The proglucagon gene encodes glucagon and several glucagon-like peptide sequences that exert diverse metabolic and cytoprotective functions focused on the integrated control of energy homeostasis. The proglucagon gene is expressed in three principal tissues: the A cells of the endocrine pancreas, the central nervous system neurons within the brain stem, and enteroendocrine cells of the small and large intestine. Nutrient ingestion is a key physiological determinant of proglucagon gene expression in islets and intestinal endocrine cells. Restriction of proglucagon gene transcription to islet and intestinal endocrine cells is achieved by coordinate expression of a diverse set of transcription factors that, in some instances, also subserve key roles in control of endocrine cell development in the gut and pancreas. Although the majority of informative experiments have focused on studies of rat islet proglucagon gene transcription, the available evidence suggests that important differences exist with respect to transcriptional control of the proglucagon gene in gut endocrine cells. Furthermore, structural and functional determinants of rat proglucagon gene expression are not identical to those utilized for control of human proglucagon gene transcription.
to mature glucagon in islet A cells; as a result, these mice develop mild hypoglycemia due to glucagon deficiency. In contrast, the liberation of an intestinal profile of PGDPs, including glicentin, oxyntomodulin, and glucagon-like peptides (GLP-1 and GLP-2), derives from expression of the enzyme PC1/2 in enteroendocrine cells of the small and large intestines.

II. PROGLUCAGON GENE EXPRESSION IN THE PANCREAS

The level of blood glucose is a major determinant of secretory activity from the islet A cell, with hyperglycemia inhibiting, and hypoglycemia stimulating, the release of glucagon into the circulation. Consistent with these findings, rats subjected to chronic hyperglycemic infusion for 5 days exhibit a significant reduction in islet proglucagon mRNA transcripts as assessed by in situ hybridization. Because hyperglycemia is frequently associated with enhanced insulin secretion, it is difficult to isolate the effects of glucose versus insulin on the islet A cell. Insulin administration inhibits proglucagon gene expression in normal and diabetic rodents; insulin-induced hypoglycemia, however, is associated with increased pancreatic proglucagon gene expression in the rat. Similarly, food deprivation leading to mild hypoglycemia is associated with induction of rat proglucagon expression.
gene expression. Studies of streptozotocin-induced diabetes in rats demonstrate increased levels of pancreatic proglucagon mRNA transcripts in insulin-deficient diabetic rats, whereas the levels of proglucagon mRNA transcripts are reduced following correction of hyperglycemia following insulin administration. Whether changes in glucose alone, independent of insulin, regulate pancreatic proglucagon gene expression remains unclear, because correction of the hyperglycemia of experimental rodent diabetes with phlorizin is not associated with significant changes in the levels of pancreatic proglucagon mRNA. Despite the dominant inhibitory effect of insulin in the regulation of islet proglucagon gene expression, mice with targeted disruption of the insulin receptor gene exhibit no abnormalities in the levels of pancreatic proglucagon mRNA transcripts.

III. PROGLUCAGON GENE TRANSCRIPTION IN ISLET CELL LINES

Proglucagon gene expression has been studied predominantly in immortalized rodent islet A cell lines, including rat RIN1056A, hamster InR1-G9 or HIT T15-G, and mouse αTC-1 cells. Incubation of RIN1056A cells with sodium butyrate induces cell cycle arrest, cell differentiation, and increased levels of proglucagon mRNA transcripts due to induction of proglucagon gene transcription. Similarly, phorbol esters activate proglucagon gene transcription in RIN1056A cells whereas the arginine-induction of rat islet proglucagon gene expression is abrogated by treatment of islets with the protein kinase C inhibitor H-7. Although cyclic adenosine monophosphate (cAMP), acting through protein kinase A (PKA), up-regulates levels of proglucagon mRNA transcripts in primary cultures of rat islets, glucagon-producing rodent islet cell lines frequently exhibit defects in cAMP-dependent signaling and fail to increase levels of proglucagon mRNA transcripts following treatment with dibutyryl cAMP or forskolin. In contrast, transfection of islet cell lines with the catalytic subunit of PKA bypasses the cAMP signaling defect and activates proglucagon gene transcription. Consistent with data from studies of mice and rats in vivo, insulin reduces the levels of proglucagon gene expression in islet cell lines via inhibition of gene transcription. Paradoxically, despite the lack of evidence implicating a direct role for glucose in rodent proglucagon gene expression in vivo or in cultures of rat islets in vitro, chronic incubation (1–5 weeks) of islet InR1-G9 cells with glucose-supplemented medium (11 mM glucose) resulted in up-regulation of proglucagon mRNA transcripts, compared to cells incubated in 5 mM glucose for comparable time periods. The glucose-stimulated induction of proglucagon mRNA transcripts was due to enhanced gene transcription, and was inhibited by cotreatment with insulin. Analysis of proglucagon mRNA decay following incubation with actinomycin reveals an estimated t_{1/2} of ~12 h in RIN1056A rat islet cells; however, factors that regulate islet proglucagon mRNA stability in vivo remain poorly understood.

IV. DELINEATION OF FUNCTIONAL DOMAINS WITHIN THE RAT PROGLUCAGON GENE PROMOTER

A majority of studies of proglucagon gene transcription have predominantly utilized the rat proglucagon gene promoter fused to heterologous reporter genes (e.g., genes encoding chloramphenicol acetyltransferase, luciferase, or growth hormone), followed by analysis of transcriptional activity in transfected islet cell lines. A majority of experiments have focused on the proximal sequences within the first 300 bp of the rat proglucagon promoter, because experiments in islet cell lines demonstrated that proglucagon promoter fusion genes containing additional 5' flanking sequences extending to ~2.3 kb exhibit levels of transcriptional activity comparable to that seen with sequences extending to ~300 bp. Structural and functional characterizations of the rat promoter through deletional and mutagenesis studies have identified distinct cis-acting domains within the proximal 300 bp of the rat proglucagon promoter (Fig. 3). These domains, designated G1 through G5, bind transcription factors present in islet cell nuclear extracts and exhibit enhancer-like properties (G2–G5) or function as an islet A cell-specific promoter (G1) in vitro. The first three domains to be identified extend from ~292 to ~256 (G3), ~192 to ~179 (G2), and ~114 to ~74 (G1). Subsequent experiments subdivided the G3 sequence into an upstream domain A (5'-CGCCTGA) and a downstream domain B (5'-GATTGAAGGTTGTA-3'), and an element partially overlapping original G1 sequences, designated G4, was identified spanning ~140 to ~100. More recently, DNA sequences located between G4 and G2, from ~169 to ~140, have been designated as the G5 element. A cAMP response element (CRE), 5'-TGACGTCA-3', is located.
upstream of G3 from -300 to -292, and a phorbol ester response element has been mapped to sequences within G2. The finding that potassium-induced membrane depolarization activates glucagon gene transcription in a calcium-dependent manner has resulted in the mapping of the “depolarization response element” to sequences within the rat glucagon gene CRE. Mutational studies of the proximal rat proglucagon promoter have identified a second calcium response element within the region spanned by G2. Similarly, the inhibitory effect of insulin on rat proglucagon gene transcription has been mapped to the more distal domain A of the G3 element, and the available data suggest that insulin also exerts its effects through mechanisms converging on more proximal sequences located within the G1 element.

V. MECHANISMS MEDIATING ISLET A CELL-SPECIFIC PROGLUCAGON GENE TRANSCRIPTION

The observation that pancreatic proglucagon gene transcription is restricted to islet A cells has focused attention on identification of DNA sequences and transcription factors that both activate transcription in the A cell and restrict proglucagon gene transcription to the A cell. The difficulty in obtaining purified populations of nonimmortalized A cells for gene transfer studies has necessitated use of immortalized islet cell lines derived from insulinomas (beta cells) or glucagonomas (A cells) for comparative studies of islet cell-specific proglucagon gene transcription. Indeed, some degree of transcriptional activation is observed following transfection of rat proglucagon promoter sequences into islet beta cell lines. The G2 and G3 elements display weak enhancer-like activity in islet, but not nonislet, cell lines, whereas the more proximal G1 element is required for restriction of transcriptional activation to the islet alpha cell lineage. Nevertheless, the results of electrophoretic mobility-shift assays or footprinting experiments using these DNA elements in conjunction with nuclear extracts from islet cell lines exhibiting different hormonal phenotypes produce comparable patterns of DNA–protein interaction, providing evidence for considerable complexity in the transcriptional specification of A cell-specific gene transcription. Furthermore, insulin and somatostatin gene enhancer sequences placed upstream of the proximal rat proglucagon promoter can activate transcription in islet cells when linked to the G1 element. Moreover DNA sequences within the proglucagon gene G3 element bind nuclear factors that also recognize related sequences within the somatostatin upstream enhancer element and the insulin gene E-1 promoter region, leading to the designation of the G3 domain A region as the pancreatic islet cell-specific enhancer sequence (PISCES) element. Given the common embryological origin of hormonally distinct yet related islet cell lineages, it is not surprising that islet hormone genes have evolved both common and unique mechanisms for specifying islet subtype-specific gene transcription.

Within the G1 proximal promoter element, at least four distinct patterns of DNA–protein complex
formation, with varying binding specificity, can be identified using nucleotide sequences from −100 to −52 as probes interacting with islet A cell nuclear extracts. The formation of several G1 complexes appears to be relatively islet cell specific, and mutations within G1 that disrupt these DNA–protein interactions also result in diminished transcriptional activity in transfected islet A cells. Within the core G1 domain, the sequence CAGATG from −83 to −78 corresponds to E-1, an “E box-related” subdomain known to be important for expression of the somatostatin, insulin, and gastrin genes in islet cells. Two additional E box motifs are located within the adjacent G4 element, E-2, from −108 to −103, and E3, from −135 to −130. Functional studies using dominant negative helix–loop–helix (HLH) proteins suggest that the E-3 box likely represents the more functionally important sequence for transcriptional regulation. Although the insulin gene E boxes function as positive regulatory elements, the HLH protein E47 represses glucagon gene transcription mediated by E box binding sites, whereas the combination of E47 and Beta2 transcription factors activated glucagon promoter activity in InR1-G9 islet cells. Although Beta2-deficient mice develop diabetes and exhibit defects in formation of enteroendocrine cell lineages, whether Beta2 plays an essential role in control of glucagon gene expression independent of A cell lineage formation remains uncertain. Although the first 75 bp of the rat proglucagon gene promoter, comprising a portion of the proximal G1 element, imparts a degree of A cell specificity to transfected reporter genes, inclusion of the entire G1 domain extending to −100 is required for optimal specificity in alpha versus beta cell lines. Sequences within the G5 element may also function to restrict proglucagon gene transcription to A cells, because sequential deletion of the G5 element modestly increases transcriptional activity of proglucagon promoter reporter genes in nonislet cell lines.

VI. ISLET PROGLUCAGON GENE TRANSCRIPTION FACTORS

The observation that the proximal rat proglucagon promoter G1 element contains several TAAT nucleotide motifs corresponding to recognition sites for homeodomain transcription factors has provided impetus for assessment of the potential role of islet homeodomain proteins in the control of proglucagon gene transcription. The first islet transcription factor cloned using TAAT element DNA probes was Isl-1 (islet 1), a LIM domain homeobox protein that binds DNA sequences in the rat insulin gene E2 region. (The acronym LIM derives from the names of proteins Lin-11, Isl-1, and Mec-3.) Isl-1 also binds to TAAT motifs within the rat proglucagon gene G1 region and is a weak transactivator of proglucagon promoter activity in cell transfection studies. Nevertheless, mice with targeted disruption of the Isl-1 gene contain insulin mRNA transcripts yet exhibit defective islet A cell formation, implicating a role for Isl-1 in islet A cell development. Furthermore, inhibition of Isl-1 expression using antisense expression vectors in hamster islet InR1-G9 cells results in reduced levels of endogenous proglucagon mRNA transcripts. Whether Isl-1 is important for proglucagon gene expression in normal islet A cells awaits loss-of-function studies in human mutations or experiments designed to inactivate Isl-1 specifically in normal alpha cells in vivo. The beta cell transcription factor Pdx-1 also binds to the G1 element and is a potent repressor of proglucagon gene transcriptional activity and proglucagon mRNA transcripts, likely via DNA binding-independent mechanisms, in islet cell lines.

The caudal family homeobox protein Cdx-2/3, also cloned as an insulin gene enhancer binding protein, binds with high affinity to AT-rich motifs within the proglucagon gene G1 element and activates the proglucagon promoter in vitro. Increased expression of Cdx-2/3 also activates expression of the endogenous rodent proglucagon gene in transfected InR1-G9 cells. Two Cdx-2/3 isoforms are detected in rodent islet cells, including full-length bioactive Cdx-2/3, and an amino-terminally truncated protein that binds to the G1 element but does not exhibit transactivation potential. Determination of whether Cdx-2/3 is essential for islet proglucagon gene transcription in normal A cells in vivo is hampered by the early embryonic lethality of mice harboring inactivating mutations in the Cdx-2/3 gene.

Both Pax6 and Pax4 are expressed in the endocrine pancreas and play divergent roles in the control of cell lineage formation and proglucagon gene transcription. The paired homeodomain protein Pax6 binds to AT-rich motifs within both the G1 and G3 proximal promoter elements. The Pax6 protein activates G1- and G3-dependent transcription and is capable of synergistic transcriptional activation through heterodimer formation with Cdx-2/3, primarily through binding to the G1 element. The Pax6-Cdx-2/3 transcriptional activation via G1 is further enhanced through interaction with the transcriptional co-activator p300. Mice with a targeted inactivation
of the Pax6 gene, or mice expressing the dominant negative Pax6 SEY\textsuperscript{NEU} allele exhibit marked abnormalities in the formation of islet cell lineages, reduced numbers of islet A cells, and decreased levels of proglucagon mRNA transcripts. Whether Pax6 is essential for proglucagon gene transcription in the adult A cell independent of its role in islet A cell development has not yet been determined.

The Pax4 gene is also essential for islet lineage development in that inactivation of the mouse Pax4 gene results in failure to form beta and delta cells, yet in increased numbers of A cells. Also, Pax4 does not appear to be expressed in mature adult islet A cells, yet it is capable of acting as a transcriptional repressor of proglucagon gene expression when ectopically expressed in islet A cell lines. Intriguingly, the repression of transcription exerted by Pax4 may be independent of DNA binding, because Pax4 isoforms function as transcriptional repressors even in the absence of a DNA-binding domain. The integrated roles of Pax6 and Pax4 in islet cell development have led to a model whereby islet lineage allocation and phenotype may be dictated by both positive (Pax6) and negative (Pax4) control of cell development and hormone gene expression. The related homeobox transcription factor Pax2 is also expressed in islet alpha cells, binds to both the G3 and G1 promoter elements, and functions as a positive regulator of proglucagon gene transcription.

Brain 4 (Brn4), a POU domain transcription factor originally isolated from a rat hypothalamic cDNA library, binds to and transactivates promoters containing a DNA octamer motif recognized by related POU domain proteins. (POU is an acronym derived from the names of three transcription factors, Pit-1, Oct-1, and Unc-86, which are all characterized by a specific DNA-binding domain.) Brain 4 is also expressed in islet A cells, binds to AT-rich sequences within the 5′ end of the G1 element, and activates rat proglucagon gene transcription. Induction of Brn4 expression in beta cell lines is associated with activation of endogenous glucagon gene expression \textit{in vitro}. Whether Brn4 is essential for proglucagon gene transcription in normal islets \textit{in vivo} remains unclear; mice with targeted disruption of the Brn4 gene do not exhibit defects in islet glucagon gene expression. Members of the Maf transcription factor family also bind to G1 and enhance proglucagon gene transcription. Maf factors are capable of enhancing Pax6 transcriptional activity via increased Pax6 binding to G1 or though protein–protein interaction with Pax6 independent of DNA binding. Although c-Maf \textit{−/−} mice have been generated via homologous recombination, a majority of c-Maf knockout embryos die on days E17.5–18.5, and the surviving mice exhibit microphthalmia; however, the status of endocrine pancreas and islet A cells in Maf \textit{−/−} mice has not yet been reported.

Members of the hepatocyte nuclear factor-3 gene family (HNF-3), currently known as the Fox (forkhead box) transcription factors, bind to the rat proglucagon gene G2 element. HNF-3\beta (FoxA2) is expressed in islet A cell lines and overexpression of HNF-3\beta results in repression of proglucagon promoter activity in islet cell lines \textit{in vitro}. Multiple HNF-3\beta isoforms can be detected in islet A cell lines that bind G2 with similar affinity, but only the full-length HNF-3\beta\textit{1} isoform represses transcriptional activity. HNF-3\beta also binds to the G3 element and transfection of a dominant negative mutant HNF-3\beta represses G3-dependent transcriptional activity in islet A cells. Targeted disruption of HNF-3\beta results in early embryonic lethality, precluding assessment of A cell formation and glucagon gene expression in the adult mouse, whereas beta-cell-specific inactivation of HNF-3\beta results in mice with hyperinsulinemic hypoglycemia, likely due to defective control of K\textsubscript{ATP} channel function.

The HNF-3 (FoxA) proteins exhibit similar patterns of DNA-binding specificity, and both HNF-3\alpha (FoxA1) and HNF-3\gamma (FoxA3) also bind to the glucagon gene G2 promoter element. Although a functional role for HNF-3\gamma in control of proglucagon gene transcription remains to be established, HNF-3\alpha activates G2-dependent proglucagon gene transcription in heterologous fibroblasts and in islet cell lines. Furthermore, HNF-3\alpha \textit{−/−} mice exhibit reduced levels of pancreatic proglucagon gene expression and a defective glucagon secretory response to hypoglycemia, implicating an essential role for HNF-3\alpha in islet proglucagon gene transcription.

VII. INTESTINAL PROGLUCAGON GENE EXPRESSION

Nutrient ingestion represents a primary determinant of proglucagon gene expression in enteroendocrine cells of the small and large intestines. Fasting reduces and feeding stimulates proglucagon gene expression in the rodent small bowel. High-fiber diets lead to up-regulation of proglucagon mRNA transcripts in the distal small bowel and colon, possibly due in part to a direct effect of fatty acids on induction of proglucagon gene expression. Indeed, luminal infusion of long-chain triglycerides into the rat jejunum or
intravenous infusion of fatty acids in parenterally fed rats stimulates intestinal proglucagon gene expression. Intestinal proglucagon gene expression is also up-regulated following major small bowel resection or induction of experimental diabetes in rodents. The mechanisms regulating intestinal proglucagon gene expression are poorly understood, although incubation of intestinal cell lines with specific nutrients such as peptones or fatty acids up-regulates proglucagon gene expression, likely through effects on proglucagon gene transcription. Peptide hormones such as gastrin-releasing peptide also stimulate intestinal proglucagon expression via activation of proglucagon gene transcription.

VIII. PROGLUCAGON GENE ENTEROENDOCRINE TRANSCRIPTION FACTORS

Compared to our understanding of islet proglucagon gene transcription, much less is known about control of proglucagon gene promoter activity in gut endocrine cells. Although the functional properties of the G1–G5 elements have been carefully defined in studies of islet-cell-specific proglucagon gene transcription, the potential importance of these proximal promoter elements in specifying intestine-specific gene transcription is less well understood. Evidence derived from analysis of proglucagon promoter activity following transfection of islet versus intestinal cell lines suggests important differences in the functional organization of proglucagon promoter elements in islet versus enteroendocrine cells. Transfection studies have identified a series of distal enhancer-like elements located between −2253 and −1292 bp upstream of the rat proglucagon gene transcription start site. This broad region of proglucagon gene 5′ flanking sequences, designated the glucagon gene upstream enhancer (GUE), appears to be functionally important for intestine-specific proglucagon gene transcription. Specific subdomains within the GUE exhibit positive and negative effects on reporter gene transcription, and GUE-derived probes bind proteins present specifically in GLUTag cell nuclear extracts. Nevertheless, proglucagon gene transcription factors that activate proglucagon gene expression specifically in gut endocrine cells have not yet been identified.

Both Cdx2/3 and Pax6 are expressed in enteroendocrine L cells, bind the G1 promoter element in electrophoretic mobility-shift assay (EMSA) experiments, and activate proglucagon gene transcription in transfected GLUTag mouse enteroendocrine cells. Mice expressing the dominant negative Pax6 SEYNEU allele exhibit markedly reduced levels of intestinal proglucagon mRNA transcripts in the small and large intestines. Whether this phenotype is principally due to the importance of Pax6 for enteroendocrine cell lineage formation or reflects an essential role for Pax6 in control of intestinal proglucagon gene expression remains unclear. In contrast to the central importance of HNF-3α for islet proglucagon gene expression, intestinal proglucagon gene expression appears normal in HNF-3α−/− mice.

IX. ANALYSIS OF ISLET AND INTESTINAL PROGLUCAGON GENE TRANSCRIPTION IN TRANSGENIC MICE

The proglucagon promoter sequences required for expression of a reporter gene in murine islets and enterocyte cells have been broadly identified in a limited number of transgenic mouse studies. A 1252-bp fragment of the rat proglucagon gene promoter and 5′ flanking region extending from the Kpn I site and including 57 bp of exon 1 sequences directed expression of a cDNA encoding SV40 T antigen to islet A cells, resulting in the formation of glucagonomas in mice that were several months old. Transgene expression was also detected in the brain, but not in enteroendocrine cells of the gut. These findings imply that DNA sequences sufficient for islet-specific expression are distinct from those required to target correct enteroendocrine-specific expression. Furthermore, transgene expression under the control of the 1252-bp rat promoter was highly restricted to islet alpha cells, indicating that sequences within this promoter region were sufficient for specification of cell-specific transgene expression. Similarly, a comparable fragment of the rat proglucagon gene promoter extending from the Xho I site to exon 1 was sufficient for directing expression of a modified transforming growth factor-β1 (TGF-β1) cDNA to islet A cells in vivo. A larger rat proglucagon promoter fragment extending to −2252 bp containing the first 58 bp of exon was also expressed in islet A cells and in brain cells. Furthermore, transgene expression was detected in enteroendocrine cells of the small and large intestines, and these mice developed glucagon-producing endocrine tumors of the colon after weeks of transgene expression. Islet hyperplasia and endocrine tumor formation were also observed in the pancreas after several weeks, suggesting that the −2252 bp of rat proglucagon
gene 5' flanking sequences contained additional information, compared to the smaller 1252-bp promoter fragment, resulting in a greater degree of transgene expression compared to that observed with the −1252-bp promoter sequence. Transgene expression was also detected in the brain stem and hypothalamus of −2252-bp rat proglucagon promoter transgenic mice.

X. HUMAN PROGLUCAGON GENE TRANSCRIPTION AND PROMOTER STUDIES IN MICE

Although a majority of studies of proglucagon gene transcription have utilized the rat promoter in transfection and transgenic experiments, there is little information available about the functional organization and activity of the human proglucagon gene promoter. Comparison of the human and rat proximal promoter sequences reveals a reasonable degree of sequence conservation within the G1–G5 promoter subdomains. Nevertheless, human proglucagon promoter and 5' flanking sequences extending to −600 bp are transcriptionally inactive following transfection of rodent islet or intestinal cell lines. Furthermore, in contrast to the data obtained with reporter genes under the control of rat proglucagon promoter sequences, several kilobases of human proglucagon gene 5' flanking sequences are not sufficient for activation of reporter gene expression in rodent islet cell lines, and human glucagon-producing islet or enteroendocrine cells have not yet been characterized and transfected with these reporter genes. The current findings indicate considerable species-specific differences in the structural and functional organization of the rat versus the human proglucagon gene promoter. Additional experimental data in support of the unique functional organization of the human proglucagon gene promoter derive from transgenic mice studies. A transgene containing the human growth hormone gene under the transcriptional control of ≈1.6 kb of the human proglucagon gene promoter was expressed in the brain stem and in enteroendocrine cells, but not in mouse pancreatic islets. These results, interpreted within the experimental limitations of using murine cells for analysis of human promoter expression, provide further evidence suggesting that the human proglucagon gene promoter has evolved distinct functional mechanisms for regulation of islet-specific proglucagon gene transcription.

XI. SUMMARY OF CURRENT KNOWLEDGE

Analyses of islet proglucagon gene expression, based on transfection experiments of rodent cell lines, transgenic mice, and physiological studies of glucose-regulation in mice and rats, have delineated specific cis-acting domains and transcription factors that coordinately regulate rat proglucagon gene transcription specifically in islet A cells. Our knowledge of the DNA sequences and transcription factors important for control of proglucagon gene expression in enteroendocrine cells or neurons is considerably more limited. Furthermore, the available data from analysis of the human proglucagon promoter imply important functional species-specific differences, suggesting that the data obtained from analysis of the rat promoter may not necessarily be applicable to our understanding of human proglucagon gene expression. It seems likely that the development of additional experimental models using newly derived human endocrine cell lines, taken together with more detailed analysis of the factors regulating human proglucagon gene transcription, will be required to reconcile the differences observed in results from studies of rat and human proglucagon promoter control.

Glossary

diabetes Metabolic syndrome characterized by an elevated blood glucose that results from a combination of insufficient insulin production and/or deficient insulin action.
enteroendocrine cells Specialized, phenotypically distinct endocrine cells; found within the mucosa of the gastrointestinal tract, they produce one or more peptide hormones.
glucagon-like peptides Two small peptides, glucagon-like peptide-1 and glucagon-like peptide-2, derived from posttranslational processing of proglucagon; exhibit sequence similarity to glucagon.
intestine The gastrointestinal tract, including the stomach and the small and large bowel tracts.
islets The islets of Langerhans; include four distinct highly specialized endocrine cell types that produce insulin (beta cells), glucagon (alpha cells), somatostatin (delta cells), or pancreatic polypeptide (PP cells).

See Also the Following Articles
Glucagon Action • Glucagon-like Peptides: GLP-1 and GLP-2 • Glucagonoma Syndrome • Glucagon Processing • Glucagon Secretion, Regulation of
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