Obesity: Mediators and Treatment Approaches

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This is the fifth of a series of six articles based on presentations at the American Diabetes Association Scientific Sessions held 6–10 June 2008 in San Francisco, California.

Obesity hormones

Zofia Zukowska (Washington, DC) discussed the peripheral actions of neuropeptide Y (NPY), an important mediator by which diet and lack of physical activity lead to weight gain. NPY is synthesized as a 97 amino acid precursor, which is processed and amidated to NPY 1–36. NPY 1–36 is cleaved by dipeptidyl peptidase (DPP)-4 to NPY 3–36, which has other biologic activities, leading to the possibility that inhibitors of DPP-4 may potentiate NPY action with potentially adverse (or beneficial) effects. NPY is contained in all sympathetic nerves together with norepinephrine, although their modes of release are somewhat dissimilar. This is, then, a major sympathetic nervous system effector, elevated in stress, hypertension, cardiac and renal failure, and malignancies, which, Zukowska stated, is the most abundant peptide in the brain and heart. There are multiple G protein–coupled receptors for NPY including y1, which is vasoconstrictive, has atherogenic effects, and acts in the brain to reduce anxiety and increase appetite (1), and y2 and y5, which are also involved in the peptide's vascular effects (2). She cited evidence that although stress with increased sympathetic tone causes lipolysis by increasing catecholamine levels, sympathetic activation may also increase NPY, leading to angiogenesis and adipogenesis causing fat cell growth. Cold stress with a fat- and sugar-enriched diet increases body weight. An experimental model of daily 10-min encounters with an aggressive mouse was also associated with increased NPY as well as increased Y2 receptor expression, seen particularly with a high-fat diet and environmental stress. Interestingly, *ob/ob* mice have a sevenfold increase in NPY expression. NPY has insulin-like effects on release of adipokines and resistin. In vivo, NPY administration by a slow-release pellet stimulates fat formation in lean mice and monkeys. The effect of stress with a high-fat diet is blocked with a y2 receptor antagonist or by deletion of the y2 receptor using local injection of a viral vector, both of which increase apoptosis and decrease proliferation of endothelial cells and adipocytes, decreasing obesity and improving insulin sensitivity and glucose tolerance. Stress-induced increased sympathetic tone, then, would lead to weight loss, but desensitization of that pathway, accompanied by upregulation of the y2 pathway, as well as increased local glucocorticoids, leads to fat accumulation (3). Interestingly, peptide YY 3–36 has effects similar to those of NPY in fat, stimulating angiogenesis and adipogenesis, although in the brain PYY has the opposing effect of inducing satiety and promoting weight loss.

Peter Arner (Karolinska, Stockholm, Sweden) discussed human obesity genes, including those influencing fatty acid combustion in muscle, adipocyte lipid metabolism, adipogenesis, and brain control of appetite and energy expenditure. Human fat cells increase lipid content under circumstances of increased insulin or decreased catecholamine levels, which increase fat uptake and decrease its release. Genetic variants in lipolysis have been documented, with a group of 311 obese and 223 nonobese women and 114 and 82 such men, showing that obesity was associated with increased insulin-induced inhibition of lipolysis and decreased norepinephrine-induced lipolysis. Resistance to catecholamine action would, Arner suggested, promote obesity. There are four catecholamine receptors, α-2A and β-1, -2, and -3, with the latter being G protein–coupled receptors and with abnormalities of the β-2 receptor associated with obesity (4). A number of other genetic polymorphisms appear to regulate adipose tissue mass (5). Using a genome-wide scan, a neuropeptide receptor involved in pain perception, GPR-74 (the G protein–coupled receptor for the morphine-modulating neuropeptides A18 famide [NPAF] and NPFF), is highly expressed in adipose tissue. NPFF decreases lipolysis in human fat cells in a dose-dependent fashion and may be as potent as insulin, appearing to act by inhibiting the signal from the β-adrenergic receptor to hormone-sensitive lipase. There are several GPR-74 polymorphisms in man, with the ATAG haplotype associated with 45% reduction in likelihood of obesity (6) and with increased lipolysis and increased adipocyte norepinephrine sensitivity, suggesting that individuals with the protective polymorphism have a greater lipolytic response to norepinephrine and decreased NPFF/NPAF response. Another question is whether there are genetic variations in the adipocyte generation involved in obesity. Growth of human adipose tissue has been thought to be regulated by adipogenesis in youth, with subsequent fat expansion only by growth of preexisting adipocytes, although above a certain obesity level adipogenesis also may occur later in life. Arner reviewed his studies with measurement of 14C (derived from atmospheric nuclear weapon testing) in adipose tissue, suggesting that adipocyte turnover is ~10% per year and that lean individuals produce new fat cells at lower rates than obese individuals (7). Genetic factors linked to greater or lesser degrees of adipogenesis may, then, play a role in human obesity.

Several studies presented at the meeting examined genetic associations of obesity. Lindgren et al. (abstract 1751) analyzed genome wide association data pertaining to obesity from >90,000 individuals, finding that variants in the fused toe (FTO) gene, which have already been described and appear to relate to hypothalamic and pancreatic islet signaling, and in the melanocortin four receptor gene, involved in another hypothalamic

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satiety receptor pathway, appear to show the strongest signals. Traurig et al. (abstract 1,752) reported that gene variants among 3,501 Pima Indians associated with obesity may alter transcription of SIM1, the human homolog of the *Drosophila* Single Minded gene, required for differentiation of hypothalamic neuroendocrine cells, and further that four of 96 morbidly obese Pima Indians had abnormalities in the SIM1 gene sequence. Scott et al. (abstract 1,763) reported that T allele carriers of the 3111T/C polymorphism of the clock gene had greater waist circumference among 207 individuals with histologically confirmed non alcoholic fatty liver disease, suggesting a role of the molecular clock in visceral obesity, although there was no association with other insulin resistance characteristics. (Abstract numbers refer to the ADA Scientific Sessions, *Diabetes* 57 [Suppl. 2], 2008).

Stephen Bloom (London, U.K.) discussed gut hormones regulating appetite. Bloom termed bariatric surgery the only currently available successful treatment of obesity, with the Swedish obese subjects study of 4,000 individuals showing that those who had the procedure maintained 25% weight loss after 10 years, with a 29% increase in mortality in matched (but not randomized) controls (8) and with similar suggestion of benefit in a retrospective matched control study of nearly 10,000 individuals undergoing such procedures (9). There are, however, 30–40% rehospitalization rates and 1–2% surgical mortality, leading Bloom to conclude, "It's expensive, it's dangerous, but it works." Bariatric surgery appears to act in part by increasing satiety, perhaps by induction of gut hormones. Ghrelin is produced in the stomach and stimulates appetite, with treatment useful in individuals with impaired appetite from cancer or renal failure, but levels typically are low in obesity, so blocking ghrelin may not be helpful, just as obese individuals typically have high leptin, with administration of this agent not effective when given as a single agent. Reduction in hunger after meals is not related to gastric distension or to nutrients in the circulation and appears to be caused by neural or hormonal signals derived from the gastrointestinal tract. Gut hormones do not exhibit downregulation of response with prolonged exposure. Three separate gut hormonal responses may be involved in weight regulation; short-lived reduction in appetite; chronic elevation, seen with gut disease; and an acute nausea response to very high gut signal levels.

Peptide YY (PYY) 36 was identified in 1982 as a peptide produced by gut endocrine cells and released into the circulation (10). Bloom's group subsequently found the peptide to be present in the distal gut, with malabsorption increasing delivery of nutrients to this site, which particularly increases PYY levels (11). PYY levels increase fivefold after major small bowel resection (12). After bariatric surgery with bypass, there is elevation in PYY. Infusion of PYY 3–36 similarly reduces food intake and hunger scores and inhibits the response to ghrelin, and Bloom suggests that ghrelin is not stimulated by the presence of food in the stomach but rather by changes in the release of gut hormones such as PYY; obese individuals have lower PYY release, potentially explaining weight differences between obese and lean individuals. PYY3–36 is rapidly cleared, rapid peaks lead to nausea, and appetite rebound occurs when levels fall. Glucagon-like peptide (GLP)-1 reduces food intake by central effects, while its DPP-4 degradation product and exendin 9–39 block the effect, increasing food intake. Interestingly, DPP-4 inhibition decreases formation of PYY3–36 from PYY1–36, and administration of the DPP-4 inhibitor vildagliptin has been reported to decrease PYY concentrations (13). Human pancreatic polypeptide decreases food intake in a fashion similar to that associated with PYY3–36.

Oxyntomodulin is a 37–amino acid gut peptide derived from the preproglucagon molecule, which does not bind to the glucagon receptor. Its initial discovery was based on reduction in gastric acid production. Oxyntomodulin is released in proportion to meal size, and levels are high in bowel disorders associated with decreased appetite. Chronic oxyntomodulin treatment decreases weight to a greater extent than seen in pair-fed animals, suggesting an effect in increasing energy expenditure. In a 4-week study of oxyntomodulin treatment in obese individuals, 2.5 kg weight loss was seen over 4 weeks, compared with a 0.5-kg decrease in placebo-treated patients. No evidence of escape from the effect was seen at the end of the study. Measurement of metabolic rate showed no change in basal levels, but activity-related energy expenditure was 9% greater, with a 26% increase in physical activity. An oxyntomodulin analog not susceptible to degradation by DPP-4, TKS1225 is being developed by thiakis, a biotech company that Bloom founded (and of which he is Chief Scientific Officer) focused on peptides regulating appetite. Onyntomodulin appears to act at the central GLP-1 receptor but also has action at the arcuate nucleus, leading to greater weight loss and less nausea than GLP-1. Its effect is additive to that of rimonabant.

Mary Dallman (San Francisco, CA) discussed effects of glucocorticoids on feeding. Insulin and glucocorticoids have in many ways opposite effects, inhibiting versus promoting gluconeogenesis, with anabolic versus catabolic actions, and reducing versus promoting food intake. Together, the two synergize or antagonize in a fashion ultimately increasing caloric intake. Adrenalectomized rats given increasing corticosterone doses lose weight as a result of its catabolic effect but with mesenteric fat accumulation, thus shifting caloric stores from peripheral to central sites and from muscle to fat. Fat intake is not increased in adrenalectomized diabetic animals, however, unless insulin is replaced, and fat intake is proportional to the dose of insulin administered, and corticosterone does not increase mesenteric fat in the absence of insulin, with an insulin dose-related increase in mesenteric fat. Effects of corticosterone are mediated in part by increasing dopamine levels over the shell of the nucleus accumbens (14). Behavioral actions of insulin depend on hepatic vagal afferents, with insulin increasing fat intake to a greater extent when infused into the splanchnic rather than the systemic circulation, while vagotomy increases fat intake, suggesting that hepatic vagal afferents to the brain are involved in inhibition of fat intake (15). It appears that fat intake alters c-Fos expression in brain sites such as the nucleus tractus solitaries and nucleus accumbens known to participate in pleasurable behaviors (16).

The function of this dual hormonal system may be related to the effect of stress and high glucocorticoids on behavior and autonomic outflow. High glucocorticoid levels stimulate insulin and food ingestion—a metabolic signal that in turn reduces the brain chronic stress–response network, which constitutes a biological explanation for the stressed individual feeling and, perhaps, functioning better with increasing food intake, thus leading to a learned behavioral pattern (17). Chronic corticosterone administration increases nonhypothalamic corticotropin-releasing factor (CRF) levels, while insulin increases fat stores, re-

ducing CRF expression. As another feedback loop in the stress system, sucrose and/or fat reduce the CRF, ACTH, and corticosterone responses to single or repeated acute stress. Sucrose ingestion inhibits paraventriclar nucleus CRF, so mesenteric fat mass may produce a metabolic feedback signal.

Studies of relationships between diabetes and obesity

Despres et al. (abstract 949) analyzed the relationship between waist circumference and BMI among 19,605 diabetic and 147,567 nondiabetic patients examined by almost 6,400 primary care physicians in 63 countries. Waist and BMI were strongly correlated, but at every BMI level waist circumference was greater in diabetic than in nondiabetic patients: by ~4 and 10 cm among men and women, respectively. The regression equations were as follows: for diabetic men, waist circumference (cm) = 33.3 + 2.1 × BMI (kg/m^2) + 0.12 × age (years); for nondiabetic men, waist circumference = 29.3 + 2.2 × BMI + 0.14 × age; for diabetic women, waist circumference = 39.3 + 1.8 × BMI + 0.09 × age; and for nondiabetic women, waist circumference = 29.4 + 2.0 × BMI + 0.12 × age. Measurement of waist circumference, then, adds information for characterization of patients' diabetes risk in all BMI categories. Iacobellis and Gerstein (abstract 1735) analyzed echocardiograms of 246 individuals and found that among the 58% with metabolic syndrome, epicardial fat thickness was 9.5 mm and 7.5 mm in men and women, respectively, which exceeds that in individuals without the syndrome. These data suggest a useful measure for risk stratification and, perhaps, for therapeutic interventions. Saydah and Eberhardt (abstract 993) analyzed data from 1999–2004 National Health and Nutrition Examination Surveys and found a sedentary lifestyle in 35% of known diabetic subjects but 26% of pre-diabetic subjects, 24% of those with undiagnosed diabetes, and 24% of those without diabetes; 7, 4, 6, and 2% of the groups, respectively, reported an inability to vigorously exercise, while 25, 17, 20, and 14% reported watching television at least 5 h daily.

Dyson et al. (abstract 1703) compared a low-carbohydrate (CHO) diet with a standard diet in 13 type 2 diabetic and 13 nondiabetic obese individuals with BMI 35 kg/m^2. Although weight loss was greater with the low-CHO diet at 3 months, at 2 years neither group had sustained weight loss or change in blood pressure or lipids, or, among the diabetic patients, in glycemia. Buscemi et al. (abstract 1746) randomized 20 overweight or obese women to two different hypocaloric diets: a low-CHO "Atkins" diet vs. a Mediterranean diet, with 8 vs. 5 kg weight loss at 60 days but 57% decreased vs. 41% increased brachial artery flow-mediated dilation at 5 days. The low-CHO diet increased interleukin-6 and 8-iso-prostaglandin F2α at 5 days, suggesting that it may acutely cause inflammation and oxidative stress. Kodama et al. (abstract 1703) presented a meta-analysis of 24 studies of type 2 diabetic patients in whom the dietary CHO-to-fat ratio was measured, showing no effect of the ratio on fasting glucose or A1C but an association of a high CHO-to-fat ratio with higher fasting insulin and higher postmeal glucose and 2-h insulin levels, suggesting reduced insulin sensitivity.

Menchikova et al. (abstract 66) compared seven older overweight to obese individuals undergoing caloric restriction with 8 kg weight loss with eight individuals beginning an exercise program and showed a similar (22 vs. 26%) improvement in insulin sensitivity using a hyperinsulinemic-euglycemic clamp. Vastus lateralis muscle biopsies showed similar mitochondrial content (based on cardiolipin content), but NADH oxidase, a measure of activity of the electron transport chain, increased only with exercise, suggesting that the apparent mitochondrial dysfunction of aging (and of insulin-resistant states) is a function of physical inactivity, while weight loss but not exercise increased citrate synthase activity, which is the regulatory step of the Krebs cycle. Paniagua et al. (abstract 1687) studied 11 abdominally obese offspring of obese type 2 diabetic parents on three 28-day diets (one high in saturated fat, one high in monounsaturated fat, and one high in CHO) and found lower postprandial free fatty acids and higher glucose with the high CHO diet, whereas glucose was lower and fatty acid levels were higher with the saturated fat diet. Lipid oxidation was lower with the high-CHO diet, which was associated with higher adipose tissue uncoupling protein-2 expression. Postprandial oxidized LDL levels were lower with the high monounsaturated fat diet.

Dietary fructose appears to be an important mediator of insulin resistance. Nagai et al. (abstract 1514) noted that peroxisome proliferator–activated receptor γ coactivator (PGC)-1β is a transcriptional coactivator for sterol response element binding protein-1c, the transcriptional regulator of hepatic lipogenesis. They reduced PGC-1β expression with targeted antisense oligonucleotides in the liver and adipose tissue of rats fed high-fructose diets for 4 weeks and found 20 and 70% reductions in plasma and liver triglyceride, respectively, and lower fasting glucose and insulin levels with increased hepatic and peripheral insulin sensitivity, suggesting that PGC-1β may be a therapeutic target for treatment of insulin-resistant states including nonalcoholic fatty liver disease, diabetes, and hypertriglyceridemia. Le et al. (abstract 35), noting that consumption of sugar-sweetened beverages containing fructose increased by ~135% from 1977 to 2001, studied 11 male offspring of type 2 diabetic patients versus 8 control subjects after standard and high-fructose diets. Fasting triglyceride increased 81 vs. 32% and insulin 17 vs. 30%, respectively, with similarly increased urate and decreased free fatty acids and ketones in both groups. Hepatic lipid content increased 103 vs. 73%. Hepatic insulin sensitivity decreased 13%, and alanine aminotransferase increased 88% in the offspring while not changing in controls. Stanhope et al. (abstract 352) randomized 23 overweight or obese individuals to fructose- or glucose-sweetened beverage consumption for 10 weeks. Abdominal computerized tomography scanning showed an increase in fat area with fructose, and fasting glucose and insulin increased 5 and 12%, with reduction in insulin sensitivity index, measured from deuterated glucose disposal and net insulin output during a glucose tolerance test; these parameters were unchanged with glucose-sweetened beverages. Yeung et al. (abstract 353) noted that the distinctive photosynthetic mechanism of corn and sugar cane selectively concentrates the 13-C isotope of carbon, measuring the C13-to-C12 ratio using mass spectroscopy in 131 individuals. Comparing those consuming >2–4 servings/week vs. ≤1–3 servings/month of sodas or sweetened juices, C13 increased with increasing consumption of these beverages and was significantly associated with waist circumference and BMI.

Gillum et al. (abstract 1552) noted that the endocannabinoid precursor N-acylphosphatidyl-ethanolamines are synthesized in the small intestine in response to ingested fat and that plasma and lymph

levels increase 50–100% following food or intraduodenal lipid infusion, with systemic administration reducing food consumption 90% and suppressing hypothalamic transcription of NPY 64% in a rodent model and with intracerebroventricular administration reducing food intake 56%, suggesting potential as a therapeutic target. Scheen et al. (abstract 101) presented 2-year results of 599 individuals receiving 20 mg daily of the cannabinoid 1 receptor antagonist rimonabant along with those of 305 receiving placebo, finding 5.5 vs. 1.2 kg weight loss and 6 vs. 2 cm reduction in waist circumference, with improvement in fasting glucose and insulin and in glucose tolerance. Nausea occurred in 13 vs. 4%, anxiety in 5 vs. 3%, and depression in 4 vs. 2%, with most of these side effects observed during the first year of treatment. Hollander et al. (abstract 330) randomized 368 type 2 diabetic patients treated with insulin monotherapy to 20 mg daily of rimonabant versus placebo for 48 weeks, with baseline a A1C of 9.1% and BMI 35 kg/m^2, and found that A1C decreased 0.9 vs. 0.2%, weight decreased 2.5 kg vs. an increase of 0.1 kg, HDL cholesterol increased 3% vs. a decrease of 7%, and triglyceride decreased 4% vs. an increase of 8%. Nausea occurred in 11 vs. 2%, anxiety in 14 vs. 4%, and depression in 10 vs. 4%.

Garvey et al. (abstract 390) randomized 206 diabetic patients to a combination of 15 mg phentermine in the morning (typical dose 15–37.5 mg daily), and 100 mg topiramate in the evening (typical anticonvulsant dose 100–200 mg daily) vs. placebo, with a 16-week A1C decrease 1.1 vs. 0.6% and weight loss 6 vs. 1%; no treatment-related serious adverse events were reported. Karnieli et al. (abstract 430) implanted a gastric stimulator in 10 obese type 2 diabetic patients, applying gastric contractility modulation signals to the antrum of the stomach during meals. At 24 weeks, A1C decreased from 8.1 to 7.3%, fasting glucose from 174 to 143 mg/dl, homeostasis model assessment of insulin resistance from 10.3 to 6.2, systolic blood pressure from 134 to 126 mmHg, weight from 103 to 98 kg, and waist circumference from 121 to 115 cm, with HDL cholesterol increasing ~9%. Kipnes et al. (abstract 573) used the same device in 12 type 2 diabetic patients for 12 weeks, with a decrease in A1C from 8.5 to 7.6% and in weight from 106 to 103 kg. The weight change did not correlate with that in A1C, perhaps indicating a weight-independent mechanism of improved glycemia.

Several studies addressed aspects of bariatric surgery. Bose et al. (abstract 1440) compared nine type 2 diabetic women 1 month after Roux-en-Y gastric bypass surgery with 10 having diet-induced weight loss, both by ~10 kg, and found similar improvement in fasting glucose and insulin but greater reduction in post–glucose load glycemia and greater increase in GLP-1, which may therefore be a consequence of the surgery rather than of the weight loss. Schernthaner et al. (abstract 257) studied 95 patients with a mean 39 kg weight loss after bariatric surgery, finding an increase in circulating endothelial precursor cells, potentially reducing atherogenesis. Tarnoff et al. (abstract 105) randomized 11 type 2 diabetic patients, 7 receiving metformin alone and 4 also receiving a sulfonylurea, to endoscopic insertion of a 61-cm duodenal-jejunal bypass impermeable fluoropolymer sleeve, fastened with a barbed metal anchor at the duodenal entrance—versus 5 having sham endoscopy. At 1 week, fasting glucose decreased 52 vs. increasing 17 mg/dl, respectively, with mean 7-point daily glucose profile decreasing 55 vs. increasing 1 mg/dl. At 12 weeks, one versus three continued to require hypoglycemic medication, with weight loss 8.5 vs. 7.8 kg. At 31 weeks, eight patients receiving the sleeve had a decrease in A1C of 2.9% from 8.9% at baseline, while three sham-treated patients had a 0.8% fall. The sleeve came loose in three patients, requiring retrieval through endoscopy; eight had abdominal pain; three had diarrhea; three had vomiting; two had hypoglycemia; and one had nausea. Bruno et al. (abstract 1741) found that two serum markers of bone turnover increased in 20 patients 18 months following Roux-en-Y gastric bypass surgery: bone-specific alkaline phosphatase from 18 to 22 ng/ml and N-telopeptide cross-linked type 1 collagen from 11 to 17 nmol/l; however, 25-hydroxy vitamin D increased from from 17 to 26 ng/ml (presumably reflecting supplementation). Both of these studies suggest that there may be harm as well as benefit from bariatric surgery, which is in keeping with Bloom's observations.

Amylin and pramlintide

Asmar et al. (abstract 1446) compared the effects of human amylin, pramlintide, and GLP-1 on gastric emptying, appetite, and food intake, finding similar reduction in all parameters in 11 type 1 diabetic individuals. There was greater gastric emptying suppression with GLP-1 than with amylin but similar reduction in food intake in 12 nondiabetic individualsl; the GLP-1 resistance in type 1 diabetes perhaps indicates action in part via stimulation of amylin secretion. Pramlintide had effects similar to those of human amylin. King et al. (abstract 549) reported use of continuous glucose monitoring to titrate prandial insulin dosing in nine pump-treated type 1 diabetic patients before and after addition of 60 μg pramlintide before each meal. Insulin dosing was adjusted to have fewer than 20% of glucose readings >170 mg/dl, fewer than 10% <70 mg/dl, and 4-h postmeal glucose within 20% of premeal glucose. At 5 weeks, A1C decreased from 7.4 to 7.1%, weight decreased 1 kg, and basal insulin decreased 11%, while the carbohydrate–to–prandial insulin dose ratio increased 8%; they suggest that in this setting prandial insulin bolus doses should not be reduced. Huffman and McLean (abstract 199) treated 11 type 1 diabetic individuals with continuous subcutaneous pramlintide infusion using an insulin pump at nine μg/h basally, titrating to 60 μg three times daily before meals over 3 weeks. Baseline vs. 12-week fasting glucose was 187 vs. 182 mg/dl, but there was a postprandial glucose increment of 24 mg/dl vs. a decrement of 17 mg/dl, with a 26% reduction in the bolus insulin–to–carbohydrate ratio. A1C decreased from 8.2 to 7.7%, and there was mean 1.4 kg weight loss, suggesting that this could be a potentially useful approach to pramlintide administration.

In a study of type 2 diabetic patients, Riddle (abstract 524) randomized 61 individuals receiving insulin glargine titrated to target fasting glucose 70–100 mg/dl to 120 μg pramlintide three times daily versus placebo for 16 weeks, finding the insulin dose to increase from 51 to 65 vs. from 48 to 57 units daily. Fasting glucose decreased from 144 to 81 vs. from 122 to 85 mg/dl, the postprandial glucose increment decreased from 55 to 30 vs. from 61 to 54 mg/dl, and A1C was reduced from 8.7 by 1.2% vs. from 8.2 by 0.5%. Body weight decreased 1 kg versus increasing 1 kg, hypoglycemia occurred in 57 vs. 55% of subjects, and nausea occurred in 39 vs. 18%. Given the small numbers and somewhat dissimilar baseline glycemia, the study can only be regarded as suggestive of benefit.

Amylin may be particularly important as a component of multiple drug regi-

mens, with interesting evidence that it may restore leptin responsiveness in obesity (18); a number of studies presented at the ADA assessed amylin-related treatments as approaches to obesity management. Nicandro et al. (abstract 1543) described phase one studies with AC2307, an amylin mimetic with increased duration of action in obese nondiabetic individuals, showing reduction in food intake. Trevaskis et al. (abstract 192) administered amylin, leptin, and protein YY (3–36) to diet-induced obese rats for 4 weeks. As single agents, amylin and leptin led to 8 and 4% weight loss, respectively, while there was no weight loss with PYY. Addition of PYY to amylin and leptin led to 10 and 9% weight loss, respectively. Amylin plus leptin led to 20% weight loss, and the triple combination led to 24% weight loss, with the latter two regimens reducing hepatic expression of the lipogenic genes stearoyl-CoA desaturase-1 and fatty acid synthase, as well as reducing fat mass to undetectable levels without reducing lean mass. Weyer et al. (abstract 1738) treated 177 overweight or obese individuals on a 40% calorie-deficit diet with 180 μg pramlintide twice daily for 2 weeks and then 360 μg twice daily (twice the current maximal daily dose) for 4 weeks. A total of 139 subjects completed this period and achieved 2–8% weight loss and were randomized to add metreleptin 5 mg twice daily, continue pramlintide alone, or change to 5 mg metreleptin twice daily alone. Of 93 evaluable participants at 20 weeks, weight loss from baseline was 13, 8, and 8%, with weight loss stabilizing after 12 weeks in the monotherapy groups but continuing at an average rate of 0.2 kg/week in the combination group. Aronne et al. (abstract 99) randomized 244 overweight or obese individuals to placebo or to 120 μg pramlintide three times daily alone or in combination with 10 mg sibutramine daily or 37.5 mg phentermine daily for 24 weeks, finding weight loss in evaluable participants of 2.1, 3.6, 11.3, and 11.3 kg, with 28, 36, 78, and 82% of subjects, respectively, achieving ≥5% weight loss.

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References

1. Eva C, Serra M, Mele P, Panzica G, Oberto A: Physiology and gene regulation of the brain NPY Y1 receptor. Front Neuroendocrinol 2006;27:308–339
2. Abe K, Tilan JU, Zukowska Z: NPY and NPY receptors in vascular remodeling. Curr Top Med Chem 2007;7:1704–1709
3. Kuo LE, Kitlinska JB, Tilan JU, Li L, Baker SB, Johnson MD, Lee EW, Burnett MS, Fricke ST, Kvetnansky R, Herzog H, Zukowska Z: Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. Nat Med 2007;13:803–811
4. Large V, Hellström L, Reynisdottir S, Lönnqvist F, Eriksson P, Lannfelt L, Arner P: Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function. J Clin Invest 1997;100:3005–3013
5. Dahlman I, Arner P: Obesity and polymorphisms in genes regulating human adipose tissue. Int J Obes (Lond) 2007; 31:1629–1641
6. Dahlman I, Dicker A, Jiao H, Kere J, Blomqvist L, van Harmelen V, Hoffstedt J, Borch-Johnsen K, Jorgensen T, Hansen T, Pedersen O, Laakso M, Arner P: A common haplotype in the G-protein-coupled receptor gene GPR74 is associated with leanness and increased lipolysis. Am J Hum Genet 2007;80:1115–1124
7. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Näslund E, Britton T, Concha H, Hassan M, Rydén M, Frisén J, Arner P: Dynamics of fat cell turnover in humans. Nature 2008; 453:783–787
8. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM: Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007 Aug 23;357:741–752
9. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC: Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–761
10. Tatemoto K: Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion. Proc Natl Acad Sci U S A 1982; 79:2514–2518
11. Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR: Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology 1985;89:1070–1077
12. Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS, Bloom SR: Release of peptide YY (PYY) after resection of small bowel, colon, or pancreas in man. Surgery 1987;101:715–719
13. Vella A, Bock G, Giesler PD, Burton DB, Serra DB, Saylan ML, Deacon CF, Foley JE, Rizza RA, Camilleri M: The effect of dipeptidyl peptidase-4 inhibition on gastric volume, satiation and enteroendocrine secretion in type 2 diabetes: a double-blind, placebo-controlled crossover study. Clin Endocrinol (Oxf) 2008; 69:737–744
14. Barrot M, Abrous DN, Marinelli M, Rougé-Pont F, Le Moal M, Piazza PV: Influence of glucocorticoids on dopaminergic transmission in the rat dorsolateral striatum. Eur J Neurosci 2001;13: 812–818
15. Warne JP, Foster MT, Horneman HF, Pecoraro NC, Ginsberg AB, Akana SF, Dallman MF: Hepatic branch vagotomy, like insulin replacement, promotes voluntary lard intake in streptozotocin-diabetic rats. Endocrinology 2007;148:3288–3298
16. Warne JP, Horneman HF, Ginsberg AB, Pecoraro NC, Foster MT, Akana SF, Dallman MF: Mapping brain c-Fos immunoreactivity after insulin-induced voluntary lard intake: insulin- and lard-associated patterns. J Neuroendocrinol 2007;19: 794–808
17. Dallman MF, Warne JP, Foster MT, Pecoraro NC: Glucocorticoids and insulin both modulate caloric intake through actions on the brain. J Physiol 2007;583: 431–436
18. Roth JD, Roland BL, Cole RL, Trevaskis JL, Weyer C, Koda JE, Anderson CM, Parkes DG, Baron AD: Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies. Proc Natl Acad Sci U S A 2008; 105:7257–7262