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Editors

# **Receptor-Targeted Therapies in Diabetes Mellitus**

**From Pathophysiology to Innovative Treatments**



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## Chapter 6

# Insulin Receptors in Hypothalamus: Key Regulators of Glucose Homeostasis and Diabetes

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### Abstract

Insulin receptors (IR) play a critical role in maintaining glucose homeostasis, particularly through central mechanisms in the hypothalamus. Hypothalamic IR signaling regulates hepatic glucose production (HGP) by modulating enzymatic activity and interacting with neural circuits. Glucose-responsive neurons in the arcuate and ventromedial regions of the hypothalamus detect fluctuations in glucose levels, initiating hormonal and behavioral responses to maintain euglycemia. Insulin's central action on  $K^+$ -ATP channels significantly reduces HGP; however, this process can be disrupted by sulfonylureas such as tolbutamide. Additionally, insulin regulates HGP through the vagus nerve and the cytokine interleukin-6 (IL-6), highlighting the roles of the autonomic nervous system and inflammatory pathways in glucose metabolism.

Advanced techniques, including adenoviral delivery and neuron-specific ablation, are used to identify the neuronal populations and mechanisms involved. This chapter explores hypothalamic IR signaling and its therapeutic potential for diabetes, emphasizing the intricate regulatory network of insulin within the central nervous system (CNS).

**Keywords:** Insulin receptors, hepatic glucose production, diabetes, glucose homeostasis

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## Abbreviations

AgRP	Agouti-related peptide
ANS	Autonomic nervous system
ARC	Arcuate nuclei
CNS	Central nervous system
cryo-EM	Cryogenic electron microscopy
DMN	Dorsomedial nucleus
ERK	Extracellular signal-regulated kinase
FOXO	Forkhead Box O
G6Pase	Glucose-6-phosphatase
GABA	Gamma-aminobutyric acid signals
GE	Glucose-excited neuron cells
G:	Glucose-inhibited neuron cells
GLP-1	Glucagon-like peptide
GLUT	Glucose transporter
GSK3	Glycogen synthase kinase 3
HGP	Hepatic glucose production
ICV	Intracerebroventricular
IL-6	Interleukin-6
IR	Insulin receptors
JNK	c-Jun NH2-terminal kinase
KATP	ATP-sensitive potassium channels
LCFA	Long-chain fatty acids
LH	Lateral hypothalamic
MAPK	Mitogen-activated protein kinase
MC4R	Melanocortin 4 receptor
MCH	Melanin-concentrating hormone
mTOR	Mechanistic target of rapamycin
NP-Y	Neuropeptide Y
NTS	Nucleus tractus solitarius
OCH	Orexin-concentrating hormone
PDK1	Phosphoinositide-dependent protein kinase-1
PEPCK P	Phosphoenolpyruvate carboxykinase
PI3K/AKT	Phosphoinositide 3-kinase
PIP3	Phosphatidylinositol-3,4,5-triphosphate
POMC	Pro-opiomelanocortin-related peptide
PTB1B	Protein tyrosine phosphatase 1B
PV	Paraventricular nucleus
RBCs	Red blood cells
SCL2A	Solute carrier family 2 members
SF-1	Steroidogenic factor 1-expressing neurons
SHC	Src homology 2 domain-containing transforming protein
SOCS3	Suppressor of cytokine signaling 3
STAT3	Signal transducer and activator of transcription 3

Tyr	Tyrosine residues
VM	Ventromedial nucleus
$\alpha$ -MSH	$\alpha$ -melanocyte-stimulating hormone

## Introduction

Insulin receptors in the hypothalamus play a pivotal role in regulating glucose homeostasis and maintaining overall metabolic balance. The hypothalamus, a critical brain region, integrates various metabolic signals and influences peripheral glucose metabolism through neural and hormonal pathways (Pan et al. 2023). Recent studies have demonstrated that insulin action in the hypothalamus significantly impacts hepatic glucose production (HGP). For example, blocking insulin signaling in the brain impairs the suppression of HGP, while central insulin administration effectively reduces HGP, independent of circulating insulin levels. This effect is mediated through KATP channels in hypothalamic neurons and the vagus nerve, linking central insulin action to liver function. Furthermore, insulin in the hypothalamus increases hepatic IL-6 expression, activating STAT3 signaling to inhibit gluconeogenesis (Petersen and Shulman, 2018). These mechanisms highlight the critical role of hypothalamic insulin signaling pathways in controlling peripheral glucose metabolism and maintaining glucose homeostasis. Dysfunction in hypothalamic insulin signaling has significant implications for metabolic disorders such as diabetes. Impairments in glucose sensing and glucose tolerance have been observed with the deletion of insulin-responsive GLUT4 in the brain, further emphasizing the hypothalamus's role in glucose regulation (Flores-Cortez et al. 2023). These findings suggest that insulin resistance in the hypothalamus can contribute to the pathogenesis of diabetes by disrupting the brain's ability to regulate glucose levels and insulin secretion (Alonge et al. 2020). Understanding the mechanisms by which insulin receptors influence glucose homeostasis could pave the way for novel therapeutic strategies to treat diabetes and other metabolic disorders (Cai et al. 2020).

## The Crucial Role of the Insulin Receptor in Glucose Regulation

Insulin, a crucial anabolic peptide hormone produced by pancreatic  $\beta$ -cells, plays a central role in regulating human metabolism. Beyond its well-established function in glucose homeostasis, insulin exerts diverse effects throughout the body (Beaupere et al. 2021). Found in all metazoans, insulin-like signaling controls evolutionarily conserved processes such as reproduction and lifespan. When insulin binds to its receptor (IR), it initiates a series of structural changes and self-phosphorylation events, activating a cascade of kinase signaling pathways (De Meyts, 2004). The PI3K/AKT pathway is pivotal in mediating insulin's metabolic effects, facilitating glucose uptake into muscle and adipose tissues by translocating GLUT4 transporters. In the liver, insulin enhances glycogen and lipid synthesis while suppressing gluconeogenesis (Savova et al. 2023). Additionally, IR signaling supports cellular growth, proliferation, and development. Alongside the PI3K/AKT pathway, the MAPK pathway mediates insulin's mitogenic effects (Rahman et al. 2021). Dysfunction in IR signaling, due to pancreatic  $\beta$ -cell loss or insulin resistance, disrupts these processes, leading

to the persistent elevation of blood glucose levels characteristic of diabetes mellitus. Understanding these pathways is crucial for developing therapies that restore proper insulin function and effectively manage metabolic disorders. Patients with diabetes face numerous complications that result in various disease states, underscoring the urgent need to target IR for diabetes treatment (Martín-Timón, 2014). Although the detailed mechanism of insulin-binding-induced IR activation is not fully understood, recent advancements in cryo-EM have expanded our knowledge by revealing various structures of ligand-bound IR, including those with insulin, peptides, and aptamers. Challenges remain, however, in elucidating how insulin accesses and triggers structural changes at apolipoprotein IR binding sites, coordinates extracellular domain conformational changes with cytoplasmic kinase domain autophosphorylation, and determines how agonists bias IR towards specific metabolic effects through functional selectivity (Zakir et al. 2023).

### **Insulin Receptor Activation: Insight and Challenges**

Insulin initiates a cascade of events upon binding to the insulin receptor (IR) in peripheral tissues, crucially activating the receptor and triggering intracellular signaling pathways. The initial steps in IR activation involve the auto-phosphorylation of specific tyrosine residues within the receptor (Le et al. 2023). Notably, three tyrosine residues Tyr1146, Tyr1150, and Tyr1151 located in the kinase activation loop of IR isoform A are sequentially phosphorylated. This process is essential for regulating the kinase activity of IR. In its inactive state, the unphosphorylated activation loop obstructs the catalytic site of the kinase, inhibiting its function by preventing substrate and ATP binding (Yunn et al. 2023). Upon insulin binding, these tyrosine residues undergo phosphorylation, causing the activation loop to move away from the catalytic site. These conformational changes enhance IR kinase activity, enabling interactions with substrates and ATP, thereby initiating downstream signaling events. Insulin also induces phosphorylation of additional tyrosine residues located in the juxtamembrane and C-terminal regions of IR (Kim and Novak, 2007). Among these, phosphorylation of Tyr960 (pY960) in the juxtamembrane creates a docking site for IR substrate proteins and SHC. This interaction facilitates IR-mediated phosphorylation of IR substrate-1 (IRS-1) and SHC, which are crucial for propagating insulin signaling within the cell. The roles of phosphorylated Tyr1316 (pY1316) and Tyr1322 (pY1322) in the C-terminal domain are less clearly understood but are implicated in regulating IR kinase activity and its interaction with adaptor proteins. Insulin receptor activation primarily triggers two major signaling pathways: the PI3K/AKT and MAPK pathways. The PI3K/AKT pathway is responsible for most of the metabolic effects induced by insulin in peripheral tissues (Tennagels et al. 2000). IRS proteins bind to the p85 regulatory subunit of PI3K, activating it to produce PIP3. PIP3 recruits PDK1 and activates AKT, which phosphorylates various downstream targets (Denley et al. 2009). These targets include GLUT4, which promotes glucose uptake; GSK3, which promotes glycogen synthesis; and mTOR, which promotes protein and lipid synthesis (Hahn and Denlinger, 2007). Additionally, AKT phosphorylates FOXO transcription factors, regulating gene expression (Lee et al. 2022). Conversely, the MAPK pathway, initiated by SHC and IR substrate proteins, regulates insulin's mitogenic effects on cell growth, proliferation, and differentiation. This pathway involves the Grb2-Sos-Ras-Raf-ERK signaling cascade. ERK phosphorylates

cytoplasmic and nuclear proteins, influencing cellular responses and acting as a transcription factor. Thus, insulin receptor activation orchestrates a complex network of signaling pathways that regulate critical metabolic and growth processes in response to insulin stimulation in peripheral tissues (Borisov et al. 2009).

## **Role of Hypothalamus in Glucose Homeostasis**

The rising global epidemic of obesity and metabolic disorders, particularly type 2 diabetes, poses a significant biomedical challenge. Obesity-related type 2 diabetes is characterized by impaired glucose homeostasis, yet the underlying mechanisms remain poorly understood (Chobot et al. 2018). Maintaining glucose homeostasis is vital for mammalian survival, as glucose is minimally stored in the body and its levels must be tightly regulated through communication with peripheral organs (Perreault et al. 2016). Interestingly, glucose levels in the central nervous system (CNS) are significantly lower than those in circulation, typically ranging between 1 mmol/L and 2.5 mmol/L, and can drop to as low as 0.5 mmol/L. The hypothalamus, a key region for glucose regulation, contains various nuclei with distinct neuronal populations that express neuropeptides and neurotransmitters essential for energy homeostasis (Roh et al. 2016). Its ability to sense and respond to fluctuations in glucose levels underscores its critical role in maintaining glucose balance (Karnani and Burdakov, 2011). These nuclei and neuronal populations are adept at detecting changes in glucose levels and other metabolic cues, integrating this information, and orchestrating appropriate physiological responses. This function is crucial not only for normal metabolic processes but also in the context of metabolic disorders (Alvarsson and Stanley, 2018). Dysregulation of hypothalamic function can contribute to the development and progression of type 2 diabetes and other metabolic conditions. Furthermore, the hypothalamus's role in glucose sensing is significant in the context of type 1 diabetes, particularly concerning the development of hypoglycemia unawareness—a dangerous condition in which patients fail to recognize symptoms of low blood sugar (Lundqvist et al. 2019). Understanding the mechanisms by which the hypothalamus senses glucose and its impact on metabolic health is therefore critical for developing novel therapeutic strategies to manage and treat diabetes and related metabolic disorders (Zhao et al. 2023).

## **Hypothalamic Glucose-Sensing Neurons: Location and Function**

Higher organisms have developed specialized sensor and effector mechanisms to maintain systemic glucose homeostasis. The brain, which consumes 60–70% of total glucose, predominantly utilizes high-affinity transporters such as GLUT-1 and GLUT-3, enabling effective glucose uptake independent of insulin. This highlights the brain's critical role in glucose surveillance. Recent evidence suggests that continuous glucose monitoring occurs through specific cell types across various brain regions, including the brainstem, corticolimbic areas, and hypothalamus. While much focus has been on neuronal glucose sensing, the role of non-neuronal cells is gaining attention. Among these regions, the hypothalamus has been identified as a central hub in the complex and distributed glucose-sensing network (Agrawal et

al. 2021). The hypothalamus comprises distinct nuclei, such as the paraventricular (PV), ventromedial (VM), lateral (LH), and arcuate (ARC) nuclei, each containing specific populations of glucose-sensing neurons. The ARC, located adjacent to the third ventricle and median eminence, houses opposing neuronal populations: orexigenic AgRP-producing neurons and anorexigenic POMC-derived neurons. Together with MC4R-expressing neurons, these form the melanocortin system, which is crucial for regulating appetite, energy expenditure, and glucose homeostasis (Bétry et al. 2018). The interaction between  $\alpha$ -MSH and AgRP at MC4Rs influences downstream pathway activation. AgRP neurons, which send inhibitory GABAergic signals to POMC neurons, also express the orexigenic neuropeptide Y (NPY). The balance between orexigenic and anorexigenic signals ultimately determines metabolic outcomes. While AgRP neurons are primarily classified as gastrointestinal (GI) neurons, POMC neurons are generally considered glucose-excitatory (GE) neurons (Deem et al. 2022). However, recent findings suggest that glucose modulation of POMC neuron activity may result from presynaptic inputs rather than direct glucose detection. ARC POMC and AgRP neurons project to various hypothalamic and extrahypothalamic regions, including the ventromedial nucleus (VMN), where neurons sense changes in extracellular glucose levels. Notably, SF1-expressing neurons in the VMN express receptors for key metabolic hormones, although only about 10% are responsive to glucose (Bell et al. 2018). The VMN is essential for regulating energy balance and initiating counter-regulatory responses to hypoglycemia. The LH is a heterogeneous structure containing various neuronal populations, including orexin and melanin-concentrating hormone (MCH) neurons. Orexin neurons are generally classified as GI, while some MCH neurons are considered GE. This area plays a vital role in regulating arousal, appetite, and reward (Chan and Sherwin, 2013).

## **Mechanism of Neuronal Glucose Sensing in the Hypothalamus**

The hypothalamus regulates blood glucose levels by sensing, integrating, and responding to fluctuations through its control of the autonomic nervous system (ANS) and the endocrine system. It contains two types of glucose-sensing neurons: GE neurons, which activate when glucose levels rise, and glucose-inhibited (GI) neurons, which activate when glucose levels drop (Routh, 2010). In the ARC, GE neurons, such as POMC neurons, respond to high glucose levels by increasing activity and releasing  $\alpha$ -MSH, which reduces appetite and increases energy expenditure. Conversely, GI neurons in the ARC, including those expressing AgRP and NPY, are activated under low glucose conditions, stimulating feeding to restore glucose levels (Jais and Brüning, 2022). The VM hypothalamic nucleus contains steroidogenic factor-1 (SF1)-expressing neurons that respond to low glucose levels by initiating processes that increase blood sugar, such as glucagon secretion and hepatic glucose production. These neurons integrate signals from GE and GI neurons to maintain glucose homeostasis (Hirschberg et al. 2020). Additionally, glucose-sensing neurons in the LH and brainstem regions, such as the nucleus of the solitary tract and the dorsal motor nucleus of the vagus, contribute to glucose regulation by transmitting signals from peripheral organs to the brain. This intricate network ensures stable blood glucose levels, which is vital for preventing metabolic disorders like diabetes (Boychuk et al. 2015).

## **Role of Hypothalamus in Regulating Hepatic Glucose Production**

The hypothalamus regulates food intake and energy expenditure by monitoring blood levels of key hormones and nutrients. The ARC, situated near the median eminence and surrounding the third ventricle, senses these metabolic signals due to its strategic location (Tran et al. 2022). The ARC contains orexigenic neurons that produce NP and AgRP, as well as anorexigenic neurons that produce POMC and cocaine-amphetamine regulated transcript ( $\alpha$ -MSH), which activate pathways that reduce food intake and increase energy expenditure via melanocortin receptors. AgRP counteracts  $\alpha$ -MSH by binding to these receptors (Bouret, 2022).

The PV nucleus produces catabolic neuropeptides and controls sympathetic output to enhance fatty acid oxidation. The VM hypothalamus senses glucose and leptin, producing brain-derived neurotrophic factor to regulate satiety and glucose homeostasis (Yu and Kim, 2012). The DMN and LH also play roles, with the LH functioning as a feeding center due to its production of MCH and orexin, which regulate appetite and energy balance (Lee et al. 2021).

## **Brain-Based Mechanism for Managing Glucose Levels**

A specialized group of neurons in the brain detects metabolic signals, including hormones like insulin and leptin, as well as nutrients such as glucose and fatty acids, primarily in the hypothalamus and brainstem. These brain regions contain neurons that adjust their excitability in response to changes in extracellular glucose levels. Two main types of glucose-sensing neurons exist: glucose-excited neurons, which activate when extracellular glucose levels rise, and glucose-inhibited neurons, which become active when glucose levels drop (Jordan et al. 2010). Glucose-excited neurons are predominantly found in the ventromedial (VM) ARC, and paraventricular nucleus (PVN). In contrast, glucose-inhibited neurons are located in the lateral hypothalamus (LH), ARC, and PVN (De Backer et al. 2016). Both types are also present in the dorsal vagal complex of the brainstem, which includes the nucleus of the solitary tract (NTS), the area postrema, and the dorsal motor nucleus of the vagus (Khodai et al. 2018).

## **Detection and Response to Glucose Change**

Maintaining stable blood glucose levels requires a rapid response to fluctuations in plasma glucose. When glucose-sensing neurons in the hypothalamus and other regions detect a potential drop in blood sugar, they initiate a core response. This detection activates a series of neural and hormonal mechanisms designed to prevent further declines in glucose levels and restore normal blood sugar levels (euglycemia) (Stanley et al. 2019).

## **Mechanism of Glucose Level Detection by Hypothalamic Neurons**

Proper management of glucose metabolism is crucial for brain physiological processes, which are monitored by glucose-detecting neurons. These neurons modify their electrical activity in response to changing glucose levels. Importantly, these neurons can directly sense glucose level

changes without relying on indirect presynaptic modulation. These specialized neurons are concentrated in the hypothalamic region and outside the hypothalamus (Yoon and Diano, 2021). The hypothalamus plays a crucial role in blood glucose regulation, as it can detect, process, and respond to changes in circulating signals. This intricate function is achieved through its influence on the ANS and the endocrine system (Fioramonti, 2023). The hypothalamus contains two types of glucose-responsive neurons: those excited by glucose and those inhibited by it. Rising glucose levels activate GE neurons, while low glucose conditions stimulate GI neurons. The ARC and VMH nuclei play important roles in understanding their glucose-detecting mechanisms and their role in glucose metabolism, particularly in hypothalamic regions (Jordan et al. 2010). The GE neurons and pancreatic  $\beta$ -cells both increase their activity when glucose levels rise. In  $\beta$ -cells, this process involves glucose uptake via GLUT2, glucose phosphorylation by glucokinase, and glucose metabolism leading to increased ATP production. This increase in ATP closes KATP channels, depolarizes the membrane, and allows calcium entry, triggering insulin release. Given these similarities, researchers have investigated the involvement of GLUT2, glucokinase, and KATP channel components (SUR1, SUR2, and Kir6.2) in central glucose sensing (Jordan et al. 2010; Thorens, 2015). GLUT2 is found in brain regions containing glucose-responsive neurons. Studies involving genetically modified mice have shown that GLUT2 in the CNS plays a role in counteracting low blood sugar (Sun et al. 2023). In pancreatic  $\beta$ -cells, glucokinase controls ATP production through glycolysis and regulates KATP channel activity. The pancreatic variant of glucokinase is also present in glucose-sensing brain areas and is involved in approximately 70% of GE neurons. Furthermore, when glucokinase was selectively reduced in cultured neurons from the VM hypothalamus, these neurons lost their ability to sense glucose (De Backer et al. 2016). In the brain, KATP channels (composed of subunits SUR1 and Kir6.2) play a crucial role in linking glucose metabolism to changes in electrical activity, particularly in the glucose-sensing regions of the hypothalamus. Electrophysiological studies have shown that inhibiting or activating KATP channels can alter how GE neurons respond to changes in glucose levels in laboratory settings and living organisms (Mc Traggart et al. 2010). Extensive research suggests that GE neurons respond to elevated extracellular glucose like pancreatic  $\beta$ -cells. This process involves increased ATP levels, which lead to the closure of KATP channels. This closure results in membrane depolarization, followed by calcium influx through voltage-gated channels, ultimately enhancing neuronal activity and neurotransmitter release (Fridyland et al. 2011). However, some evidence also suggests the presence of alternative glucose-sensing mechanisms in neurons that may not rely on KATP channels or GLUT2.

### **Hormonal, Physiological and Behavioural Responses to Restore Euglycemia**

The brain relies heavily on glucose for fuel, necessitating precise regulation of blood sugar levels (glucose homeostasis) through hormonal and physiological responses to prevent hypoglycemia, which is rare in healthy individuals (Mergenthaler et al. 2013). However, diabetes mellitus, particularly in patients treated with insulin, can lead to frequent hypoglycemic episodes, which may result in confusion, seizures, and even coma or death (Spargue et al. 2011). In healthy individuals, blood sugar levels are maintained through predictable responses activated by the sympathetic nervous system, with physiological and

behavioral reactions occurring at specific glucose thresholds (Stanley et al. 2019). Three primary protective mechanisms are initiated: insulin production decreases as pancreatic  $\beta$ -cells reduce output, glucagon production increases from pancreatic  $\alpha$ -cells, and the adrenal medulla releases more epinephrine into the bloodstream (Sprague and Arbeláez, 2011; Senthilkumaran et al. 2024). As glucose levels fall within the normal range (4.4-4.7 mmol/L or 80-85 mg/dL), the pancreas reduces insulin production, promoting glucose production while decreasing its use by non-brain tissues. If levels drop below normal (3.6-3.9 mmol/L or 65-70 mg/dL), counterregulatory hormones, such as glucagon and epinephrine, stimulate glucose production in the liver and limit glucose use in insulin-sensitive tissues. At even lower levels (2.8-3.0 mmol/L or 50-55 mg/dL), symptoms of hypoglycemia appear, and brain function becomes impaired below 2.8 mmol/L or 50 mg/dL. In poorly controlled diabetics, these thresholds shift higher, while individuals with frequent low blood sugar or excessive insulin production may develop lower thresholds. These mechanisms prompt individuals to consume carbohydrates to restore normal blood sugar levels (euglycemia) (Verhulst et al. 2022). Unlike glucagon and epinephrine, which act quickly, growth hormone and cortisol have a delayed impact during hypoglycemia. Research using controlled hormone suppression and replacement techniques has revealed time-dependent effects; for instance, when cortisol levels were kept low, glucose production decreased, and utilization increased after 6 hours, resulting in lower blood glucose levels after 9.5 hours, despite unchanged glucagon, insulin, and growth hormone levels (Stanley et al. 2019). A study comparing healthy adults with patients lacking growth hormone and cortisol due to hypopituitarism found that the hormone-deficient group had lower blood glucose levels starting 2.5 hours after insulin infusion began, becoming statistically significant by 12 hours. However, both groups recovered quickly from hypoglycemia once insulin infusion stopped, indicating that growth hormone and cortisol do not play a crucial role in the immediate correction of low blood sugar (Stanley et al. 2019; Defeo et al. 1989).

### **Involvement of the Autonomous Nervous System and Inflammatory Pathways**

The CNS plays a crucial role in the development of diabetes, which is primarily a disorder of peripheral tissues. The hypothalamus, a key structure within the CNS, is central to regulating glucose levels due to its position at the intersection of neuroendocrine and autonomic systems. Emerging evidence suggests that hypothalamic inflammation significantly disrupts glucose homeostasis. Although the exact cause of this inflammation remains unclear, it is closely linked to various forms of cellular stress, including endoplasmic reticulum stress, RNA stress, oxidative damage, and autophagy defects. These stress factors can trigger or enhance the activation of pro-inflammatory NF- $\kappa$ B pathways. The effectiveness of anti-inflammatory treatments and therapies targeting these pathways in alleviating diabetic symptoms indicates their potential for managing the widespread disease and its complications. The underlying mechanisms of hypothalamic inflammation involve multiple dynamic processes (Inoue, 2016).

### **Influence of Insulin on HGP via Vagal Nerve**

The liver plays a crucial role in maintaining overall glucose balance by regulating glucose production based on energy needs. Insulin, present in high concentrations in portal blood, is the primary regulator of HGP. In diabetes, increased HGP is correlated with elevated fasting blood glucose levels. Insulin directly influences liver cells to control HGP (Sharabi et al. 2018). When insulin binds to its receptors, it activates a signaling cascade involving PI3K, IRS, PDK1, and Akt, which suppresses HGP. Consequently, mice lacking liver-specific insulin receptors or having impaired PI3K signaling exhibit high insulin levels and glucose intolerance, along with reduced insulin-mediated suppression of HGP. Meanwhile, insulin regulates HGP through both direct and indirect pathways (Petersen and Shulman, 2018). While direct control occurs via insulin receptors in the liver, indirect regulation involves insulin's effect on other organs. Studies have shown that insulin can still partially suppress HGP even when PI3K signaling is inhibited in the liver. Moreover, research comparing I.V. and I.P. insulin administration revealed that the magnitude of insulin levels reflects direct insulin action on liver cells. These findings suggest that the relationship between insulin and HGP regulation is more complex. Insulin indirectly inhibits HGP through two main mechanisms. First, it decreases the release of glycerol and free fatty acids from adipose tissue, which are essential materials and energy sources for gluconeogenesis. Second, it reduces the expression of key genes involved in gluconeogenesis in the liver, especially those encoding PEPCK and G6Pase (Inoue et al. 2016; Egerton et al. 2017). The vagus nerve plays a crucial role in how central insulin action regulates HGP. Cutting the hepatic branch of the vagus nerve reduces the HGP-suppressing effect of ICV insulin administration. The vagus nerve typically maintains steady activity, but studies in anesthetized rats show that blood glucose increases enhance this activity, while insulin increases inhibit it. HGP is also lowered by ICV  $\alpha$ -MSH administration. Furthermore, administering diazoxide (a KATP channel activator that hyperpolarizes neurons) to the dorsal motor nucleus of the vagus suppresses HGP. These findings suggest that HGP suppression may result from vagus nerve activation (Matsuhisa et al. 2000). The vagus nerve's influence extends beyond HGP regulation to broader hepatic glucose metabolism. This is evidenced by insulin resistance in vagotomized rats, increased hepatic glycogen synthase activity following vagal stimulation in rabbits, and enhanced glucose utilization in perfused rat livers when the vagus is stimulated in the presence of insulin. Notably, the insulin resistance induced by vagotomy in rats can be mitigated by intraportal administration of acetylcholine. However, this suggests that the control of HGP by central insulin action cannot be explained solely by the direct effect of acetylcholine released by the vagus on liver cells (Matsuhisa et al. 2000; Kistner et al. 2022; Ellingsgaard et al. 2020; Nieto-Vazquez et al. 2008; Erta et al. 2012; Febbraio et al. 2004; De Melo Madureira et al. 2022).

### **Conclusion**

This chapter explores the intricate mechanisms underlying glucose homeostasis, emphasizing the critical role of the insulin receptor (IR) and its activation in regulating blood glucose levels. The insulin receptor is essential for glucose uptake and metabolism, and its proper activation is crucial for maintaining euglycemia. Despite advancements in understanding IR function,

challenges remain in optimizing therapeutic targeting, necessitating further research to enhance diabetes management strategies. The hypothalamus's role in glucose regulation is also examined, highlighting its function through glucose-sensing neurons that monitor glucose levels and adjust hepatic glucose production accordingly. This central control illustrates the hypothalamus's significant influence on metabolic processes. Additionally, mechanisms involved in detecting glucose changes and initiating appropriate physiological responses to stabilize glucose levels are discussed. The interplay between hormonal, physiological, and behavioral responses, along with contributions from the autonomic nervous system and inflammatory pathways, is essential for restoring euglycemia. Lastly, the cytokine IL-6's role in modulating insulin's effects sheds light on the regulatory network affecting insulin sensitivity and glucose metabolism, paving the way for future research on glucose-related disorders.

## References

- Agrawal, R., Reno, C. M., Sharma, S., Christensen, C., Huang, Y., & Fisher, S. J. (2021). Insulin action in the brain regulates both central and peripheral functions. *American Journal of Physiology-Endocrinology and Metabolism*, 321(1), E156–E163.
- Alonge, K. M., D'Alessio, D. A., & Schwartz, M. W. (2021). Brain control of blood glucose levels: Implications for the pathogenesis of type 2 diabetes. *Diabetologia*, 64(1), 5–14.
- Alvarsson, A., & Stanley, S. A. (2018). Remote control of glucose-sensing neurons to analyze glucose metabolism. *American Journal of Physiology-Endocrinology and Metabolism*, 315(3), E327–E339.
- Beaupere, C., Liboz, A., Fève, B., Blondeau, B., & Guillemain, G. (2021). Molecular mechanisms of glucocorticoid-induced insulin resistance. *International Journal of Molecular Sciences*, 22(2), 623.
- Bell, B. B., Harlan, S. M., Morgan, D. A., Guo, D. F., & Rahmouni, K. (2018). Differential contribution of POMC and AgRP neurons to the regulation of regional autonomic nerve activity by leptin. *Molecular Metabolism*, 8, 1–12.
- Bétry, C., Thobois, S., Laville, M., & Disse, E. (2018). Deep brain stimulation as a therapeutic option for obesity: A critical review. *Obesity Research & Clinical Practice*, 12(3), 260–269.
- Borisov, N., Aksamitiene, E., Kiyatkin, A., Legewie, S., Berkhout, J., Maiwald, T., Kaimachnikov, N. P., Timmer, J., Hoek, J. B., & Kholodenko, B. N. (2009). Systems-level interactions between insulin–EGF networks amplify mitogenic signaling. *Molecular Systems Biology*, 5(1), 256.
- Bouret, S. G. (2022). Developmental programming of hypothalamic melanocortin circuits. *Experimental & Molecular Medicine*, 54(4), 403–413.
- Boychuk, C. R., Gyarmati, P., Xu, H., & Smith, B. N. (2015). Glucose sensing by GABAergic neurons in the mouse nucleus tractus solitarius. *Journal of Neurophysiology*, 114(2), 999–1007.
- Cai, M., Liao, Z., Zou, X., Xu, Z., Wang, Y., Li, T., Li, Y., Ou, X., Deng, Y., Guo, Y., Peng, T., & Li, M. (2020). Herpes Simplex Virus 1 UL2 inhibits the TNF- $\alpha$ -mediated NF- $\kappa$ B activity by interacting with p65/p50. *Frontiers in Immunology*, 11, 549.
- Chan, O., & Sherwin, R. (2013). Influence of VMH fuel sensing on hypoglycemic responses. *Trends in Endocrinology & Metabolism*, 24(12), 616–624.
- Chobot, A., Górowska-Kowolik, K., Sokołowska, M., & Jarosz-Chobot, P. (2018). Obesity and diabetes—Not only a simple link between two epidemics. *Diabetes/Metabolism Research and Reviews*, 34(7), e3042.
- D'souza, A. M., Neumann, U. H., Glavas, M. M., & Kieffer, T. J. (2017). The glucoregulatory actions of leptin. *Molecular Metabolism*, 6(9), 1052–1065.
- De Backer, I., Hussain, S. S., Bloom, S. R., & Gardiner, J. V. (2016). Insights into the role of neuronal glucokinase. *American Journal of Physiology-Endocrinology and Metabolism*, 311(1), E42–E55.

- De Melo Madureira, Á. N., de Oliveira, J. R. S., & de Menezes Lima, V. L. (2022). The role of IL-6 released during exercise to insulin sensitivity and muscle hypertrophy. *Mini Review in Medicinal Chemistry*, 22(18), 2419–2428.
- De Meyts, P. (2004). Insulin and its receptor: Structure, function and evolution. *BioEssays*, 26(12), 1351–1362.
- Deem, J. D., Faber, C. L., & Morton, G. J. (2022). AgRP neurons: Regulators of feeding, energy expenditure, and behavior. *The FEBS Journal*, 289(8), 2362–2381.
- Defeo, P., Perriello, G., Torlone, E., Ventura, M. M., Santeusano, F., Brunetti, P., Gerich, J. E., & Bolli, G. B. (1989). Demonstration of a role for growth hormone in glucose counter-regulation. *American Journal of Physiology*, 256, E835–E843.
- Denley, A., Gymnopoulos, M., Kang, S., Mitchell, C., & Vogt, P. K. (2009). Requirement of phosphatidylinositol (3,4,5) trisphosphate in phosphatidylinositol 3-kinase-induced oncogenic transformation. *Molecular Cancer Research*, 7(7), 1132–1138.
- Dilworth, L., Facey, A., & Omoruyi, F. (2021). Diabetes mellitus and its metabolic complications: The role of adipose tissues. *International Journal of Molecular Sciences*, 22(14), 7644.
- Edgerton, D. S., Kraft, G., Smith, M., Farmer, B., Williams, P. E., Coate, K. C., Printz, R. L., O'Brien, R. M., & Cherrington, A. D. (2017). Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. *JCI Insight*, 2(6), e91863.
- Ellingsgaard, H., Seelig, E., & Timper, K. (2020). GLP-1 secretion is regulated by IL-6 signalling: A randomised, placebo-controlled study. *Diabetologia*, 63, 362–373.
- Erta, M., Quintana, A., & Hidalgo, J. (2012). Interleukin-6, a major cytokine in the central nervous system. *International Journal of Biological Sciences*, 8(9), 1254–1266.
- Febbraio, M. A., Hiscock, N., Sacchetti, M., Fischer, C. P., & Pedersen, B. K. (2004). Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes*, 53(7), 1643–1648.
- Fioramonti, X. (2023). A new role for hypothalamic glucose-sensing neurons in hypoglycemia unawareness. *Diabetes*, 72(8), 1055–1056.
- Flores-Cortez, Y. A., Barragán-Bonilla, M. I., Mendoza-Bello, J. M., & Espinoza-Rojo, M. (2023). Insulin: A connection between pancreatic  $\beta$  cells and the hypothalamus. *World Journal of Diabetes*, 14(2), 76–91.
- Hahn, D. A., & Denlinger, D. L. (2007). Meeting the energetic demands of insect diapause: Nutrient storage and utilization. *Journal of Insect Physiology*, 53(8), 760–773.
- Hirschberg, P. R., Sarkar, P., Teegala, S. B., & Routh, V. H. (2020). Ventromedial hypothalamus glucose-inhibited neurones: A role in glucose and energy homeostasis? *Journal of Neuroendocrinology*, 32(1), e12773.
- Inoue, H. (2016). Central insulin-mediated regulation of hepatic glucose production [Review]. *Endocrine Journal*, 63(1), 1–7.
- Jais, A., & Brüning, J. C. (2022). Arcuate nucleus-dependent regulation of metabolism—Pathways to obesity and diabetes mellitus. *Endocrine Reviews*, 43(2), 314–328.
- Jordan, S. D., Könnner, A. C., & Brüning, J. C. (2010). Sensing the fuels: Glucose and lipid signaling in the CNS controlling energy homeostasis. *Cellular and Molecular Life Sciences*, 67(19), 3255–3273.
- Karnani, M., & Burdakov, D. (2011). Multiple hypothalamic circuits sense and regulate glucose levels. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 300(1), R47–R55.
- Khodai, T., Nunn, N., Worth, A. A., Feetham, C. H., Belle, M. D. C., Piggins, H. D., & Luckman, S. M. (2018). PACAP neurons in the ventromedial hypothalamic nucleus are glucose inhibited and their selective activation induces hyperglycaemia. *Frontiers in Endocrinology*, 9, 632.
- Kim, S. K., & Novak, R. F. (2007). The role of intracellular signaling in insulin-mediated regulation of drug metabolizing enzyme gene and protein expression. *Pharmacology & Therapeutics*, 113(1), 88–120.
- Kistner, T. M., Pedersen, B. K., & Lieberman, D. E. (2022). Interleukin 6 as an energy allocator in muscle tissue. *Nature Metabolism*, 4(2), 170–179.
- Le, T. K. C., Dao, X. D., Nguyen, D. V., Luu, D. H., Bui, T. M. H., Le, T. H., Nguyen, H. T., Le, T. N., Hosaka, T., & Nguyen, T. T. T. (2023). Insulin signaling and its application. *Frontiers in Endocrinology*, 14, 1226655.
- Lee, J., Raycraft, L., & Johnson, A. W. (2021). The dynamic regulation of appetitive behavior through lateral hypothalamic orexin and melanin concentrating hormone expressing cells. *Physiology & Behavior*, 229, 113234.

- Lee, S. H., Park, S. Y., & Choi, C. S. (2022). Insulin resistance: From mechanisms to therapeutic strategies. *Diabetes & Metabolism Journal*, 46(1), 15–37.
- Li, R. J. W., Zhang, S.-Y., & Lam, T. K. T. (2020). Interaction of glucose sensing and leptin action in the brain. *Molecular Metabolism*, 39, 101011.
- Lundqvist, M. H., Almby, K., Abrahamsson, N., & Eriksson, J. W. (2019). Is the brain a key player in glucose regulation and development of type 2 diabetes? *Frontiers in Physiology*, 10, 457.
- Martín-Timón, I. (2014). Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World Journal of Diabetes*, 5(4), 444.
- Matsuhisa, M., Yamasaki, Y., Shiba, Y., Nakahara, I., Kuroda, A., Tomita, T., Iida, M., Ikeda, M., Kajimoto, Y., Kubota, M., & Hori, M. (2000). Important role of the hepatic vagus nerve in glucose uptake and production by the liver. *Metabolism*, 49(1), 11–16.
- McTaggart, J. S., Clark, R. H., & Ashcroft, F. M. (2010). The role of the KATP channel in glucose homeostasis in health and disease: More than meets the islet. *The Journal of Physiology*, 588(17), 3201–3209.
- Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: The role of glucose in physiological and pathological brain function. *Trends in Neuroscience*, 36(10), 587–597.
- Nieto-Vazquez, I., Fernández-Veledo, S., & Lorenzo, M. (2008). Dual role of interleukin-6 in regulating insulin sensitivity in murine skeletal muscle. *Diabetes*, 57(12), 3211–3221.
- Obici, S., Feng, Z., Morgan, K., Stein, D., Karkanas, G., & Rossetti, L. (2002). Central administration of oleic acid inhibits glucose production and food intake. *Diabetes*, 51(2), 271–275.
- Pan, S., Worker, C. J., & Feng Earley, Y. (2023). The hypothalamus as a key regulator of glucose homeostasis: Emerging roles of the brain renin-angiotensin system. *American Journal of Physiology-Cell Physiology*, 325(1), C141–C154.
- Perreault, K., Lagacé, J. C., Brochu, M., & Dionne, I. J. (2016). Association between fat-free mass and glucose homeostasis: Common knowledge revisited. *Ageing Research Reviews*, 28, 46–61.
- Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. *Physiological Reviews*, 98(4), 2133–2223.
- Rahman, M. S., Hossain, K. S., Das, S., Kundu, S., Adegoke, E. O., Rahman, M. A., Hannan, M. A., Uddin, M. J., & Pang, M.-G. (2021). Role of insulin in health and disease: An update. *International Journal of Molecular Sciences*, 22(12), 6403.
- Roh, E., Song, D. K., & Kim, M. S. (2016). Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Experimental & Molecular Medicine*, 48(3), e216.
- Routh, V. H. (2010). Glucose sensing neurons in the ventromedial hypothalamus. *Sensors*, 10(10), 9002–9025.
- Savova, M. S., Mihaylova, L. V., Tews, D., Wabitsch, M., & Georgiev, M. I. (2023). Targeting PI3K/AKT signaling pathway in obesity. *Biomedicine & Pharmacotherapy*, 159, 114244.
- Senthilkumar, M., Koch, C., Herselman, M. F., & Bobrovskaya, L. (2024). Role of the adrenal medulla in hypoglycaemia-associated autonomic failure: A diabetic perspective. *Metabolites*, 14(2), 100.
- Sharabi, K., Tavares, C. D., Rines, A. K., & Puigserver, P. (2015). Molecular pathophysiology of hepatic glucose production. *Molecular Aspects of Medicine*, 46, 21–33.
- Sohn, J. W., & Ho, W. K. (2020). Cellular and systemic mechanisms for glucose sensing and homeostasis. *Pflügers Archiv - European Journal of Physiology*, 472(11), 1547–1561.
- Sprague, J. E., & Arbeláez, A. M. (2011). Glucose counterregulatory responses to hypoglycemia. *Pediatric Endocrinology Review*, 9(1), 463–473.
- Stanley, S., Moheet, A., & Seaquist, E. R. (2019). Central mechanisms of glucose sensing and counterregulation in defense of hypoglycemia. *Endocrine Reviews*, 40(3), 768–788.
- Sun, B., Chen, H., Xue, J., Li, P., & Fu, X. (2023). The role of GLUT2 in glucose metabolism in multiple organs and tissues. *Molecular Biology Reports*, 50(8), 6963–6974.
- Tennagels, N., Bergschneider, E., Al-Hasani, H., & Klein, H. W. (2000). Autophosphorylation of the two C-terminal tyrosine residues Tyr 1316 and Tyr 1322 modulates the activity of the insulin receptor kinase *in vitro*. *FEBS Letters*, 479(1–2), 67–71.
- Thorens, B. (2015). GLUT2, glucose sensing and glucose homeostasis. *Diabetologia*, 58, 221–232.
- Tran, L. T., Park, S., Kim, S. K., Lee, J. S., Kim, K. W., & Kwon, O. (2022). Hypothalamic control of energy expenditure and thermogenesis. *Experimental & Molecular Medicine*, 54(4), 358–369.

- Verhulst, C. E. M., Fabricius, T. W., Teerenstra, S., Kristensen, P. L., Tack, C. J., McCrimmon, R. J., Heller, S., Evans, M. L., Amiel, S. A., Pedersen-Bjergaard, U., & de Galan, B. E. (2022). Glycaemic thresholds for counterregulatory hormone and symptom responses to hypoglycaemia in people with and without type 1 diabetes: A systematic review. *Diabetologia*, 65(10), 1601–1612.
- Yoon, N. A., & Diano, S. (2021). Hypothalamic glucose-sensing mechanisms. *Diabetologia*, 64(5), 985–993.
- Yu, J. H., & Kim, M.-S. (2012). Molecular mechanisms of appetite regulation. *Diabetes & Metabolism Journal*, 36(6), 391.
- Yunn, N. O., Kim, J., Ryu, S. H., & Cho, Y. (2023). A stepwise activation model for the insulin receptor. *Experimental & Molecular Medicine*, 55(10), 2147–2161.
- Zakir, M., Ahuja, N., Surksha, M. A., Sachdev, R., Kalariya, Y., Nasir, M., Kashif, M., Shahzeen, F., Tayyab, A., Khan, M. S. M., Junejo, M., Manoj Kumar, F., Varrassi, G., Kumar, S., Khatri, M., & Mohamad, T. (2023). Cardiovascular complications of diabetes: From microvascular to macrovascular pathways. *Cureus*, 15(9), e45835.
- Zhao, X., An, X., Yang, C., Sun, W., Ji, H., & Lian, F. (2023). The crucial role and mechanism of insulin resistance in metabolic disease. *Frontiers in Endocrinology*, 14, 1149239.