Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Effects of Anterior Pituitary Adenomas' Hormones on Glucose Metabolism and Its Clinical Implications

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Abstract: Pituitary adenomas have recently become more common and their incidence is increasing yearly. Functional pituitary tumors commonly secrete prolactin, growth hormones, and adrenocorticotropic hormones, which cause diseases such as prolactinoma, acromegaly, and Cushing's disease, but rarely secrete luteinizing, follicle-stimulating, thyroid-stimulating, and melanocyte-stimulating hormones. In addition to the typical clinical manifestations of functional pituitary tumors caused by excessive hormone levels, some pituitary tumors are also accompanied by abnormal glucose metabolism. The effects of these seven hormones on glucose metabolism are important for the treatment of diabetes secondary to pituitary tumors. This review focuses on the effects of hormones on glucose metabolism, providing important clues for the diagnosis and treatment of related diseases.

Keywords: pituitary adenoma, glucose metabolism, prolactin, growth hormones, glucocorticoids

Introduction

The incidence of pituitary adenomas, which are common benign tumors of the anterior pituitary gland, is increasing annually, accounting for approximately 14% of all intracranial tumors.[1] Approximately a third to a half (36–54%) of pituitary tumors are nonfunctional.[2–5] Nonfunctioning adenomas do not secrete hormones and may cause mass effects such as visual deficits, hypopituitarism, or headaches. Some nonfunctional adenomas may not cause symptoms and are incidentally discovered during neuroimaging.[6] The other half of pituitary adenomas (46–64%) are functional tumors that secrete hormones.[7–9] The common secreted hormones are prolactinoma (PRL; 32–51%), growth hormones (GH; 9–11%), and adrenocorticotropic hormones (ACTH; 3–6%). The less commonly secreted hormones are thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and melanocyte-stimulating hormone (MSH). Functional adenomas cause clinical symptoms mediated by the excessive secretion of hormones, leading to acromegaly, Cushing's disease (CD), galactorrhea, hypogonadism, and other symptoms.

Pituitary tumors are often accompanied by impaired glucose tolerance or diabetes mellitus, which is often an early manifestation of these tumors. The presence of glucose metabolism disorders further increases the risk of cardiovascular disease-associated morbidity and mortality in patients with pituitary tumors.[10] In addition, diabetes mellitus may also affect the treatment plan for patients with pituitary tumors because the therapeutic agents for pituitary tumors may affect glucose metabolism.[11] In this review, we highlight the roles of seven hormones in glucose metabolism respectively and provide basic theoretical support for the clinical diagnosis and treatment of related glucose metabolism disorders.

PRL and Glucose Metabolism

The main manifestations of prolactinoma are hypogonadism and galactorrhea. In women, hypogonadism can lead to irregular menstruation, amenorrhea, sexual dysfunction, infertility, and reduced intersex bone mineral production.[12]

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Patients who suffer from hyperprolactinemia often have fractures due to decreased bone mineral density.[13] Moreover, large PRL-producing tumors can cause compressive symptoms, including headaches, vision changes, and hydrocephalus.[14,15]

PRL is a polypeptide hormone that is released by lactating cells from the anterior pituitary. Hypothalamus controls PRL secretion differently from other pituitary hormones because it is primarily suppressed by extracting dopamine from the tuberoinfundibular dopamine neurons (TIDA).[16] Moreover, as prolactin receptors (PRLRs) are present in almost all organs, PRL affects more physiological processes than other pituitary hormones.[17] Therefore, PRL plays several roles in endocrine metabolism and growth and development, water and electrolyte balance, and brain and behavior.[16,18,19]

PRL is not conducive to glucose metabolism in patients with prolactinoma who often have obesity and metabolic disorders.[20,21] Compared to healthy individuals, individuals with hyperprolactinemia often have glucose intolerance and decreased insulin sensitivity.[22–24] Data from female mouse studies showed that long-term high PRL levels are associated with increased appetite, weight gain, obesity, insulin resistance, and glucose intolerance, supporting the notion that high PRL levels are detrimental to metabolic homeostasis.[25,26] Moreover, hyperprolactinemia has been associated with impaired metabolism in a study using the euglycemic hyperinsulinemic clamp technique,[27] as well as an increase in the homeostatic model assessment (HOMA) index[28] and a reduction of insulin sensitivity index (ISI)[29] in both obese and lean patients.

Hyperprolactinemia increases blood glucose levels via two mechanisms. Hyperprolactinemia leads to hypoadiponectin. Adiponectin can enhance insulin-mediated inhibition of hepatic gluconeogenesis[30] and improve insulin sensitivity by stimulating glucose uptake and fatty acid oxidation of fat and muscle cells,[31,32] supporting the notion that patients with hyperprolactinemia may exhibit biochemical signs of both metabolic syndromes and insulin resistance.[33] Hyperprolactinemia can also induce gonadotropin suppression, which may indirectly induce insulin resistance in both men and women.[34,35]

In conclusion, prolactinomas and hyperglycemia may occur in the same patient, requiring a comprehensive hypoglycemic treatment in accordance with the patient's blood glucose levels.

GH and Glucose Metabolism

Acromegaly is a clinical syndrome characterized by the excessive secretion of GH, which usually occurs in pituitary adenomas.[36] Typical facial features of acromegaly include thickened lips, enlarged nose and ears, nasolabial folds, and lordosis.[37] The incidence of diabetes in patients with acromegaly is higher than that in the general population. More than 50% of patients diagnosed with acromegaly develop impaired glucose metabolism.[38] Moreover, the presence or absence of diabetes is an important predictor of increased mortality in acromegaly.[39]

GH plays a direct role in glucose metabolism. It induces insulin resistance, leading to impaired glucose metabolism.[40] Patients with acromegaly are characterized by reduced insulin sensitivity and impaired hepatic and extrahepatic insulin activity.[41,42] GH mediates the action of insulin mainly by regulating p85α[43] in fat tissues (Figure 1). Excessive GH levels promote the expression of p85α, which reduces the activity of insulin-mediated phosphoinositide 3-kinase (PI3K), leading to insulin resistance.[44] In patients with obesity, the inhibition of GH activity reverses insulin resistance.[45] In addition, GH acts on the liver,[46] skeletal muscles,[47] brain,[48] kidneys,[49] and other organs, leading to insulin resistance and increased glucose output.

The indirect effect of GH on glucose metabolism is mediated by insulin-like growth factor 1 (IGF-1), a peptide hormone with a 50% homology to proinsulin. Similar to insulin, IGF-1 enhances glucose uptake and oxidative/non-oxidative glucose metabolism, which is positively correlated with the dose of IGF-1. GH binds to GH receptors, which are primarily located in hepatic cells, leading to the synthesis and secretion of IGF-1 in the liver, which improves insulin sensitivity.[50,51] Moreover, IGF-1 can inhibit endogenous (mainly liver) glucose production, but is not as effective as insulin,[52–54] and acts on the IGF-1 receptors in the brain[55] to increase insulin sensitivity[56] and decrease food intake.[57]

Although the direct and indirect roles of GH in glucose regulation are opposites, the overall effect is still the result of direct action. On the one hand, chronic excessive GH can cause insulin resistance, and these roles largely offset the favorable effect of IGF-1 on insulin sensitivity. On the other hand, IGF-1 is not as effective as insulin, and IGF-1 resistance is also observed in skeletal muscles.[58]

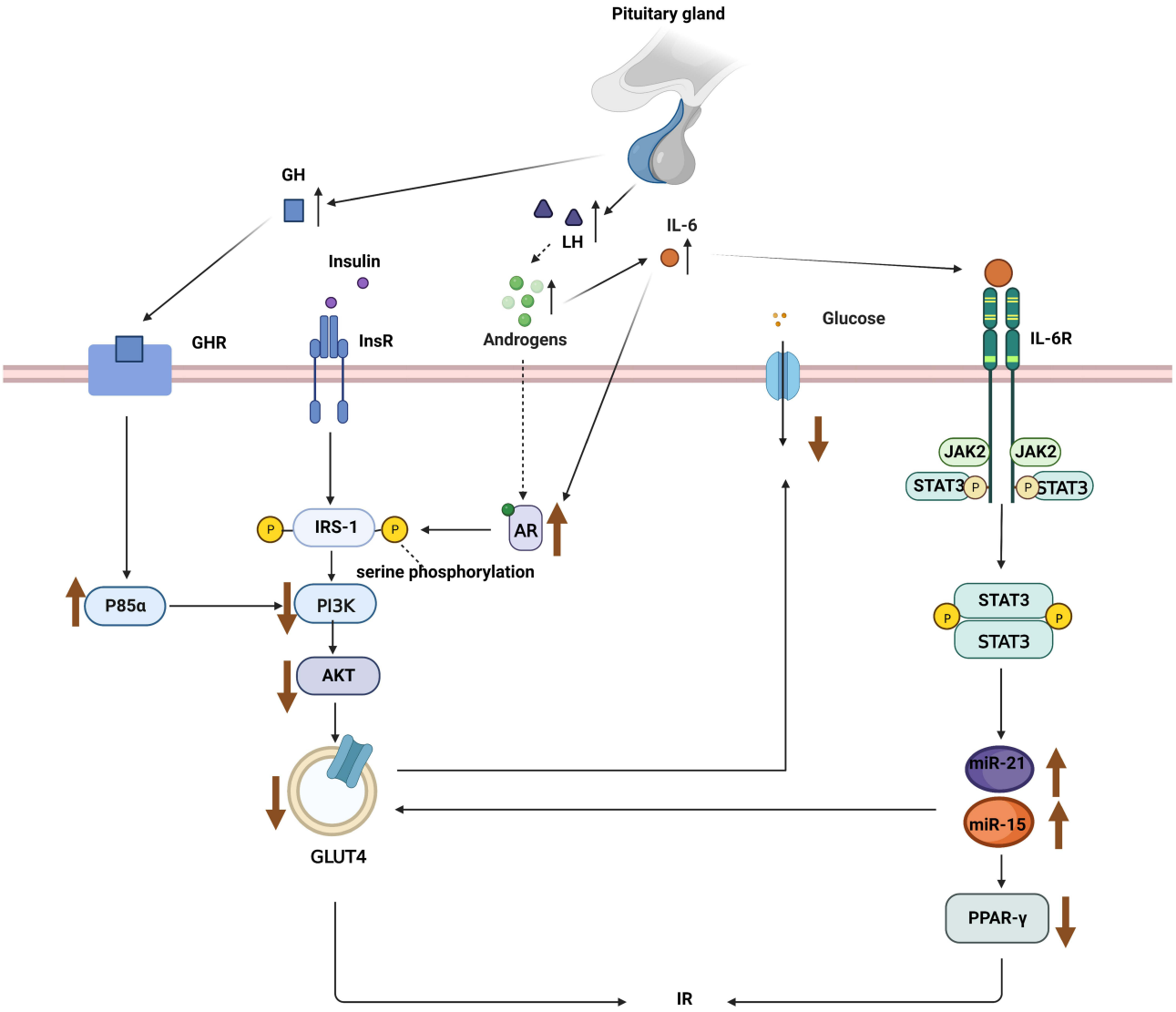

Figure 1 The regulation mechanism of luteinizing hormone (LH) and growth hormone (GH) on glucose homeostasis. LH indirectly affects glucose homeostasis by interfering with related signaling pathways through androgens and inflammatory mediators, while GH interferes with insulin signaling through p85α.
Abbreviations: IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; GLUT4, glucose transporter 4; AR, androgen receptor; JAK2, Janus tyrosine kinase 2; STAT3, signal transducers and activators of transcription 3; PPAR-γ, peroxisome proliferator activated receptor γ; IL-6, interleukin 6.

In conclusion, GH is implicated in the pathogenesis of diabetes and its extensive effects are important in the diagnosis, prevention, and treatment of diabetes. The hypoglycemic treatment for acromegaly is the same as that for diabetes. Generally, lowering GH levels increases insulin sensitivity, and glycemic control ensues.[59]

ACTH and Glucose Metabolism

Cushing syndrome (CS) is a general condition caused by excessive secretion of cortisol from the adrenal gland. The most common cause of CS is ACTH-secreting pituitary tumors called CD, accounting for about 80–85%.[60] Typical symptoms of CS include full moon face, buffalo back, centripetal obesity, purple stripes, hypertension and hypokalemia, osteoporosis, and diabetes. Moreover, alterations in glucose metabolism are present in 50% of patients with CD.[61]

To the best of our knowledge, few studies have investigated the direct relationship between ACTH and glucose homeostasis, reporting that ACTH regulates glucose metabolism mainly through downstream glucocorticoids (GCs). Here, we discuss the effects of GCs on glucose metabolism from the following aspects (Figure 2).

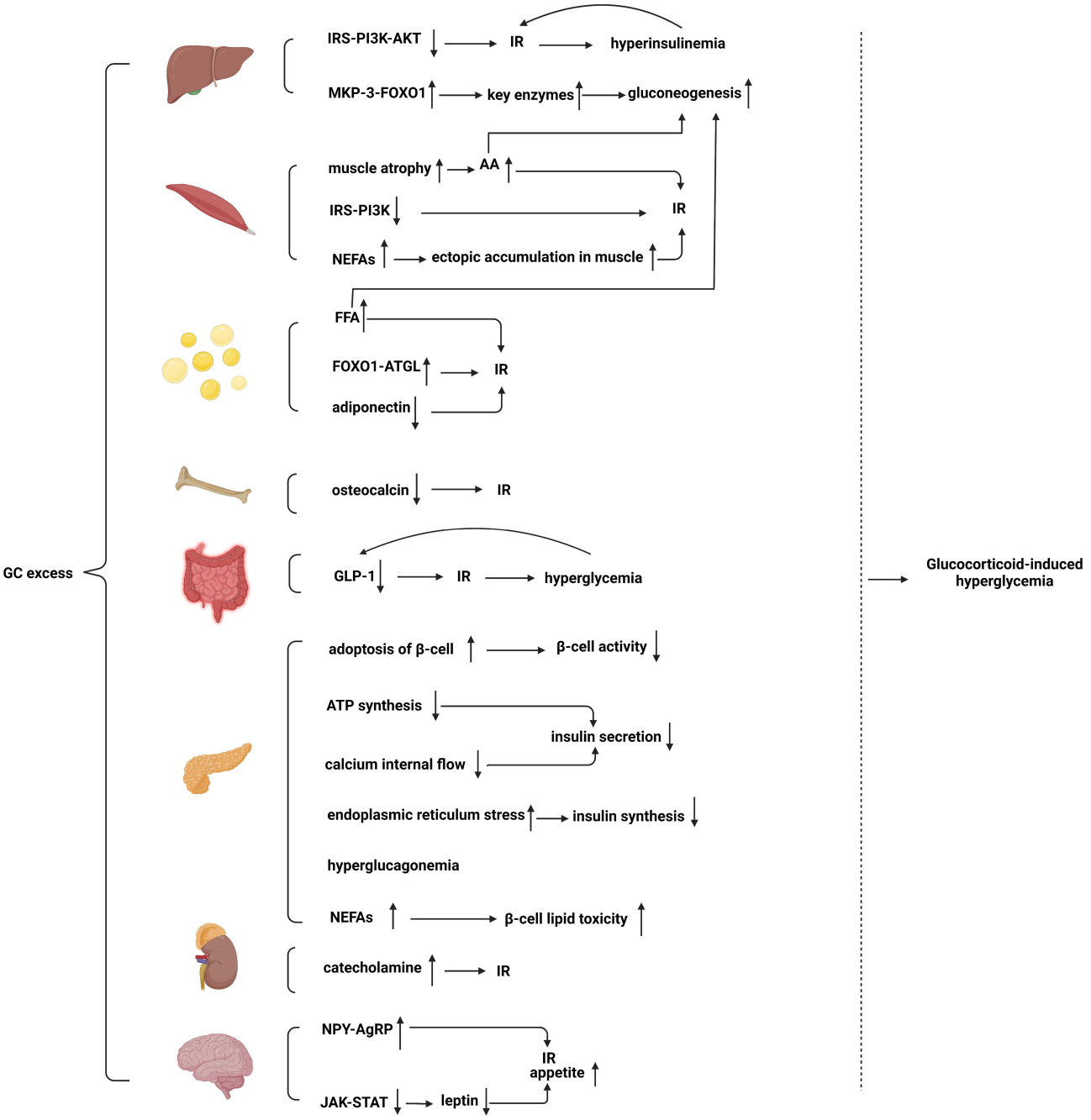

Figure 2 Excessive GCs act on the above-mentioned organs to induce glucose metabolism disorders and eventually lead to hyperglycemia.
Abbreviations: IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; MKP-3, mitogen-activated protein kinase phosphatase-3; FOXO1, forkhead box protein O1; AA, amino acid; FFA, free fatty acids; NEFAs, non-esterified fatty acids; ATGL, adipose triglyceride lipase; NPY, nerve peptide Y; AgRP, agouti-related protein; JAK, Janus tyrosine kinase; STAT, signal transducers and activators of transcription.

Hepatic tissue plays a major role in regulating glucose levels. The first key pathway is the regulation of key gluconeogenic enzymes. GCs act on target genes of gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.[62] A study has suggested that GC-induced forkhead box protein O1 (FOXO1) upregulation stimulates hepatic glucose output.[63] GCs upregulate FOXO1 by promoting mitogen-activated protein kinase phosphatase-3 (MKP-3) expression, a liver gluconeogenic activator.[64] Moreover, Gluconeogenesis is further induced by lipolysis in adipose tissues and protein hydrolysis in the skeletal muscles.[65] The second key pathway is insulin resistance mediated by the overexpression of GCs. Impaired phosphorylation of the downstream messenger of the insulin cascade

(IRS-PI3K-AKT) in rats treated with GCs leads to compensatory hyperinsulinemia, which in turn increases insulin resistance in the liver through a vicious pre-cycle.[66] GCs increase the blood glucose level by its effects on the liver as described above.

The skeletal muscle accounts for approximately 80% of insulin-mediated glucose uptake. GCs directly hinder insulin signaling in skeletal muscle cells to inhibit glucose uptake, thereby leading to GC-induced diabetes. Dexamethasone decreases the activity and expression of insulin substrate 1 (IRS1) and phosphoinositide-3-kinase regulatory subunit 1 (PI3Kr1) in rodent skeletal muscle cells,[67] which are the primary target genes for skeletal muscle glucocorticoid receptor (GR), and further inhibits insulin-induced glucose transporter 4 (GLUT4) recruitment to skeletal muscle surfaces.[68,69] In addition to the above mechanisms, patients with long-term exposure to corticosteroid drugs can develop extensive muscle atrophy, leading to the development of myopathy.[70] In these patients, increased muscle proteolysis and passivated protein synthesis lead to elevated serum amino acid levels,[71–73] which can indirectly impede glycogen synthesis and glucose transport.[74] GCs also increase the circulation of non-esterified fatty acids (NEFAs) from adipose tissue and its ectopic accumulation[75] in skeletal muscles, further exacerbating insulin resistance.[76] In addition, elevated serum amino acids and NEFAs also provide substrates for liver gluconeogenesis.

GCs play various roles in adipose tissues[77] such as the promotion of lipolysis and insulin-antagonistic mechanisms.[78] Exposure to GCs causes systemic elevated fatty acid and triglycerides levels, leading to insulin resistance[66] and increased hepatic gluconeogenesis.[65] To date, accumulating evidence has indicated that 5 days of exposure to prednisolone results in increased levels of basal free fatty acids (FFA) and disruption of insulin-mediated inhibition of FFA, which induces increases in insulin and fasting glucose levels, suggesting that GCs induce insulin resistance.[79] In vitro tests also have suggested that excessive exposure to GCs results in insulin resistance.[77] Moreover, lipolysis can provide glycerol and fatty acids as gluconeogenic substrates, which in turn provide energy for gluconeogenesis and increase allosteric activation of gluconeogenesis by increasing hepatic acetyl Coenzyme A.[77] GC-induced decrease in insulin signaling in fatty tissue is also associated with reduced glucose uptake. A previous study has reported that prednisolone may indirectly activate adipose triglyceride lipase (ATGL) transcription via FOXO1, suggesting that GCs block the insulin signaling pathway to prevent insulin-mediated inhibition.[79] In addition, excessive levels of GCs can reduce adiponectin expression and secretion levels in fatty tissue.[30] Because adiponectin enhances fatty acid oxidation in the muscles and insulin inhibition of hepatic gluconeogenesis,[31,32] excessive GCs increase glucose and insulin resistance.

Osteocalcin is a bone-derived hormone whose non-carboxylated form (Glu-OC) is essential to glucose and energy metabolism.[80] Osteocalcin is an insulin-sensitizing hormone released from osteoblasts.[81] Interestingly, osteocalcin-deficient mice develop abnormal glucose tolerance and insulin resistance owing to reduced insulin expression and pancreatic β-cell proliferation.[82] Osteocalcin mediates its functions both directly and indirectly. Glu-OC directly activates the putative receptor GPRC6A (G protein-coupled receptor, family C, group 6, member A) in the pancreas, leading to insulin production and β-cell proliferation.[83] Glu-OC indirectly increases insulin secretion through glucagon-like peptide-1 (GLP-1)[84] in a mechanism that may be referred to as bone-gut-metabolism flow. Moreover, Glu-OC negatively affects glucose metabolism independent of GLP-1, possibly by activating FOXO1 and the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α).[85] Notably, long-term exposure to GCs induces a reduction in circulating osteocalcin, leading to insulin resistance.[86] Therefore, these findings demonstrate the role of bones in regulating energy metabolism.

GLP-1 is synthesized from intestinal enteroendocrine L-cells and secreted after nutrient intake.[87] GLP-1 mainly exhibits insulinotropic effects but has many other roles, such as stimulating β-cell proliferation and reducing insulin resistance, inhibiting gastric emptying, glucagon release, and food intake.[88] Moreover, hypercortisolemia may affect the incretin system because excessive GCs cause a decrease in GLP-1 secretion. Accumulating evidence further indicates that dexamethasone reduces cyclic adenosine monophosphate (cAMP) production, which in turn impairs protein kinase A activity and ultimately GLP-1 secretion.[89] GC-induced reduction of GLP-1 action ultimately leads to insulin resistance and impaired glucose tolerance, which accelerates the development of diabetes and further increases blood glucose levels,[90] which in turn leads to decreased GLP-1 secretion, creating a vicious cycle.[91]

GCs impair β-cell activity and affect insulin secretion and synthesis. A study on human and mouse islets in vitro indicated that prednisolone decreases β-cell activity by inducing apoptosis of β-cells and that blocking GRs reverses this effect.[92,93] Furthermore, chronic hypercortisolism results in pancreatic β-cell dysfunction. Excessive GCs lead to reduced

ATP synthesis and calcium internal flow by decreasing the expression levels of type 2 glucose transporters and glucose kinases, leading to impaired metabolism in β-cells and glucose uptake, and ultimately to reduced insulin secretion.[94] Treatment with prednisolone in INS1 (rat pancreatic β-cell line) induces endoplasmic reticulum stress and impairs the biosynthesis and secretion of insulin. In rats, chronic high GCs levels lead to hyperglucagonemia by affecting the function and mass of pancreatic cells,[95,96] which also increases blood glucose levels. In addition to the aforementioned mechanism of GC-induced β-cell failure, GC-induced increase in NEFAs can lead to β-cell lipid toxicity, which further increases blood glucose levels.[97]

Pheochromocytoma is associated with preoperative diabetes mellitus.[98] The literature suggests that catecholamine leads to pheochromocytoma-associated diabetes by impairing insulin sensitivity and secretion.[99] These effects are mediated by complex mechanisms, including the direct action of catecholamine, the subsequent inhibition of glucose uptake in muscle cells, and high concentrations of FFA.[100–102] Cortisol is important for the adrenal myelin, which synthesizes, stores, and secretes catecholamine in chromaffin cells. Excessive cortisol levels aggravate adrenaline-mediated glucose homeostasis.[103]

GCs also mediate the development of obesity and diabetes partly by inducing the hypothalamic arcuate nucleus to stimulate appetite.[104] GCs can stimulate appetite and induce insulin resistance in animals by upregulating the mRNA of nerve peptide Y (NPY) and agouti-related protein (AgRP).[105,106] However, physiologically, leptin inhibits appetite through leptin signaling in NPY-AgRP neurons.[107] In rats, GCs impede the effects of leptin by impairing the leptin-dependent Janus tyrosine kinase (JAK)-signal transducers and activators of the transcription(STAT) signaling pathway in the hypothalamus.[108]

In conclusion, it is imperative to carefully assess the phenotype of patients with CS with impaired glucose tolerance and, if possible, conduct accurate insulin secretion and sensitivity tests before initiating treatment because CS further impairs glucose tolerance.[109]

Gonadotropin and Glucose Metabolism

In most cases, gonadotropin is characterized by the secretion of physiologically inactive hormones, therefore, its release does not cause any clinical symptoms. Functional gonadotroph-secreting tumors are scarce and account for only 0.2% of pituitary adenomas.[110] Therefore, the diagnosis of gonadotropinomas is most usually based on the immunohistochemical analysis. However, in rare cases, gonadotropinomas secrete bioactive hormones, including LH and FSH.[111,112] In vivo, functional gonadotropin adenomas are associated with changes in hormone levels. In patients with gonadotropinomas, estradiol levels are usually high whereas LH levels are low because of negative feedback from estrogen or damage to normal glands from pituitary tumors.[113] Moreover, premenopausal women with functional gonadotropin adenomas have clinical manifestations of oligomenorrhea, amenorrhea, galactorrhea, or infertility whereas men usually have enlarged testicles or hypogonadism.[112]

We found little literature on changes in glucose metabolism caused by functional gonadotropin tumors, therefore, we will elucidate the independent role of FSH and LH in glucose metabolism respectively.

FSH and Glucose Metabolism

FSH adenomas can induce typical clinical manifestations of excessive hormone levels, which vary by age and sex, such as menstrual dysfunction and spontaneous ovarian hyperstimulation syndrome, enlarged male testicles, and precocious puberty in children of the same sex.

FSH receptor (FSHR) is a class A G-protein-coupled receptor rich in leucine repeats belonging to the glycoprotein hormone receptor (GPHRs) subfamily. GPHRs consist of FSHR and LH/choriogonadotropin receptor (LH/CGR). FSH binds to and activates FSHR on the surface of female ovarian granulosa cells and male testicular Sertoli cells, leading to folliculogenesis and spermatogenesis, respectively.[114] Extragonadal tissues, including fat tissues,[115] the biliary epithelium,[116] liver tissues,[117] and bone[118] also express functional FSHR, which may be associated with glucose metabolism.

Animal experiments show that FSH induces gluconeogenesis to increase blood glucose levels. In mice, FSH enhances gluconeogenesis through G-protein-coupled receptor kinase 2 (GRK2) in the livers.[119] Moreover, increasing evidence indicates that FSH levels are positively correlated with the homeostasis model of assessment-insulin resistance (HOMA-IR) and glucose.[120] However, data from clinical studies also showed that FSH was negatively correlated with HOMA-IR during the menopausal transition. In contrast to previous animal studies, a cross-sectional study suggested that FSH is a protective

factor.[121,122] Women with premenopausal polycystic ovary syndrome (PCOS), who have lower FSH levels,[123] are more likely to suffer from insulin resistance and diabetes,[122] supporting the notion that FSH is a protective factor. Consistently, a case-control study has also reported the same conclusion.[124]

Although FSH is involved in various mechanisms of glucose metabolism, its effect on glucose metabolism is controversial in animal experiments and clinical trials, and its role requires further exploration.

LH and Glucose Metabolism

LH is produced and released by the anterior pituitary gland and plays an important role in female follicular growth stimulation, oocyte maturation, ovulation, and estrogen production.[125] Androgen hypersecretion in PCOS is mainly due to LH hypersecretion and can result in insulin resistance and diabetes in women with PCOS.[126,127] LH hypersecretion leads to increased synthesis and secretion of androgens, interfering with the insulin signaling pathway (IRS-1-PI3K-Akt-Glut) in peripheral tissues.[128] It is mainly manifested as significantly increased serine phosphorylation of insulin receptor substrate-1 (IRS-1) stimulated by insulin (p-IRS-1 S636/639) and significantly decreased phosphorylation of insulin-stimulated Akt (p-AKT S473), as well as downregulated glucose transport genes including glucose transporter 2 (GLUT2) and GLUT-4. LH increases blood glucose levels via the insulin resistance mechanism described above.

In addition to mediating insulin resistance via the above pathway, some studies have shown that androgens are closely related to inflammatory factors.[129,130] Chronic inflammation is also an important mechanism of insulin resistance. A recent study has reported elevated interleukin 6 (IL-6) levels in PCOS due to chronic inflammation.[131] IL-6 can promote androgen receptors, leading to insulin resistance.[132] In PCOS,[133] IL-6 can also mediate the JAK2/STAT3 signaling pathway whose activation can stimulate the expression of miR-21 and miR-155 to downregulate the expression of peroxisome proliferator-activated receptor γ(PPAR-γ) and GLUT4, thereby indirectly causing insulin resistance.[131] In addition to IL-6, the levels of tumor necrosis factor-α (TNF-α), IL-1α, and other inflammatory cytokines are significantly increased whereas IL-4, IL-10, and other anti-inflammatory cytokines are significantly decreased in women with PCOS,[128] which can further lead to insulin resistance (Figure 1).

Collectivize, most studies have shown that LH causes insulin resistance through hyperandrogenemia and inflammation, which increase blood glucose levels. Although the exact mechanism by which excessive levels of androgens cause inflammatory states remains unclear, we speculate that LH has a glycemic effect.

TSH and Glucose Metabolism

Pituitary thyrotropin-secreting tumors (TSH tumors) are characterized by the spontaneous secretion of TSH, which is not affected by the negative feedback of thyroid hormones. Oversecretion of thyroxine (T4) and triiodothyronine (T3) due to continued overstimulation of TSH is classified as "central hyperthyroidism".[134] The clinical presentation of patients with TSH tumors is similar to the signs and symptoms of hyperthyroidism, often accompanied by compression of the optic chiasm and pituitary cells, resulting in visual defect or loss and impaired anterior pituitary. However, some patients with untreated TSH tumors have no symptoms.[134,135]

Some studies have shed new light on the relationship between excess TSH, hepatic gluconeogenesis, and insulin resistance. TSH inhibits cAMP-regulated transcriptional coactivators 2 (CRTC2) phosphorylation and upregulates p-CREB (cAMP-response element binding protein) by activating the TSHR/cAMP/ protein kinase A (PKA) pathway. CRTC2 then enters the nucleus to bind p-CREB, resulting in increased PEPCK and G6P expression, which can promote hepatic gluconeogenesis.[136] A linear regression analysis has suggested that TSH is also independently and positively associated with HOMA-IR.[137] Moreover, recent in vitro studies in mice have reported that TSH stimulates nuclear factor-kappa B (NF-κB) DNA-binding activity via the CAMP-PKA-dependent pathway to increase TNF-α transcriptional activity.[138,139] The possible mechanisms by which TNF-α impairs insulin signal transduction include downregulating the expression of IRS-1, inhibiting tyrosine phosphorylation of IRS-1, and increasing serine/threonine phosphorylation of IRS-1. Reduced tyrosine phosphorylation and downregulation of IRS-1 expression inhibit PI3K activity, causing insulin resistance and downregulation of GLUT4 expression.[140] In summary, the molecular mechanism of TSH-induced glucose metabolism disorders are mediated by gluconeogenesis and insulin resistance (Figure 3).

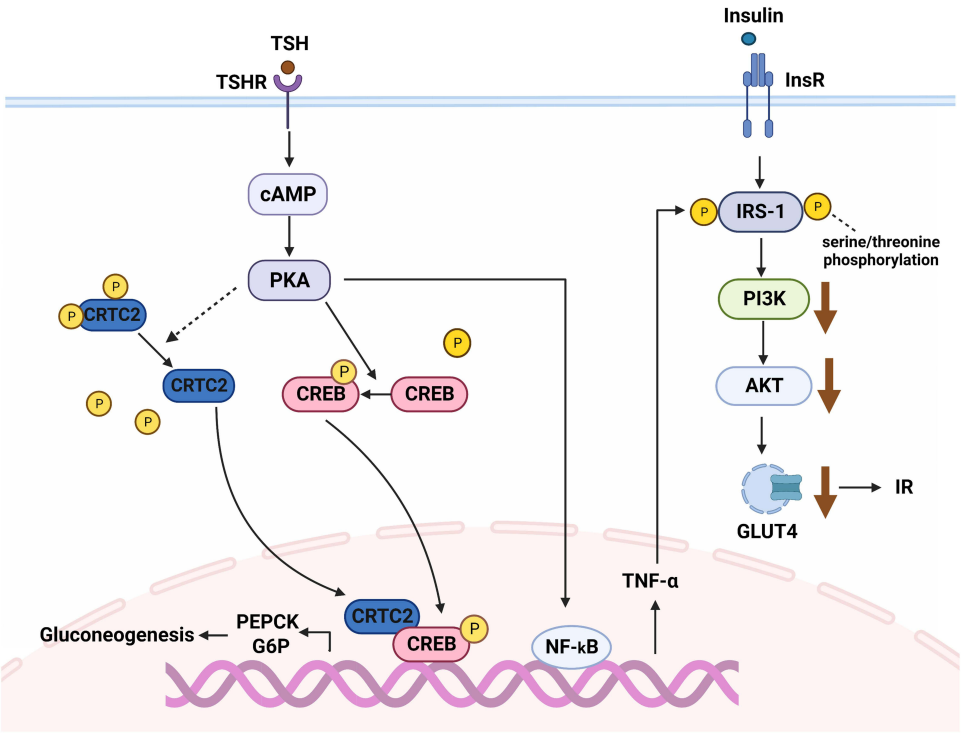

Figure 3 The regulatory mechanism of thyroid stimulating hormone (TSH) on glucose metabolism. TSH induces gluconeogenesis and insulin resistance through the TSHR/cAMP/PKA pathway.

Abbreviations: CRTC2, cAMP-regulated transcriptional coactivators 2; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; PEPCK, phosphoenolpyruvate carboxykinase; G6P, glucose-6-phosphatase; PKA, protein kinase A; TSHR, thyroid stimulating hormone receptor; IRS-1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase.

In addition to TSH, peripheral excessive thyroid hormone levels also influence blood glucose. Under a physiological state, thyroid hormones affect glucose metabolism by hindering insulin activity and promoting hepatic gluconeogenesis and glycogenolysis. In contrast, thyroid hormones can also upregulate the gene expression of phosphoglycerate kinase and GLUT-4 to promote glycolysis. They can enhance glucose processing and use in peripheral tissues via a synergistic action with insulin.[141] Therefore, under a physiological state, thyroid hormones have a dual effect on glucose metabolism. However, patients with hyperthyroidism exhibit elevated blood glucose levels. A large clinical trial suggested that impaired glucose tolerance is mainly the result of insulin resistance in the liver of patients with hyperthyroidism.[142] Mechanistically, increased blood glucose levels may be caused by altered transcription and translation of genes related to gluconeogenesis and glycogen metabolism[143] and increased GLUT2 expression on the liver cell membrane.[141] In adipose tissues, thyroid hormones accelerate insulin degradation by promoting lipolysis and increasing the concentration of FFA.[144] Moreover, severe thyrotoxicosis can irreversibly destroy pancreatic tissues, thereby disrupting glucose homeostasis.[145]

In conclusion, we summarized various pathophysiological mechanisms of TSH tumors in regulating glucose metabolism, mainly from the perspective of TSH and thyroid hormones, which may provide a therapeutic strategy for treating hyperglycemic TSH tumors.

MSH and Glucose Metabolism

Three types of MSH (α-, β-, and γ-, MSH) are secreted by the adenohypophysis. These peptide hormones are derived from proopiomelanocortin (POMC). MSH stimulates the conversion of tyrosine into melanin within melanocytes, leading to hyperpigmentation. In addition, owing to the wide distribution of its receptors, MSH also has a variety of biological activities, including energy homeostasis, food intake, and inflammatory cytokine release.[146]

Among the receptors of MSH, melanocortin 3 receptor (MC3-R)[147] and melanocortin 4 receptor (MC4-R) are involved in energy metabolism, and MC4-R is highly involved in food intake and energy expenditure.[148] Moreover, α-MSH can bind to MC4R to reduce insulin release and increase insulin sensitivity.[149] The absence of or mutations in the POMC system can lead to the development of obesity and diabetes in animals and humans. In mice, α-MSH deficiency leads to the development of type 2 diabetes.[150] In humans, mutations in β-MSH can also lead to overeating and obesity,[151] which can lead to the accumulation of adipose tissue in the body. Adipose tissue promotes insulin resistance and type 2 diabetes by releasing FFA, inflammatory cytokines, and other factors.[152] Inflammatory factors, such as TNF-α and IL-6, play an important role in insulin resistance. A previous study has shown that α-MSH inhibits the transcription of pro-inflammatory cytokines, such as IL-6 and TNF-α, by blocking the nuclear translocation of NF-κB.[153] Therefore, α-MSH can increase insulin sensitivity by downregulating inflammatory factors in the adipose tissues of obese mice, alleviating the effects of obesity (Figure 4).

In conclusion, the melanocortin system can suppress appetite and reduce body weight, which in turn can reduce blood glucose and lipid levels. These changes can impede the progression of type 2 diabetes and may act as therapeutic targets. These previous studies suggest that α-MSH or its analogs may be useful for the treatment of obesity and type 2 diabetes. However, inevitably, there are certain side effects, such as effects on the cardiovascular system.[154] Therefore, follow-up studies are needed to comprehensively determine the components and effects of this system and their potential as therapeutic targets.

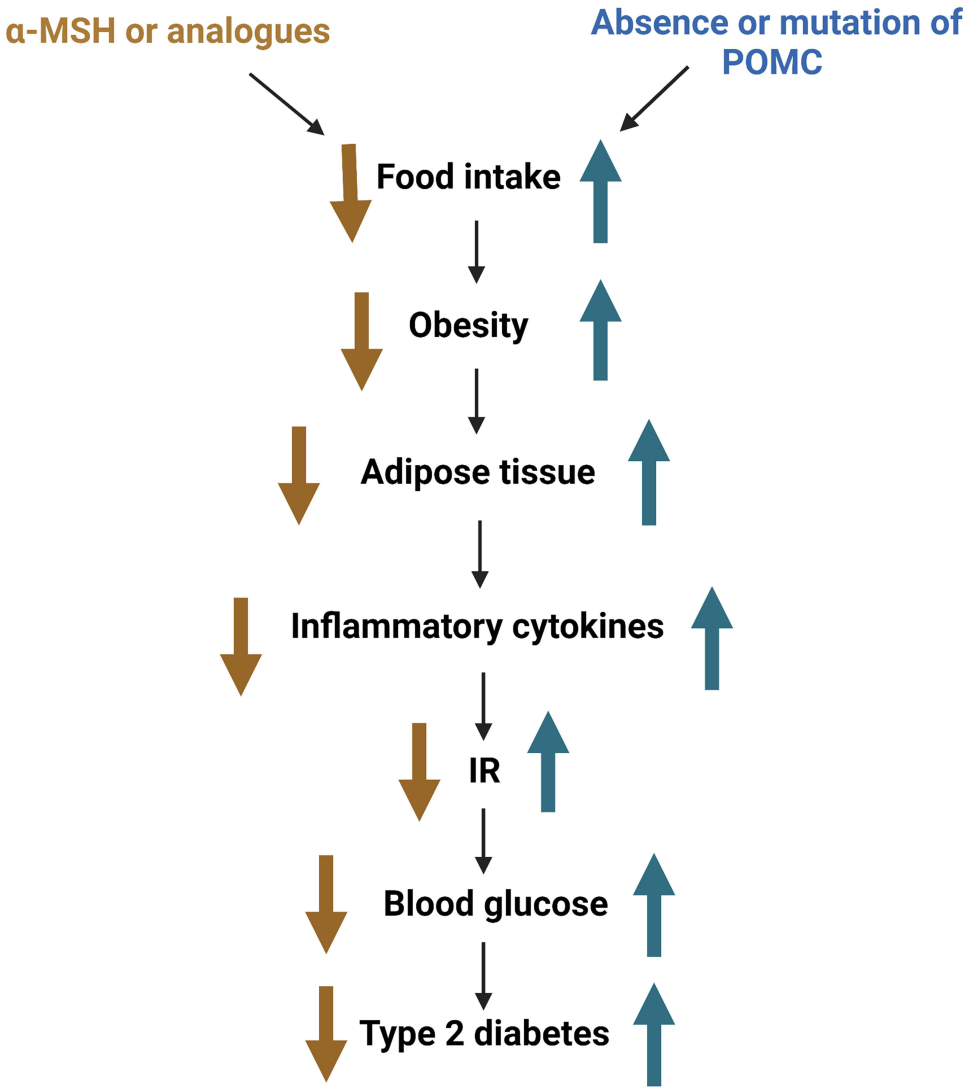

Figure 4 Relationship between the melanocortin system and diabetes.
Abbreviation: POMC, proopiomelanocortin.

Prospects of Treatment

Excessive secretion of seven hormones in pituitary tumors plays an important role in the regulation of glucose metabolism. In patients with pituitary tumors, diabetes increases the mortality rate and affects the choice of drugs for the treatment of these tumors. Several drugs have been found to affect glucose metabolism. In the first-line treatment of acromegaly, first-generation long-acting somatostatin analogs, such as octreotide, inhibit insulin secretion, which may potentially affect glucose homeostasis in patients with acromegaly.[155] However, a meta-analysis has shown that the change in glycated hemoglobin level during treatment with octreotide class is ≤0.5%,[156] indicating that the effect of octreotide on glucose metabolism is modest. Long-acting pasireotide, a second-generation somatostatin analog, is associated with frequent complications, such as hyperglycemia and diabetes, compared to first-generation somatostatin analogs.[157] The incidence of hyperglycemic events in the pasireotide group (28.7%) was significantly higher than that in the octreotide group (8.3%).[158] Second-line treatment for acromegaly involves GH receptor antagonists such as pegvisomant. Compared with octreotide, pegvisomant has a more favorable effect on glucose homeostasis, especially in reducing fasting blood glucose levels, improving glucose tolerance, and increasing insulin sensitivity.[159,160] In patients with prolactinoma, dopamine agonists, including bromocriptine (BRC) and cabergoline, are the standard treatment of choice.[161,162] The use of both agents results in significant improvements in blood glucose levels, regardless of the presence or absence of hyperprolactinemia.[163] In particular, rapidly released BRC can induce improvements in glucose tolerance and weight loss,[164] and BRC-quick release has been approved as a complementary therapy for type 2 diabetes mellitus in the United States.[165] In patients with CD, the first choice of treatment is surgical resection of pituitary adenoma, however, some patients often require drug treatment for various reasons. Drugs targeting pituitary corticotropin adenomas should inhibit tumor growth and reduce ACTH secretion. However, only pasireotide is currently approved for patients with failed or inoperable surgery.[166] Pasireotide can not only treat acromegaly but also inhibit ACTH synthesis and release. However, pasireotide also inhibits insulin secretion, thereby affecting glucose homeostasis. Moreover, six percent of patients discontinue treatment because of hyperglycemia.[167] Therefore, new drugs are needed to treat CD.

In this review, we summarized the pharmacological treatment of several common pituitary adenomas and their effects on glucose metabolism. Therefore, accurate metabolic assessment and monitoring of blood glucose levels before and after treatment should be performed when necessary. Interestingly, most pituitary adenomas show improvement in glucose metabolism after treatment and do not require additional hypoglycemic therapy. However, hypoglycemic therapy is needed if the blood glucose level of some patients is poorly controlled or if it is still not corrected after treatment for pituitary tumors. In general, hypoglycemic treatment is similar to that observed in patients with diabetes. However, attention should be paid to the effects of some hypoglycemic drugs on primary diseases and the interactions between drugs. In conclusion, we need to balance benefits and risks to determine the best treatment for patients.

Conclusions and Prospects

In summary, this study reviews the effects of seven complex pituitary hormones on glucose metabolism via different mechanisms. Our review indicates that excessive hormone levels would lead to an imbalance of blood glucose homeostasis, and abnormal blood glucose levels might be the early manifestation of some diseases, which provides clues for the early diagnosis and treatment of related diseases. New drugs based on the above mechanism need to be explored further. Compared to other reviews, the present review is more extensive and comprehensive. However, the roles of some hormones remain controversial and require further study.

Abbreviations

PRL, prolactin; GH, growth hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; MSH, melanocyte-stimulating hormone; TIDA, tuberoinfundibular dopamine neurons; PRLRs, prolactin receptors; HOMA, homeostatic model assessment; ISI, insulin sensitivity index; BMI, body mass index; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide 3-kinase; IGF-1, insulin-like growth factor 1; CS, Cushing's syndrome; CD, Cushing's disease; ACT, cortisol-secreting adrenocortical tumor; GC, glucocorticoid; FOXO1, forkhead box protein O1; IRS1, insulin substrate 1; PI3Kr1, phosphoinositide-3-kinase

regulatory subunit 1; AKT, protein kinase B; GLUT4, glucose transporter 4; GLUT2, glucose transporter 2; NEFAs, non-esterified fatty acids; FFA, free fatty acids; ATGL, adipose triglyceride lipase; GPRC6A, G protein-coupled receptor, family C, group 6, member A; GLP-1, glucagon-like peptide-1; CAMP, cyclic adenosine monophosphate; IGT, impaired glucose tolerance; GR, glucocorticoid receptor; UPR, unfolded protein response; NPY, nerve peptide Y; AgRP, agouti-related protein; JAK, Janus tyrosine kinase; STAT, signal transducers and activators of transcription; FSHR, follicle-stimulating hormone receptor; GPHRs, glycoprotein hormone receptors; CGR, choriogonadotropin receptor 2; GRK2, G-protein-coupled receptor kinase 2; PCOS, polycystic ovary syndrome; IL-6, interleukin 6; PPAR-γ, peroxisome proliferator activated receptor γ; TNF-α, tumor necrosis factor-α; IL-18, interleukin 18; T4, thyroxine; T3, triiodothyronine; CRTC2, cAMP-regulated transcriptional coactivators 2; CREB, cAMP-response element binding protein; PEPCK, phosphoenolpyruvate carboxykinase; G6P, glucose-6-phosphatase; PKA, protein kinase A; NF-κB, nuclear factor-kappa B; TyG, triglyceride glucose; POMC, proopiomelanocortin; MC3-R, melanocortin 3 receptor; MC4-R, melanocortin 4 receptor; MKP-3, mitogen-activated protein kinase phosphatase-3; PGC1α, peroxisome proliferator-activated receptor-γ coactivator-1α; BRC, bromocryptotine.

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Author Contributions

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Disclosure

The authors report no conflicts of interest in this work.

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