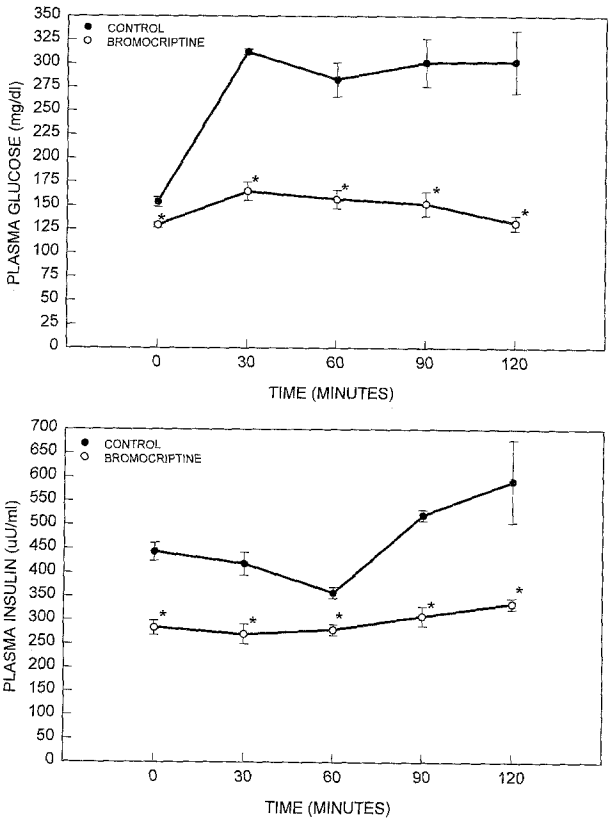

Fig 1. Effect of bromocriptine on diurnal glucose tolerance. Animals were administered glucose (2 g/kg BW) at light onset following 5 weeks of treatment with (○) bromocriptine (500 μg per animal) or (●) vehicle, and plasma glucose and insulin levels were monitored over the next 2 hours. *Significant difference from control ($P < .01$).

Recently, it was demonstrated that physiologic increases (to 750 μmol/L) of FFA are necessary for a period of 4 to 6 hours to substantially inhibit insulin-stimulated glucose uptake (via decreasing glycogen synthesis and carbohydrate oxidation).[25] Moreover, several hours of increased plasma FFA concentration and skeletal muscle lipoprotein lipase activity are required to inactivate pyruvate dehydrogenase in skeletal muscle[33,34] and thus lead to decreased glucose oxidation and transport.[20-22,25] In the present study, bromocriptine-induced inhibition of lipolysis and FFA oxidation was measured during the middle of the daily peak of plasma FFA levels, which extends for 8 to 10 hours during the dark period of the day in the obese Syrian hamster.[19] Moreover, bromocriptine reduces this nocturnal 8- to 10-hour peak in plasma FFA level by 50%.[19] This reduction in nocturnal FFA mobilization and oxidation may in part account for the subsequent increase in diurnal insulin-stimulated glucose disposal[19] and improved glucose tolerance (present study). Decreased FFA oxidation decreases intracellular levels of acetyl coenzyme A (CoA), NADH/NAD ratio, and citrate, thereby relieving their inhibitory influences on glucose oxidation and transport (and subsequent glycogen formation).[20,21] Elevated levels of intracellular fatty acyl-CoA may also inhibit glycogen synthase directly.[25,35]

The reduction in basal hepatic glucose output produced by bromocriptine may also result in part from its inhibition of FFA oxidation. The basal rate of FFA oxidation is enhanced in obesity, which can be expected to increase hepatic glucose output by inhibiting pyruvate dehydrogenase, stimulating pyruvate carboxylase, and providing adenosine triphosphate and a key positive modulator, acetyl CoA, to drive gluconeogenesis.[23,36] Furthermore, increases in plasma FFA levels may contribute to the obesity-associated resistance to insulin suppression of hepatic glucose production.[21-23] It is interesting that in the present study nocturnal hepatic glucose output was reduced by 28% without a decrease in plasma glucose level. Since hepatic glucose output equals peripheral glucose uptake in the steady-state fasting condition, it follows that in absolute terms peripheral glucose uptake was also reduced by treatment. This may seem at variance with a bromocriptine-induced improvement in insulin-stimulated glucose disposal, until one realizes that the plasma insulin level was concurrently dramatically reduced (by 75%) by treatment. Much higher levels of insulin are required to maintain a normal basal rate of tissue glucose clearance than are necessary to inhibit hepatic glucose output.[21] Bromocriptine treatment substantially increases insulin-stimulated glucose disposal during insulin infusion, which produces hyperinsulinemia in control and bromocriptine-treated hamsters.[19]

Bromocriptine treatment produced a large reduction in body fat stores of the Syrian hamster without altering daily energy intake (or fecal energy[37]) or end-treatment total metabolic rate. However, the decreased weight gain of bromocriptine-treated animals with a concurrent equivalent daily energy intake relative to controls (Table 1) argues that total energy expenditure may have been increased by bromocriptine during some portion of the drug treatment period. The increased fattening of female hamsters transferred from long to short daily photoperiods also occurs without an increase in food consumption.[8-10] After 6 to 8 weeks on short daily photoperiods, body fat increases tend to stabilize. Therefore, it will be more instructive in future studies to follow energy balance and intermediary metabolism during the course of treatment to delineate the time course of these interactive relationships. Previous studies have demonstrated that bromocriptine treatment strongly inhibits lipogenesis[15,18] and markedly enhances protein turnover[19] in the hamster, so body fat may be reduced without reducing energy intake by shifting energy utilization away from lipid synthesis toward protein turnover, which is a significant contributor to total energy expenditure.[38,39] Such a shift in metabolism has been demonstrated to be part of the natural annual cycle of metabolism in mammals.[7,40] Available evidence suggests that bromocriptine inhibits hepatic lipogenesis by blocking prolactin augmentation[15] and vagal mediation[41,42] of insulin-stimulated lipogenesis. However, inasmuch as bromocriptine can bind specifically to hepatocyte plasma membrane and influence glucose metabolism,[43] a direct effect of the drug on hepatic lipogenesis cannot be precluded. Bromocriptine may also regulate hepatic lipogenesis (and overall metabolism) by influencing hypothalamic neuroendocrine control systems (see below). Bromocriptine reduces hyperinsulinemia in these hamsters[18,19] (and the present study), and this influence may also reduce lipogenesis. In obese pigs and human subjects, bromocriptine reduces body fat without a substantial loss of lean body mass.[44,45] Bromocriptine may preserve lean body mass by increasing protein synthesis and reducing amino acid deamination and excretion.[19,44]

Bromocriptine may reduce the nocturnal peak in plasma FFA[19] and nocturnal lipolysis, FFA oxidation, and hepatic glucose output in hamsters by influencing central (hypothalamic) circadian systems known to regulate these activities. Basal and 2-deoxyglucose–induced circadian increases in plasma FFA and glucose are abolished by suprachiasmatic nuclei (SCN) lesions in the rat.[46] A plethora of data indicate that the SCN are a circadian pacemaker regulating numerous neuroendocrine and metabolic activities in vertebrates.[47,48] Bromocriptine may influence the SCN directly or may modulate circadian activities in other hypothalamic areas that are influenced by the SCN and involved in metabolism such as (but not limited to) the arcuate, ventromedial, lateral, or paraventricular nuclei.[46] Evidence for bromocriptine interaction with such metabolic regulatory systems comes from several separate sets of data. (1) Bromocriptine inhibits the circadian peak in hepatic lipogenic responsiveness to insulin.[15] (2) Bromocriptine induces shifts in cortisol rhythms (which are normally tightly synchronized to the daily photoperiod and locomotor activity rhythm and regulated by the SCN[47]) in animals allowed to feed ad libitum and held on a photoperiod.[19] (3) Bromocriptine treatment produces the same metabolic changes in almost every detail in the hamster as the naturally occurring seasonal changes in metabolism shown

to be directed by interactions of circadian neuroendocrine rhythms.[18,26,49] (4) The magnitude of effectiveness of bromocriptine in producing its metabolic effects depends on the time of day of its administration (A.H. Cincotta, unpublished data, July 1993).

Bromocriptine is a pleiotropic neuromodulator influencing many different neurotransmitter activities.[50] However, as it relates to this study, the significant sympatholytic activities of the molecule may be particularly germane. Bromocriptine is both a presynaptic D_2 dopamine receptor agonist and a presynaptic α_2-adrenergic receptor agonist in central and peripheral neurons, resulting in substantial inhibition of noradrenaline synthesis and secretion.[50-55] Bromocriptine also reduces circulating levels of dopamine β-hydroxylase[56,57] and inhibits adrenal release of noradrenaline.[58,59] At postsynaptic sites, bromocriptine is a powerful D_2 dopamine agonist and an α_1-adrenergic antagonist.[60,61] Bromocriptine may inhibit nocturnal lipolysis, FFA oxidation, and hepatic glucose output by altering daily changes in the dopamine to noradrenaline activity ratio in hypothalamic and peripheral centers known to regulate these metabolic activities. For instance, bromocriptine may attenuate the ventromedial hypothalamic noradrenergic drive to stimulate lipolysis and hepatic glucose production.[62,63] Peripherally, bromocriptine not only reduces sympathetic and circulating noradrenaline levels, but also acts as an α_1-adrenergic receptor antagonist and α_2 agonist in target tissues, including liver and adipose,[43,64] where it may thereby inhibit hepatic glucose production and lipolysis, respectively.[43,65]

Some of bromocriptine's activities are probably a consequence of its potent inhibitory effects on prolactin secretion.[60] Prolactin is an important liporegulatory hormone with substantial time-of-day–dependent effects on both lipogenesis and lipolysis.[66] In a migratory sparrow, prolactin levels are greatest in the afternoon during the migratory period, and injections at this time of day promote increased lipogenesis during the day and increased fat mobilization at night when migration occurs.[67] In obese insulin-resistant female Syrian hamsters held on 10-hour daily photoperiods, plasma prolactin levels peak near light offset[19] and account for increased hepatic lipogenesis about 14 hours later.[15,16] Prolactin also stimulates lipolysis, but with a much reduced lag period (1 to 2 hours after administration). Therefore, prolactin at light offset can increase nocturnal lipolysis and subsequent diurnal lipogenesis. Bromocriptine alters the daily rhythm of prolactin[19] and may be expected to reduce both lipid activities in part by shifting the daily peak of plasma prolactin to a time of day when it does not support these metabolic activities and to a time of day when it peaks naturally in seasonally lean hamsters.

The seasonal obese insulin-resistant condition in animals in the wild is a tactic evolved for survival in a cyclic environment and contains all the elements of the thrifty gene hypothesis.[68] Seasonal increases in lipid production and storage (associated with insulin resistance and hyperinsulinemia) provide an energy source during long periods of low food availability or to fuel migration or subsequent protein synthesis associated with reproductive recrudescence, pregnancy, and lactation.[6,7,69,70] The associated hepatic and muscle insulin resistance may function to shunt glucose away from (lipid-utilizing) muscle, ensuring an adequate supply to tissues with an obligatory requirement for it (eg, brain) during seasonal periods of low carbohydrate availability or during starvation (eg, migration, over wintering, or hibernation).[3] Changes in the organization of circadian neuroendocrine activities regulating metabolism are responsible for the expression of this seasonal condition.[4,5,11,12,49] Evidence suggests that bromocriptine inhibits the seasonal development of this condition in part by impacting this neuroendocrine organization. Moreover, preliminary data indicate that such bromocriptine action can produce similar changes in metabolism of age-associated obesity and type II diabetes in humans.[45]

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