

Our topic of study for this **Review Paper** is the **interaction between insulin and dopamine signalling!**

**Background:**

Insulin resistance ↑; blood-sugar levels ↑; dopamine levels may exhibit a complex pattern of alteration (↓/↑); probability of diabetes and psychological disorders ↑;

**Criteria for primary sources** to base the paper upon:

- **Relevance:** Sources must **directly** investigate the interplay between insulin and dopamine signalling pathways.
- **Recentness:** Prioritize studies **published within the last 5 years** to ensure up-to-date information unless the resource is ground-breaking or extremely important.
- **Methodology:** Prioritize experiments with **robust methods**, including controlled conditions, sample size justification, and statistical analysis.
- **Peer Review:** Choose articles published in **reputable journals** with a rigorous peer-review process.
- **Brain Region Specificity:** Focus on studies examining insulin and dopamine signalling interactions in specific brain regions relevant to our research question. Select studies exploring the neural circuits involved in insulin and dopamine signalling interactions, as this may provide a more comprehensive understanding. (This is not discussed yet, but note that affected brain areas include the striatum, midbrain, and more)

**List of studies to reference:**

**Human Research:**

1. Stephanie Kullmann, Dominik Blum, Benjamin Assad Jaghutriz, Christoph Gassenmaier, Benjamin Bender, Hans-Ulrich Häring, Gerald Reischl, Hubert Preissl, Christian la Fougère, Andreas Fritzsche, Matthias Reimold, Martin Heni, Central Insulin Modulates Dopamine Signaling in the Human Striatum, *The Journal of Clinical Endocrinology & Metabolism*, Volume 106, Issue 10, October 2021, Pages 2949–2961, <https://doi.org/10.1210/clinem/dgab410>
2. Thanarajah, S. E., Iglesias, S., Kuzmanovic, B., Rigoux, L., Stephan, K. E., Brüning, J. C., Tittgemeyer, M. (2019). Modulation of midbrain neurocircuitry by intranasal insulin. *NeuroImage*, 194, 120-127. ISSN 1053-8119. <https://doi.org/10.1016/j.neuroimage.2019.03.050>
3. Sauerzopf, U., Weidenauer, A., Dajic, I., Bauer, M., Bartova, L., Meyer, B., Nics, L., Philippe, C., Pfaff, S., Pichler, V., Mitterhauser, M., Wadsak, W., Hacker, M., Kasper, S., Lanzenberger, R., Pezawas, L., Praschak-Rieder, N., & Willeit, M. (2021). Disrupted relationship between blood glucose and brain dopamine D2/3 receptor binding in patients with first-episode schizophrenia. *NeuroImage: Clinical*, 32, 102813. <https://doi.org/10.1016/j.nicl.2021.102813>
4. Mansur, R. B., Delgado-Peraza, F., Subramaniapillai, M., Lee, Y., Iacobucci, M., Nasri, F., Rodrigues, N., Rosenblat, J. D., Brietzke, E., Cosgrove, V. E., Kramer, N. E., Suppes, T., Raison, C. L., Fagiolini, A., Rasgon, N., Chawla, S., Nogueras-Ortiz, C., Kapogiannis, D., & McIntyre, R. S. (2021). EXPLORING BRAIN INSULIN RESISTANCE IN ADULTS WITH BIPOLAR DEPRESSION USING EXTRACELLULAR VESICLES OF NEURONAL ORIGIN. *Journal of Psychiatric Research*, 133, 82. <https://doi.org/10.1016/j.jpsychires.2020.12.007>

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5. Carnell, S., Steele, K. E., Thapaliya, G., Kuwubara, H., Aghababian, A., Papantoni, A., Nandi, A., Brašić, J. R., Moran, T. H., & Wong, D. F. (2023). Milkshake Acutely Stimulates Dopamine Release in Ventral and Dorsal Striatum in Healthy-Weight Individuals and Patients with Severe Obesity Undergoing Bariatric Surgery: A Pilot Study. *Nutrients*, 15(12), 2671.  
<https://doi.org/10.3390/nu15122671>
6. Julia P. Dunn, Robert M. Kessler, Irene D. Feurer, Nora D. Volkow, Bruce W. Patterson, Mohammad S. Ansari, Rui Li, Pamela Marks-Shulman, Naji N. Abumrad; Relationship of Dopamine Type 2 Receptor Binding Potential With Fasting Neuroendocrine Hormones and Insulin Sensitivity in Human Obesity. *Diabetes Care* 1 May 2012; 35 (5): 1105–1111.  
<https://doi.org/10.2337/dc11-2250>

#### Animal Research:

1. Kleinridders, A., Cai, W., Cappellucci, L., Ghazarian, A., Collins, W. R., Vienberg, S. G., Pothos, E. N., & Kahn, C. R. (2015). Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proceedings of the National Academy of Sciences of the United States of America*, 112(11), 3463-3468. <https://doi.org/10.1073/pnas.1500877112>
2. Chiu, S., Chen, C., & Cline, H. T. (2008). Insulin Receptor Signaling Regulates Synapse Number, Dendritic Plasticity, and Circuit Function In Vivo. *Neuron*, 58(5), 708-719.  
<https://doi.org/10.1016/j.neuron.2008.04.014>
3. Patel, J. C., Stouffer, M. A., Mancini, M., Nicholson, C., Carr, K. D., & Rice, M. E. (2019). Interactions between insulin and diet on striatal dopamine uptake kinetics in rodent brain slices. *The European Journal of Neuroscience*, 49(6), 794. <https://doi.org/10.1111/ejn.13958>
4. Morris, J., Bomhoff, G., Gorres, B., Davis, V., Kim, J., Lee, P., Brooks, W., Gerhardt, G., Geiger, P., & Stanford, J. (2011). Insulin resistance impairs nigrostriatal dopamine function. *Experimental Neurology*, 231(1), 171-180. <https://doi.org/10.1016/j.expneurol.2011.06.005>

#### Locked but may be relevant (no summary):

1. Lammers, N. M., Trinko, R., Opland, D. M., Figee, M., Ackermans, M. T., Booij, J., Schuurman, P. R., Fliers, E., Denys, D., DiLeone, R. J., & Serlie, M. J. (2018). Striatal dopamine regulates systemic glucose metabolism in humans and mice. *Science Translational Medicine*.  
<https://doi.org/aar3752>

2. Haltia, L. T., Rinne, J. O., Merisaari, H., Maguire, R. P., Savontaus, E., Helin, S., Någren, K., & Kaasinen, V. (2007). Effects of intravenous glucose on dopaminergic function in the human brain in vivo. *Synapse*, 61(9), 748-756. <https://doi.org/10.1002/syn.20418>

**Review Articles for Reference, not to be cited (?):**

1. Kleinridders, A., Pothos, E.N. Impact of Brain Insulin Signaling on Dopamine Function, Food Intake, Reward, and Emotional Behavior. *Curr Nutr Rep* 8, 83–91 (2019).  
<https://doi.org/10.1007/s13668-019-0276-z>
2. Patel JC, Carr KD, Rice ME. Actions and Consequences of Insulin in the Striatum. *Biomolecules*. 2023; 13(3):518. <https://doi.org/10.3390/biom13030518>
3. Lam, M. P., Soares, C. N., Munoz, D. P., Milev, R., & De Felice, F. G. (2019). Insulin Resistance as a Shared Pathogenic Mechanism Between Depression and Type 2 Diabetes. *Frontiers in Psychiatry*, 10. <https://doi.org/10.3389/fpsyg.2019.00057>
4. Nguyen, T. T. L., Chan, L. C., Borreginne, K., Kale, R. P., Hu, C., & Tye, S. J. (2018). A review of brain insulin signaling in mood disorders: From biomarker to clinical target. *Neuroscience & Biobehavioral Reviews*, 92, 7-15. <https://doi.org/10.1016/j.neubiorev.2018.05.014>
5. Christian Hölscher (2020) Brain insulin resistance: role in neurodegenerative disease and potential for targeting, *Expert Opinion on Investigational Drugs*, 29:4, 333-348, DOI: 10.1080/13543784.2020.1738383

**Details of research papers:** This section provides a concise overview of the significant findings and methodologies of the chosen papers. Please note that it only covers part of the discussed research.

1. "Central Insulin Modulates Dopamine Signaling in the Human Striatum"

**Objective:**

Investigate the impact of centrally administered insulin on dopaminergic activity in the striatum and overall neural activity in healthy, normal-weight individuals.

**Methods:**

- Employed a randomized, placebo-controlled, blinded, crossover trial design.
- Utilized a PET/MRI hybrid scanner for simultaneous [11C]-raclopride-PET and resting-state functional MRI.
- Administered intranasal insulin or placebo on separate days to 10 healthy, normal-weight men.

**Key Findings:**

- Increased [11C]-raclopride binding potential in the ventral and dorsal striatum post-central insulin administration, suggesting reduced synaptic dopamine levels.
- Lower resting-state striatal activity was observed 15 and 30 minutes after nasal insulin compared to placebo.
- More robust functional connectivity in the mesocorticolimbic circuitry 45 minutes after intranasal insulin in individuals with a pronounced insulin-induced effect on dopamine levels.

**Conclusions:**

This study reveals that central insulin modulates dopaminergic tone in the striatum, influencing regional brain activity and connectivity. The findings deepen our understanding of the insulin-dopamine interaction and its role in regulating whole-body metabolism.

**Implications:**

- Acknowledges the sensitivity of dopaminergic pathways to body weight and metabolic states.
- Aligns with animal studies indicating the importance of insulin in dopamine neuron function and its potential implications in insulin-resistant states.

**Methodological Strengths:**

- Effective use of PET/MRI hybrid scanner for simultaneous neuroimaging.
- Rigorous trial design with randomized, placebo-controlled, blinded, crossover methodology.

**Future Considerations:**

- Explore potential clinical implications of the observed insulin-induced changes in dopaminergic activity, especially in metabolic disorders and obesity.

- Consider the need for further studies to elucidate the long-term effects of central insulin on dopaminergic signalling and its implications for overall brain function and metabolism.
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## 2. "Modulation of Midbrain Neurocircuitry by Intranasal Insulin"

### Objective:

Examine time- and dose-dependent effects of intranasal insulin on functional connectivity of the dopaminergic midbrain in humans.

### Methods:

- Utilized intranasal administration and task-free functional MRI in a repeated-measures design.
- Factors included dose (placebo, 40 IU, 100 IU, 160 IU), time (7 points during a 90-minute post-intervention interval), and group (low vs. high HOMA-IR).

### Key Findings:

Identified a three-way interaction in functional connectivity between the midbrain and ventromedial prefrontal cortex.

Systemic insulin sensitivity modulates the temporal course and dose-dependent effects of intranasal insulin on midbrain functional connectivity.

### Conclusions:

This study suggests that altered insulin sensitivity may impact dopaminergic projections of the midbrain, potentially contributing to the dysregulation of reward-related and motivational behaviour in obesity and diabetes.

### Implications:

- Highlights the connection between altered insulin sensitivity and dysregulation of reward-related behaviour.
- Provides guidance for designing future human studies utilizing intranasal insulin administration.

### Future Considerations:

- Explore the clinical implications of altered insulin sensitivity on dopaminergic midbrain function.
- Consider the time courses of midbrain functional connectivity for designing future studies.

### 3. "Disrupted Relationship Between Blood Glucose and Brain Dopamine D2/3 Receptor Binding in Patients With First-Episode Schizophrenia"

#### Objective:

Explore the relationship between blood glucose levels and brain dopamine signalling in drug-naïve patients with first-episode psychosis.

#### Methods:

- Utilized positron emission tomography to quantify blood glucose levels and binding of the dopamine D2/3 receptor agonist radioligand (+)-[11C]-PHNO.
- Examined 15 medication-naïve patients and 27 healthy volunteers.

#### Key Findings:

- Identified two clusters of significant interaction between blood glucose levels and diagnosis on (+)-[11C]-PHNO binding-potential values.
- Positive relationship between blood glucose levels and binding-potential values in healthy volunteers.
- A negative relationship was observed in patients with first-episode psychosis in the right ventral tegmental area, with similar but less significant behaviour in the ventral striatum and pallidum.

#### Conclusions:

This study suggests a disturbed relationship between blood glucose and brain dopamine D2/3 receptor binding in patients with first-episode schizophrenia. The reversal in the relationship may reflect an underlying pathogenic alteration linking altered dopamine signalling and dysfunctional glucose homeostasis in schizophrenia.

#### Implications:

- Highlights disturbed glycemic control as an intrinsic feature of schizophrenia.
- Provides insights into the interplay between dopamine signalling and glucose homeostasis in psychosis.

#### Future Considerations:

- Investigate the clinical implications of disrupted glucose-dopamine relationships in schizophrenia.

- Consider the potential therapeutic relevance for addressing both dopamine dysregulation and glucose homeostasis in the treatment of first-episode psychosis.
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#### **4. "Insulin Resistance in Brain Alters Dopamine Turnover and Causes Behavioral Disorders"**

##### **Significance:**

Both types 1 and 2 diabetes are associated with increased risks of age-related cognitive function decay and mood disorders, especially depression. This study investigates whether brain-specific knockout of the insulin receptor (NIRKO) in mice causes behavioural changes and explores the mechanistic link.

##### **Key Findings:**

- NIRKO mice exhibit age-related anxiety and depressive-like behaviour.
- Altered mitochondrial function, aberrant monoamine oxidase (MAO) expression, and increased dopamine turnover in the mesolimbic system contribute to behavioural changes.
- Treatment with MAO inhibitors reverses anxiety and depressive-like behaviours in NIRKO mice.

##### **Mechanistic Insights:**

- Brain insulin resistance in NIRKO mice leads to mitochondrial dysfunction, reduced oxidative activity, increased reactive oxygen species, and elevated lipid and protein oxidation in the striatum and nucleus accumbens.
- Increased levels of MAO A and B contribute to elevated dopamine turnover in affected brain areas.
- Changes in MAO A and B are directly linked to the loss of insulin signalling, as demonstrated in cultured neurons and glial cells.

##### **Implications:**

- Demonstrate a potential molecular link between central insulin resistance and behavioural disorders.
  - Highlight the importance of insulin action in regulating neuronal signalling and plasticity.
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#### **5. "Insulin Receptor Signaling Regulates Synapse Number, Dendritic Plasticity, and Circuit Function In Vivo"**

##### **Summary:**

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Insulin receptor signalling's role in synaptic plasticity has been postulated, yet its function in the central nervous system (CNS) remains unclear. This study investigates the impact of insulin receptor signalling on visual system function by recording light-evoked responses in optic tectal neurons in living *Xenopus* tadpoles. Tectal neurons expressing dominant-negative insulin receptor (dnIR) or subjected to insulin receptor knockdown exhibit significantly smaller light-evoked responses. The study explores the effects on synapse density, dendritic arbour structural plasticity, and circuit function.

**Key Findings:**

- Tectal neurons expressing dnIR or subjected to insulin receptor knockdown show significantly smaller light-evoked responses.
- dnIR-expressing neurons exhibit reduced synapse density as assessed by electron microscopy (EM).
- Decreased AMPA miniature excitatory postsynaptic current (mEPSC) frequency is observed in dnIR-expressing neurons.
- Experience-dependent dendritic arbour structural plasticity is altered in dnIR-expressing neurons.
- Paired-pulse responses suggest unaffected synaptic vesicle release probability.
- Synapse maturation, assessed by AMPA/NMDA ratio and ultrastructural criteria, remains unaffected by dnIR expression.

**Implications:**

Insulin receptor signalling regulates circuit function and plasticity by controlling synapse density. The study provides insights into the role of insulin receptor signalling in shaping the structural and functional aspects of neural circuits *in vivo*.

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**6. "Exploring Brain Insulin Resistance in Adults with Bipolar Depression Using Extracellular Vesicles of Neuronal Origin"**

**Objective:**

To directly explore the potential role of neuronal insulin signalling in adults with bipolar depression using plasma extracellular vesicles enriched for neuronal origin (NEVs).

**Methods:**

- Leveraged plasma samples from a randomized, double-blind, placebo-controlled, 12-week clinical trial evaluating infliximab as a treatment for bipolar depression.

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- Isolated NEVs using immunoprecipitation against the neuronal marker L1CAM from baseline and weeks 2, 6, and 12 (endpoint) samples.
- Measured NEV biomarkers related to neuronal insulin signaling using immunoassays.
- Assessed neuronal insulin signalling at its first node (IRS-1) and along both the canonical (Akt, GSK-3 $\beta$ , p70S6K) and alternative (ERK1/2, JNK, p38-MAPK) pathways.
- A subset of participants ( $n = 27$ ) underwent whole-brain magnetic resonance imaging (MRI) at baseline and endpoint.

### **Key Findings:**

- Pre-treatment NEV biomarkers of insulin signaling are independently associated with cognitive function and MRI measures.
- Association between IRS-1 phosphorylation at serine site 312 (pS312-IRS-1), an indicator of insulin resistance, and cognitive dysfunction was mediated by ventromedial prefrontal cortex (vmPFC) volume.
- Patients treated with infliximab, a tumour necrosis factor-alpha antagonist with known insulin-sensitizing properties, showed enhanced protein phosphorylation from the alternative pathway.
- Infliximab responders had significant increases in phosphorylated JNK levels.
- Treatment with infliximab resulted in increased MRI measures of brain volume.
- Treatment-related changes in dorsolateral prefrontal cortex volume were mediated by changes in biomarkers from the insulin alternative pathway.

### **Conclusions:**

The findings support brain insulin signaling as a target for further mechanistic and therapeutic investigations in bipolar depression.

### **Implications:**

- Highlights the potential role of brain insulin signaling in bipolar depression.
- Suggests a link between insulin resistance, inflammatory processes, and treatment response in bipolar depression.

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## **7. "Interactions Between Insulin and Diet on Striatal Dopamine Uptake Kinetics in Rodent Brain Slices"**

### **Abstract:**

This study explores the interactions between insulin and diet on striatal dopamine uptake kinetics in rodent brain slices, focusing on the caudate putamen and nucleus accumbens core. The research

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investigates the functional consequences of acute insulin exposure and chronic diet-induced changes in insulin on dopamine transporter (DAT) activity after evoked dopamine release.

**Key Findings:**

- Insulin (30 nM) increased both Cpeak and Vmax in the caudate putamen and nucleus accumbens core of ad-libitum fed (AL) rats, dependent on insulin receptor and PI3-kinase activity.
- A pure effect of insulin on uptake was unmasked in mice lacking striatal acetylcholine, revealing increased Vmax causing a decrease in Cpeak.
- Diet influenced Vmax, being lower in food-restricted (FR) versus AL rats.
- The effects of insulin on Cpeak and Vmax were amplified by food restriction but blunted by obesogenic (OB) diet, aligning with opposite consequences of these diets on insulin levels and insulin receptor sensitivity.

**Additional Information:**

Insulin and diet have marked effects on dopamine (DA) transmission in the brain. Insulin increases evoked striatal DA release indirectly via cholinergic interneurons (ChIs) but enhances DA transporter activity and DA uptake directly by activating insulin receptors coupled to the PI3K / Akt pathway. Food restriction (FR) or obesogenic (OB) diets that produce lower or higher plasma insulin respectively decrease DA release and uptake, relative to an ad-libitum (AL) diet. Moreover, insulin-induced increases in DA release and uptake are enhanced with FR but blunted with OB diets.

**Implications:**

The study reveals acute and chronic effects of insulin and diet on dopamine release and uptake, impacting brain reward pathways. These findings contribute to understanding the intricate interplay between insulin, diet, and dopamine dynamics in the basal ganglia circuitry.

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**8. "Milkshake Acutely Stimulates Dopamine Release in Ventral and Dorsal Striatum in Healthy-Weight Individuals and Patients with Severe Obesity Undergoing Bariatric Surgery: A Pilot Study"**

**Abstract:**

This pilot study investigates the acute effects of a highly palatable milkshake on dopamine release in the ventral and dorsal striatum. Positron emission tomography (PET) imaging with [11C]raclopride was employed to assess striatal dopamine receptor binding before and after the consumption of the palatable meal. The study includes 11 females, with 6 having severe obesity and 5 having a healthy weight. Those with severe obesity underwent assessments pre- and 3 months post-vertical sleeve gastrectomy (VSG).

**Key Findings:**

- Post-meal dopamine receptor binding decreased in the ventral striatum, posterior putamen, and anterior caudate, indicating meal-stimulated dopamine release.
- Changes in the caudate and putamen were disproportionately driven by meal-associated changes in the healthy-weight group.
- Baseline (pre-meal) dopamine receptor binding was lower in severe obesity compared to the healthy-weight group.
- Baseline dopamine receptor binding and dopamine release did not change from pre- to post-surgery in the severe obesity group.

**Implications:**

The study suggests that the consumption of a highly palatable milkshake acutely stimulates dopamine release in both the ventral and dorsal striatum. This phenomenon is proposed to contribute to the overconsumption of highly palatable foods, particularly in the context of obesity.

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**9. "Insulin Resistance Impairs Nigrostriatal Dopamine Function"**

**Abstract:**

This study investigates the impact of insulin resistance, induced by a high-fat diet modeling early-stage Type 2 Diabetes, on nigrostriatal dopamine function in young adult Fischer 344 rats. The research examines the effects of the diet on dopamine release, clearance, and iron deposition in the substantia nigra, focusing on the nigrostriatal pathway affected in Parkinson's disease (PD) and parkinsonism.

**Key Findings:**

- Rats fed a high-fat diet (60% calories from fat) for 12 weeks exhibited insulin resistance compared to chow-fed controls.
- In vivo electrochemistry revealed attenuated potassium-evoked dopamine release and diminished dopamine clearance in the striatum of the high-fat diet group.
- Magnetic resonance imaging indicated increased iron deposition in the substantia nigra of the high-fat group.
- Alterations in the expression of proteins involved in iron metabolism were observed in the substantia nigra of the high-fat group compared to chow-fed animals.
- Nigrostriatal dopamine release correlated with the degree of insulin resistance.
- Striatal dopamine uptake and turnover decreased with high-fat feeding.

**Implications:**

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The study suggests that insulin resistance induced by a high-fat diet impairs nigrostriatal dopamine function, providing insights into the potential links between Type 2 Diabetes and Parkinson's disease. The observed alterations in iron metabolism may contribute to the impairment of nigrostriatal dopamine function.

#### **Research Highlights:**

- High fat-fed animals exhibit attenuated nigrostriatal DA release in vivo.
  - Nigrostriatal DA release is correlated with the degree of insulin resistance.
  - Striatal DA uptake and turnover are decreased with high fat feeding.
  - High fat feeding increases measures of iron deposition in the substantia nigra.
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#### **10. "Relationship of Dopamine Type 2 Receptor Binding Potential With Fasting Neuroendocrine Hormones and Insulin Sensitivity in Human Obesity"**

##### **Objective:**

The study aims to explore the relationship between midbrain dopamine (DA) neurons, involved in reward and motivation, and hormones regulating food intake (insulin, leptin, and acyl ghrelin [AG]) in obesity. The central DA type 2 receptor (D2R) availability is assessed, and associations with metabolic measures and insulin sensitivity are investigated.

##### **Research Design and Methods:**

- Fasting levels of insulin, leptin, and AG, along with BMI and insulin sensitivity index (SI), are examined in lean and obese females.
- D2R availability is measured using positron emission tomography and [18F]fallypride, a radioligand competing with endogenous DA.
- Regional regression analyses are performed to identify associations between metabolic measures and D2R availability in specific brain regions.

##### **Key Findings:**

- Negative associations are observed between AG and D2R in clusters involving the striatum and inferior temporal cortices.
- Extensive negative relationships are found between AG and D2R in the caudate, putamen, ventral striatum (VS), amygdala, and temporal lobes.
- SI is negatively associated with D2R in the VS, while insulin is not.
- BMI and leptin show positive associations with D2R availability in the caudate.

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- Leptin and AG exhibit associations consistent with their opposite effects on DA levels (decreasing and increasing, respectively).
- After adjusting for BMI, AG maintains a significant relationship in the VS.

**Conclusions:**

The findings provide evidence for an association between neuroendocrine hormones and DA brain signaling in obese females. The increased D2R availability in obese subjects may reflect relatively reduced DA levels competing with the radioligand.

**Implications:**

This study contributes to understanding the interplay between neuroendocrine hormones and dopamine signaling in the context of obesity, shedding light on potential mechanisms underlying reward and motivation in this population.

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