

Article

Schizophrenia

Brain Insulin Action and Metabolic Dysregulation in Schizophrenia: From Mechanistic Insights to Novel Interventions

Metabolic dysfunction is highly prevalent in individuals with schizophrenia, resulting in increased morbidity and mortality rates compared to the general population. While antipsychotic medications contribute substantially to this risk, there are intrinsic pathophysiological mechanisms at play as well. One emerging hypothesis implicates abnormal brain insulin signaling, which is involved in the regulation of several neuroendocrine, metabolic, and cognitive processes. In schizophrenia, disrupted insulin signaling pathways or the presence of brain insulin resistance may contribute to both metabolic dysregulation and core neuropsychiatric symptoms, including cognitive deficits. Exploring the interplay between metabolic dysfunction and brain insulin resistance in schizophrenia warrants further investigation as it represents a unique opportunity for both mechanistic inquiry and the development of novel therapeutic strategies that can improve metabolic and cognitive outcomes in this population.

AgRP: Agouti-related protein; AMPK: 5'AMP-activated protein kinase; ASL: Arterial spin labelling; CNS: central nervous system; CART: cocaine-amphetamine-regulated-transcript; DAT: Dopamine transporter; GLP-1RA: Glucagon-like peptide-1 receptor agonist; INI: Intranasal Insulin; IRS-1: insulin receptor substrate-1; MRI: Magnetic resonance imaging; NPY: Neuropeptide Y; POMC: pro-opiomelanocortin; rCBF: Regional cerebral blood flow; rsfMRI: resting state functional MRI; TNF- α : Tumor Necrosis Factor- α

Brain Insulin Action and Metabolic Dysregulation in Schizophrenia: From Mechanistic Insights to Novel Interventions

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Metabolic Dysfunction in Schizophrenia

Schizophrenia is a chronic and severely debilitating psychiatric illness that affects approximately 1% of the population.^{1,2} Patients with schizophrenia are additionally afflicted by higher rates of cardiometabolic comorbidities compared to the general population, including nearly twice the rate of obesity, a 5-6-fold increased risk of developing type 2 diabetes mellitus, and a 3-6-fold increased risk of cardiovascular disease.^{3,4} Consequently, schizophrenia is associated with a 15-20-year shorter life expectancy than the general population.^{3,5} These cardiometabolic disturbances also have significant implications for self-esteem, quality of life, and cognitive functioning, worsening functional outcomes (**Figure 1**). Importantly, growing evidence highlights a close link between metabolic health and cognitive functioning; patients with comorbid metabolic syndrome perform worse on measures of cognition compared to those without metabolic syndrome.⁶⁻⁹ Furthermore, as illness course and antipsychotic treatment

continue, the worsening metabolic profile has deleterious effects on cognitive functioning.^{10,11}

Growing evidence highlights a close link between metabolic health and cognitive functioning.

The etiology of cardiometabolic comorbidities in schizophrenia is believed to be multifactorial, arising from a complex interplay of unhealthy lifestyle factors, reduced access to medical care, and metabolic side effects of antipsychotic medications. At the same time, the consistent presence of metabolic abnormalities in drug-naïve and first-episode patients suggests there may be an intrinsic vulnerability as well.¹² This has led to the hypothesis that schizophrenia and metabolic disorders may share common pathophysiological mechanisms, and improving metabolic health may confer cognitive benefits.

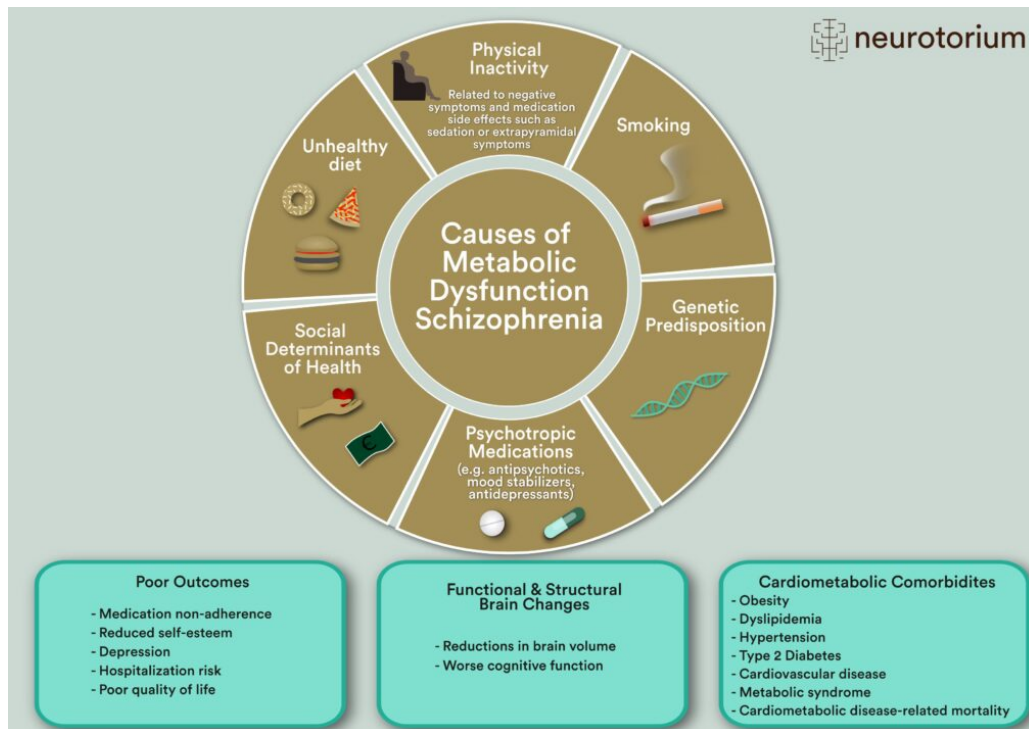


Figure 1. Causes and consequences of metabolic dysfunction in schizophrenia

Patients with schizophrenia experience high rates of cardiometabolic comorbidities such as obesity, dyslipidemia, hypertension, type 2 diabetes, and cardiovascular disease. The etiology of these comorbidities is multifactorial, arising from a complex interplay of intrinsic and extrinsic factors, including genetic predispositions, physical inactivity, unhealthy diet, high smoking rates, poorer socioeconomic status, as well as antipsychotic medication side effects. Beyond the devastating medical sequelae, these comorbidities also contribute to medication non-adherence, low self-esteem, decreased quality of life, and worse cognitive functioning.

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Brain insulin action: a proposed unifying link underlying cognitive and metabolic dysfunction in schizophrenia

In recent years, brain insulin resistance has been positioned at the crossroads of cognitive and metabolic disorders.¹³ Brain insulin action is a novel area of investigation as the brain was long considered to be an insulin-insensitive organ. However, it is now well-recognized that insulin is also abundantly present within the central nervous system (CNS),¹⁴ with wide

expression of insulin receptors in brain regions such as the hypothalamus, midbrain dopamine neurons, striatum, prefrontal cortex, and hippocampus.¹⁵ Insulin in the brain is involved in the regulation of several neuroendocrine, metabolic, and cognitive processes,^{13,16} many of which are notably disrupted in schizophrenia (**Figure 2**).

For example, insulin action within the hypothalamus suppresses hepatic glucose production,¹⁷⁻¹⁹ promotes satiety, reduces appetite, and increases energy expenditure.^{20,21} Insulin also modulates mood, supports memory formation through synaptic plasticity and stimulating long-term potentiation, and promotes neuronal survival by triggering the release of neurotrophic factors.^{16,22-25}

Causes of impaired brain insulin signaling in schizophrenia

Our understanding of impaired brain insulin action in schizophrenia is still in its infancy; however, it is likely a multilevel process involving both intrinsic illness-related mechanisms and antipsychotic exposure (**Figure 3**).²³

Genetic/neurobiological causes of brain insulin resistance:

Several genetic studies show overlap between schizophrenia and diabetes, with shared variants in genes regulating insulin signaling,

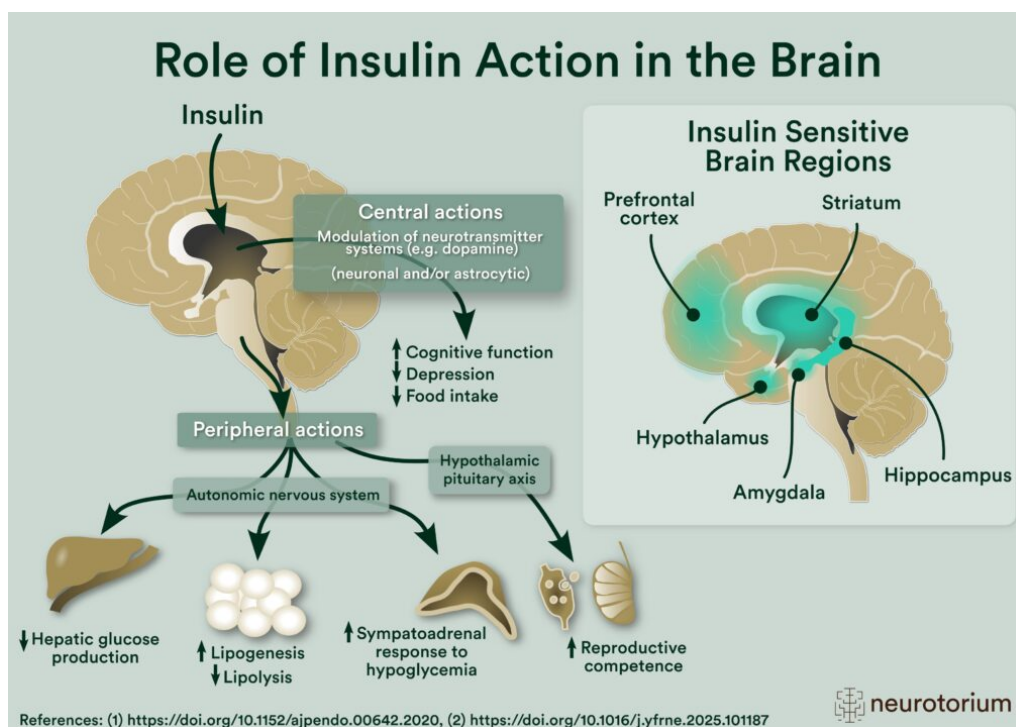


Figure 2. Brain insulin action in relation to peripheral and central outcomes.

Insulin receptors are widely expressed throughout the brain, with high concentrations in regions such as the prefrontal cortex, striatum, hippocampus, hypothalamus and amygdala. Insulin acting within these brain regions exerts several downstream central and peripheral actions.

including the Akt pathway, which is involved in glucose homeostasis. Reduced Akt1 activation, mRNA expression, and protein levels have been observed in the hippocampus, frontal cortex, and blood of patients with schizophrenia compared to healthy controls.²³ In parallel, mitochondrial dysfunction, increased oxidative stress, and decreased levels of antioxidant products in schizophrenia may disrupt neuronal insulin sensitivity by damaging membrane lipids and insulin receptor components, as well as impairing intracellular signaling cascades such as the Akt pathway.²⁶

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protein levels have been observed in the hippocampus, frontal cortex, and blood of patients with schizophrenia compared to healthy controls.²³

Peripheral causes of brain insulin resistance:

In addition, several systemic metabolic disturbances are present in schizophrenia that act synergistically to drive central insulin resistance. For example, schizophrenia is characterized by greater inflammation and elevated inflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, and

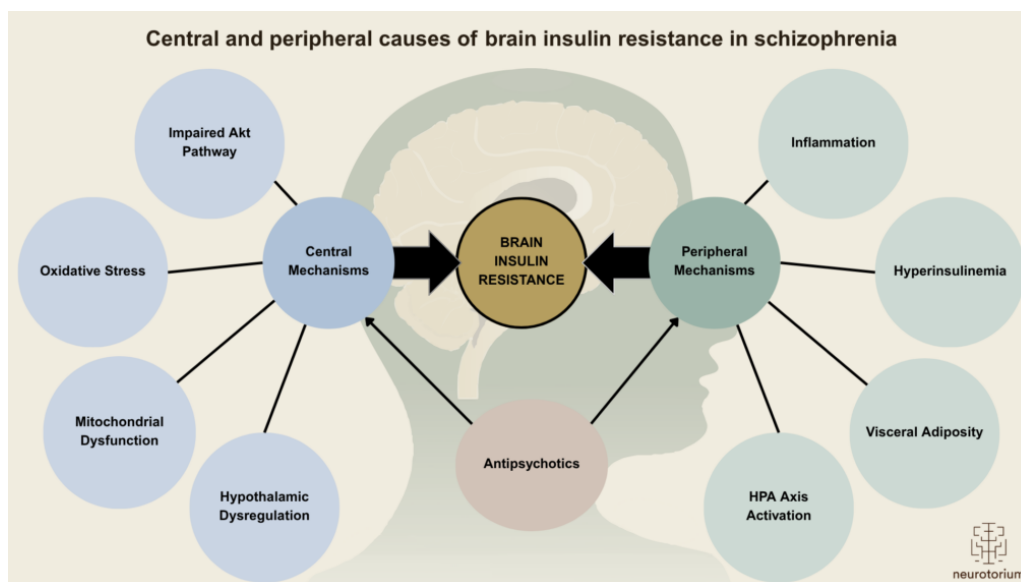


Figure 3. Central and peripheral causes of brain insulin resistance in schizophrenia

Multiple interconnected pathways may underlie impaired brain insulin signaling in schizophrenia. These include both central/neurobiological mechanisms (i.e., neuroinflammation, mitochondrial dysfunction, Akt pathway dysfunction, oxidative stress) and peripheral mechanisms (i.e., visceral adiposity, increased insulin release, chronic stress, and inflammation). Additionally, antipsychotic medications exacerbate both peripheral and central mechanisms, contributing to increased appetite and weight gain, increased insulin release, increased hepatic glucose production, and decreased glucose uptake by skeletal muscle.

tumor necrosis factor-alpha (TNF- α).²⁷ These have been implicated in the pathogenesis of insulin resistance and hyperinsulinemia. Hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, characterized by abnormal cortisol release and stress response, further perpetuates inflammation and oxidative stress.²⁸ Altogether, these disruptions contribute to the development of metabolic abnormalities, including peripheral insulin resistance that eventually leads to brain insulin resistance.^{23,29}

Hypothalamic-pituitary-adrenal (HPA)-axis dysregulation, characterized by abnormal cortisol release and stress response, further perpetuates inflammation and oxidative stress.²⁸

Consequences of impaired brain insulin signaling in schizophrenia

Brain consequences: Insulin in the brain increases dopamine transporter (DAT) surface expression and dopamine reuptake in the ventral tegmental area and striatum.^{26,30,31} Impaired insulin action may contribute to increased dopamine availability, which in turn may relate to the development of positive symptoms.³² Central insulin dysregulation may also underlie the close relationship between cognitive dysfunction in mental illness. To this point, intranasal insulin (INI), a way of directly stimulating the brain with insulin, has been shown to improve verbal memory and visuospatial function, in healthy controls and in

Alzheimer's disease.^{33,34} Interestingly, despite demonstrated improvements with INI in these cognitive domains in other populations, no beneficial effects were observed in the three studies published to date exploring the use of INI in antipsychotic-treated patients with schizophrenia.³⁵⁻³⁷ These findings may allude to brain insulin resistance in this population and the postulated anti-insulin effects of antipsychotics in the brain, which may limit pro-cognitive effects of various interventions.³⁸

Peripheral consequences: In line with the physiological effects of insulin action in the brain, central insulin resistance has been associated with long-term adiposity, glucose dysregulation, and reduced peripheral insulin sensitivity, thus implicating it in the development of metabolic disorders such as obesity and diabetes.³⁹ As such, this phenotype may help explain the alarmingly high rates of metabolic disorders seen in people with schizophrenia. It is important to recognize the circular relationship between peripheral and central insulin resistance. Central insulin resistance impairs appetite control and glucose regulation, promoting weight gain and peripheral insulin resistance. At the same time, peripheral insulin resistance leads to hyperinsulinemia and inflammation which can compromise blood-brain barrier integrity and insulin signaling in the brain.

It is important to recognize the circular relationship between peripheral and central insulin resistance.



The contributing role of antipsychotics on impaired brain insulin signaling

Antipsychotic treatment may exacerbate intrinsic brain insulin resistance through direct effects on insulin signaling pathways, as well as through the secondary effects of peripheral metabolic abnormalities. For example, D2 antagonism by antipsychotics results in an increase hypothalamic AMPK activation and inhibits the ability of central insulin to suppress endogenous glucose production.^{40,41} At the same time, antipsychotics also act directly on peripheral D2-receptors expressed on pancreatic beta cells.⁴² These receptors act as autocrine regulators to inhibit glucose-stimulated insulin secretion. Consequently, antipsychotics may induce hyperinsulinemia, which has been demonstrated in healthy control studies with acute antipsychotic administration.⁴³ This hyperinsulinemia may lead to insulin resistance, hinder insulin transport across the blood-brain barrier, and impair central insulin action and its downstream effects. Furthermore, preclinical studies have demonstrated that central infusion of olanzapine results in an acute upregulation of NPY and AgRP mRNA expression.⁴⁰ Upregulation of NPY may subsequently lead to disruptions in central insulin action and its physiologic suppression of appetite and endogenous glucose production. Finally, while increased inflammation may be intrinsic to the illness itself, antipsychotics may also contribute to and exacerbate the inflammation seen in patients, which in turn may potentiate weight gain and insulin resistance.⁴⁴ Overall, these illness-related and treatment-induced processes converge to create a state of impaired insulin action which may contribute to greater cognitive dysfunction and

heightened metabolic risk in this population.

Increased inflammation may be intrinsic to the illness itself, antipsychotics may also contribute to and exacerbate the inflammation seen in patients, which in turn may potentiate weight gain and insulin resistance.⁴⁴

Therapeutic Implications and Future Directions

Deficits in brain insulin signaling present a unique opportunity that can be leveraged for both mechanistic inquiry and the development of novel therapeutic strategies in schizophrenia.

From the research standpoint, exploring brain insulin signaling can offer valuable insights into the pathophysiology of schizophrenia and metabolic comorbidities. However, studying insulin action in the human brain is still quite new and is limited to the use of proxy indicators. Multi-modal neuroimaging, combined with INI as a pharmacological challenge, is currently the most widely-published way to reliably, non-invasively, and safely examine the effects of insulin in the brain across healthy controls and various patient populations (e.g., obesity, type 2 diabetes, and Alzheimer's disease).⁴⁵ Approaches include resting state functional magnetic resonance imaging (rs-fMRI), arterial spin labeling (ASL), and task-based fMRI. Interestingly, these MRI-based outcome measures have been correlated with

physiological and behavioural changes as well. For example, INI has been found to increase functional connectivity between the anterior medial prefrontal cortex and hypothalamus, but only in individuals with preserved peripheral insulin sensitivity. INI has also consistently been found to reduce regional cerebral blood flow (rCBF) in the hypothalamus,^{46,47} and this change in hypothalamic blood flow has been positively correlated with change in insulin sensitivity.⁴⁸ Thus, this neuroimaging-based assay of brain insulin action can be utilized to further our understanding of impaired brain insulin signaling in relation to metabolic outcomes in schizophrenia relative to healthy individuals, and to disentangle the potential modulatory effects of antipsychotic medications.

From a clinical standpoint, this paradigm can also be used to assess whether metabolic interventions may reverse or improve brain insulin resistance in patients with schizophrenia and subsequently result in cognitive and metabolic improvements. Central insulin-sensitizers (i.e., drugs that increase the availability of insulin in the brain) such as metformin and glucagon-like-peptide 1 receptor agonists (GLP-1RAs) stand out as potential candidates for this purpose. Indeed, these agents have been investigated in antipsychotic-treated patients with schizophrenia and have shown efficacy in reducing body weight and mitigating other metabolic aberrations.^{49,50} Future treatment studies may consider assessing whether these medications intended for cardiometabolic improvement have potential neuroprotective effects as well.

Conclusions

To summarize, growing evidence suggests that brain insulin resistance may play a key role in the pathophysiology of schizophrenia, particularly in relation to cognitive dysfunction, dopaminergic dysregulation, and the high burden of metabolic comorbidity. This represents a promising area of investigation in schizophrenia research that can provide us with greater insights into the underlying illness neurobiology and initiate new streams of work to uncover novel therapeutic strategies to treat both the illness and its metabolic comorbidities.

Growing evidence suggests that brain insulin resistance may play a key role in the pathophysiology of schizophrenia, particularly in relation to cognitive dysfunction, dopaminergic dysregulation, and the high burden of metabolic comorbidity.

References

1. Sadock BJ, Kaplan HI, Sadock VA. xv, 1470 p. (Wolter Kluwer/Lippincott Williams & Wilkins, Philadelphia, 2007).
2. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophr Res.* 2008;102(1-3):1-18.
3. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J.* 2005;150(6):1115-21.
4. Rajkumar AP, Horsdal HT, Wimberley T, Cohen D, Mors O, Borglum AD, et al. Endogenous and Antipsychotic-



Related Risks for Diabetes Mellitus in Young People With Schizophrenia: A Danish Population-Based Cohort Study. *Am J Psychiatry*. 2017;174(7):686-94.

5. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.

6. Bora E, Akdede BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. *Psychol Med*. 2017;47(6):1030-40.

7. Li C, Zhan G, Rao S, Zhang H. Metabolic syndrome and its factors affect cognitive function in chronic schizophrenia complicated by metabolic syndrome. *J Nerv Ment Dis*. 2014;202(4):313-8.

8. Lindenmayer JP, Khan A, Kaushik S, Thanju A, Praveen R, Hoffman L, et al. Relationship between metabolic syndrome and cognition in patients with schizophrenia. *Schizophrenia Research*. 2012;142(1-3):171-76.

9. Maksyutynska K, Stogios N, Prasad F, Gill J, Hamza Z, De R, et al. 274. The Impact of Metabolic Dysregulation on Cognition in Mood Disorders: A Systematic Review and Meta-Analysis. *Biological Psychiatry*. 2023;93(9):S204.

10. MacKenzie NE, Kowalchuk C, Agarwal SM, Costa-Dookhan KA, Caravaggio F, Gerretsen P, et al. Antipsychotics, Metabolic Adverse Effects, and Cognitive Function in Schizophrenia. *Front Psychiatry*. 2018;9:622.

11. Morgan VA, McGrath JJ, Jablensky A, Badcock JC, Waterreus A, Bush R, et al. Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis. *Psychol Med*. 2014;44(10):2163-76.

12. Chen DC, Du XD, Yin GZ, Yang KB, Nie Y, Wang N, et al. Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia: Relationships with clinical phenotypes and cognitive deficits. *Psychological Medicine*. 2016;46(15):3219-30.

13. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiol Rev*. 2016;96(4):1169-209.

14. Dakic T, Jevdjovic T, Lakic I, Ruzicic A, Jasnic N, Djurasevic S, et al. The Expression of Insulin in the Central Nervous System: What Have We Learned So Far? *International Journal of Molecular Sciences*. 2023;24(7):6586.

15. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature*. 1978;272(5656):827-9.

16. Agrawal R, Reno CM, Sharma S, Christensen C, Huang Y, Fisher SJ. Insulin action in the brain regulates both central and peripheral functions. *American Journal of Physiology-Endocrinology and Metabolism*. 2021;321(1):E156-E63.

17. Dash S, Xiao C, Morgantini C, Koulajian K, Lewis GF. Intranasal insulin suppresses endogenous glucose production in humans compared with placebo in the presence of similar venous insulin concentrations. *Diabetes*. 2015;64(3):766-74.

18. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat Med*. 2002;8(12):1376-82.

19. Filippi BM, Yang CS, Tang C, Lam TK. Insulin activates Erk1/2 signaling in the dorsal vagal complex to inhibit glucose production. *Cell Metab*. 2012;16(4):500-10.

20. Yang CS, Lam CK, Chari M, Cheung GW, Kokorovic A, Gao S, et al. Hypothalamic AMP-activated protein kinase regulates glucose production. *Diabetes*. 2010;59(10):2435-43.

21. Loh K, Zhang L, Brandon A, Wang Q, Begg D, Qi Y, et al. Insulin controls food intake and energy balance via NPY neurons. *Molecular Metabolism*. 2017;6(6):574-84.

22. Hallschmid M. Intranasal insulin. *Journal of Neuroendocrinology*. 2021;33(4).

23. Agarwal SM, Caravaggio F, Costa-Dookhan KA, Castellani L, Kowalchuk C, Asgariroozbehani R, et al. Brain insulin action in schizophrenia: Something borrowed and something new. *Neuropharmacology*. 2020;163:107633.

24. Feldman DE. Synaptic mechanisms for plasticity in neocortex. *Annu Rev Neurosci*. 2009;32:33-55.

25. Wozniak M, Rydzewski B, Baker SP, Raizada MK. The cellular and physiological actions of insulin in the central nervous system. *Neurochem Int*. 1993;22(1):1-10.

26. Murray AJ, Rogers JC, Katshu MZUH, Liddle PF, Upthegrove R. Oxidative Stress and the Pathophysiology and Symptom Profile of Schizophrenia Spectrum Disorders. *Frontiers in Psychiatry*. 2021;Volume 12 - 2021.

27. Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, et al. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology*. 2011;152(4):1314-26.

28. Mikulska J, Juszczak G, Gawrońska-Grzywacz M, Herbet M. HPA Axis in the Pathomechanism of Depression and Schizophrenia: New Therapeutic Strategies Based on Its Participation. *Brain Sci*. 2021;11(10).

29. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. *Cell*. 2008;135(1):61-73.

30. Nash AI. Crosstalk between insulin and dopamine signaling: A basis for the metabolic effects of antipsychotic drugs. *J Chem Neuroanat*. 2017;83-84:59-68.

31. Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, et al. Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. *Nat Commun*. 2015;6:8543.



32. Mebel DM, Wong JC, Dong YJ, Borgland SL. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased reuptake. *Eur J Neurosci.* 2012;36(3):2336-46.
33. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Haring HU. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiol Rev.* 2016;96(4):1169-209.
34. Novak V, Milberg W, Hao Y, Munshi M, Novak P, Galica A, et al. Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. *Diabetes Care.* 2014;37(3):751-9.
35. Li J, Li X, Liu E, Copeland P, Freudenreich O, Goff DC, et al. No effect of adjunctive, repeated dose intranasal insulin treatment on body metabolism in patients with schizophrenia. *Schizophr Res.* 2013;146(1-3):40-5.
36. Fan X, Copeland PM, Liu EY, Chiang E, Freudenreich O, Goff DC, et al. No effect of single-dose intranasal insulin treatment on verbal memory and sustained attention in patients with schizophrenia. *J Clin Psychopharmacol.* 2011;31(2):231-4.
37. Fan X, Liu E, Freudenreich O, Copeland P, Hayden D, Ghebremichael M, et al. No effect of adjunctive, repeated-dose intranasal insulin treatment on psychopathology and cognition in patients with schizophrenia. *J Clin Psychopharmacol.* 2013;33(2):226-30.
38. Pearson-Leary J, Jahagirdar V, Sage J, McNay EC. Insulin modulates hippocampally-mediated spatial working memory via glucose transporter-4. *Behav Brain Res.* 2018;338:32-39.
39. Heni M. The insulin resistant brain: impact on whole-body metabolism and body fat distribution. *Diabetologia.* 2024;67(7):1181-91.
40. Martins PJ, Haas M, Obici S. Central nervous system delivery of the antipsychotic olanzapine induces hepatic insulin resistance. *Diabetes.* 2010;59(10):2418-25.
41. Kowalchuk C, Teo C, Wilson V, Chintoh A, Lam L, Agarwal SM, et al. In male rats, the ability of central insulin to suppress glucose production is impaired by olanzapine, whereas glucose uptake is left intact. *J Psychiatry Neurosci.* 2017;42(6):424-31.
42. Rubí B, Ljubicic S, Pournourmohammadi S, Carobbio S, Armanet M, Bartley C, et al. Dopamine D2-like receptors are expressed in pancreatic beta cells and mediate inhibition of insulin secretion. *J Biol Chem.* 2005;280(44):36824-32.
43. Teff KL, Rickels MR, Grudziak J, Fuller C, Nguyen HL, Rickels K. Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. *Diabetes.* 2013;62(9):3232-40.
44. Prestwood TR, Ballon JS, Asgariroozbehani R, Wu S, Agarwal SM, Hahn MK, et al. Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia. *Behavioural Brain Research.* 2021;402:113101.
45. Stogios N, Wu S, Hahn M, Emami Z, Navagnanavel J, Korann V, et al. Exploring the effects of an insulin challenge on neuroimaging outcomes: A scoping review. *Frontiers in Neuroendocrinology.* 2025;77:101187.
46. Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Haring H-U, et al. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes care.* 2015;38(6):1044-50.
47. Heni M, Wagner R, Willmann C, Jaghutriz BA, Vosseler A, Kubler C, et al. Insulin Action in the Hypothalamus Increases Second-Phase Insulin Secretion in Humans. *Neuroendocrinology.* 2020;110(11-12):929-37.
48. Heni M, Wagner R, Kullmann S, Veit R, Mat Husin H, Linder K, et al. Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. *Diabetes.*