In male rats, the ability of central insulin to suppress glucose production is impaired by olanzapine, whereas glucose uptake is left intact

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Background: Insulin receptors are widely expressed in the brain and may represent a crossroad between metabolic and cognitive disorders. Although antipsychotics, such as olanzapine, are the cornerstone treatment for schizophrenia, they are associated with high rates of type 2 diabetes and lack efficacy for illness-related cognitive deficits. Historically, this risk of diabetes was attributed to the weight gain propensity of antipsychotics, but recent work suggests antipsychotics can have weight-independent diabetogenic effects involving unknown brain-mediated mechanisms. Here, we examined whether antipsychotics disrupt central insulin action, hypothesizing that olanzapine would impair the well-established ability of central insulin to suppress hepatic glucose production. **Methods:** Pancreatic euglycemic clamps were used to measure glucose kinetics alongside a central infusion of insulin or vehicle into the third ventricle. Male rats were pretreated with olanzapine or vehicle per our established model of acute olanzapine-induced peripheral insulin resistance. Groups included (central–peripheral) vehicle–vehicle ($n = 11$), insulin–vehicle ($n = 10$), insulin–olanzapine ($n = 10$) and vehicle–olanzapine ($n = 8$). **Results:** There were no differences in peripheral glucose or insulin levels. Unexpectedly, we showed that central insulin increased glucose uptake, and this effect was not perturbed by olanzapine. We replicated suppression of glucose production by insulin (clamp relative to basal: $77.9\% \pm 13.1\%$, all $p < 0.05$), an effect abolished by olanzapine (insulin–olanzapine: $7.7\% \pm 14\%$). **Limitations:** This study used only male rats and an acute dose of olanzapine. **Conclusion:** To our knowledge, this is the first study suggesting olanzapine may impair central insulin sensing, elucidating a potential mechanism of antipsychotic-induced diabetes and opening avenues of investigation related to domains of schizophrenia psychopathology.

Introduction

Antipsychotics are the mainstay treatment for schizophrenia and are rapidly increasing in on- and off-label use, including in older adults and in youth.^{1–3} However, antipsychotics are associated with adverse metabolic effects, including weight gain, dyslipidemia and type 2 diabetes.⁴ Olanzapine and clozapine confer the greatest risk.⁵ Moreover, clozapine, and possibly also olanzapine, appear to be the most efficacious agents,⁶ precluding avoidance of their use in the most severely ill individuals. Young patients treated with antipsychotics also have rates of glucose intolerance up to 55%,⁷ with a recent meta-analysis confirming higher exposure-adjusted incidences of type 2 diabetes in antipsychotic-exposed youth than in healthy

or psychiatric controls.⁸ The strength of this association in patients with schizophrenia is exemplified by 3- to 5-fold higher prevalence of type 2 diabetes than in the general population.⁹ These adverse effects have also garnered additional concern given well-established findings that patients with schizophrenia die 20 years earlier than the general population, a finding directly attributable to cardiovascular disease.⁹

Though antipsychotic-induced adverse metabolic effects are highly concerning, the mechanisms are not yet well understood. Initially, it was believed that the glucose dysregulation associated with antipsychotic use was associated with their weight gain propensity. However, in rodents, a single dose of antipsychotics (hence avoiding weight gain) reliably causes acute impairments in insulin sensitivity (liver

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and peripheral).^{10–14} Similarly, healthy humans who had been administered 1–9 days of olanzapine (and interestingly enough also aripiprazole — an agent considered to be less metabolically active) showed perturbations in glucose homeostasis before weight change.^{15–17} This finding indicates that antipsychotics can directly affect glucose regulation separate from and in addition to their effects on weight gain.

The vast majority of the existing literature has focused on antipsychotic effects on peripheral insulin action, with evidence consistently pointing to the liver as the target organ for antipsychotic-induced dysregulation^{10–13} and suggesting impaired insulin action upon adipose tissue¹⁸ and skeletal muscle.¹⁹ However, antipsychotics exert therapeutic effects through the brain, an insulin-sensitive organ that is now also identified as a key regulator of whole body and energy homeostasis.^{20,21} Insulin receptors are expressed in many brain areas, and abnormalities in brain insulin signalling have been reported in patients with schizophrenia, with evidence suggesting that antipsychotics may also disrupt these pathways.²² Linking these disruptions to metabolic dysfunction, it is now well established that insulin, separate from its effects on liver receptors, regulates hepatic glucose production in rodents via hypothalamic insulin receptors.^{23,24} Moreover, intranasal insulin administration to healthy humans decreases endogenous glucose production.²⁵ Increased endogenous glucose production is the main source of hyperglycemia in individuals with diabetes²⁶ and thus a hallmark of underlying pathophysiology of this serious medical illness.

Recent work by our laboratory as well as others has begun building evidence suggesting antipsychotics may be causing glucose disturbances via centrally mediated mechanisms.^{12,27–29} Notably, most studies examining acute glucose dysregulation by these agents have used hyperinsulinemic-euglycemic clamps.^{10,11,14,30} This clamp design uses an elevated level (hyperinsulinemic) of continuous intravenous insulin, which crosses into the brain, exerting both peripheral and central effects. Thus, in this design, it remains inconclusive whether antipsychotics could be altering insulin action at the level of the brain or periphery. To address this issue, in the present study we used the pancreatic euglycemic clamp method. During a pancreatic euglycemic clamp, a peripheral infusion of somatostatin blocks endogenous production of insulin, which is then replaced at “basal” levels via a peripheral insulin infusion. Replacement of insulin within physiologic “basal” levels, at a level which does not cross into the central nervous system, allows separate manipulation of central insulin concentrations via an intracerebroventricular (ICV) infusion. Under these conditions central insulin is established to suppress hepatic glucose production;^{23,24} thus we set out to examine if olanzapine administration could abolish central insulin action on suppression of glucose production, supporting antipsychotic-induced central insulin resistance.

Methods

Our study protocol was approved by the Centre for Addiction and Mental Health Animal Care Committee and follows Canadian Council on Animal Care guidelines. Healthy male

Sprague-Dawley rats (300–325 g; Harlan) were kept on a 12-hour light/dark cycle with free access to food and water. Testing was conducted during the light cycle, with all protocols initiated between 8 am and 9 am.

Intracerebroventricular cannulation

Animals were pair-housed and given a 7-day adaptation period before ICV cannulation. Animals were anesthetized with inhaled isoflurane and a nonsteroidal anti-inflammatory (5 mg/kg; Merial) injected as an analgesic. Using a stereotaxic frame (Kopf and Tujunga), we used a stainless steel guide (HRS Scientific) to insert a cannula into the third cerebral ventricle at the following coordinates: anterior–posterior –2.5 mm, medial–lateral 0.0 mm, and dorsal–ventral –8.0 mm. The cannula was secured using 4 stainless steel screws (Lomat) fixed to the skull and held down using dental cement (Jet Repair) and kept patent with a stainless steel obturator (HRS Scientific). We administered buprenorphine (0.3 mg/kg) for postoperative analgesia, and animals were housed individually after surgery.

Vessel cannulation

After a 7-day recovery period from ICV surgery, vascular catheterization was performed. Animals were anesthetized with inhaled isoflurane, and polyethylene catheters (PE-50, Cay Adams) capped with 2.5 cm of silastic tubing (Dow Corning Corp.) were introduced and advanced to the right atrium and aortic arch of the jugular vein and carotid artery, respectively. The catheter lines were externalized dorsally and blocked with a pin. We administered buprenorphine (0.3 mg/kg) during cannulation and once postsurgery for analgesia. Animals were allowed a 4- to 5-day recovery period before performance of the euglycemic clamps.

Pancreatic euglycemic clamp

To ensure equal nutritional status, all rats were restricted to about 60 kcal of food the night before the 210-minute pancreatic euglycemic clamp procedure (Fig. 1). Rats received a primed, continuous ICV infusion of insulin (total dose 30 μ U, previously established to decrease glucose production;²³ 0.3 μ L/hr) or saline into the third ventricle throughout the 210-minute duration. A primed, continuous infusion of 3- H^3 -glucose (0.4 mCi/min) also began at 0 minutes and continued throughout the clamp to assess glucose kinetics. At 90 minutes, the clamp phase was initiated via a continuous intravenous infusion of somatostatin (3 μ g/kg/min) and exogenous insulin (1 mU/kg/min) to replace insulin at basal levels. A glucose infusion was also initiated at 90 minutes and adjusted as needed to maintain euglycemia. According to our established protocol,¹⁴ a single subcutaneous injection of olanzapine (2 mg/kg) or vehicle at 90 minutes was administered, directly preceding commencement of the clamp phase (i.e., peripheral insulin infusion). We chose the olanzapine dosage based on 70% D_2 receptor occupancy, a measure of clinical therapeutic efficacy, and based on acute induction of hepatic and peripheral insulin resistance

during a hyperinsulinemic euglycemic clamp.¹⁴ Notably, no single antipsychotic agent possesses therapeutic serum levels to guide dosing, and D_2 occupancies remain the gold standard to determine clinically effective doses. Samples were taken at 10-minute intervals to measure plasma glucose, insulin and 3- H^3 -glucose-specific activity (to determine glucose production and utilization). The 4 experimental groups (ICV-peripheral) were as follows: vehicle-vehicle ($n = 11$), insulin-vehicle ($n = 10$), insulin-olanzapine ($n = 10$) and vehicle-olanzapine ($n = 8$). Plasma samples were stored at -80°C for subsequent glucose tracer and insulin analysis.

Laboratory analysis

We measured plasma glucose with an Analox GM9 glucose analyzer. Plasma radioactivity from [3- H] glucose was determined after deproteinization with barium hydroxide and zinc sulfate and subsequent evaporation to remove tritiated water. We analyzed insulin by radioimmunoassay specific for rat insulin (Cedarlane).

We calculated the glucose infusion rate based on the glucose infusion pump rate and the animal's body weight. This measure is an indication of whole body insulin sensitivity and is representative of both glucose production and uptake; a high glucose infusion rate suggests high sensitivity to insulin. Glucose turnover (rate of appearance [Ra]) was calculated using the steady state formula ($Ra = \text{tracer infusion rate} \div \text{specific activity}$). In the basal state (0–90 min), the total rate of glucose appearance corresponds to endogenous glucose production. Endogenous glucose production, a measure of hepatic insulin sensitivity, was calculated by subtracting the exogenous glucose infusion rate from the total rate of glucose appearance during the clamp (90–210 min). At a steady state glucose disappearance (R_d) is equivalent to the rate of glucose appearance, and at euglycemia glucose disappearance corresponds to tissue glucose utilization because renal glucose clearance is zero.³¹ Glucose utilization repre-

sents both insulin-dependent and -independent uptake into peripheral tissues. Data are presented as average values of samples taken between 60 and 90 minutes for basal and between 190 and 210 minutes for clamp values of the pancreatic euglycemic clamp, as these final time points represent a steady state.

Statistical analysis

Statistical analysis was done using SAS/STAT software version 9.4. We conducted a series of mixed-model, repeated-measures analyses to determine whether glucose, insulin, glucose infusion rate, glucose production and glucose utilization values changed over the course of the experiment, differed across treatment groups and changed differentially over time across the groups. If a significant group $\times$ time interaction was found indicating that the magnitude of difference between the 2 treatment groups changed over time, we constructed a series of linear contrasts to further explore the nature of the interaction. This model tested for group effects in the clamp period while controlling for the average of the basal period. If a significant group effect was found, we performed post hoc t tests as applicable with Bonferroni adjustments for multiple comparisons. For percent glucose suppression (basal relative to clamp), we used a one-way ANOVA; if a group effect was found to be significant, we controlled for multiple comparisons using the Bonferroni method. We considered results to be significant at $p < 0.05$. Data are reported as means with standard deviations.

Results

Basal phase

We tested for group and group $\times$ time effects during the basal period and found no significant differences for any parameters. More specifically, during the basal period, peripheral

Fig. 1: Experimental protocol describing the pancreatic euglycemic clamp with intracerebroventricular (ICV) insulin and acute olanzapine treatment.

insulin (Fig. 2A) and glucose (Fig. 2B) levels did not differ among the treatment groups. There were also no differences in glucose utilization (Fig. 3) or glucose production (Fig. 4) during this time period (60–90 min).

Steady state

Results are reported testing for time and treatment interaction during steady state clamp (190–210 min), controlling for basal values. There were no significant time $\times$ group interactions determined among any of our parameters of interest, and thus we removed the time $\times$ group interaction from the model. There were no between-groups differences in periph-

eral insulin (Fig. 2A) or glucose (Fig. 2B) levels during the clamp phase when controlling for basal phase. There was a significant group effect in glucose infusion rate (Fig. 5), which is a measure of whole body insulin sensitivity ($F_{3,38} = 3.80$, $p < 0.001$). Glucose infusion rate was increased in the insulin–vehicle group compared with the vehicle–vehicle ($p < 0.001$) and vehicle–olanzapine groups ($p = 0.002$). With co-administration of olanzapine, the glucose infusion rate for insulin–olanzapine was no longer significantly increased (Fig. 5). There was a significant group effect in the measure of glucose utilization ($F_{3,38} = 6.60$, all $p < 0.01$; Fig. 3). Glucose utilization during the clamp, controlling for basal phase, was significantly increased in both groups that received central

Fig. 2: Plasma levels of (A) insulin and (B) glucose throughout the basal and euglycemic clamp period. There was no statistically significant difference noted in either outcome between the treatment groups ($n = 8$ –11). INS = insulin; OLA = olanzapine; VEH = vehicle.

Fig. 3: Effect of intracerebroventricular insulin with or without olanzapine (2 mg/kg) on glucose utilization. Controlling for basal phase values, glucose utilization during the clamp was significantly increased with both groups that received central insulin (INS–VEH and INS–OLA) relative to VEH–VEH ($p = 0.025$ v. INS–VEH; $p = 0.024$ v. INS–OLA) and VEH–OLA ($p = 0.014$ v. INS–OLA; $p = 0.015$ v. INS–VEH) ($n = 8$ –11). * $p < 0.05$. INS = insulin; OLA = olanzapine; VEH = vehicle.

Fig. 4: Effect of intracerebroventricular insulin with or without olanzapine (2 mg/kg) on glucose production. Controlling for basal phase values, INS–VEH significantly decreased glucose production relative to other treatment groups ($p = 0.015$ v. VEH–VEH; $p < 0.001$ v. INS–OLA; $p = 0.010$ v. VEH–OLA). With coadministration of OLA (INS–OLA), this decrease was no longer present ($n = 8$ –11). * $p < 0.05$. INS = insulin; OLA = olanzapine; VEH = vehicle.

insulin (the insulin–vehicle and insulin–olanzapine groups) compared with the vehicle–vehicle ($p = 0.025$ v. insulin–vehicle; $p = 0.024$ v. insulin–olanzapine) and vehicle–olanzapine groups ($p = 0.014$ v. insulin–olanzapine; $p = 0.015$ v. insulin–vehicle; Fig. 3). There was also a significant group effect in the measure of hepatic glucose production ($F_{3,37} = 7.37$, $p < 0.001$; Fig. 4). Hepatic glucose production was significantly lower in the insulin–vehicle group than in the other treatment groups ($p = 0.015$ v. vehicle–vehicle; $p < 0.001$ v. insulin–olanzapine; $p = 0.010$ v. vehicle–olanzapine; Fig. 4). Accordingly, ICV insulin significantly suppressed hepatic glucose production (clamp relative to basal: $77.9\% \pm 13.1\%$, all $p < 0.05$; Fig. 6). This suppression of hepatic glucose production was no longer observed when olanzapine was coadministered (clamp relative to basal: insulin–olanzapine $7.7\% \pm 14\%$; Fig. 6). In summary, olanzapine administration abolished the ability of ICV insulin to suppress hepatic glucose production during the clamp phase (Fig. 6). Conversely, olanzapine had no apparent effect on ICV insulin-mediated increases in glucose utilization (Fig. 3).

Discussion

Using euglycemic pancreatic clamps, we replicated seminal findings that central insulin suppresses hepatic glucose production in rodents.^{23,24} In addition, to our knowledge, for the first time we show that the widely prescribed antipsychotic olanzapine perturbs central insulin action, directly abolishing the well-established ability of central insulin to suppress hepatic glucose production. This suggests that olanzapine may induce insulin resistance at the level of the hypothalamus, elucidating a potential underlying mechanism of centrally mediated antipsychotic-induced metabolic perturbations.

Fig. 5: Effect of intracerebroventricular insulin with or without olanzapine (2 mg/kg) on the glucose infusion rate, a measure of insulin sensitivity. Glucose infusion rate was increased in the INS–VEH group relative to VEH–VEH ($p < 0.001$) and VEH–OLA ($p < 0.002$). With co-administration of olanzapine, the glucose infusion rate for INS–OLA was no longer significantly increased and reduced the glucose infusion rate to the level of the VEH–VEH control ($n = 8–11$). * $p < 0.05$. INS = insulin; OLA = olanzapine; VEH = vehicle.

Intriguingly, in contrast to the pronounced effect of olanzapine administration on peripheral and hepatic insulin sensitivity during hyperinsulinemic euglycemic clamp conditions,^{10,11,14,30} olanzapine in the absence of central insulin administration had no effect during basal pancreatic clamp conditions on any parameters of glucose kinetics compared with vehicle administration. In fact, olanzapine treatment looks remarkably like manipulations that block central nutrient sensing and dorsal vagal complex insulin action.^{24,32} Interventions inhibiting central nutrient or insulin sensing have no effect on glucose kinetics in absence of the nutrient or insulin stimulus in a pancreatic clamp, but inhibit the ability of these stimuli to suppress hepatic glucose production.^{24,32} Thus, these differing results during our experimental design compared with previous studies administering antipsychotics during a hyperinsulinemic clamp may be associated with the difference in clamp technique used (i.e., hyperinsulinemic v. basal insulin). To our knowledge, the only 2 published studies that found no effect of olanzapine on hepatic glucose production in rodents used either a pancreatic basal clamp (peripheral infusion of insulin 1 mU/kg/min)³³ or measured glucose production following a central olanzapine injection under basal conditions (no insulin infusion).³⁴ These 2 studies used techniques that (in contrast to the hyperinsulinemic euglycemic clamp or an ICV insulin infusion) do not induce elevated central insulin. Furthermore, acute central olanzapine administration in rodents was found to induce hyperglycemia only in a postprandial state (where one would expect elevated physiologic levels of insulin or glucose that reach the brain) in association with increases in key gluconeogenic enzymes in the liver.²⁸ This effect was not observed in fasted rodents receiving a central olanzapine infusion.²⁸ Our data, taken together with the aforementioned evidence, suggest that a central insulin

Fig. 6: Effect of a single, subcutaneous dose of olanzapine (2 mg/kg) on the ability of insulin to suppress glucose production (%). INS–VEH significantly suppressed glucose production, but this suppression was abolished in the INS–OLA group, which did not differ in suppression values from VEH–VEH and VEH–OLA ($n = 8–11$). * $p < 0.05$. INS = insulin; OLA = olanzapine; VEH = vehicle.

stimulus (and possibly other nutrient stimulation) may at least in part be necessary to observe olanzapine-induced perturbations at the level of the liver.

Although it is possible that a higher dose of olanzapine would have shown impaired hepatic glucose production by itself while also reversing the effects of centrally administered insulin, this remains to be tested, and the findings of Albaugh and colleagues³³ argue against this. They used a similar peripheral infusion rate of insulin (1 mg/kg/min) during a pancreatic euglycemic clamp, and despite a higher dose of olanzapine preceding the clamp procedure (10 mg/kg via gavage) they found no effects of olanzapine compared with vehicle on glucose production.³³

The cellular and molecular mechanisms by which olanzapine could be disrupting central insulin action are unknown. Central insulin is known to decrease activity of 5'AMP-activated protein kinase (AMPK),³⁵ a central regulator of energy homeostasis. Hypothalamic AMPK is activated in low-energy status, and inactivation of AMPK results in suppression of hepatic glucose production with no change in glucose uptake.³⁶ Central and peripheral olanzapine administration is found to increase hypothalamic AMPK activation in association with hepatic insulin resistance and increased hepatic glucose production.^{12,28,37} Thus, it is tempting to speculate that olanzapine could be impairing insulin-mediated inhibition of AMPK, which would be expected to impair suppression of hepatic glucose production with no effect on glucose utilization.

Central insulin also influences key orexigenic hypothalamic pathways linked to hepatic glucose production (e.g., down-regulation of neuropeptide Y [NPY] and agouti-related protein [AgRP]),^{38–40} which may be disrupted by antipsychotics. Interestingly, olanzapine acutely infused into the third ventricle increases hypothalamic NPY and AgRP expression, with concomitant hepatic insulin resistance noted during hyperinsulinemic clamp experiments.¹² In turn, ICV NPY infusion impairs the effects of high levels of circulating insulin to suppress hepatic glucose production.⁴¹ Although the mechanism of how NPY alters hepatic glucose production is unclear, this may suggest that antipsychotic-induced upregulation of NPY could explain the abolishment of central insulin action leading to impaired inhibition of hepatic glucose production.

When postulating a mechanism, we should also consider the fact that antipsychotics, in particular newer, second-generation agents, antagonize a number of neurotransmitter systems implicated in energy homeostasis, such as histamine (H_1) and serotonin ($5HT_{2c}$).⁴² Activation or agonism of hypothalamic H_1 and $5HT_{2c}$ pathways has been linked to improvements in insulin sensitivity,^{43,44} which in the case of H_1 augments central insulin-mediated suppression of hepatic glucose production.⁴³ Antipsychotics also antagonize the D_2 receptor, which is implicated in glucose homeostasis. For example, bromocriptine, a D_2 agonist, is now indicated for the treatment of diabetes.⁴⁵ However, although the D_2 receptor represents the common property by which antipsychotics exert therapeutic effects (and not all antipsychotics dysregulate hepatic glucose production¹⁰), it is unlikely that D_2 blockade on its own accounts for disruption of hepatic glucose production, but rather may act in synergy with other mechanisms.

An additional unprecedented finding from this study is that ICV insulin infusion also resulted in an increase in glucose uptake relative to the basal phase. The effect of ICV insulin on glucose uptake is unexpected, as previous studies failed to find an effect of ICV insulin on glucose utilization.^{23,32} A potential explanation for this previously undescribed result is the difference in ICV insulin infusion rate in our study. We used the same total ICV insulin dose as Obici and colleagues,²³ but during a shorter clamp duration (210 min v. 360 min), resulting in a higher infusion rate. To the best of our knowledge, a dose–response effect of ICV insulin on glucose utilization has not been examined and may have played a role in our study result. It is also important to note that olanzapine appears to spare the pathway through which central insulin increases glucose utilization. This intriguing finding could suggest that development of intranasal formulations of antipsychotic drugs (i.e., currently available for loxapine) may have advantages over systemic (i.e., oral or intramuscular) administration by possibly circumventing adverse metabolic effects on glucose utilization.

Limitations

Only male rats were used in this study. There are sex differences in regards to adverse effects of antipsychotics; female rats have increased propensity for antipsychotic-induced weight gain and hyperphagia compared with male rats. However, the role of sex in direct (weight-independent) effects of antipsychotics on glucose homeostasis is unknown. Thus, the possibility exists that males and females might regulate glucose homeostasis differently, but early observations suggest that acute olanzapine-induced induction of insulin resistance is sex-independent.¹² Cannulae placement was not verified; however, our ability to replicate central insulin-mediated suppression of hepatic glucose production acts as a positive control. Another potential limitation is that our study investigated only a single acute dose of olanzapine. In reality, antipsychotics are taken repeatedly, often over a lifetime, and we do not know how antipsychotics would affect central insulin sensing in a chronic dosing scenario. However, we might speculate that central insulin sensing would remain affected, as Boyda and colleagues^{46,47} have found persistent glucose dysregulation and insulin resistance (without tolerance or sensitization) with repeated olanzapine administration in rats. Finally, we did not investigate specific pathways in this study. Potential mechanisms have been speculated and will be investigated in future experiments.

Conclusion

Our work supports the concept that olanzapine can induce central insulin resistance to alter hepatic glucose metabolism. Specifically, olanzapine abolishes the ability of central insulin to suppress hepatic glucose production, resulting in the inappropriate production of glucose. An increase in endogenous glucose production is a hallmark of type 2 diabetes, resulting in devastating medical consequences, such as microvascular/macrovascular disease.⁴⁸ Moreover, hyperglycemia and central insulin resistance have been linked to cognitive deficits.^{49,50} Worsening cognitive function is especially concerning for people with

schizophrenia, as cognitive deficits represent a core domain of psychosis; hence antipsychotic-induced central insulin resistance could exacerbate this aspect of schizophrenia psychopathology.⁵¹ Our finding of antipsychotic-induced central insulin resistance may also in part explain why existing trials examining intranasal insulin for weight gain attenuation⁵² or cognitive functioning in patients with schizophrenia taking antipsychotics⁵³ have been unsuccessful, as central insulin resistance would potentially impair any metabolic or cognitive benefits of intranasal insulin. Thus, further investigations into the mechanisms underlying antipsychotic-induced centrally mediated glucose perturbations are critical to develop effective antipsychotic treatments minimizing adverse metabolic effects and/or targeted interventions in the face of metabolic dysregulation. For example, some postulated mechanisms may be amendable to therapeutic interventions (e.g., central histamine blockade), whereas others may not (e.g., D₂ blockade). Taken together, future preclinical rodent studies examining postulated pathways and chronic dosing paradigms to examine sensitization, or conversely, tolerance to this adverse effect will be clinically relevant and important. Furthermore, direct translation of our novel findings into humans using the pancreatic euglycemic clamp combined with the use of intranasal insulin may hold the potential to unravel the complexities underlying the metabolic vulnerability and possibly psychopathology that characterizes schizophrenia.

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