Reduction of body fat stores by inhibition of prolactin secretion

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Summary. Reductions of prolactin secretion by bromocriptine treatment for 24 days reduced fat stores (abdominal and epididymal fat depots) in hamsters by 25–49% compared with control animals. However, body weights and food consumption were not affected. These results further substantiate an important role for prolactin in regulation of fat metabolism and indicate that bromocriptine might be used to decrease fat stores.
Key words. Bromocriptine; prolactin; fat stores.

An enormous effort has been made to understand lipid metabolism and the causes of obesity. Although much has been learned regarding the synthesis, transport, storage and mobilization of fat, the utilization of this knowledge for practical means of controlling body fat stores has not been entirely successful. A primary maxim that apparently still governs most thinking is the simplistic notion that the amount of body fat is little more than the net consequence of energy input and energy output. However, ecological and physiological research on animals under natural conditions indicate that there are other important determinants of fat stores as important as food availability and immediate energy requirements. In a migratory sparrow, for example, fat stores are greatest when the birds are most active (during the migratory seasons) and least during summer when food may be plentiful and activity low[1,2]. Evidence such as this suggests an important role for neuroendocrine mechanisms in control of fat stores, and prolactin is thought to have a central place in this mechanism[3–5]. Injections of prolactin have been shown to stimulate lipogenesis and body fat stores in representative species of all the major vertebrate classes[6], including the Syrian hamster[7], provided the injections are made during a sensitive interval of the day. The present study in Syrian hamsters tests the possibility that drug-induced reduction of prolactin secretion might reduce fat stores.

Reproductively mature (Experiment 1: 3–4 months old; Experiment 2: 7 months old) male hamsters (b.wt: 100–150 g) were caged in pairs, fed ad libitum, maintained at 23 °C and provided with 14-h daily photoperiods (light onset: 08.00 h). The hamsters were injected (i.p.) daily at 08.00 and 14.00 with equal amounts of bromocriptine in peanut oil (see table for dosages) or peanut oil (controls). Bromocriptine treatment (600 µg/day) reduced blood prolactin concentrations in hamsters over a 24-h period by about 80%[8]. Food consumption was monitored daily. After 24 days of treatment, the animals were killed by an overdose of sodium pentobarbital to obtain body weights, abdominal and epididymal fat pad weights, and testes and seminal vesicles weights. Seasonal changes in abdominal and epididymal fat pad weights correlate well with changes in total body fat stores of the Syrian hamster[9,10]. Therefore, these fat depots were used as indices of body fat stores. Statistical differences between the control and experimental groups were tested by Student's t-test.

Results and discussion. Bromocriptine dramatically reduced indices of body fat stores at both the highest (600 µg/hamster/day) and lowest (15 µg) dosages tested (table). Weights of abdominal fat depots were reduced by 25–49% compared with controls among the highest dosage experimental groups. The lowest dosage reduced the abdominal fat pad by 38% and the epididymal fat pad by 33%. However, bromocriptine treatment did not alter body weights (either final body weights or percent increase in body weight over the injection period), food consumption, or reproductive indices (paired testes weights, seminal vesicle weights, and vas deferens plus epididymus weights) (table 1). In a recent experiment, bromocriptine (600 µg/day) significantly reduced abdominal fat depots by 50% compared with controls (0.41 g ± 0.06 versus 0.85 g ± 0.13, respectively) after only 10 days of injections.

A reduction of lipid synthesis probably accounts for much of the decrease in body fat stores resulting from bromocriptine treatment. Bromocriptine injections for 5 days dramatically reduced lipogenesis and completely blocked lipogenic responsiveness to insulin in isolated hepatocytes of the Syrian hamster[8]. Bromocriptine also severely reduced the insulin receptor number in the liver[11]. Prolactin replacement in bromocriptine-treated hamsters completely reversed the bromocriptine inhibition of both the lipogenic responses to insulin and the insulin receptor number. Although it has long been recognized that insulin is a primary hormone in regulating lipid metabolism, the above demonstrations are the first to show that prolactin has a critical permissive role in the lipogenic activities of insulin.

It seems curious that bromocriptine-induced losses in fat stores were not reflected in a concurrent loss in body weight. Increases in body weight have in fact been reported as a result of bromocriptine treatment (high dosages) in Syrian hamsters[12]. It also seems interesting that a reduction of nearly 50% of the fat stores did not entail any reduction in food consumption. Thus the reduction in fat stores is not a direct consequence of reduced

Reduction in boy fat stores by bromocriptine injections

Treatment	n	Body weight (% increase over injection period)	Indices of body fat stores: Epididymal fat pad (g)	Epididymal fat pad (%b.wt)	Abdominal fat pad (g)	Abdominal fat pad (%b.wt)	Liver weight (g)	Food consumption (g/day/animal)	Reproductive indices: Paired testes (g)	Seminal vesicles (g)	Vas deferens + epididymus (g)
Experiment 1 (3–4 months of age)											
Control	9	11.5 ± 4.0	1.73 ± 0.06	1.37 ± 0.05	0.84 ± 0.03	0.67 ± 0.03	5.2 ± 0.2	8.8 ± 0.2	4.0 ± 0.1	1.62 ± 0.08	0.98 ± 0.10
Bromocriptine (600 µg/day)	10	16.3 ± 2.4	1.17 ± 0.07[1]	0.93 ± 0.05[1]	0.43 ± 0.02[1]	0.38 ± 0.01[1]	5.3 ± 0.3	8.8 ± 0.2	3.9 ± 0.1	1.68 ± 0.10	0.90 ± 0.10
Experiment 2 (7 months of age)											
Control	8	3.3 ± 0.9	1.35 ± 0.07	1.10 ± 0.05	0.96 ± 0.08	0.77 ± 0.06	4.9 ± 0.5	10.4 ± 0.3	3.5 ± 0.2	1.42 ± 0.05	0.84 ± 0.05
Bromocriptine (600 µg/day)	8	5.4 ± 1.2	1.07 ± 0.09[2]	0.76 ± 0.04[1]	0.72 ± 0.07[2]	0.54 ± 0.04[1]	5.6 ± 0.7	11.2 ± 0.3	3.6 ± 0.2	1.53 ± 0.06	0.78 ± 0.06
Bromocriptine (200 µg/day)	7	3.0 ± 1.1	1.08 ± 0.05[1]	0.90 ± 0.05[1]	0.75 ± 0.08	0.63 ± 0.08	5.0 ± 0.3	9.8 ± 0.3	3.3 ± 0.2	1.57 ± 0.03	0.79 ± 0.05
Bromocriptine (15 µg/day)	8	1.6 ± 1.2	0.91 ± 0.06[1]	0.86 ± 0.05[1]	0.60 ± 0.04[1]	0.56 ± 0.04[1]	4.5 ± 0.2	9.2 ± 0.5	3.3 ± 0.1	1.40 ± 0.07	0.76 ± 0.06

[1] Significantly less than control ($p < 0.01$). [2] Significantly less than control ($p < 0.05$).

caloric intake. This conclusion is consonant with another in which prolactin was shown to stimulate fattening in unfed fish[13]. The possibility of a shift from fat synthesis to increased protein synthesis in bromocriptine-treated animals deserves further study.

Because insulin has many other vital activities, reduction of insulin itself is not a practical way to reduce fat stores. However, reduction of prolactin secretion has been practiced extensively in obstetrics and gynecology with few deleterious side-effects. The low dose of bromocriptine used in this study is equivalent on a weight basis to that used in humans for such purposes[14]. Thus a selective suppression of insulin's lipogenic activities by reducing prolactin secretion may offer a practical means for treating obesity.

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Inhibition by SMS 201-995 of normal mammary gland growth in mice

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Summary. Twice daily s.c. injection of 5 ng or 50 ng of SMS 201-995 between 25 and 55 days of age induced a significant retardation of normal mammary gland growth in C3H/He virgin mice, associated with the reduced plasma GH level. Meanwhile, plasma prolactin level and the pattern of estrous cycle were affected little by SMS treatments. The results indicate an involvement of GH in normal mammary gland growth in mice.

Key words. GH; mammary gland; mice; prolactin; somatostatin.

Somatostatin was initially isolated from the hypothalamus[2] and subsequently found in the gastrointestinal tracts and pancreatic islets[3]. Somatostatin and its analogs have widespread physiological roles including the suppression of the secretion of hormones from gut and pancreas, gastric acid secretion and pancreatic exocrine secretion[3–6]. However, the most representative action of somatostatin is the inhibition of pituitary growth hormone (GH) secretion[2, 7, 8] and most analogs are more potent and longer acting than the native molecule[9, 10].

Despite the accumulation of a considerable amount of data, the question of the role of GH in mammary gland growth is still far from being conclusively answered. Exogenous administration of GH from different species, as used in previous studies, is likely to be one of the factors preventing reliable interpretation of the results. In this paper, we studied the effects of chronic administration of SMS 201-995, a somatostatin analog, on mammary gland growth and the circulating levels of GH and prolactin in virgin mice.

Materials and methods. Animals and treatments. A highly inbred strain of C3H/He mice maintained in our laboratory were used. At 25 days of age, virgin mice were divided into 3 groups. The 1st, 2nd and 3rd groups received twice daily (08.00 and 17.00) s.c. injections of 0.05 ml physiological saline, 5 ng SMS 201–995 (Sandoz Ltd., Basel, Switzerland) and 50 ng SMS, respectively,

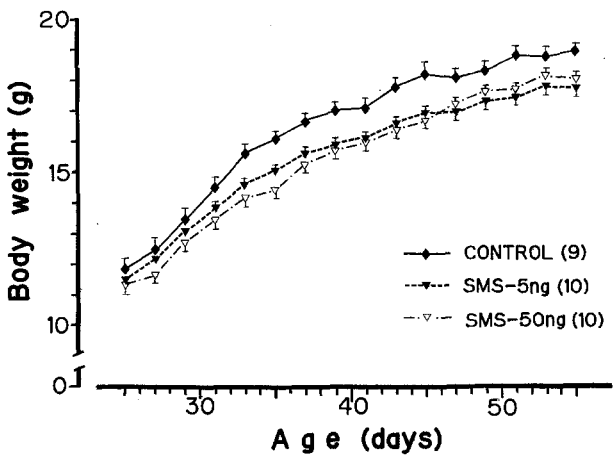

Figure 1. Body weight change in each group (Mean ± SEM). Each dose of SMS, dissolved in 0.05 ml physiological saline, was injected subcutaneously twice daily between 25 and 54 days of age and once on the morning of day 55. Control received vehicle only. Number of mice weighed is indicated in the parentheses.