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Cerebral Insulin Resistance in Gifted Individuals: Relationships between High Cognitive Ability and Cerebral Metabolic Alterations

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Abstract

Introduction: *Cerebral insulin resistance is a phenomenon associated with metabolic alterations in the brain, often related to diseases such as Alzheimer's, type 2 diabetes mellitus (DM) and cognitive disorders. Gifted individuals exhibit unique characteristics, such as greater neural connectivity and intense brain energy demands, which raises the question of their possible vulnerability or resilience to brain insulin resistance.*

Objective: *The aim of this article on insulin resistance, cognitive function, and giftedness is to review recently published data derived from human studies, including clinical trials.*

Methods: *We conducted a literature review followed by a synthesis of neurobiological components of the mechanisms involved in brain insulin and giftedness, to generate an understanding of this association and thus spark new research interests.*

Results: *In research with cognitively normal participants, insulin resistance was associated with worse global cognition, as well as verbal episodic memory and executive function, but several neurobiological components are involved.*

Discussion: *Diabetes appears to be associated with cognitive decline in some cognitive domains more than others, particularly executive function, working memory and attention. Most cross-sectional and longitudinal clinical studies show an association between insulin resistance and cognition in older people. Furthermore, they use only a single or global cognitive test, and there is little information about which specific cognitive domains are involved.*

Conclusion: *Scientific investigation of this topic can not only deepen our knowledge about metabolism and cognition, mas also guide practical strategies to protect mental and physical health of this group.*

Keywords: *brain insulin, giftedness, insulin resistance.*

1. Introduction

Cerebral insulin resistance is a phenomenon associated with metabolic changes in the brain, often related to diseases such as Alzheimer's, type 2 diabetes mellitus (DM) and cognitive disorders. [1] Gifted individuals exhibit unique characteristics, such as greater neural connectivity and intense brain energy demands, which raises the question of their possible vulnerability or resilience to brain insulin resistance. [1]

Insulin performs unique nonmetabolic functions in the brain. Whereas both insulin and its mRNA have been detected in the central nervous system (CNS), it is now known that this hormone is also synthesized in several regions of the brain, brain endothelial cells and blood-brain barrier (BBB) function, and those related to behavioral effects, such as cognition in pathological states of mental and organic health.

Insulin resistance in the brain has been associated with long-term adiposity and an unfavorable distribution of adipose tissue, implicating it in the pathogenesis of subgroups of obesity and pre-DM that are characterized by distinct patterns of body fat distribution. [4] Insulin is synthesized by a subpopulation of neurons in the cerebral cortex and neural progenitor cells in the hippocampus. Complementing the slow supply of insulin to the brain from pancreatic beta cells, insulin released locally by neurons provides a rapid means of regulating local

microcircuits, effectively modulating synaptic transmission and energy homeostasis on demand from neural networks. [5]

Modulation of insulin production by brain neurons via glucagon-like peptide 1 (GLP-1) agonists may be useful in combating diabetes, obesity and neurodegenerative diseases. Concomitantly, insulin's ability to modify stress and fear, appetite and eating behavior, and cognitive function in healthy and diseased individuals highlights its potential in the therapeutic and mechanistic exploration of highly prevalent psychiatric, metabolic, and cognitive conditions. such as mood disorders, obesity and Alzheimer's disease (AD). [6] However, inconsistencies in study designs, dosages, and outcome measures necessitate standardized methodologies to better understand the central action of insulin. [7]

2. Objectives

The purpose of this article on insulin resistance, cognitive function, and giftedness is to review recently published data derived from human studies, including clinical trials. To contribute to the understanding of the interactions between high cognitive ability and brain metabolic health, and to identify possible risk factors that can be used in preventive interventions for gifted individuals, and to offer a perspective on current knowledge gaps and future directions in the field.

3. Methodology

We performed a review of the literature published in the electronic library PubMed. The search terms were: “Insulin [title] and (brain or cognition or dementia). We reviewed citation titles, abstracts, and full manuscripts when necessary to exclude publications that were not original research, not directly relevant to the brain and insulin pathways, or with a small sample size and limited power to detect associations (<75 people total).

This search yielded 146 articles, of which 26 met the predetermined inclusion and exclusion criteria. Among the nine studies that specifically examined insulin resistance and cognitive dysfunction and/or decline, eight studies suggested an association, but some only in subanalyses. We performed a synthesis of neurobiological components of the mechanisms involved in brain insulin and giftedness, to generate understanding of this association and thus awaken new research interests.

4. Results

Overall, these studies show that central insulin resistance, reflected by higher CSF insulin or HOMA-IR, is associated with poorer cognitive performance and increased odds of developing AD pathology (elevated CSF total and p-tau levels). [8] Among individuals with cognitive dysfunction, one study demonstrates that insulin resistance is associated with lower global cognition only in women and in those without the APOEε4 allele. [9] In studies of cognitively normal participants, insulin resistance has been associated with poorer global cognition, as well as verbal episodic memory and executive function, but multiple neurobiological components are involved. [10]

4.1. Neurobiological Components

4.1.1 Cerebral angiogenesis

Neuroimaging studies have shown that insulin affects brain activity, cerebral blood flow, and functional connectivity in regions such as the hypothalamus, amygdala, and insula. [11] Both are involved in the stimulation of hypoxia-inducible factor (HIF) in angiogenesis and can be activated by the insulin signaling pathway. Thus, the PI3K and MAPK pathways communicate between the insulin signaling pathway and the angiogenesis pathway in the brain. [11]

Cerebral blood flow (CBF) dynamics at the onset of hypoglycemia may play a key role in hypoglycemia unawareness; however, there is currently a paucity of techniques that can monitor CBF in adults with high temporal resolution. [12]

One study found through diffuse correlation spectroscopy (DCS) that cerebral blood flow increased by 42% after insulin injection with a delay of 17 ± 10 min, while the onset of hypoglycemia symptoms was delayed by 24 ± 11 min. [13]

The onset of CBF mechanisms precedes the onset of hypoglycemia symptoms in non-diabetic individuals with normal hypoglycemia awareness.[14] The two canonical downstream pathways involved in mediating the insulin signaling pathway are the phosphoinositide-3 kinase cascades (PI3K) and mitogen-activated protein kinase (MAPK). In the brain, they should be similar to those in the periphery. The PI3K and MAPK pathways play important roles in angiogenesis. [14]

4.1.2 Blood-brain barrier

The BBB is a selective, semipermeable barrier around the microvasculature in the brain. It plays a crucial role in brain health by tightly controlling molecular passage between the bloodstream and the brain. [15]

The primary (but probably not the only) mechanism that allows insulin to enter the brain is receptor-mediated transcytosis, binding to insulin receptors at the BBB, and movement occurs through endothelial cells into the extracellular space of the brain. [15] In certain specialized regions of the brain, such as the arcuate nucleus of the hypothalamus, the BBB appears to be less dense.16 Similar to animals, insulin is present in the cerebrospinal fluid (CSF) of humans. This compartment is accessible for investigations of transport processes to the brain. The presence of insulin in human CSF indicates that the hormone is transported from the bloodstream to the central nervous system. [16]

Insulin transport is not equally effective in all individuals. There appear to be a number of situations that facilitate or hinder this transport, ultimately influencing the availability of insulin in the brain: insulin penetration into the CSF is lower in obese individuals.[16] In addition, changes in blood glucose levels acutely modulate the transport of peptide hormones, including insulin, into the CSF.[17] Thus, alterations in the transport process across the BBB that require the insulin receptor may be responsible for the observed variations in insulin transport into the human CSF. In line, decreased transport efficiency has been identified in individuals presenting systemic insulin resistance. [17]

Aging is also associated with a reduction in insulin transport into the CSF. [18] This decline may contribute to impaired insulin action in the brain, predisposing individuals to age-related cognitive dysfunction and neurodegenerative diseases. [18] Insulin signaling on the human BBB using the human cerebral microvascular endothelial cell line (hCMEC/D3) as a well-established in vitro model. [19] Short-term insulin stimulation increased cell proliferation via the canonical phosphoinositide-

3 kinase/protein kinase signaling pathways, kinase B and mitogen-activated protein kinase, demonstrating that insulin signaling is involved in the regulation of biological responses in the human BBB. [20]

Insulin rapidly increased the tight junction integrity of hCMEC/D3 cells via the phosphoinositide-3 kinase/protein kinase B/glycogen synthase kinase-3 β signaling pathway. Inhibition of insulin/factor. Inhibition of insulin/insulin-like growth factor-1 receptor kinase by AG1024 blocked the increase in tight junction integrity.[19] High insulin/high glucose treatment (as a model of hyperglycemia and hyperinsulinemia) synergistically reduced tight junction integrity in hCMEC/D3 cells. [20]

4.1.3 Human brain insulin approaches

Insulin receptors are expressed in the human brain on neurons and other cell types (astrocytes), teleologically arguing for a role for insulin in the brain. Tanycytes, a type of cell that express the insulin receptor, are necessary for insulin uptake. [20]

Several techniques are used to stimulate brain insulin action in clinical research. The most physiological way is to measure the response to endogenous insulin that is released in response to food intake. [20]

Several additional postprandial factors make it difficult to dissect the specific effects of insulin from other effects. A more selective approach is intravenous insulin infusion during hyperinsulinemic-euglycemic glucose clamps. [21]

However, this technique also fails to differentiate between peripheral and cerebral effects. One approach frequently used in clinical research to overcome this challenge is the administration of insulin by nasal spray. [21]

This route delivers a substantial amount of insulin to the brain, while only small amounts enter the bloodstream. [21]

The amount of insulin absorbed into the bloodstream is not sufficient to induce hypoglycemia and probably does not contribute significantly to the cerebral effects induced. However, this insulin spillover must be taken into account when studying the potential impact of brain insulin on peripheral metabolism. [21] Modern neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) facilitated investigations into the effects of insulin on brain function. [21]

MEG measures the magnetic fields produced by the brain's electrical activity. Early studies using MEG demonstrated the impact of insulin on neuronal activity and related the effects of insulin on the brain to body weight, metabolic factors, and genetic factors. [22] PET allows the assessment of metabolic processes, and most studies investigating the effects of insulin in the brain used the tracer fluorodeoxyglucose (FDG) to measure glucose uptake in the brain under insulin stimulation. [22]

Most studies on insulin action in the human brain have used fMRI. In contrast to MEG, it provides higher spatial resolution not only for cortical but also subcortical regions. [22] Magnetic resonance imaging (fMRI) identifies and quantifies functional aspects, and thus insulin-induced changes in regional brain activity and brain networks are identified. [22]

A study using MEG identified the clinical relevance of insulin action in the brain for the first time, linking brain insulin resistance with peripheral insulin resistance, genetic predisposition, and weight loss success in obese adults. [22]

Although MEG is a suitable tool for measuring brain activity primarily in cortical areas, fMRI provides high spatial resolution for both cortical and subcortical regions. [22] Thus, insulin action can be detected in all regions relevant to feeding behavior, which include regions deep within the brain, such as the hypothalamus, midbrain, and brainstem, as well as regions within the striatum. [22] fMRI studies have shown significant insulin-induced attenuation predominantly in the occipital and prefrontal cortical regions and the hypothalamus, successfully localizing insulin-sensitive brain regions in healthy, mostly normal-weight individuals. [22]

4.1.4 Insulin resistance in the human brain

There are a substantial number of people with reduced or even absent brain response to insulin, a condition called 'brain insulin resistance,' and several studies have shown that blood measures of insulin resistance were related to a decreased risk of cognitive impairment/dementia. [23] This condition is most commonly associated with overweight and obesity. Other factors have also been linked to brain insulin resistance, including normal aging, circulating NEFA levels, and several common genetic polymorphisms, most of which were discovered through their association with body weight. [23]

Further evidence for the effects of insulin on the human brain comes from functional studies; they are experimental studies of nasal administration of insulin that improved memory, altered eating behavior, and affected mood.

The insula is implicated in a wide range of functions and plays a significant role in regulating the body's homeostasis. Furthermore, it is involved in the perception of bodily states, such as hunger and satiety, making it also essential for eating behavior.[24] The hypothalamus is made up of several nuclei, some of which are essential for the energy homeostasis of the entire body, for the eating behavior and body weight. [24]

4.1.5 Insulin and biomarkers of brain structure and function

Increased perivascular space (EPVS) in the basal ganglia is commonly found on MRI in senility and is associated with cognitive decline and impairment. [25] A cross-sectional study examined the correlation between insulin resistance and EPVS among 235 participants and showed that insulin resistance insulin (by HOMA-IR) was associated with an increased risk of moderate/severe EPVSs, after controlling for cardiovascular risk factors. [25]

In a longitudinal study of cognitively normal adults with MCI, it was associated with gene sequencing for exons involved in insulin resistance to brain insulin, using data from clinical evaluations, neuropsychological tests and fMRI scans, and observed that certain insulin resistance genes can lead to neuronal disconnections in the brain that further impair cognition. [25] The DLB group had more regional deficits in connectivity on fMRI, characterized by (presumably synaptic) disconnections in cerebellar-frontal-temporal regions, compared with the cognitively normal group. [26]

More severe SVPE and decreased regional connections by fMRI may reveal underlying mechanisms for cognitive impairment induced by insulin resistance. [26]

Elevated levels of insulin in the blood or brain are also associated with increased cerebral glucose metabolism in cerebral cortices and hippocampal regions, which may be involved in cognition. [26]

4.1.6 Dopamine and Insulin

Dysfunctional signaling in midbrain reward circuits perpetuates diseases characterized by compulsive overconsumption of rewarding substances, such as substance abuse, binge eating disorder, and obesity. [27]

Dopaminergic activity in the ventral tegmental area (VTA) serves as an index of how rewarding stimuli are perceived and triggers behaviors necessary to obtain future rewards. [27]

The evolutionary link between reward and the pursuit and consumption of palatable foods ensured the survival of an organism, and the hormonal systems that regulate appetite developed concomitantly to regulate motivated behaviors, but these same mechanisms are activated in the regulation of directed behavior to reward around food, drugs, alcohol and social interactions.[27] Understanding how hormonal regulation of VTA dopamine output alters motivated behaviors is essential to leveraging therapies that target these hormonal systems to treat addiction and disordered eating.[27]

The metabolic hormones ghrelin, glucagon-like peptide-1, amylin, leptin and insulin regulate behaviors toward food and drugs of abuse through mechanisms underlying the VTA, highlighting similarities and differences in how these hormones modulate VTA dopamine signaling. [27]

Leptin acts by suppressing food restraint activity involves coding of food stimuli by VTA DA neurons at a millisecond level. Presenting key mechanisms linking metabolic information to reward signaling. [28]

In the presence of insulin, glucose levels must decrease further before GE neurons respond. Thus, the set point for detecting glucose deficit and initiating compensatory mechanisms would be reduced. [28]

The VMH is required for the counterregulatory response to hypoglycemia (CRR) that increases hepatic gluconeogenesis to restore euglycemia28 Furthermore, the VMH also restricts the hepatic glucose production during euglycemia and stimulates peripheral glucose uptake. [28]

4.1.7 Dopamine and Giftedness

Dopamine has long been considered a volume transmitter that diffuses after release to mediate effects on many cells over a large area and on a time scale with both fast and slow coding mechanisms for dopamine volume transmission.[29]

Recording and fMRI studies have found that dopamine encodes events on the order of hundreds of milliseconds and that dopamine neuron activity is regulated on similarly rapid time scales, with subsecond encodings for dopamine. [29]

The firing of dopamine axons causes the release of dopamine with very fast kinetics, and this release activates dopamine receptors with a signaling speed of tens of milliseconds. [29] Extracellular dopamine levels are highly variable spatially and temporally, with critical points of dopamine peaks of short duration. Receptors can be evenly distributed on target cells, just clustered "synaptically," or be arranged in any way in between. Electron microscopy studies have found that approximately 30% of dopamine varicosities are associated with postsynaptic specializations, and so it is possible that these specializations align exactly with the scarce sites of dopamine release. [30]

The precise distribution of the two main families of dopamine receptors (D1 and D2) in relation to secretory sites still needs to be clarified, and in gifted individuals they present a more organized distribution in quantity and specific regions. Dopamine is detected at critical points after release, diffusion is confined, and striatal D2 receptors are rapidly activated. [30]
A synapse-like organization with postsynaptic GABA receptors and clusters of nearby synaptic or perisynaptic dopamine receptors may be a way to support rapid dopamine encoding. [30]

4.1.8 Giftedness

Intelligence is highly heritable and an important determinant of health and well-being. Recent genome-wide meta-analyses have identified 24 genomic loci linked to variation in intelligence, but several biological factors influence overall intelligence. [30-37] In gene set analysis, six gene sets from the Gene Ontology were significantly associated with intelligence: neurogenesis, neuron differentiation, central nervous system neuron differentiation, regulation of nervous system development, positive regulation of central nervous system development, and nervous and regulation of synapse structure or activity. [30-37] Conditional analysis indicated that there were three independent associations: regulation of nervous system development, differentiation of central nervous system neurons, and regulation of synapse structure or activity, which together accounted for the associations of the other sets. [30-37]

When linking gene-based P values to tissue-specific gene sets, we observed strong associations with gene expression in multiple brain areas, particularly the frontal cortex. [30-37] In single-cell gene expression set analyses of the brain, we found significant associations of striatal medium spiny neurons and pyramidal neurons in the hippocampal CA1 and cortical somatosensory regions. [30-37] Conditional analysis showed that the independent association signal in brain cells was driven by medium spiny neurons, neuroblasts, and CA1 pyramidal neurons. [30-37]

Intelligence has been associated with a wide variety of human behaviors and brain anatomy. [30-37]

A meta-analysis showed negative genetic correlations between intelligence and Attention Deficit Disorder (ADHD), depressive symptoms, and Alzheimer's disease. [30-37] Studies on the genetic background of intelligence focus on dopaminergic genes (DRD2, DRD4, COMT, SLC6A3, DAT1, CCKAR) and the adrenergic system (ADRB2, CHRM2), as well as neutrophil (BDNF) and oxidative stress genes (LTF, PRNP). [30-37]

Dopaminergic, oxidative stress, and neutrophil BDNF genes are directly related to neurodevelopmental dysfunctions that impact the reward system and hormonal systems of cortisol, vasopressin, melatonin, and oxytocin and justify a possible link and new window of approach for the influence of insulin on states of high intelligence such as giftedness. [30-37]

4.1.9 Giftedness and High Brain Demand

Brain insulin resistance has been associated with neurodegenerative and metabolic diseases, such as Alzheimer's and type 2 diabetes. However, its impact on gifted individuals

(IQ ≥ 130), who have greater brain energy demands and high neural connectivity, remains unexplored. [30-37]

Although there are still no studies dedicated to the topic, the hypothesis that gifted individuals may be more vulnerable (or resilient) to this condition is intriguing and deserves attention. [30-37] Gifted individuals have highly connected brains, with greater metabolic activity in crucial areas such as the hippocampus (responsible for memory), the prefrontal cortex (executive functions and planning) and the nucleus accumbens (reward and motivation). [30-37]

These regions directly depend on high glucose levels and effective insulin signaling. [30-37] Brain insulin plays a role beyond glucose metabolism, modulating neurotransmitters such as dopamine, which are essential for motivation, learning and pleasure. [30-37]

This high energy demand and intense use of these circuits make it plausible that changes in brain insulin signaling can significantly impact the cognitive and emotional performance of gifted individuals. [30-37]

4.1.10 Glucagon System 1 (GLP-1)

GLP-1 is a peptide secreted by the intestine that acts through the GLP-1 receptor, and the primary function of GLP-1 is to aid in reducing postprandial glucose levels, and studies demonstrate the ability of GLP-1 to act in the brain to alter glucose regulation.[24-30] Evidence for a central GLP-1 system and the effects of brain GLP-1 on regulating multiple facets of glucose homeostasis, including glucose tolerance, insulin production, sensitivity to insulin, hepatic glucose production, muscular glucose uptake, and connections of the central GLP-1 system with the intestine. [24-30]

This pathophysiological condition accompanies an acutely impaired modulation of peripheral metabolism in response to insulin action in the brain, particularly in the postprandial state. [24-30]

4.1.11 Insulin Growth Factor-1 (IGF-1)

Insulin-like growth factor-1 (IGF-1) is a hormone that mediates the effects of human growth hormone and is also neuroprotective by promoting neurogenesis and inhibiting apoptosis. [24-30]

Reduced IGF-1 levels are associated with several neurodegenerative conditions. Because most IGF-1 binds to IGF-binding proteins (IGFBPs), including IGFBP3 which contributes to tau phosphorylation, we examined studies on IGF and its binding proteins in association with cognition. [24-30]

Kimoto A et al., evaluated patients with AD and analyzed serum levels of IGF-1, and found positive correlations between IGF-1 and the MMSE and dementia scale, especially in the subscales of recall, verbal fluency and attention. [24-30]

4.1.12 Ghrelin

Peripherally administered ghrelin activates GHSRs in the VTA and induces bimodal effects on mesolimbic dopamine neurotransmission depending on food consumption states. [24-30] Ghrelin induces orexigenic behavior by activating growth hormone secretagogue 1 receptors (GHSRs) in the ventral tegmental area (VTA) as well as in the hypothalamus, suggesting the involvement of the mesolimbic dopaminergic system in the action of ghrelin. [24-30]

Ghrelin was administered to rats peripherally (3 nmol, iv) as well as locally into the VTA (0.3 nmol). Dopamine in the nucleus accumbens (NAc) shell was measured by microdialysis.Peripheral ghrelin decreased dopamine levels in the NAc when food was removed after ghrelin administration. [24-30]

This inhibitory effect was mediated by GABA(A) and N-methyl-D-aspartate (NMDA) receptors in the VTA. In contrast, when animals consumed food after ghrelin administration, dopamine levels increased robustly. [24-30]

This stimulating effect was mediated by NMDA receptors, but not by GABA(A) receptors, in the VTA. Importantly, both the inhibitory and stimulatory effects of ghrelin primarily required activation of GHSRs in the VTA. [24-30]

Furthermore, local injection of ghrelin into the VTA induced dopamine release in the NAc and food consumption, supporting the local action of ghrelin in the VTA. Consumption of regular or palatable food without systemic ghrelin administration induced an increase in dopamine levels in the NAc via activation of mu opioid receptors in the VTA. [28]

Systemic administration of ghrelin (3 nmol) followed by no food induced a decrease in dopamine levels through activation of kappa opioid receptors in the VTA. [24-30] Systemic administration of ghrelin followed by consumption of regular food induced an increase in dopamine levels through preferential activation of mu opioid receptors, whereas systemic administration of ghrelin followed by consumption of palatable food suppressed the increase in dopamine levels. of dopamine through preferential activation of kappa opioid receptors. [24-30]

Thus, natural food reward and systemic ghrelin activate mu and kappa opioid receptor pathways in the VTA, respectively, resulting in opposing influences on dopamine release in the NAc. [24-30]

Furthermore, systemic ghrelin induces switching of the dominant opioid receptor pathway for highly rewarding foods from mu to kappa, resulting in suppression of the mesolimbic dopaminergic system. [24-30]

5. Discussion

Diabetes has emerged as a modifiable risk factor and has been associated with cognitive impairment, cognitive decline, and dementia, including dementia attributed to AD. Several studies have now shown a 50% increased risk of dementia among people with diabetes, compared to those without. Furthermore, diabetes appears to be associated with cognitive decline in some cognitive domains more than others, particularly executive function, working memory, and attention.

Most cross-sectional and longitudinal clinical studies show an association between insulin resistance and cognition in older people. Furthermore, they use only a single or global cognitive test, and there is little information about which specific cognitive domains are implicated.

For example, a population-based study of 1028 cognitively normal participants tested cognitive performance associated with insulin resistance using the Digit Symbol Substitution (DSS) subtest of the Wechsler Adult Intelligence Scale, a sensitive measure of cognitive dysfunction, and found a worse performance in DSS. Thus, a simple perceptual speed test may be informative in clinical practice to detect cognitive dysfunction in elderly individuals with insulin resistance. [31-35]

Glucose hypometabolism was independently associated with anosognosia in AD, particularly in the posterior cingulate cortex and right angular gyrus. Anosognosia was associated with conversion from MCI to AD within 5 years. [31-35]

Anosognosia in AD is related to cerebral glucose hypometabolism. [35] Furthermore, anosognosia independently predicts conversion from MCI to AD. The absence of anosognosia may be clinically useful in identifying those patients who are unlikely to convert from MCI to AD.[35]

To have an impact on science and ultimately on clinical care and public health (dementia prevention), future research needs to identify and characterize the biological and environmental mechanisms involved in insulin resistance and cognitive impairment. [31-35]

Studies should focus on humans, with an emphasis on large and diverse population-based and community-based cohorts. In the sample, participants would have a spectrum of metabolic dysfunction, from normoglycemia (controls) to insulin resistance and pre-diabetes to diabetes, and an IQ test to assess giftedness and even their possible impairments with acquired cognitive deficits. [31-35]

Prospective, longitudinal assessments should include detailed phenotyping, with performance-based cognitive testing across domains, biospeciment collection (for novel blood biomarkers of insulin resistance, epigenetic markers of cognitive decline), functional neuroimaging, and assessments of a variety of medical factors (vascular) and environmental (social and behavioral).

An fMRI and physical activity study showed that the exercise program resulted in enhanced insulin action in the brain to the level of a healthy weight person, demonstrated by increased insulin-induced striatal activity and strengthened hippocampal functional connectivity. Improved brain insulin action correlated with increased mitochondrial respiration in skeletal muscle, reductions in visceral fat, hunger, and improved cognition. [31-35]

Mediation analyses suggest that enhanced brain insulin response helps mediate the peripheral effects of exercise, leading to healthier body fat distribution and reduced perception of hunger. [31-35]

One study showed that an 8-week exercise intervention in sedentary individuals can restore insulin action in the brain.

Therefore, the ameliorative benefits of exercise on brain insulin resistance may provide an objective therapeutic target in humans in the challenge of reducing diabetes risk factors. [31-35]

In Practical Applications, prevention with identification early detection of metabolic risks in gifted individuals. Education with awareness of the impact of lifestyle on cognitive health. And treatment aims to develop strategies to improve brain metabolic function, integrating nutrition, exercise, and stress management techniques. [31-35]

6. Conclusion

Although there are no specific studies, the hypothesis that gifted individuals may be more vulnerable or resilient to brain insulin resistance is based on their high energy demands and lifestyle factors. Scientific investigation of this topic can not only deepen our knowledge of metabolism and cognition but also guide practical strategies to protect the mental and physical health of this group. If confirmed, brain insulin resistance in gifted individuals could be transformed into a factor of care to ensure that exceptional individuals reach their full potential, preserving their performance and quality of life.

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