New Pathogenic Concepts in Type 2 Diabetes Mellitus

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INTRODUCTION

Optimal management of type 2 diabetes mellitus (DM) requires an understanding of the pathophysiology of the disease. In the previous manual of this volume, the classic defects of insulin resistance and inadequate insulin secretion were reviewed. This manual reviews the recent findings that the incretin system (gut hormones involved in glucose metabolism) and adipokines (cytokines derived from adipose tissue) play an important role in many of the abnormalities seen in patients with type 2 DM. Adipokines may also be involved in vascular inflammation, endothelial dysfunction, and thrombosis, all of which have been linked to atherosclerosis and vascular events.

INCRETIN INFLUENCES ON GLUCOSE HOMEOSTASIS

Incretin hormones are gut peptides produced by enteroendocrine cells and secreted in response to feeding. Incretins modulate pancreatic hormone secretion in a glucose-dependent fashion to help maintain glucose homeostasis (Figure 1). The significant incretin hormones identified to date are glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide; GIP) and glucagon-like peptide-1 (GLP-1).

Initial interest in gut hormones began at the turn of the 20th century, with the discovery of “secretin” by Bayliss and Starling. Interest was rekindled in the 1960s with the development of radioimmunoassays for insulin, which allowed precise quantification of serum insulin levels during different physiologic conditions. An early and important observation was that for the same serum glucose level, insulin levels were 50% to 70% higher when the glucose load was administered orally as opposed to intravenously. It was subsequently discovered that the gut-derived hormones GIP and GLP-1 mediated this augmented response to feeding, which is now known as the incretin effect. Incretin actions that have been documented in humans are shown in the Table.

GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE SYNTHESIS, SECRETION, AND METABOLISM

GIP was initially discovered in the 1930s as a substance that decreased gastric acid secretion and motility in the denervated dog stomach and was subsequently shown to be the first substance with incretin activity in humans. GIP is a 42-amino acid peptide hormone synthesized in and secreted from the enteroendocrine K cells, which exist throughout the duodenum and jejunum but are found in highest numbers in the proximal duodenum. GIP is cleaved from a 153-amino acid precursor, preproGIP, by prohormone convertase 1/3 and is secreted in response to the presence of fats and, to a lesser extent, carbohydrate in the gut. Once released, circulating GIP\(_{1-42}\) has a very short half-life of approximately 7 minutes and is rapidly degraded via N-terminal cleavage by dipeptidyl peptidase-4 (DPP-4). This short half-life may play a role in limiting systemic exposure and makes the therapeutic use of GIP difficult. Both the active hormone and its inactive metabolite, GIP\(_{3-42}\), are renally excreted.

Physiologic Actions

The primary action of GIP is to amplify glucose-dependent insulin secretion. This action is mediated by a highly specific GIP receptor on the pancreatic beta cell. The GIP receptor is a type II G protein-coupled receptor belonging to the same superfamily as secretin, glucagon, and vasoactive intestinal peptide. Binding of GIP to its receptor induces production of cyclic adenosine monophosphate (cAMP) by adenylate cyclase–activating protein kinase. The net effect is membrane depolarization as a result of inhibition of ATP-sensitive potassium channels, increased amplitude of depolarization-evoked calcium ion flow via opening of L-type calcium channels, and potentiation of calcium-mediated exocytosis of insulin via a non–calcium concentration-dependent mechanism.
The GIP receptor is also present on adipocytes, suggesting that GIP may have a role in adipose metabolism. Indeed, early experiments in cell culture and animals showed that GIP exposure (via infusion or incubation) resulted in an increase in lipoprotein lipase, a decrease in circulating triglycerides, increased fatty acid accumulation by adipocytes, and increased incorporation of labeled glucose into lipids within the adipocyte. Conversely, in experiments with GIP receptor knockout mice, which are unable to respond to circulating GIP, the mice demonstrated a decrease in adiposity while on a high-fat diet and preferred use of fat as an energy source rather than accumulation in adipocytes. When the GIP receptor knockout mice were crossed with leptin-deficient ob/ob mice, the resulting double knockout mice had reduced weight gain and reduced adiposity as compared with the ob/ob mice with normal GIP receptors, despite no change in food intake.

**Impaired Effects in Type 2 DM**

Most studies have found the levels of circulating GIP in patients with type 2 DM to be normal in both the fasting and postprandial states. However, in patients with type 2 DM and in many nondiabetic first-degree relatives of patients with type 2 DM, there is a decreased incretin response to GIP. The cause of this resistance has been difficult to elucidate in animal models as well as in human studies. Although initially suggested to be a result of a defect in the GIP receptor, no polymorphism yet identified has been linked with diabetes or defective signaling of the receptor.

Another suggested mechanism is rapid desensitization or decreased expression of the receptor. One suggested pathway is hyperglycemic suppression of peroxisome proliferator–activated receptor gamma (PPARγ) transcription. Such an inducible defect in receptor expression is compatible with the finding of a defect in the responsiveness to GIP in other types of diabetes. Also strongly supporting this mechanism is the recent finding that in subjects with type 2 DM, near euglycemia restores GIP sensitivity. This resistance to the incretin effect of GIP could play a role in the relative insulin deficiency..

**Table. Incretin Actions Documented in Humans**

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td></td>
</tr>
<tr>
<td>Increase glucose-dependent insulin secretion</td>
<td>+</td>
</tr>
<tr>
<td>Inhibit glucagon secretion</td>
<td>+</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Inhibit gastric emptying</td>
<td>+</td>
</tr>
<tr>
<td>Increase gastric acid production</td>
<td>+</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Inhibit food intake</td>
<td>+</td>
</tr>
<tr>
<td>Promote postprandial satiety and weight loss</td>
<td>+</td>
</tr>
</tbody>
</table>

GLP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1.

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**Figure 1.** Binding of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to their respective receptors causes increased formation of cyclic adenosine monophosphate (cAMP), with resultant activation of protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factors (cAMP-GEF2 in particular, also known as Epac2). Increased PKA activation results in decreasing activation of adenosine triphosphate (ATP)-sensitive potassium channels (KATP channel), inhibition of delayed rectifying potassium channels (Kv channel), and increased activity of L-type calcium channels. cAMP-GEF2 promotes release of intracellular calcium stores via calcium-induced calcium release to further stimulate calcium-dependent exocytosis. Increased intracellular calcium and glucose accelerate ATP generation, thus increasing substrate for cAMP production and providing energy for exocytosis. cAMP = adenylate cyclase; ADP = adenosine diphosphate; ER = endoplasmic reticulum; G = G protein–coupled receptor; IP3 = inositol 1,4,5-trisphosphate; RYR = ryanodine receptor. (Adapted with permission from Baldissera FGA, Holst JJ. Glucagon-related peptides in the human gastrointestinal mucosa. Diabetologia 1984;26:223–8.)
noted in type 2 DM. It may also help explain the delay in postprandial insulin release seen in early diabetes and prediabetic states.

**GLUCAGON-LIKE PEPTIDE-1**

*Synthesis, Secretion, and Metabolism*

GLP-1 has been far more studied and has more therapeutic potential than GIP. GLP-1 is derived from proglucagon, a large peptide that contains the amino acid sequences for glucagon, GLP-1, GLP-2, and several other peptides. Proglucagon is found in many tissues and is cleaved variably, in a tissue-specific manner dependent on which prohormone convertase is present.28–30 In the enteric neurons of the distal ileum and colon, proglucagon converts GLP-1 and GLP-2.30 In contrast to the pancreas, GLP-1 is cleaved within the L cell and undergoes N-terminal truncation and amidation to produce GLP-1_{7-36}-amide, which is the physiologic incretin. Of the cleavage products of proglucagon produced in the L cells, only GLP-1 has been established as an incretin.3 GLP-1_{7-36}-amide has a very low affinity for the GLP-1 receptor and acts as an incretin only at supraphysiologic doses.29,32,33 GLP-1_{7-36}-amide rises precipitously with meal ingestion, whereas serum levels of GLP-1_{1-36}-amide, an active intermediate in the amidation reaction, remain relatively stable.33 All active compounds described from this point are collectively referred to as GLP-1.

GLP-1 levels begin to rise shortly after food ingestion. The mechanism of GLP-1 release in humans has not been fully elucidated, although there is evidence for a neural stimulus, particularly in the early phase of GLP-1 secretion.4,34 Direct contact of nutrients with the L cells of the duodenum stimulates brisk GLP-1 release.35 However, GLP-1 levels begin to rise shortly after food ingestion, long before nutrient transit to the location of most of the L cells in the distal ileum and colon.6,38 In procedures that shorten the transit of nutrients (eg, Roux-en-Y gastric bypass, jejunocolic bypass, biliopancreatic bypass surgery for morbid obesity), the release of GLP-1 is increased in the immediate postoperative period.6,8,37,38 Like GIP, GLP-1 is rapidly degraded by DPP-4, producing the degradation products GLP-1_{9-37} and GLP-1_{9-36}-amide.9 GLP-1 and its degradation products are renally cleared, with an effective half-life of 2 to 5 minutes.9,34

**Physiologic Actions**

Much like GIP, GLP-1 acts through a highly specific receptor on the beta cell, and the postreceptor cascade of events is thought to be the same, with the only difference being the receptor itself.13 When both receptors are activated, there is an additive effect. On a per molecule basis, GLP-1 is a more potent insulin secretagogue than GIP. However, at circulating physiologic levels, GIP and GLP-1 contribute equally to the incretin effect in normal individuals.37,38

GLP-1 is also essential for normal glucagon regulation. After ingestion of a carbohydrate meal, glucagon levels decrease dramatically in nondiabetic subjects,39 an effect that cannot be explained by increased insulin levels alone.40 In the postprandial period, GLP-1 suppresses glucagon release from the pancreatic alpha cells and this action is blocked by exendin_{9-39}-amide, an antagonist at the GLP-1 receptor.41 The postreceptor cascade for this action is not fully understood.

In the central nervous system (CNS), GLP-1 promotes satiety. Although much of the research in this area has been done in rats using intraventricular infusion of GLP-1,31 evidence from human trials using peripheral infusion of GLP-1 also demonstrated decreased food intake, without food aversion.42 Another mechanism proposed and investigated in rats allows peripheral GLP-1 to gain access to the CNS directly via the subfornical organ and the area postrema.43 Anatomically, these areas of the brain are very similar in rats and in humans and have been implicated in the action of other satiety signals and in drinking behavior.44,45

**Impaired Effects in Type 2 DM**

Unlike GIP, the incretin response to GLP-1 is preserved in type 2 DM,22 but there is a small decrement in the postprandial release of GLP-1 in persons with impaired glucose tolerance (IGT) or type 2 DM as compared with normoglycemic controls.46–48 Individuals with IGT and type 2 DM demonstrate reduced GLP-1 responses about 60 to 120 minutes following ingestion of a meal.46–48 Thus, in the late phase following a meal, a relative hypoinsulinemia results that is due, at least in part, to the decrease in GLP-1 augmentation of insulin release.

Much like the insulin incretin effect, the glucagonostatic effect of GLP-1 is glucose-dependent and is decreased in type 2 DM.41 The high glucagon levels promote glycogenolysis in the fed state, contributing to postprandial hyperglycemia. High insulin levels, either endogenous or pharmacologic, decrease the glycemic excursion but do not reduce the hyperglucagonemia.49

**THERAPEUTIC POTENTIAL**

Therapeutically, incretins represent a new class of antihyperglycemic therapy in type 2 DM. Early studies
with native GLP-1 showed improved glycemic control, but therapeutic use was hampered by the short half-life of the hormone. Exenid-4, a GLP-1 receptor agonist isolated from the saliva of the Gila monster (Heloderma suspectum), resists DPP-4 degradation and as a result has a longer biologic half-life. Exenatide, a synthetic form of exendin-4 that mimics the biologic actions of native GLP-1, has been approved by the U.S. Food and Drug Administration (FDA) for treatment of type 2 DM. As would be expected from a GLP-1 receptor agonist, postprandial glucagon levels are reduced and insulin responses are normalized. Although there is interest in the therapeutic potential of GIP, it is unclear how to restore GIP sensitivity in type 2 DM, and pharmacologic agents targeting the incretin system have yet to show a benefit beyond that explained by their actions on GLP-1. Furthermore, given the ana- bolic effect of GIP on adipocytes in an animal model, perhaps visceral adipocytes in particular, it is unclear whether enhancement or blockade of GIP would be of benefit in management of type 2 DM.

**ROLE OF ADIPOSE TISSUE AND ENDOTHELIAL DYSFUNCTION IN TYPE 2 DIABETES**

Normal endothelial function protects against atherosclerosis and is involved in the regulation of blood pressure so as to assure tissue perfusion while avoiding hypertensive damage. Many complications of both type 2 DM and metabolic syndrome, particularly atherosclerosis, are associated with derangements of endothelial function, and endothelial dysfunction has been documented in patients with type 2 DM as well as individuals with insulin resistance or at high risk for developing type 2 DM. Major influences on endothelial function as well as glucose homeostasis are products of visceral adipose tissue, known in the aggregate as adipokines. Conceptually, one can think of “healthy” adipose tissue as producing adipokines that are anti-inflammatory and that promote glucose and fatty acid oxidation, and “unhealthy” adipose tissue (as is encountered in type 2 DM and metabolic syndrome) as producing adipokines that promote inflammation and thrombosis.

**NORMAL ENDOTHELIAL FUNCTION**

Normal endothelial cells generate both vasodilatory and vasoconstrictive signal molecules locally. The most potent vasodilatory influence is nitric oxide (NO), which is produced when l-arginine is oxidized by the NADPH-dependent NO synthase (NOS). NO stimulates guanylate cyclase, thereby increasing the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP generation lowers the intracellular calcium ion concentration, and in vascular smooth muscle this effect causes vascular relaxation. NO also inhibits platelet aggregation by a cGMP-dependent mechanism as well as inhibits the proliferation of smooth muscle cells.

Insulin promotes NO synthesis via activation of the PI3K and Akt pathways, and it stimulates recruitment and growth of vascular smooth muscle cells via activation of MAPK. Impaired insulin action in insulin-resistant states such as type 2 DM and metabolic syndrome frequently results in derangements of both the PI3K and Akt pathways.

**ENDOTHELIAL DYSFUNCTION**

Endothelial dysfunction results from increased generation of free radicals exacerbated by impaired generation of antioxidant defense; the resultant state of increased oxidative stress promotes or causes hypertension, hypercoagulability, and vascular inflammation. Excessive generation of reactive oxygen species by endothelium depletes NO and is thought to be of primary importance in DM-associated vascular pathophysiology. Superoxide increases markedly during episodic hyperglycemia and is generated by the action of multiple NADPH-dependent oxidases, including xanthine oxidase, lipooxygenase, mitochondrial oxidases, and NOS. Superoxide reduces NO bioactivity and interferes with NO synthesis. Furthermore, superoxide stimulates vascular smooth muscle cell proliferation and recruits inflammatory modulators to vessel walls. Superoxide dismutase, which normally degrades superoxide and thereby protects against oxidative stress, is depleted and subnormally active. Additionally, asymmetric dimethylarginine, an endogenous competitive inhibitor of NOS, is significantly increased in DM-associated hypertension.

In the presence of hyperglycemia, excessive glycolysis leads to intracellular accumulation of diacylglycerol, which activates PKC. Activation of PKC reduces NOS activity and augments production of the potent vasoconstrictor endothelin-1. PKC also stimulates the expression of vascular endothelial growth factor, epithelial growth factor, and transforming growth factor, which promote growth and proliferation of vascular smooth muscle cells. Peptides exposed to hyperglycemia can form nonenzymatically glycated advanced glycosylation end products, which consume NO and
increase susceptibility of low-density lipoprotein (LDL) cholesterol to oxidation. Advanced glycosylation end products have also been shown to increase generation of inflammatory cytokines (eg, interleukin-1 [IL-1], tumor necrosis factor-α [TNF-α]) and to stimulate growth and proliferation of vascular smooth muscle cells. Additionally, excessive intracellular glucose activates the aldose reductase pathway, in which glucose is reduced to sorbitol at the expense of NADPH depletion. Consequently, NADPH-dependent NOS and glutathione reductase functions are impeded.

ADIPOKINES

Rather than being an inert storage bin for triglycerides, adipose tissue is now known to be a metabolically active organ that secretes bioactive peptides, or adipokines, that influence inflammation, coagulation, and endothelial function as well as glucose and lipid metabolism (Figure 2). Well-characterized adipokines include leptin, adiponectin, and resistin; each has been implicated in the pathogenesis of metabolic syndrome, type 2 DM, and increased cardiovascular risk even independent of type 2 DM. Inflammatory cytokines, notably IL-6 and TNF-α, derive from macrophages in visceral adipose tissue and induce hepatic production of fibrinogen and C-reactive protein, the latter of which is a well-recognized independent predictor of risk for type 2 DM and cardiovascular disease (Figure 3). The prothrombotic plasminogen activator inhibitor 1, an inhibitor of thrombolysis, is also produced by visceral adipose tissue, elevated in metabolic syndrome and type 2 DM, and associated with increased risk for type 2 DM.

Most adipokines are increased in obesity-related insulin resistance in both humans and animal models, with visceral fat accounting for more than subcutaneous adipose tissue. Weight reduction is associated with reduced serum levels of IL-6, TNF-α, resistin, and leptin and with increased levels of adiponectin. A focus on the known actions of the adipokines is important in appreciating the contribution of visceral adipose tissue to health and its deranged function in the pathophysiology of metabolic syndrome and type 2 DM.

Adiponectin

Adiponectin is a 247-amino acid peptide produced uniquely by mature adipocytes. Important effects of adiponectin include increased insulin sensitivity with improved GLUT-4–mediated glucose transport and glucose oxidation by myocytes, improved glucose and fatty acid uptake by adipocytes, and suppressed hepatic gluconeogenesis and glycogenolysis. As compared with nondiabetic control subjects, patients with type 2 DM have decreased serum adiponectin levels.

Serum adiponectin circulates as a full-length peptide (fAd) and as a proteolytic cleavage fragment consisting of the globular C-terminal domain (gAd), which may have enhanced bioactivity. Two receptors for adiponectin have been described, with different affinity for the 2 circulating forms of adiponectin. The adipoR1 receptor, which is most abundant in skeletal muscle, has a high affinity for gAd but very low affinity for fAd. The adipoR2 receptor, which is mainly expressed in the liver, has intermediate affinity for both forms of adiponectin. Vascular endothelium predominantly expresses mRNA for the adipoR1 receptor, suggesting a signaling role for gAd in vascular tissue.

Adiponectin and endothelial function. Human and animal studies have established a link between adiponectin and endothelial function. Human studies measuring blood flow in the forearm during reactive hyperemia show a strong direct correlation between adiponectin and endothelium-dependent vasodilation. Knockout mouse models devoid of adiponectin expression show severe derangement of endothelial function and associated smooth muscle hyperproliferation and intimal thickening. In one study, intimal thickening was attenuated when fAd adiponectin was experimentally replaced. In another study, a mouse model with total apolipoprotein E deficiency, usually associated with severe atherosclerosis, demonstrated a 30% decrease in plaque formation, compared with control mice, after being transfected with adiponectin-expressing adenovirus.
Adiponectin and inflammation. Adiponectin favorably modulates the interactions of vascular and inflammatory cells so as to minimize atherosclerotic damage. The fAd variant of adiponectin inhibits the expression of adhesion molecules (vascular cell adhesion molecule-1 [VACM-1], E-selectin, and intercellular adhesion molecule-1 [ICAM-1]) on the luminal surface of endothelial cells. The adhesion molecules normally recruit inflammatory cells to a “foothold” in lipid-laden plaque, so reduced expression of these molecules results in less inflammatory plaque. In addition, fAd suppresses leukocytic colony formation, reduces phagocytic activity, and reduces macrophage secretion of TNF-α. Furthermore, gAd inhibits the generation of reactive oxygen species within endothelial cells, resulting in reduced oxidation of LDL cholesterol. Oxidation of LDL cholesterol is regarded as being of key importance in the genesis of inflammatory atherosclerotic plaque.

Adiponectin and insulin sensitivity. Adiponectin was first linked to insulin sensitivity in 2001. gAd increases the rate of skeletal muscle fatty acid oxidation, an event indirectly linked to lower plasma glucose concentration. The connection between fatty acid oxidation and glucose homeostasis is that fatty acid oxidation reduces the intracellular triglyceride content; high levels of muscle triglyceride are known to interfere with insulin-stimulated PI3K activation of GLUT-4 translocation and facilitated glucose transport. The net result of an adiponectin-poor, intramyocellular-enriched triglyceride state is muscle resistance to insulin action.

Additionally, adiponectin activates PPARα and PPARγ, which are ligand-activated transcription factors and members of the superfamily of nuclear hormone receptors regulating glucose and lipid metabolism. In animal models, administration of adiponectin results in accelerated fatty acid oxidation and energy consumption via PPARγ activation. Increased fatty acid oxidation leads to depletion of intracellular triglycerides and free fatty acids in liver and skeletal muscle cells, which is associated with improved insulin action in these tissues.

Adiponectin also improves insulin sensitivity via the activation of AMP-activated protein kinase (AMPK). Skeletal muscle, liver, adipose tissue, and pancreatic islet beta cells all play a major role in the maintenance of energy balance and the pathogenesis of insulin resistance and type 2 DM. The integration and coordination of the individual roles and functions of these organs requires a common mediator capable of balancing energy requirements. AMPK acts as a major “toggle switch” between system energy generation versus consumption, as it promotes the energy-producing (ATP-generating) processes of fatty acid and glucose uptake and oxidation and inhibits the ATP-consuming processes of gluconeogenesis, lipogenesis, and protein synthesis. gAd activates AMPK via phosphorylation in skeletal muscle, and fAd activates AMPK in the liver. Activation of AMPK may be a common pathway by which adipokines improve insulin sensitivity, as leptin has been shown to exert a similar action.

Leptin

Leptin is a 16-kDa cytokine-like peptide product of the ob gene produced by adipose tissue and known...
to be involved in the regulation of food intake and energy expenditure. Immunoactive serum leptin is proportional to whole-body adipose mass; thus, serum leptin concentration is a reflection of the degree of “fatness.” Genetic syndromes in which leptin is grossly absent (eg, generalized lipoatrophy) result in severe insulin resistance.

Leptin receptors in the arcuate nucleus of the hypothalamus appear to be of principal importance in satiety signaling. In animal models, injection of leptin into this region inhibits food intake. Most forms of human obesity are associated with elevated serum leptin, implying a certain degree of CNS resistance.

Resistin

Resistin is a 12.5-kDa cysteine-rich polypeptide secreted by adipocytes. Steppan et al studied resistin in rodent models and found that serum resistin is elevated in 2 different genetic models of obesity and in a diet-induced model of diabetes and obesity. In these studies, administration of resistin was associated with reduced insulin sensitivity in wild-type mice. Conversely, neutralization of resistin by a monoclonal antibody was associated with lower mean glycemia and improved insulin sensitivity. Additionally, these authors have shown decreased resistin gene transcription and expression following thiazolidinedione therapy.

Resistin increases expression of IL-1, IL-6, IL-12, TNF-α, ICAM-1, VCAM-1, and CCL2 (chemokine [C-C motif] ligand 2), which in aggregate represent
activation of inflammation and leukocyte chemotaxis and migration from blood through vessel walls. Activation of inflammation is associated with impaired insulin action and endothelial function, both of which are germane to metabolic homeostasis and long-term complications of type 2 DM.

**RENNIANGIOTENSIN SYSTEM COMPONENTS**

Several constituents of the renin-angiotensin system, including renin, angiotensin I and II, angiotensin-converting enzyme, and angiotensin receptor types 1 and 2 (AT1, AT2) are expressed and secreted by adipose tissue. In general, activity of the renin-angiotensin system is heightened by the presence of obesity, with a twofold higher expression of the AT1 gene in adipocytes of obese, hypertensive women as compared with the adipocytes of obese, normotensive women. The effect of angiotensin II on adipocytes is principally inhibition of cell differentiation of preadipocytes to mature adipocytes, an effect reversible by administration of an angiotensin II receptor blocker. A reduced number of mature adipocytes has been cited as a factor contributing to the development of type 2 DM.\(^\text{157}\)

**SUMMARY**

The role of gut hormones in the regulation of several metabolic processes, including the control of satiety, gastric emptying, and energy utilization, has been an increasingly important topic of research, and a number of potential therapeutic options have been investigated. GLP-1 has been at the forefront of this research, and evidence clearly has shown the vital role this incretin plays in beta cell function. The chief effect of GLP-1 is glucose-dependent augmentation of insulin release in response to oral feeding—the so-called incretin effect. In addition, GLP-1 promotes satiety, delays gastric emptying, and suppresses glucagon.

Adiponectin improves insulin action and exerts anti-inflammatory effects on hepatocytes and vascular endothelium. The adiponectin-poor adipocyte, by contrast, produces IL-6 and TNF-\(\alpha\), which oppose the glucose-lowering effects of insulin and promote vascular inflammation and thrombosis, as well as hypertension. Modern treatment of type 2 DM and prediabetes must now address visceral adiposity and endothelial function as zealously as it targets insulin supply and demand.

**REFERENCES**


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