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# Expanding the understanding of insulin resistance in brain and periphery

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## Abstract

Insulin resistance is a central feature of metabolic disorders such as type 2 diabetes (T2D). While studies on this disorder have largely been linked to glucose metabolism and intracellular signaling, recent advances reveal that insulin resistance extends beyond traditional glucose regulatory pathways, impacting multiple organs including the brain, contributing to cognitive dysfunction and neurodegenerative diseases such as Alzheimer's disease (AD). This opinion revisits insulin resistance through molecular, cellular, and systemic perspectives, emphasizing the intersection between peripheral and brain insulin resistance (BIR), the role of the blood–brain barrier (BBB), and emerging biomarkers. Furthermore, we integrate insights from multi-omics and neuroimaging studies to refine our understanding, advocating for a broader perspective that informs early detection and intervention in metabolic and neurodegenerative diseases.

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Declaration of interests

The authors declare that they have no conflicts of interest.

Declaration of generative AI and AI-associated technologies in the writing process

During the preparation of this opinion article, the authors used ChatGPT4o in order to improve language and readability. After using this tool, the authors reviewed and edited the content as much as needed and take full responsibility for the content of the publication.

## Insulin resistance: beyond its roles in metabolic disorders

Metabolic disorders such as T2D, obesity, and cardiovascular disease contribute an immense burden on healthcare systems worldwide. In both T2D and obesity, **insulin resistance** (see Glossary) is a common pathology, frequently linked to metabolic tissues such as the liver, fat, and muscle [1]. In simplistic terms, insulin resistance is viewed as a condition in which body cells, particularly cells in muscle, fat, and liver, become unresponsive to insulin, leading to a cascade of metabolic dysfunction, including impaired glucose homeostasis and dyslipidemia. While traditionally defined by impairment in systemic glucose homeostasis and defects in insulin signaling pathways, our understanding of insulin resistance has significantly expanded. Recent advances in molecular biology and cross-disciplinary research have not only illuminated the complex etiology and systemic impact of insulin resistance in obesity and T2D, but also revealed downstream effects beyond classical glucose uptake pathways, including the closely interconnected processes such as lipid metabolism, mitochondrial function, and inflammatory signaling.

The advent of advanced technologies – including single-cell and spatial transcriptomics, noninvasive imaging, and the study of secreted factors – is transforming our understanding of insulin resistance. Moreover, newly developed drugs such as the glucagon-like peptide-1 receptor agonists (GLP-1RAs) exhibit remarkable effects on weight management and peripheral insulin resistance, all reshaping treatment approaches for T2D. In addition, we now know that the brain can also be susceptible to insulin resistance, manifesting as brain insulin resistance (BIR) [2], which impacts on brain health, cognition, and metabolism, contributing to metabolic dysfunction and accelerating neurodegeneration, including AD. Drugs originally designed for T2D are being repurposed for neurodegenerative diseases with underlying BIR, and are proving to be beneficial [3].

Although the defining pathology of AD involves amyloid β and tau, BIR is also a prominent feature, affecting approximately 90% of individuals with AD [4]. Not only does T2D double the risk of developing AD [5], but conversely, AD itself has been linked to increased risk of T2D [6]. However, insulin resistance can occur in either the brain or the periphery independently, highlighting the need to study them as distinct but potentially interacting processes. In addition, limited understanding of the etiology and primary consequences of BIR remains a major obstacle to its study. While BIR broadly affects cellular metabolism, its effects vary depending on cell type and brain region [7–9].

Recent advances reveal that insulin resistance plays a broader role in brain health and aging than previously thought, presenting opportunities for advancing treatments and aiding in prevention. This opinion article aims to explore key molecular players and critical links between central and peripheral insulin resistance. In this opinion article we identify research gaps and propose potential therapeutic strategies using cutting-edge technologies to address insulin resistance in health and aging-related diseases.

## Expanding the classical repertoires of molecular mechanisms of insulin resistance

The classical view of insulin signaling describes how it binds to the insulin receptor (IR), a tyrosine kinase receptor, triggering autophosphorylation and recruitment of insulin receptor substrate (IRS) proteins. This initiates a signaling cascade through the phosphatidylinositol 3-kinase (PI3K), which regulates key metabolic processes, including translocation of glucose transporter 4 (GLUT4) to the cell surface for glucose uptake [10]. Defects in this pathway are central to the development of insulin resistance (Figure 1).

In recent decades, research has expanded our understanding of the molecular landscape involved in insulin signaling and its dysregulation in insulin resistance (Figure 1). Canonical components such as fatty acids, forkhead box protein O1, isoforms of protein kinase C, subunits of PI3K (regulatory p85 and catalytic p110), and mitochondrial reactive oxygen species (ROS) [11] all remain fundamental to insulin signaling transduction. While these factors are foundational to classical insulin signaling, ongoing studies continue to expand this repertoire. Additional cellular and molecular players in insulin signaling pathways have been revealed, including transcriptional and mitochondrial mechanisms that increase the complexity of insulin signaling and offer potential therapeutic interventions for managing insulin resistance.

### Advancements in our understanding of metabolic pathways of insulin resistance

Beyond its traditional cytoplasmic signaling roles, the IR has recently been shown to translocate to the nucleus, where it interacts with RNA polymerase II and binds to gene promoters, directly regulating transcription [12]. This mechanism links insulin signaling to long-term gene expression changes, particularly in lipid metabolism and protein synthesis. This finding highlights a previously unexplored role of insulin, suggesting long-term effects on insulin resistance beyond its immediate receptor signaling defects.

Emerging evidence shows a strong link between neurodegenerative diseases and metabolic disorders, including T2D. For instance, biliverdin reductase-A (BVR-A), a key reductase in heme degradation, integrates insulin signaling with mitochondrial function through GSK3β phosphorylation to promote neuroprotection [13]. In peripheral tissues, BVR-A dynamically responds to insulin [14], whereas its reduction in rodent models of obesity and diabetes impairs both insulin signaling [15] and mitochondrial activity, contributing to cognitive decline [13]. These findings suggest BVR-A as a potential biomarker and therapeutic target for neurodegenerative diseases.

Impaired lipid metabolism also contributes to insulin resistance. Lipidomic studies suggest specific lipid metabolites, in particular sphingolipids and phospholipids, contribute to insulin resistance [16]. Hypercaloric diets promote the accumulation of ceramides and sphingomyelins, both of which can interfere with insulin pathways to promote insulin resistance. Importantly, as lipid alteration also plays a role in the early onset of AD, this might suggest an alternative link between the accelerated AD risk in T2D [17].

Building on these emerging insights, additional regulatory layers such as **post-translational modifications** [18], nucleotide signaling, and epigenetic alterations have also been implicated in insulin resistance. Studies have identified over 1000 dysregulated phosphorylation sites in T2D [19], highlighting the complexity of insulin signaling regulation. Nucleotides such as ATP and NADH can affect insulin action through purinergic receptors and AMP-activated protein kinase (AMPK) regulation, and may serve as biomarkers of insulin resistance [20], though the precise mechanisms remain unclear. Epigenetic profiling has revealed distinct DNA methylation patterns in both blood and brain, linking insulin resistance to AD [21]. Together, these findings point towards the importance of identifying additional key factors in insulin resistance and the urgent need to elucidate the mechanisms involved.

## Tissue-specific insulin resistance

Dissecting the specific effects of IR knockout (KO) versus downstream signaling defects is essential for understanding tissue-specific insulin resistance. Conditional IR KO models using Cre–LoxP technology have been instrumental in advancing this field [22], while tamoxifen-inducible systems now offer temporal control of IR deletion, mitigating potential developmental effects.

While IR KO models have offered important insights for studying tissue-specific insulin signaling, they also introduce complexities such as compensatory adaptations that can complicate interpretation. For instance, early-life IR KO can cause neonatal lethality due to developmental abnormalities rather than insulin resistance *per se* [23]. In liver-specific IR KO models, compensatory changes in other tissues are often overlooked, and inducible KO models require careful tamoxifen optimization to ensure efficient gene inactivation [24].

A notable limitation of Cre-based models is the lack of strict tissue and cell type specificity. For example, endothelial Cre lines vary in specificity: Tek–Cre is widely used for pan-endothelial expression, while Cdh5–Cre, in particular Cdh5–Cre$^{ERT2}$, offers high specificity for brain and peripheral vasculature [25]. Through single-cell studies, recently developed tools such as Slco1c1-based Cre lines have enabled precise brain endothelial IR KO, providing insights into brain insulin transport [26]. These improved IR KO models have uncovered alternative mechanisms of insulin transport into the hypothalamus [27] and demonstrated that insulin signaling in specific cells types – such as microglia [9], endothelial cells [25], and tanycytes [26] – regulates neuroinflammation, barrier function, and amyloid clearance, highlighting insulin resistance as a broader dysfunction that extends traditional metabolic regulation.

Emerging technologies, including clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) [28] and advanced adeno-associated virus (AAV)-based gene editing [29], now enable more efficient tissue- and cell-type-specific gene manipulations with fewer confounders. While still in the early stages of refinement, these rapidly evolving tools hold promise for advancing our mechanistic understanding of insulin resistance at the cellular level.

## Central–peripheral intersection of insulin resistance

### Defining and measuring BIR

Both peripheral and central insulin resistance (i.e., BIR) involve altered IR expression, reduced insulin sensitivity, and dysregulated downstream signaling. However, unlike peripheral insulin resistance, BIR does not always overtly affect blood glucose, as demonstrated in brain or hypothalamic IR KO models [30]. While early studies linked brain insulin action to reduced food intake [31], direct evidence of insulin-dependent glucose uptake into the brain remains limited [32]. Although GLUT4 is insulin-responsive in astrocytes and neurons, most brain GLUTs (GLUT1/3) are insulin-independent [33]. For these reasons, the brain has traditionally been considered insulin-insensitive due to glucose utilization via insulin-independent mechanisms [34]. However, it is now widely recognized that the brain is highly insulin-responsive, with IR contributing to diverse roles, including neural function, metabolism, and cognition.

Measuring BIR remains challenging due to the absence of clear glucose-mediated markers, unlike what is observed in peripheral insulin resistance. Current assessments rely on noninvasive neuroimaging in combination with insulin stimulation (see later discussion) or on molecular analysis from post-mortem tissues. As no standardized metric exists, BIR is typically inferred from various factors, including IR expression and sensitivity, insulin availability, and downstream signaling markers (see Outstanding questions). Another distinction is that BIR is uniquely impacted by insulin availability at the BBB, adding an extra layer of regulation beyond pancreatic β-cell secretion in T2D [35]. The BBB also restricts drug entry into the brain, complicating treatment for metabolic, neurodegenerative, and aging-related disorders. In obesity, reduced P-glycoprotein expression can impair BBB function and metabolic regulation [36], potentially diminishing the efficacy of transport of both drugs and endogenous compounds across the BBB.

### Central mediators of BIR: the BBB

The BBB is more than just a barrier to bypass for brain access. It is an active, highly regulated component of the **neurovascular unit (NVU)**, flexibly adapting to central demand (Figure 2). First, the BBB facilitates metabolic hormone transport, including insulin, to act within the brain, which affects both peripheral metabolism and cognitive function. Insulin transport is tightly regulated and can be impaired in conditions like diabetes, obesity, AD, and aging [35]. Dysregulated BBB transport could be one of the primary insults contributing to pathogenesis of these disease conditions; however, this has yet to be confirmed due to our limited understanding of the molecular players involved. The IR expressed on the BBB is not required for insulin transport into the brain [37]. Nevertheless, studies have shown that direct brain insulin delivery, bypassing the BBB, can ameliorate disease-related impairments, highlighting the importance of insulin BBB transport [38].

Second, the BBB responds to circulating insulin, regulating brain endothelial pathways and relaying signals to the brain, and can occur independently of transport across the BBB. Brain endothelial cells express the highest IR levels among brain cell types [39], and IR signaling within endothelial cells can regulate processes such as vasoreactivity,

inflammation, and angiogenesis [40]. IR expression at the BBB is reduced in AD [37], though whether similar deficits occur at the mRNA or protein levels in metabolic diseases remains unclear. Experimental models with endothelial IR deficiency demonstrate impaired BBB integrity and disrupted signaling transduction [25]. Notably, brain endothelial cells can regulate neuroinflammation and brain insulin signaling [25,41] without requiring blood-to-brain penetration of insulin.

Brain insulin access is regionally regulated [42], adding spatial complexity to BIR. The hypothalamus, a key site for metabolic regulation, can acquire insulin via tanycytes rather than via brain endothelial cells [26]. Importantly, hypothalamic insulin signaling influences systemic metabolism, regulating hepatic glucose production, adipose function, and whole-body energy balance [43]. Overall, the BBB and hypothalamic tanycytic barrier should be considered as active contributors to both BIR and peripheral insulin resistance.

## Central mediators of BIR: local insulin synthesis

Traditionally, insulin was thought to be exclusively produced by the pancreas, but emerging evidence suggests local synthesis within the brain [44], opening further avenues of research. Early studies detected immunoreactive insulin in neurons at both the mRNA and protein levels [45], with secretion mechanisms similar to those of pancreatic β-cells [46]. However, this idea remained controversial, partly due to limited molecular tools. Notably, early reports indicated that brain insulin synthesis was restricted to neurons, with no evidence supporting a glial origin [47].

Studies utilizing advanced tools such as single-cell RNA-sequencing (scRNA-seq) have now identified *Ins2* expression in the choroid plexus (ChP) [48], a cerebrospinal fluid (CSF)-producing epithelial cell structure within the ventricle system. Unlike pancreatic insulin, which is glucose-regulated, ChP-derived insulin responds to serotonergic signaling [44], suggesting a distinct and localized function rather than systemic glucose control [49]. Functionally, brain-derived insulin is implicated in neuroprotection, neuronal glucose uptake, growth hormone regulation, and appetite control [50]. While its contribution to overall brain insulin availability remains unclear, given that BBB transport primarily regulates widespread insulin levels, local synthesis of insulin may fine-tune signaling within specific cell types.

A remaining key question is whether brain-derived insulin influences insulin resistance either centrally or peripherally. Beyond its role in glucose metabolism, brain insulin signaling modulates neurotransmission, particularly through dopamine and serotonin pathways implicated in mood and cognition [7,51–53]. Further, BIR is associated with mitochondrial dysfunction, oxidative stress, and neuroinflammation [8,9,13], all of which contribute to synaptic deficits and cognitive impairment. While these processes may involve cellular glucose metabolism, they do not necessarily impact systemic glucose homeostasis, emphasizing the need to determine alternative mechanisms of BIR.

### Peripheral mediators of BIR and therapeutic implications

Among the various physiological pathways connecting the brain and peripheral metabolic organs, the **gut–brain axis** has gained increasing attention for its potential role in insulin resistance and neurodegenerative diseases. In 2023, an expert forum recognized the potential role of the gut microbiome in T2D pathophysiology, warranting further exploration [54]. Cross-sectional studies have linked lower microbiome diversity in stool samples to greater peripheral insulin resistance [55], with reduced butyrate-producing bacteria implicated in T2D. Similarly, AD has also been associated with reduced gut microbial diversity [56], suggesting potential shared gut-related mechanisms between metabolic and neurodegenerative diseases. Although the specific pathways remain unclear, early-life microbiota composition can shape long-term outcomes in metabolism and brain function by influencing β-cell development, insulin sensitivity, and immune responses [57]. Supporting this idea, animal studies have shown that diet-induced obesity leads to hypothalamic BIR, indicated by impaired phosphorylation of IR and IRS1; these effects are reversed by antibiotic-induced alterations to the gut microbiome [58], directly implicating microbial signals in central insulin regulation.

GLP-1RAs are widely used for improving peripheral insulin sensitivity by activating central appetite-regulating circuits. There is also growing interest in their effects in neurodegenerative disease, though mechanisms underlying their beneficial effects on BIR remain unclear. Despite differential BBB penetration [59], GLP-1RAs may act via transport through non-BBB interfaces such as tanycytes [60] or vagal afferents [61]. Intriguingly, GLP-1RAs also impact the gut microbiota, in that semaglutide alters microbiota composition and reverses high-fat diet (HFD)-induced BIR in mice [62], highlighting a gut–brain contribution. Given their appetite-suppressing and cardiometabolic effects, GLP-1RAs are often considered as pharmacological mimetics of caloric restriction. Recently, lithocholic acid (LCA), a gut-derived metabolite, was found to mimic the antiaging effects of caloric restriction [63], raising the possibility that part of GLP-1RA's effects on brain function and BIR may be mediated by LCA or other microbial metabolites. Notably, as some GLP-1RAs have cognitive and anti-neuroinflammatory benefits [3] despite their limited BBB penetration, the BBB-mediated peripheral-to-central crosstalk becomes even more important to understand.

## Research gaps and technological advancements

In clinical practice, peripheral insulin resistance is commonly assessed using a homeostatic model assessment for insulin resistance (HOMA-IR), which estimates systemic insulin sensitivity based on fasting glucose and insulin levels, largely reflecting hepatic insulin resistance [64]. Another common approach is a **hyperinsulinemic–euglycemic clamp**, where a constant intravenous insulin infusion is administered, and glucose infusion is adjusted to maintain normal blood glucose, reflecting net insulin sensitivity in target tissues [65]. These methods primarily assess peripheral insulin resistance and do not directly capture BIR; thus, measurement of BIR requires alternative approaches. We go on to discuss the technologies developed to overcome these challenges.

## Challenges in interpreting tissue-specific IR KO models

Rodent models remain essential for studying insulin resistance. HFD-induced obesity in rodents leads to insulin resistance over a period of weeks to months, while genetically predisposed models such as ob/ob and db/db mice are also widely used to model insulin resistance [66]. However, the validity and translational relevance of these models, including genetically manipulated IR mice, continue to be debated.

A major challenge in interpreting tissue-specific IR KO models is distinguishing between true insulin resistance from IR deficiency or inactivation. Systemic feedback and compensatory adaptations in non-targeted tissues complicate interpretations. For instance, liver-specific IR KO models develop hepatic insulin resistance but also exhibit compensatory hyperinsulinemia, which secondarily affects muscle insulin sensitivity [67], suggesting that systemic feedback is activated when liver IR signaling is impaired. Furthermore, these models often induce more severe disruption than is typically observed in human insulin resistance, limiting their direct translational relevance. Therefore, findings from these models should be interpreted with caution.

Despite these caveats, tissue-specific IR deletion has provided valuable insights into insulin signaling in various tissues and cell types. However, there is a growing need to study insulin action and insulin resistance across multiple tissues and cell types in a comprehensive and unbiased manner, particularly in the context of single-cell biology and spatial transcriptomics. Questions remaining include addressing the preferentially altered transcripts in the insulin signaling pathway and how they change during T2D.

## Studying insulin resistance across cell types through single-cell genomics

Advances in scRNA-seq and spatial transcriptomics (Figure 3) have enabled deeper classification of insulin-sensitive tissues such as liver and adipose tissue, both of which exhibit complex cellular heterogeneity. While it is known that insulin resistance alters gene expression in multiple cell types within these tissues, integrated single-cell and spatial approaches have provided a much more granular view. For example, combined scRNA-seq and spatial transcriptomic analyses have identified over 60 distinct cell types in human white adipose tissue, uncovering immune cell types enriched under insulin resistance and obesity [68]. These tools enable the revelation of a high-resolution landscape of adipose tissue during the development of insulin resistance. Spatial transcriptomics further enhance this landscape by integrating gene expression data with tissue architecture, allowing for the mapping of cell-type-specific transcriptional responses within their native microenvironment. In human white adipose tissue, distinct clusters of mature adipocytes have been identified, including one cluster termed Adipo$^{PLIN}$, which exhibits a unique transcriptional response to insulin and may contribute to insulin resistance [69]. Together, these findings highlight the importance of retaining the spatial context when studying tissue-specific insulin resistance, and underscore how cellular diversity, molecular heterogeneity, and local microenvironments collectively shape susceptibility to insulin resistance and metabolic dysfunction.

## Data-driven pathway identification

**Multi-omics** integrate genomics, transcriptomics, proteomics, metabolomics, and lipidomics, offering a comprehensive snapshot of insulin resistance across systems and tissues. For instance, metabolomic profiling of fecal and plasma samples has identified microbial carbohydrate metabolism markers correlated with HOMA-IR, suggesting potential therapeutic targets [70]. Plasma-based multi-omics analyses (metabolomics, lipidomics, and proteomics) have also revealed distinct metabolic responses to acute exercise in insulin-resistant individuals, identifying alterations in energy metabolism, oxidative stress, and immune signaling pathways [71]. Additionally, inflammatory responses, respiratory viral infection, and host–microbe interactions have been identified as key predictors of progression from prediabetes to early T2D [72]. In particular, IL-1RA and C-reactive protein (CRP) have emerged as early molecular signatures of glucose dysfunction, linking systemic inflammation to onset of T2D [72].

Beyond systemic metabolic changes, gut microbiota-derived metabolites and immune signals may also influence brain insulin signaling, highlighting a need to further explore gut–brain interactions in BIR. These longitudinal multi-omics studies demonstrate the potential to identify precursors of insulin resistance years before clinical diagnosis [72], supporting early intervention strategies. Overall, these integrative multi-omics analyses offer powerful tools to uncover molecular mechanisms, discover biomarkers, and pinpoint therapeutic targets associated with T2D and BIR.

In addition to molecular signatures identified by multi-omics, extracellular vesicles (EVs) have emerged as promising biomarkers for BIR. In particular, neuron-derived EVs (NDEVs) can carry insulin signaling components such as phosphorylated IRS1, potentially reflecting physiological and pathological processes in neural cells that can be modulated by brain insulin signaling [73]. While neurons and pancreatic islet cells share overlapping markers, recent studies have shown that NDEVs can be selectively enriched using surface proteins such as L1CAM [74]. Additionally, NDEVs typically range from 30 nm to 150 nm, whereas islet-derived EVs are larger (100–1000 nm), enabling further separation based on size. These advances help to address challenges in biomarker specificity. Studies have identified altered IRS1 phosphorylation in EVs from individuals with neurodegenerative diseases, though further validation is needed to establish their diagnostic utility (Table 1) [75]. Nevertheless, integrating EV analysis with other molecular biomarkers may offer deeper insights into the role of BIR in T2D and AD [73,75].

Several interventions aimed at improving brain insulin sensitivity have been shown to alter insulin signaling biomarkers in NDEVs. These include responses to intranasal insulin (INI) [76], pharmacotherapy for neurodegenerative and psychiatric diseases [77], and dietary intervention for weight loss [78,79]. Interestingly, weight-loss-induced improvements in peripheral insulin sensitivity were associated with increased NDEV insulin signaling biomarkers, even in cognitively healthy older adults [79], suggesting a link between peripheral and BIR. Similarly, short-term aerobic exercise has been shown to enhance NDEV insulin signaling biomarkers during glucose stimulation in individuals with prediabetes, suggesting that improvement in brain insulin signaling may precede weight

loss [80]. Whether NDEVs can serve as reliable and specific biomarkers for BIR with the potential to predict metabolic disease progression and cognitive decline remains an important question for future studies.

## Studying BIR in humans using neuroimaging methods

Characterizing BIR in humans requires advanced neuroimaging technologies capable of assessing insulin's effects on brain metabolism, neural activity, functional connectivity, and neurotransmitter signaling. Tools such as magnetoencephalography (MEG), **functional MRI (fMRI)**, and positron emission tomography (PET) provide valuable insights into brain insulin action, though defining BIR *in vivo* depends on the specific methods employed.

The first human study linking BIR to obesity used MEG in combination with a hyperinsulinemic–euglycemic clamp. In this study, normal-weight participants exhibited increased cerebrocortical activity, whereas obese individuals showed a blunted response, a pattern correlating with body weight, metabolic parameters, and genetic factors [81]. This response can predict weight loss nearly 10 years later [82], with brain insulin sensitivity being particularly associated with reductions in visceral fat mass.

PET imaging enables analysis of insulin's effects on both brain metabolism and neurotransmission, offering valuable insights into BIR. Most PET studies primarily use fluorodeoxyglucose as a tracer to measure insulin-stimulated glucose uptake [83], while raclopride has been used to explore insulin's effects on dopamine transmission [53]. Individuals with obesity often display a paradoxically elevated insulin-stimulated brain glucose uptake during a hyperinsulinemic–euglycemic clamp, likely due to astrocyte-mediated inflammatory responses. A meta-analysis examining 31 PET studies found that insulin resistance affects brain glucose metabolism differently depending on metabolic state: fasting conditions show brain glucose hypometabolism, while hyperinsulinemic conditions show increased glucose metabolism [83]. Despite these differences, the exogenous insulin-induced change in brain glucose uptake predicts overall metabolic health, resembling the MEG study [84]. Supporting this, animal models reveal that insulin resistance causes region- and cell-type-specific dysfunction in the hypothalamus, with some regions becoming hyperactivated [85], significantly influencing energy balance, body weight regulation, and feeding behavior [86].

Although the hyperinsulinemic–euglycemic clamp is the gold standard for assessing whole-body insulin sensitivity, it cannot distinguish central from peripheral effects. INI administration offers a direct alternative to deliver insulin to the brain with minimal peripheral exposure and avoiding hypoglycemia. Neuroimaging studies have shown that INI influences mesolimbic dopamine signaling [87], altering regional neural activity and enhancing functional connectivity [88]. Together, these findings suggest INI as a valuable tool for studying central insulin action independent of peripheral confounds.

Finally, fMRI, with its superior spatial resolution, has become the primary technique for assessing the INI effects in the human brains. Insulin-responsive regions include the prefrontal cortex, hippocampus, striatum, insula, and hypothalamus, areas essential for energy metabolism, eating behavior, reward, mood, and decision-making [88]. INI has

been shown to enhance learning and memory [87], increase hippocampal blood flow [89], and improve functional connectivity [90]. Notably, hippocampal insulin sensitivity declines with age, particularly in women [89]. Prefrontal insulin action appears more influenced by cognitive control over eating rather than peripheral insulin sensitivity [91], and this central–peripheral interaction is further modulated by the menstrual cycle [92]. Collectively, these findings underscore the value of fMRI in elucidating central insulin action and monitoring the development of BIR.

Neuroimaging-based changes in regional brain activity and functional connectivity following INI administration are increasingly being used as biomarkers of BIR in humans [88]. BIR is region-specific and can emerge rapidly following a high-calorie intake, leading to exaggerated or blunted brain responses [93]. In individuals with overweight or obesity, INI elicits diminished responses in the hypothalamus and hippocampus, but exaggerated response in the insula and prefrontal cortex [82,94]. Dysregulated insulin signaling in these regions is associated with unfavorable fat distribution, increased food craving, hunger, and impaired glucose and lipid metabolism [82,95].

Conversely, improved brain insulin sensitivity is linked to better metabolic and behavioral outcomes [95,96]. Aerobic exercise enhances insulin sensitivity in the mesolimbic system, increasing striatal activity and hippocampal connectivity, both correlating with cognitive and metabolic benefits [96]. Similarly, weight loss and SGLT2 inhibitors restore brain insulin sensitivity [95]. These findings highlight the potential of neuroimaging-based techniques for early, personalized interventions targeting brain insulin signaling to prevent T2D and cognitive decline, both of which represent major healthcare burdens.

## Concluding remarks

In this opinion article we have aimed at highlighting the need to expand the understanding of insulin resistance, emphasizing its roles beyond systemic glucose metabolism (Figure 1) and its relevance in BIR, including in neurodegenerative diseases such as AD. Several points need to be addressed further in the context of central–peripheral interactions (see Outstanding questions), particularly around the role of the BBB in mediating metabolic communications between brain and periphery. Expanding our ability to predict and treat insulin resistance, both peripherally and in the brain, and identifying its underlying etiology across organs and cell types, will be essential for early intervention and therapeutic development.

Insulin resistance is increasingly recognized as a complex, multisystem process that contributes to disease comorbidities across peripheral and central systems. From an evolutionary perspective, insulin resistance may have originally evolved as an adaptive mechanism to protect the cells from nutrient overload, oxidative stress, and inflammation, restricting excessive energy intake and preventing metabolic toxicity. For decades investigators have generated a wealth of data contributing to our current understanding of insulin resistance; however, a critical challenge remains in identifying when and how it transitions from an adaptive response to a pathological state, particularly in the brain. Addressing these questions requires a cross-disciplinary approach that integrates molecular

biology, big data, and systems medicine to reveal the mechanisms linking metabolic dysfunction to neurodegenerative and psychiatric diseases.

Future research must prioritize the identification of early biomarkers and therapeutic targets that address both peripheral and BIR. By broadening our understanding of insulin resistance across organs, cell types, and metabolic pathways, we can pave the way for personalized interventions that mitigate its progression and associated consequences, both peripherally and centrally. This expanded perspective holds the potential to not only improve metabolic health but also to redefine treatment strategies for neurodegenerative and age-related diseases.

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## Glossary

**Functional MRI (fMRI)**
a neuroimaging technique that measures brain activity by detecting changes in blood flow, based on the principle that active brain regions can consume more oxygen, causing a detectable increase in blood flow which can be captured by the blood-oxygen-level-dependent (BOLD) signal.

**Gut–brain axis**
bidirectional communication between gut and brain, involving hormonal and metabolic signals.

**Hyperinsulinemic–euglycemic clamp**
a method for measuring insulin resistance, involving a simultaneous and continuous intravenous infusion of insulin to raise insulin levels while maintaining normal blood glucose levels through a variable glucose infusion. The glucose infusion rate at steady state reflects the sensitivity of target tissues to insulin.

**Insulin resistance**
a condition in which body cells do not respond properly to insulin, leading to impaired glucose uptake. Insulin resistance is a central feature of type 2 diabetes and metabolic syndrome, but is now also considered a hallmark of neurodegenerative disease such as Alzheimer’s disease.

**Multi-omics**
the integration of multiple omics studies; it can be used to study genotype–phenotype relationships.

**Neurovascular unit (NVU)**
a tightly regulated brain network consisting of many brain cells, including neurons, astrocytic endfeet, microglia, pericytes, and endothelial cells, collectively playing a key

role in the regulation of brain homeostasis and transport of signaling molecules across the blood–brain barrier.

**Post-translational modifications**

chemical modifications that occur after a protein has been synthesized and can significantly increase the functional diversity and impact the protein's function.

## References


1. Petersen MC and Shulman GI (2018) Mechanisms of Insulin action and insulin resistance. Physiol. Rev. 98, 2133–2223 [PubMed: 30067154]
2. Arnold SE et al. (2018) Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat. Rev. Neurol. 14, 168–181 [PubMed: 29377010]
3. Nowell J et al. (2023) Incretin and insulin signaling as novel therapeutic targets for Alzheimer's and Parkinson's disease. Mol. Psychiatry 28, 217–229 [PubMed: 36258018]
4. Talbot K et al. (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J. Clin. Invest. 122, 1316–1338 [PubMed: 22476197]
5. Luchsinger JA et al. (2004) Hyperinsulinemia and risk of Alzheimer disease. Neurology 63, 1187–1192 [PubMed: 15477536]
6. Janson J et al. (2004) Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 53, 474–481 [PubMed: 14747300]
7. Chen W et al. (2022) Insulin action in the brain: cell types, circuits, and diseases. Trends Neurosci. 45, 384–400 [PubMed: 35361499]
8. Chen W et al. (2023) Loss of insulin signaling in astrocytes exacerbates Alzheimer-like phenotypes in a 5xFAD mouse model. Proc. Natl. Acad. Sci. U. S. A. 120, e2220684120 [PubMed: 37186836]
9. Chen W et al. (2024) Loss of insulin signaling in microglia impairs cellular uptake of Aβ and neuroinflammatory response exacerbating Alzheimer-like neuropathology. bioRxiv, Published online August 22, 2024. 10.1101/2024.08.22.609112
10. Saini V (2010) Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World J. Diabetes 1, 68–75 [PubMed: 21537430]
11. White MF and Kahn CR (2021) Insulin action at a molecular level – 100 years of progress. Mol. Metab. 52, 101304 [PubMed: 34274528]
12. Hancock ML et al. (2019) Insulin receptor associates with promoters genome-wide and regulates gene expression. Cell 177, 722–736 e722 [PubMed: 30955890]
13. Lanzillotta C et al. (2024) Biliverdin reductase-A integrates insulin signaling with mitochondrial metabolism through phosphorylation of GSK3beta. Redox Biol. 73, 103221 [PubMed: 38843768]
14. Cimini FA et al. (2023) Dynamic changes of BVRA protein levels occur in response to insulin: a pilot study in humans. Int. J. Mol. Sci. 24, 7282 [PubMed: 37108445]
15. Cimini FA et al. (2019) Reduced biliverdin reductase-A levels are associated with early alterations of insulin signaling in obesity. Biochim. Biophys. Acta Mol. basis Dis. 1865, 1490–1501 [PubMed: 30826467]
16. Green CD et al. (2021) Sphingolipids in metabolic disease: the good, the bad, and the unknown. Cell Metab. 33, 1293–1306 [PubMed: 34233172]
17. Baloni P et al. (2022) Multi-omic analyses characterize the ceramide/sphingomyelin pathway as a therapeutic target in Alzheimer's disease. Commun. Biol. 5, 1074 [PubMed: 36209301]
18. Yang YH et al. (2023) Roles of protein post-translational modifications in glucose and lipid metabolism: mechanisms and perspectives. Mol. Med. 29, 93 [PubMed: 37415097]
19. Batista TM et al. (2020) A cell-autonomous signature of dysregulated protein phosphorylation underlies muscle insulin resistance in type 2 diabetes. Cell Metab. 32, 844–859 e845 [PubMed: 32888406]

20. Liu K et al. (2022) The mechanisms of nucleotide actions in insulin resistance. J. Genet. Genomics 49, 299–307 [PubMed: 35134563]
21. Sarnowski C et al. (2023) Multi-tissue epigenetic analysis identifies distinct associations underlying insulin resistance and Alzheimer's disease at CPT1A locus. Clin. Epigenetics 15, 173 [PubMed: 37891690]
22. Bruning JC et al. (1998) A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. Mol. Cell 2, 559–569 [PubMed: 9844629]
23. Joshi RL et al. (1996) Targeted disruption of the insulin receptor gene in the mouse results in neonatal lethality. EMBO J. 15, 1542–1547 [PubMed: 8612577]
24. Reinert RB et al. (2012) Tamoxifen-induced Cre-loxP recombination is prolonged in pancreatic islets of adult mice. PLoS One 7, e33529 [PubMed: 22470452]
25. Konishi M et al. (2017) Endothelial insulin receptors differentially control insulin signaling kinetics in peripheral tissues and brain of mice. Proc. Natl. Acad. Sci. U. S. A. 114, E8478–E8487 [PubMed: 28923931]
26. Porniece Kumar M et al. (2021) Insulin signalling in tanycytes gates hypothalamic insulin uptake and regulation of AgRP neuron activity. Nat. Metab. 3, 1662–1679 [PubMed: 34931084]
27. Rhea EM et al. (2018) Insulin transport across the blood-brain barrier can occur independently of the insulin receptor. J. Physiol. 596, 4753–4765 [PubMed: 30044494]
28. Haurwitz RE et al. (2010) Sequence- and structure-specific RNA processing by a CRISPR endonuclease. Science 329, 1355–1358 [PubMed: 20829488]
29. Ueki K et al. (2023) Establishment of pancreatic beta-cell-specific gene knockout system based on CRISPR-Cas9 technology with AAV8-mediated gRNA delivery. Diabetes 72, 1609–1620 [PubMed: 37625131]
30. Bruning JC et al. (2000) Role of brain insulin receptor in control of body weight and reproduction. Science 289, 2122–2125 [PubMed: 11000114]
31. Air EL et al. (2002) Acute third ventricular administration of insulin decreases food intake in two paradigms. Pharmacol. Biochem. Behav. 72, 423–429 [PubMed: 11900815]
32. Hasselbalch SG et al. (1999) No effect of insulin on glucose blood-brain barrier transport and cerebral metabolism in humans. Diabetes 48, 1915–1921 [PubMed: 10512354]
33. Koepsell H (2020) Glucose transporters in brain in health and disease. Pflugers Arch. 472, 1299–1343 [PubMed: 32789766]
34. Milstein JL and Ferris HA (2021) The brain as an insulin-sensitive metabolic organ. Mol. Metab. 52, 101234 [PubMed: 33845179]
35. Banks WA et al. (2022) Evidence for an alternative insulin transporter at the blood-brain barrier. Aging Pathobiol. Ther. 4, 100–108 [PubMed: 36644126]
36. Vendelbo J et al. (2018) Increasing BMI is associated with reduced expression of P-glycoprotein (ABCB1 gene) in the human brain with a stronger association in African Americans than Caucasians. Pharm. J. 18, 121–126
37. Leclerc M et al. (2023) Cerebrovascular insulin receptors are defective in Alzheimer's disease. Brain 146, 75–90 [PubMed: 36280236]
38. Stanley M et al. (2016) The effects of peripheral and central high insulin on brain insulin signaling and amyloid-beta in young and old APP/PS1 mice. J. Neurosci. 36, 11704–11715 [PubMed: 27852778]
39. Rhea EM et al. (2022) Insulin resistance in peripheral tissues and the brain: a tale of two sites. Biomedicines 10, 1582 [PubMed: 35884888]
40. Escudero CA et al. (2017) Pro-angiogenic role of insulin: from physiology to pathology. Front. Physiol. 8, 204 [PubMed: 28424632]
41. Chen MB et al. (2020) Brain endothelial cells are exquisite sensors of age-related circulatory cues. Cell Rep. 30, 4418–4432 e4414 [PubMed: 32234477]
42. Banks WA and Kastin AJ (1998) Differential permeability of the blood-brain barrier to two pancreatic peptides: insulin and amylin. Peptides 19, 883–889 [PubMed: 9663454]

43. Choi JH and Kim MS (2022) Homeostatic regulation of glucose metabolism by the central nervous system. Endocrinol. Metab. (Seoul) 37, 9–25 [PubMed: 35255598]
44. Mazucanti CH et al. (2019) Release of insulin produced by the choroid plexis is regulated by serotonergic signaling. JCI Insight 4, e131682 [PubMed: 31647782]
45. Singh BS et al. (1997) Insulin gene expression in immortalized rat hippocampal and pheochromocytoma-12 cell lines. Regul. Pept. 69, 7–14 [PubMed: 9163577]
46. Madadi G et al. (2008) Regulation of brain insulin mRNA by glucose and glucagon-like peptide 1. Biochem. Biophys. Res. Commun. 376, 694–699 [PubMed: 18809381]
47. Weyhenmeyer JA and Fellows RE (1983) Presence of immunoreactive insulin in neurons cultured from fetal rat brain. Cell. Mol. Neurobiol. 3, 81–86 [PubMed: 6136329]
48. Dani N et al. (2021) A cellular and spatial map of the choroid plexus across brain ventricles and ages. Cell 184, 3056–3074 e3021 [PubMed: 33932339]
49. Dakic T et al. (2023) The expression of insulin in the central nervous system: what have we learned so far? Int. J. Mol. Sci. 24, 6586 [PubMed: 37047558]
50. Lee J et al. (2020) Insulin synthesized in the paraventricular nucleus of the hypothalamus regulates pituitary growth hormone production. JCI Insight 5, e135412 [PubMed: 32644973]
51. Rhea EM et al. (2024) State of the science on brain insulin resistance and cognitive decline due to Alzheimer's disease. Aging Dis. 15, 1688–1725 [PubMed: 37611907]
52. Kullmann S et al. (2016) Brain insulin resistance at the cross-roads of metabolic and cognitive disorders in humans. Physiol. Rev. 96, 1169–1209 [PubMed: 27489306]
53. Kullmann S et al. (2021) Central insulin modulates dopamine signaling in the human striatum. J. Clin. Endocrinol. Metab. 106, 2949–2961 [PubMed: 34131733]
54. Byndloss M et al. (2024) The gut microbiota and diabetes: research, translation, and clinical applications – 2023 Diabetes, Diabetes Care, and Diabetologia Expert Forum. Diabetes 73, 1391–1410 [PubMed: 38912690]
55. Chen Z et al. (2021) Association of insulin resistance and type 2 diabetes with gut microbial diversity: a microbiome-wide analysis from population studies. JAMA Netw. Open 4, e2118811 [PubMed: 34323983]
56. Jemimah S et al. (2023) Gut microbiome dysbiosis in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. PLoS One 18, e0285346 [PubMed: 37224131]
57. Hill JH et al. (2025) Neonatal fungi promote lifelong metabolic health through macrophage-dependent beta cell development. Science 387, eadn0953 [PubMed: 40048508]
58. Soto M et al. (2018) Gut microbiota modulate neurobehavior through changes in brain insulin sensitivity and metabolism. Mol. Psychiatry 23, 2287–2301 [PubMed: 29910467]
59. Rhea EM et al. (2023) Brain uptake pharmacokinetics of albiglutide, dulaglutide, tirzepatide, and DA5-CH in the search for new treatments of Alzheimer's and Parkinson's diseases. Tissue Barriers 12, 2292461 [PubMed: 38095516]
60. Imbernon M et al. (2022) Tanycytes control hypothalamic liraglutide uptake and its anti-obesity actions. Cell Metab. 34, 1054–1063 e1057 [PubMed: 35716660]
61. Zhang T et al. (2022) An inter-organ neural circuit for appetite suppression. Cell 185, 2478–2494 e2428 [PubMed: 35662413]
62. Duan X et al. (2024) Semaglutide alleviates gut microbiota dysbiosis induced by a high-fat diet. Eur. J. Pharmacol. 969, 176440 [PubMed: 38402930]
63. Qu Q et al. (2024) Lithocholic acid phenocopies anti-ageing effects of calorie restriction. Nature, Published online December 18, 2024. 10.1038/s41586-024-08329-5
64. Ghosh S and Collier A (2012) Section 1 – Diagnosis, classification, epidemiology and biochemistry. In Churchill's Pocketbook of Diabetes ((2nd edn)) (Ghosh S and Collier A, eds), pp. 1–49, Churchill Livingstone
65. DeFronzo RA et al. (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am. J. Phys. 237, E214–E223
66. Turner N et al. (2013) Distinct patterns of tissue-specific lipid accumulation during the induction of insulin resistance in mice by high-fat feeding. Diabetologia 56, 1638–1648 [PubMed: 23620060]

67. Michael MD et al. (2000) Loss of insulin signaling in hepatocytes leads to severe insulin resistance and progressive hepatic dysfunction. Mol. Cell 6, 87–97 [PubMed: 10949030]
68. Massier L et al. (2023) An integrated single cell and spatial transcriptomic map of human white adipose tissue. Nat. Commun. 14, 1438 [PubMed: 36922516]
69. Backdahl J et al. (2021) Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. Cell Metab. 33, 2301 [PubMed: 34731657]
70. Takeuchi T et al. (2023) Gut microbial carbohydrate metabolism contributes to insulin resistance. Nature 621, 389–395 [PubMed: 37648852]
71. Contrepois K et al. (2020) Molecular choreography of acute exercise. Cell 181, 1112–1130 e1116 [PubMed: 32470399]
72. Zhou W et al. (2019) Longitudinal multi-omics of host-microbe dynamics in prediabetes. Nature 569, 663–671 [PubMed: 31142858]
73. Kapogiannis D et al. (2019) Association of extracellular vesicle biomarkers with Alzheimer disease in the Baltimore Longitudinal Study of Aging. JAMA Neurol. 76, 1340–1351 [PubMed: 31305918]
74. Manolopoulos A et al. (2025) Extracellular vesicles: translational research and applications in neurology. Nat. Rev. Neurol., Published April 3, 2025. 10.1038/s41582-025-01080-z
75. Blommer J et al. (2023) Extracellular vesicle biomarkers for cognitive impairment in Parkinson's disease. Brain 146, 195–208 [PubMed: 35833836]
76. Mustapic M et al. (2019) Extracellular vesicle biomarkers track cognitive changes following intranasal insulin in Alzheimer's disease. J. Alzheimers Dis. 69, 489–498 [PubMed: 30958348]
77. Mansur RB et al. (2021) Exploring brain insulin resistance in adults with bipolar depression using extracellular vesicles of neuronal origin. J. Psychiatr. Res. 133, 82–92 [PubMed: 33316649]
78. Cleary JA et al. (2025) Neuron-derived extracellular vesicles as a liquid biopsy for brain insulin dysregulation in Alzheimer's disease and related disorders. Alzheimers Dement. 21, e14497 [PubMed: 39822132]
79. Kapogiannis D et al. (2024) Brain responses to intermittent fasting and the healthy living diet in older adults. Cell Metab. 36, 1900–1904 [PubMed: 39019039]
80. Malin SK et al. (2025) Two weeks of exercise alters neuronal extracellular vesicle insulin signaling proteins and pro-BDNF in older adults with prediabetes. Aging Cell 24, e14369 [PubMed: 39421964]
81. Tschritter O et al. (2006) The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. Proc. Natl. Acad. Sci. U. S. A. 103, 12103–12108 [PubMed: 16877540]
82. Kullmann S et al. (2020) Brain insulin sensitivity is linked to adiposity and body fat distribution. Nat. Commun. 11, 1841 [PubMed: 32296068]
83. Jensen NJ et al. (2025) Relation of insulin resistance to brain glucose metabolism in fasting and hyperinsulinemic states: a systematic review and meta-analysis. J. Clin. Endocrinol. Metab. 110, e525–e537 [PubMed: 39185744]
84. Rebelos E et al. (2021) Brain insulin sensitivity is linked to body fat distribution–the positron emission tomography perspective. Eur. J. Nucl. Med. Mol. Imaging 48, 966–968 [PubMed: 33029655]
85. Konner AC and Bruning JC (2012) Selective insulin and leptin resistance in metabolic disorders. Cell Metab. 16, 144–152 [PubMed: 22883229]
86. Klockener T et al. (2011) High-fat feeding promotes obesity via insulin receptor/PI3K-dependent inhibition of SF-1 VMH neurons. Nat. Neurosci. 14, 911–918 [PubMed: 21642975]
87. Hallschmid M (2021) Intranasal insulin. J. Neuroendocrinol. 33, e12934 [PubMed: 33506526]
88. Kullmann S et al. (2020) Central nervous pathways of insulin action in the control of metabolism and food intake. Lancet Diabetes Endocrinol. 8, 524–534 [PubMed: 32445739]
89. Wagner L et al. (2023) Brain insulin responsiveness is linked to age and peripheral insulin sensitivity. Diabetes Obes. Metab. 25, 2171–2180 [PubMed: 37046367]

90. Kullmann S et al. (2017) Intranasal insulin enhances brain functional connectivity mediating the relationship between adiposity and subjective feeling of hunger. Sci. Rep. 7, 1627 [PubMed: 28487570]
91. Wagner L et al. (2022) Sex differences in central insulin action: effect of intranasal insulin on neural food cue reactivity in adults with normal weight and overweight. Int. J. Obes. 46, 1662–1670
92. Hummel J et al. (2023) Brain insulin action on peripheral insulin sensitivity in women depends on menstrual cycle phase. Nat. Metab. 5, 1475–1482 [PubMed: 37735274]
93. Kullmann S et al. (2025) A short-term, high-caloric diet has prolonged effects on brain insulin action in men. Nat Metab. 7, 469–477 [PubMed: 39984682]
94. Kullmann S et al. (2015) Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. Diabetes Care 38, 1044–1050 [PubMed: 25795413]
95. Tiedemann LJ et al. (2022) Insulin sensitivity in mesolimbic pathways predicts and improves with weight loss in older dieters. Elife 11, e76835 [PubMed: 36170006]
96. Kullmann S et al. (2022) Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. JCI Insight 7, 161498

## Outstanding questions

What roles do non-glucose metabolism pathways, such as nucleoside and heme metabolism, play in insulin resistance, and how do they integrate with classical insulin signaling?

How does the BBB contribute to insulin transport and resistance, and can modulating its function enhance insulin delivery to the brain?

Which cell types are most sensitive to insulin resistance, and how does their dysregulation drive systemic metabolic dysregulation?

Does brain-derived insulin influence insulin resistance? If so, are its effects restricted to central insulin resistance or can they be peripheral?

How do specific gut microbiota populations regulate insulin resistance through center-to-periphery communication, and can microbiome-targeted intervention provide sustainable therapeutic bene fits?

Are there any reliable biomarkers, such as blood EVs or plasma-based multi-omic signatures, that can predict the progression of insulin resistance in humans?

How can we establish standardized criteria for measuring BIR using neuroimaging and multi-omics approaches?

## Highlights

The current view of insulin resistance focuses primarily on classical insulin-sensitive tissues such as muscle, fat, and liver, often overlooking the brain.

Advances in molecular biology and cross-disciplinary research including the brain provide new perspectives on insulin resistance.

Previously overlooked metabolic pathways and emerging evidence on central–peripheral interactions reveal a more complex network regulating insulin action.

The reviewed findings highlight the need for a broader, integrative framework for insulin resistance in the context of big data, systems medicine, and disease comorbidity.

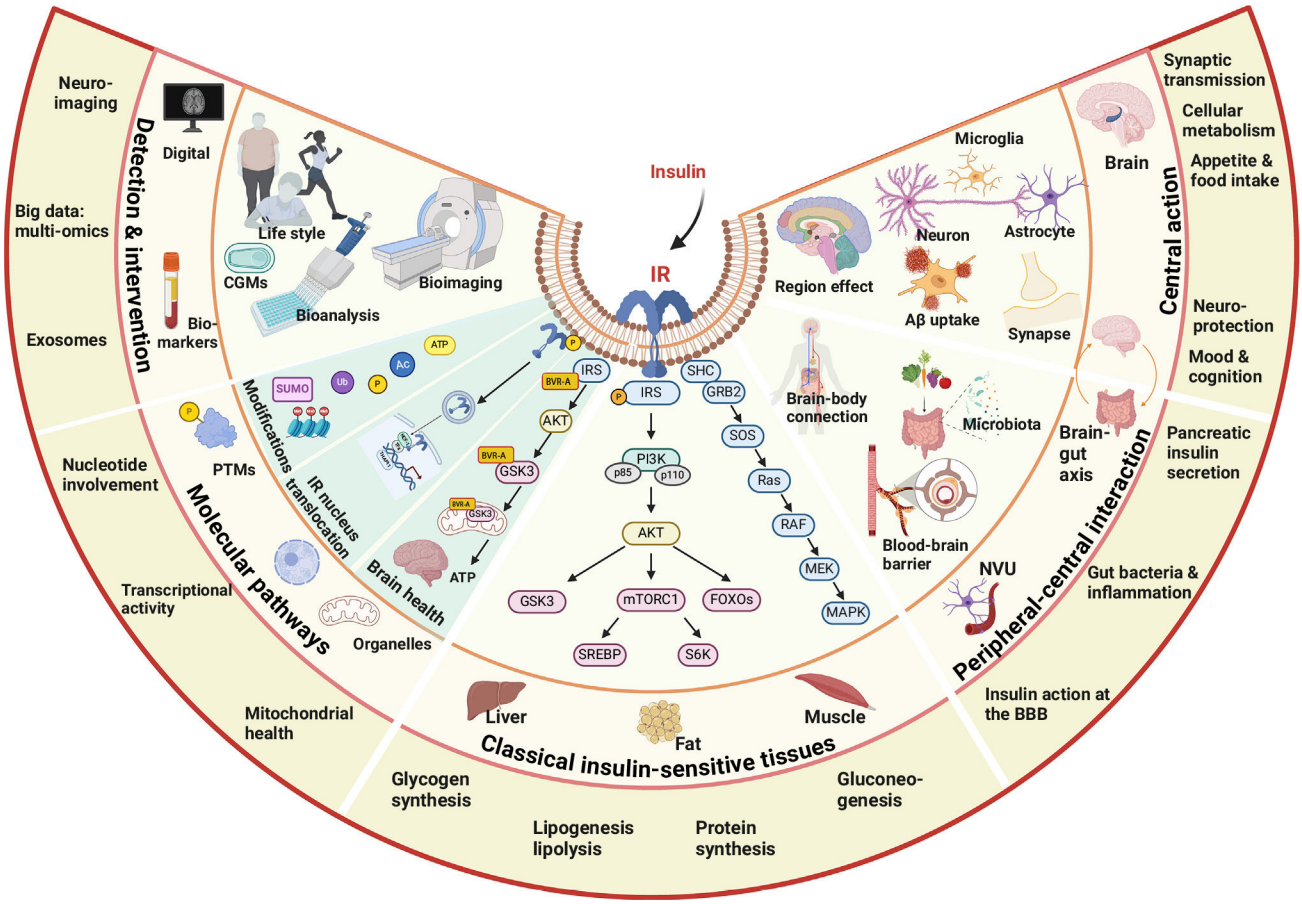


**Figure 1. Insulin signaling: beyond the cell surface.**

At the heart of insulin signaling is the cell surface insulin receptor (IR in figure). This critical protein maintains insulin signaling as needed and guides the next steps. Beyond these critical, well-established signaling pathways, additional signaling pathways and roles for the IR have been identified in recent years, including translocation to the nucleus and action within this organelle, signaling to the mitochondria through recently discovered mediators, and its role in post-translational modifications. There is increasing evidence for peripheral–central interactions, mediated in part by the blood–brain barrier (BBB) and the gut microbiome. The central actions of insulin and the IR are continually being updated, with regulation of synaptic transmission, appetite, and cognition. Advanced diagnostic technologies are being developed to better detect insulin resistance within the brain, which has proved difficult to do in humans. Other technologies are being developed to better capture some of these associations and interactions with insulin resistance. These advancements indicate a continual evolution in our understanding of insulin resistance. Abbreviations: AKT, Ser/Thr kinase; CGM, continuous glucose monitor; G SK3, a serine/threonine protein kinase; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTORC1, mammalian target of rapamycin complex 1; NVU, neurovascular unit; PTM, post-translational modification; SHC, Src homology and collagen; SREBP, sterol regulatory element-binding protein. Figure created with BioRender.

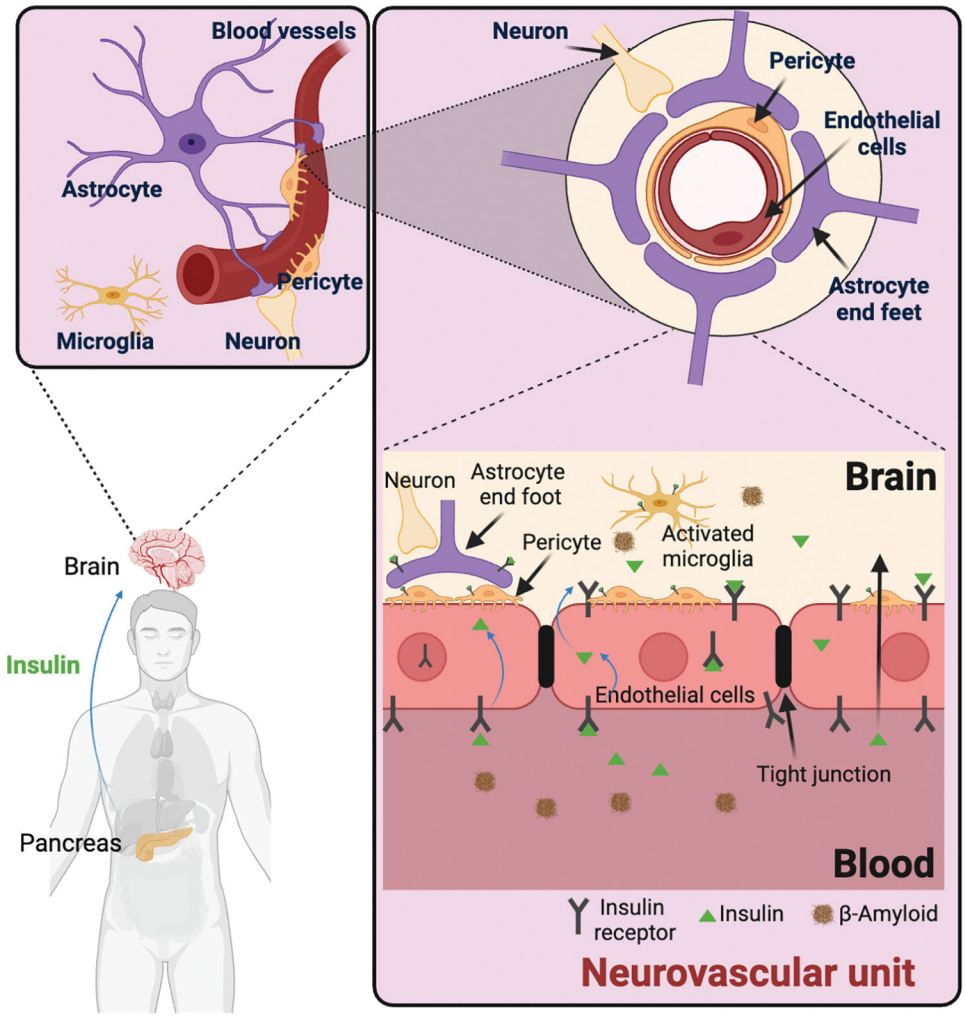


**Figure 2. Peripheral–central axis at the neurovascular unit (NVU).**

Pancreas-derived insulin crosses the blood–brain barrier (BBB), which is a part of the NVU. The NVU consists of a network of cells, including brain endothelial cells connected by tight junctions, limiting passive permeability of substrates, pericytes, astrocytic endfeet, microglia, and neurons. The insulin receptor (IR) is expressed in all cell types of the NVU, but is most abundantly expressed in brain endothelial cells. While this receptor is critical for signaling within brain endothelial cells, it is not required for insulin transport across the BBB. The IR present in endothelial cells, astrocytes and microglia has been shown to affect brain insulin signaling, likely playing a role in the etiology of brain insulin resistance (BIR). Figure created with BioRender.

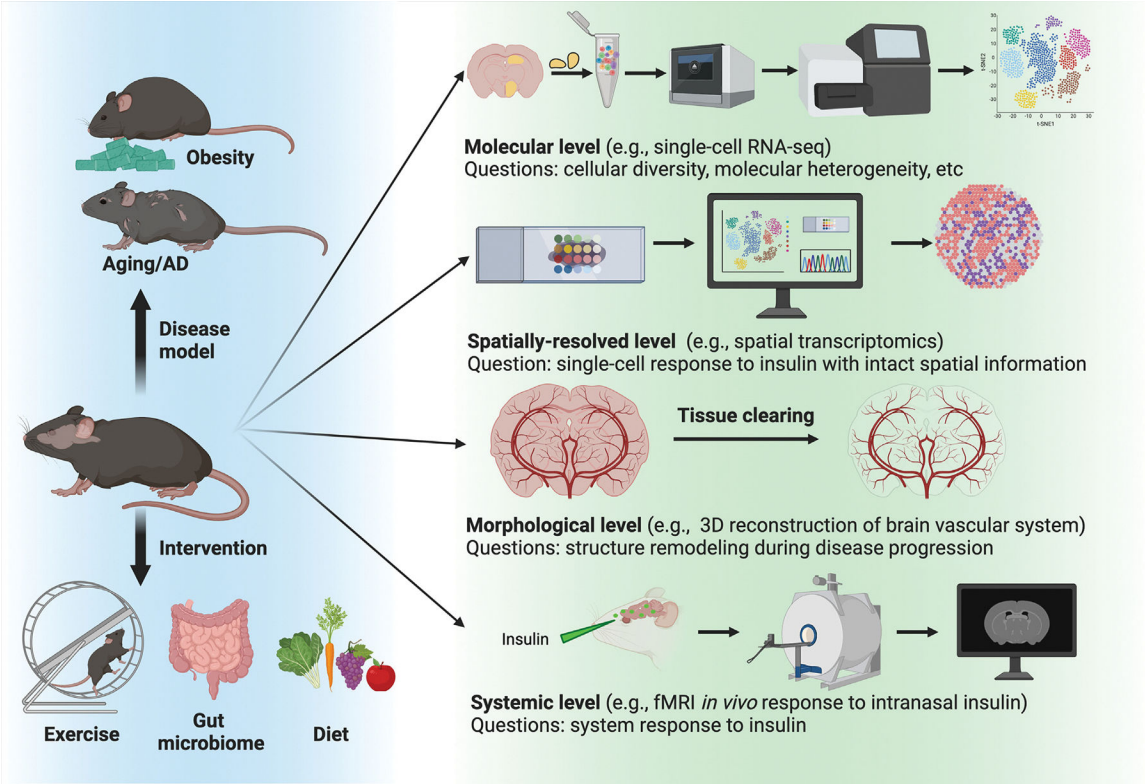


**Figure 3. Advanced neuroscience tools to study insulin action in the brain.**

Emerging tools allow investigators to advance our current understandings about the action of insulin within the brain. These tools offer the opportunity to assess not only brain insulin resistance (BIR) in diseased states such as aging, Alzheimer's disease (AD), or diet-induced obesity, but also the attenuation of BIR through various interventions including exercise, alteration of the gut microbiome, and diet. Advanced tools allow investigators to assess insulin action in the brain on multiple levels. Significant improvements have been made not only in single-cell transcriptomics data but also with spatial resolution, allowing researchers to dissociate cell types and regions involved in the overall response to disease or intervention. At the morphological level, the 3D contribution of the vasculature can be linked to disease, identifying changes in structural remodeling, coupled with histological protein expression. Finally, at the systemic level, advancements in imaging have allowed us to visualize the functional response to a stimulus, including intranasal insulin, allowing investigators to better understand the involvement of BIR in disease and intervention response. Abbreviation: fMRI, functional magnetic resonance imaging. Figure created with B ioRender.

**Table 1.**

Tools for assessing BIR *in vivo*[a]

| Selected neuroimaging techniques | Potential biomarkers (in extracellular vesicles) |
|---|---|
| fMRI | $pSer^{312}$-IRS1 |
| PET | pTyr-IRS1 |
| PET MRI | $pERK_{1/2}$ |
| MEG | pJNK |
| | pp38 |
| | $pSer^{473}$AKT |

[a]This table presents a selection of tools for assessing BIR; it is not exhaustive, and additional methods may be relevant.