Reduced insulin-receptor mediated modulation of striatal dopamine release by basal insulin as a possible contributing factor to hyperdopaminergia in schizophrenia

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Abstract

Schizophrenia is a severe and chronic neuropsychiatric disorder which affects 1% of the world population. Using the brain imaging technique positron emission tomography (PET) it has been demonstrated that persons with schizophrenia have greater dopamine transmission in the striatum compared to healthy controls. However, little progress has been made as to elucidating other biological mechanisms which may account for this hyperdopaminergic state in this disease. Studies in animals have demonstrated that insulin receptors are expressed on midbrain dopamine neurons, and that insulin from the periphery acts on these receptors to modify dopamine transmission in the striatum. This is pertinent given that several lines of evidence suggest that insulin receptor functioning may be abnormal in the brains of persons with schizophrenia. Post-mortem studies have shown that persons with schizophrenia have less than half the number of cortical insulin receptors compared to healthy persons. Moreover, these post-mortem findings are unlikely due to the effects of antipsychotic treatment; studies in cell lines and animals suggest antipsychotics enhance insulin receptor functioning. Further, hyperinsulinemia – even prior to antipsychotic use – seems to be related to less psychotic symptoms in patients with schizophrenia. Collectively, these data suggest that midbrain insulin receptor functioning may be abnormal in persons with schizophrenia, resulting in reduced insulin-mediated regulation of dopamine transmission in the striatum. Such a deficit may account for the hyperdopaminergic state observed in these patients and would help guide the development of novel treatment strategies. We hypothesize that, (i) insulin receptor expression and/or function is reduced in midbrain dopamine neurons in persons with schizophrenia, (ii) basal insulin should reduce dopaminergic transmission

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in the striatum via these receptors, and (iii) this modulation of dopaminergic transmission by basal insulin is reduced in the brains of persons with schizophrenia.

Introduction

Why dopamine and potential biological modulators of dopamine levels are relevant to schizophrenia

Schizophrenia is a severe and chronic mental illness which affects 1% of the population, ranking as one of the leading causes of disability worldwide [1,2]. While the cause of schizophrenia is currently unknown, the “dopamine (DA) hypothesis of schizophrenia” has been the most enduring idea in psychiatry for the last fifty-years [3]. Before the advent of advanced brain imaging, it was hypothesized that abnormally high levels of the neurochemical DA would be present in the brains of persons with schizophrenia [4]. Using the brain imaging technique positron emission tomography (PET) the DA hypothesis of schizophrenia has been strongly supported. Namely, with PET it has been shown that persons with schizophrenia demonstrate: (i) increased endogenous DA levels in the striatum [5,6], (ii) increased DA release in response to psychostimulants [7,8], and (iii) increased DA synthesis capacity [9,10]. Moreover, data suggests that conventional treatment with antipsychotics may not reduce the abnormally high striatal DA levels observed in these patients – leaving the underlying disease pathology unaltered and patients vulnerable to relapse given complete antipsychotic discontinuation [11].

Arguably, the finding of increased dopaminergic transmission as revealed with PET is one of the most consistent and replicated brain imaging findings in schizophrenia [12]. Despite this knowledge, little progress has been made in terms of understanding the potential mechanisms by which increased levels of DA may exist in schizophrenia. A better understanding of the biological mechanisms which regulate striatal DA levels *in vivo* is an important first step to understanding how such mechanisms may be abnormal in the brains of persons with schizophrenia.

Peripheral insulin acting on insulin receptors in the brain modulates striatal dopamine levels

Insulin receptors (IRs) are expressed throughout the brain and are activated by circulating insulin, affecting brain function, behavior, and cognition [13–16]. Historically, the brain has been considered an “insulin-insensitive” organ [16]. This is because neurons can obtain glucose without insulin, via insulin-independent transporters [16]. Thus, in the mammalian brain insulin may play a greater role as a neuromodulator than as a regulator of glucose utilization. For example, insulin has been shown to modify classical DA mediated reward behaviors [17]. Thus, while type 2 diabetes alters brain glucose metabolism to some extent [18,19], it is not assumed that the role and function of IRs in the periphery and the brain – and how they are affected by peripheral insulin resistance – is the same. For example, experimental diabetes in rodents has been found to alter the expression of IRs in peripheral tissues but not in the brain [20,21].

Notably, IRs are expressed on midbrain DA neurons (substantia nigra/ventral tegmental area; SN/VTA) [17,22], and insulin from the periphery can act on these receptors to modify DA levels in the striatum [23,24]. Specifically, several animal studies suggest that IR activation on midbrain DA neurons acts to inhibit DA synthesis and release into the striatum [22,24–26] (see Fig. 1). In turn, insulin can modify DA-dependent behaviors which are relevant to the pathophysiology of schizophrenia, such as sensitivity to DA release in response to psychostimulants [27–29]. Collectively, this evidence suggests that enhancing IR signaling in the SN/VTA may reduce DA levels in the striatum. Thus, for persons with schizophrenia enhanced IR activation should reduce striatal DA levels (improving symptoms), while reduced IR signaling should enhance striatal DA levels (worsening symptoms).

Relationship between central and peripheral insulin concentrations in relation to insulin resistance

In type 2 diabetes, peripheral insulin secretion is increased as a compensatory mechanism to restore normal glucose tolerance [30]. For example, mice with a 50% reduction in IR expression demonstrate normal glucose tolerance due to compensatory increases in plasma insulin [31–33]. Thus, overt glucose intolerance in the periphery does not need to necessarily accompany alterations in central or peripheral IR expression [30,34]. Conversely, several lines of evidence suggest that peripheral glucose metabolism can be altered by changes in central IR [35–37] and $D_{2/3}R$ functioning [38,39].

We assume that states of hyperinsulinemia (as observed in type 2 diabetes) promote more basal insulin to enter the brain, producing greater activation of central IRs. At least in humans, it has been demonstrated that insulin concentrations in cerebral spinal fluid (CSF) are correlated with concentrations in plasma [40,41]. Animal research supports that increases in peripheral insulin generally results in increased concentrations in the brain [42–46] – although this process can be reduced by ageing, fasting, obesity, and diabetes [40,41,47,48]. However, it should be noted that correlations between central and peripheral concentrations of insulin have not always been observed in animals [49,50]. Given the human data, we hypothesize that increased basal insulin levels in the periphery should generally result in greater insulin concentrations in the brain. In theory, this would result in more activation of IRs in the SN/VTA and thus inhibit DA release into the striatum.

Greater insulin resistance and fasting levels of insulin are related to less endogenous dopamine in the striatum of healthy persons measured with PET

Several lines of evidence in animals and humans suggest that insulin resistance and/or diabetes is related to less striatal DA synthesis [51–56] and metabolism [52,55,57–61]. Using PET and particular radioligands for $D_{2/3}R$, it is possible to achieve direct estimates of endogenous DA occupying $D_{2/3}R$ in humans *in vivo*. This is possible because these radiotracers are sensitive to changes in endogenous DA – competing with DA for binding to $D_{2/3}R$ at baseline [62]. By comparing the percent change in the binding of a radioligand between a baseline PET scan and a scan under acute DA depletion, it is possible to quantify levels of endogenous DA occupying $D_{2/3}R$ at baseline [63,64]; in healthy persons and those with neuropsychiatric diseases [6,65,66]. Acute DA depletion can be achieved in humans by

inhibiting dopamine synthesis via the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine (AMPT).

Using the D_{2/3}R radiotracer [¹¹C]-(+)-PHNO, and the DA depletion paradigm, we have demonstrated in healthy non-obese persons that greater insulin resistance is correlated with less endogenous DA levels in the ventral striatum/nucleus accumbens (VS) ($r^2 = .71$) [67]. Specifically, greater fasting levels of insulin were correlated with less endogenous DA levels in this region ($r^2 = .72$) [67]. These findings are consistent with previous PET studies which have employed other D_{2/3}R radiotracers to examine the relationship between baseline D_{2/3}R availability and insulin sensitivity [68,69]. Moreover, these results are consistent with previous [¹¹C]-(+)-PHNO studies examining the relationship between baseline D_{2/3}R availability and body mass index [70,71].

Collectively, this data in conjunction with the animal literature suggests that states of hyperinsulinemia, with or without the presence of diabetes, may be related to less DA signaling in the striatum. It is hypothesized that this is due to the enhanced activation of midbrain IRs by greater circulating fasting levels of insulin.

Brain insulin receptors and insulin receptor signaling may be reduced in schizophrenia

Several lines of evidence suggest that there is abnormal IR functioning in the brains of persons with schizophrenia [72]. Post-mortem studies have demonstrated that persons with schizophrenia have dramatically reduced IR concentrations (–50%) and IR cellular signaling compared to healthy controls in the dorsolateral prefrontal cortex [73,74]. Importantly, these reductions in IR expression and function are not easily attributable to the potential effects of chronic antipsychotic exposure. This is because studies in animals and cell lines suggest antipsychotics used in the treatment of schizophrenia enhance IR-mediated cell signaling [72,74]. For example, brain IR knockout mice demonstrate increased intracellular glycogen synthase kinase-3 β (GSK-3 β) activity [75]. It has been hypothesized that GSK-3 β activity is increased in schizophrenia and antipsychotics have been shown to consistently decrease GSK-3 β signaling [76]. Importantly, several DA mediated behaviors relevant to schizophrenia can be inhibited by blocking GSK-3 β signaling [77]. Notably, one study observed that IR knockout in the brains of mice results in behavioral disturbances such as increased anxiety and depression-like behaviors [78].

Collectively, these data suggest that IR signaling is reduced in the brains of persons with schizophrenia. However, no post-mortem or *in vivo* brain imaging study has examined whether IR expression and/or signaling is reduced in midbrain DA neurons of persons with schizophrenia. This can most certainly be tested. If IR expression levels were found to be reduced in midbrain DA neurons in schizophrenia patients, this in turn could result in a reduction in insulin-mediated modulation of DA levels in the striatum, and could potentially account for the hyperdopaminergia observed therein. Importantly, what current data suggests is that current antipsychotics may work to enhance IR signaling in the brain.

Relationship between peripheral hyperinsulinemia and symptoms in persons with schizophrenia

It is well established that metabolic abnormalities exist in persons with schizophrenia and their first degree-relatives [79–81]. Moreover, differences in metabolic functioning may even differentiate subtypes of patients with schizophrenia and their clinical course [82]. Importantly, higher fasting serum levels of insulin – and in turn peripheral insulin resistance – has been related to less psychotic symptoms in patients with schizophrenia. This has been observed in patients who are: (i) neuroleptic naïve first-episode [83], (ii) acutely-ill inpatients [84], and (iii) chronically treated outpatients [85]. Importantly, antipsychotics induce diabetes and weight gain [86], and it has been suggested that clinical response to these drugs may be related to a “metabolic threshold,” i.e. the more antipsychotic induced weight-gain the greater reduction in psychotic symptoms [87]. Notably, the antipsychotic which is believed to be the most efficacious for treatment-resistant schizophrenia – clozapine [88] – confers the greatest weight-gain risk [86]. Historically, before the use of antipsychotics, increasing peripheral insulin and inducing insulin comas were noted as being temporarily efficacious for reducing psychotic symptoms in patients with schizophrenia [89]. However, several problems exist in interpreting these early findings, especially with regards to the reliability of the diagnosis of schizophrenia in these studies [90]. Thus, while persons with schizophrenia are more likely to have a metabolic disorder [91], states of hyperinsulinemia (either prior to treatment or antipsychotic induced) seem to be related to better clinical outcomes. These data beckon the examination of the role of peripheral insulin on DA functioning in the brains of persons with schizophrenia.

To our knowledge, no study has examined whether insulin or glucose concentrations in the CSF are correlated with those in plasma in patients with schizophrenia – medication naïve or otherwise. This represents an important avenue of investigation to verify our assumption that peripheral hyperinsulinemia in patients relates to greater insulin concentrations in the brain. Moreover, it would be important to conclusively demonstrate that antipsychotic administration (and DA depletion) can alter central concentrations of insulin and glucose, not just peripheral [67,92,93].

Future PET studies to determine the effect of metabolic status on striatal dopamine levels in persons with schizophrenia

Future PET studies should determine whether hyperinsulinemia and/or type-2 diabetes in persons with schizophrenia results in, (i) reduced endogenous DA levels at striatal $D_{2/3}R$, (ii) reduced dopamine synthesis capacity, and (iii) reduced psychostimulant induced striatal DA release. This can be accomplished by comparing healthy controls and patients with schizophrenia both with and without such metabolic abnormalities.

Using in vivo PET imaging to determine whether IR-mediated modulation of striatal DA release is abnormal in persons with schizophrenia

We hypothesize that midbrain IR functioning is reduced in the brains of persons with schizophrenia. This would result in a reduced ability of basal insulin to modify midbrain DA neurons and thus DA transmission into the striatum. A deficit in midbrain IR signaling may potentially account for the hyperdopaminergic state observed in the striatum of these

patients. If this hypothesis were correct, the following could be observed using *in vivo* PET imaging: (i) that removal of basal insulin (under euglycemia) enhances dopaminergic transmission in the striatum (and *vice versa*), and (ii) that the modulation of dopaminergic transmission by basal insulin is reduced in the brains of persons with schizophrenia. In other words, under euglycemia the presence of basal insulin should reduce striatal DA to a lesser extent in patients with schizophrenia, while in the absence of basal insulin an enhanced increase in DA levels should be observed.

It would be possible to determine the modulatory effects of basal insulin on DA levels in the brain using an insulin-suppression paradigm. Such a paradigm has been previously employed with humans in conjunction with PET imaging [18,19]. Specifically, it was used with the radiotracer [^{18}F]-FDG to investigate if basal insulin modulates brain glucose utilization in healthy persons [19] and if such utilization is altered in persons with diabetes [18]. In this design participants receive two scans – in a double-blind, counter-balanced order – under one of two conditions: (i) acute insulin suppression plus infused saline, or, (ii) acute insulin suppression plus infused insulin.

Using a DA radioligand for $\text{D}_{2/3}\text{R}$, PET scans pre and post basal insulin suppression would allow for the measurement of insulin mediated changes in striatal DA release. This would thus allow for the determination of how basal insulin modulates DA levels in the brain. This paradigm would potentially offer a probe for midbrain IR functioning which, once validated in healthy humans, could determine whether there is abnormal DA modulation by basal insulin in the brains of persons with schizophrenia.

Clarifying our hypotheses

Our purpose for writing this “midbrain IR-deficiency hypothesis” of schizophrenia was not to propose a main-cause or *sine qua non* of the disease. Rather, our purpose for writing was to provide falsifiable hypotheses which may partially account for the increased striatal DA often observed in these patients. Similarly, we do not claim that increased striatal DA is the main or ultimate cause of schizophrenia – although this has been proposed [94]. For our purposes, increased striatal DA is simply an observable neurochemical abnormality often associated with the disease. Thus, providing plausible mechanisms for how this striatal hyper-dopaminergia may arise, given falsifiable hypotheses with brain imaging, provides a means to potentially advance our understanding of the disease and develop new therapeutic strategies.

Our “midbrain IR-deficiency hypothesis” developed from the following points of observation. Namely, (i) IRs on midbrain DA neurons can modulate striatal DA release, (ii) IR-expression and function may be reduced throughout the brain of persons with schizophrenia, (iii) metabolic abnormalities co-occur in persons with schizophrenia even before antipsychotic treatment, and (iv) hyperinsulinemic states – which are exacerbated by antipsychotic administration – may be related to both reduced striatal DA levels and improved psychotic symptoms in persons with schizophrenia. However, how ubiquitous brain IR deficiency affects global brain functioning in schizophrenia, and the mechanisms by

which reduced brain IR expression may occur in the first place, is beyond the scope of our theory. We leave such speculations to further evidence and research.

The extent of striatal D_{2/3}R blockade by antipsychotics *in vitro* and *in vivo* still represents the best correlates of clinical response in persons with schizophrenia [95–100]. However, recent evidence suggests that there is a proportion of patients with schizophrenia who do not appear to have increased striatal DA, and do not respond to conventional antipsychotic treatment [101,102]. This suggests that there may be a subgroup of patients with schizophrenia for whom increased striatal DA transmission is not relevant to the manifestation of the clinical symptomatology. In fact, the earliest study examining striatal DA levels in schizophrenia found that those patients with the greatest striatal DA demonstrated the greatest improvement given antipsychotic treatment [5]. Thus, our “midbrain IR-deficiency hypothesis” may only apply to a subgroup of patients: those who have increased striatal DA and classically respond to antipsychotics. More research is needed to better understand the potential “subtypes” of schizophrenia [103]. Such research will likely be guided by elucidating brain-specific biomarkers associated with clinical non-response to antipsychotics [104].

Falsifying our hypotheses

Our hypotheses presented herein are strongly dependent on the data which suggests that activation of IRs in the SN/VTA reduces DA release into the striatum. However, there are inconsistencies in the literature. One study found that acute insulin administration into the SN/VTA could increase spike-firing frequency of these neurons by 50% [105]; an effect which would presumably result in increased striatal DA release. Moreover, this increase in spike-firing was lost in mice lacking IRs selectively in the SN/VTA. Interestingly, spontaneous spike-firing frequency in the SN/VTA was not altered in the IR knock-out mice. Further research is required to elucidate the mechanisms by which IR activation and inhibition may regulate the functioning of the SN/VTA neurons, and in turn striatal DA release.

The strength of a hypothesis can often (but not always) be judged by how well it fits with other known theories examining the same phenomenon of interest. Multiple theories for the cause(s) of the symptoms of schizophrenia have been proposed. We have focused on adding to the DA hypothesis of schizophrenia, which ultimately suggests that the positive (or psychotic) symptoms of the disease results from exaggerated striatal DA transmission [106,107]. However, other theories (which are not mutually exclusive to the DA hypothesis, nor with each other) have been proposed to explain the symptomatology of the disease. These include theories of glutamatergic-excitotoxicity [108], reduced GABA-interneuron functioning [109], reduced cortical synaptic plasticity [110], and neuroinflammation [111]. It is beyond the scope of the current outline to delineate how our “midbrain IR-deficiency hypothesis” relates to all known theories of schizophrenia. However, it is most certainly possible to link our hypotheses with other hypotheses of schizophrenia.

Conclusions

We hypothesized that IR expression and/or function may be reduced in midbrain DA neurons in persons with schizophrenia. We also hypothesized that this would result in a reduced ability of basal insulin to modify DA levels in the striatum – potentially accounting for the striatal hyperdopaminergia observed in these patients. We propose that by using PET imaging with radioligands for D_{2/3}R it can be possible to validate or disprove our hypotheses. Such future PET studies will help us better understand how striatal DA levels may be modulated *in vivo* by neuroendocrine factors in healthy persons and persons with neuropsychiatric diseases like schizophrenia.

References

1. Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. *Eur Arch Psychiatry Clin Neurosci.* 2000; 250:274–85. [PubMed: 11153962]
2. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* 2005; 2:31.
3. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III— the final common pathway. *Schizophr Bull.* 2009; 35:549–62. [PubMed: 19325164]
4. Meltzer HY, Stahl SM. The dopamine hypothesis of schizophrenia. *Schizophr Bull.* 1976; 2:19–76. [PubMed: 779020]
5. Abi-Dargham A, Rodenhiser J, Printz D, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci.* 2000; 97:8104–9. [PubMed: 10884434]
6. Kegeles LS, Abi-Dargham A, Frankle WG, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry.* 2010; 67:231–9. [PubMed: 20194823]
7. Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M. Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. *Biol Psychiatry.* 2009; 65:1091–3. [PubMed: 19167701]
8. Laruelle M. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *Q J Nucl Med.* 1998; 42:211–21. [PubMed: 9796369]
9. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F]/[(11)C]-DOPA PET studies. *Schizophr Bull.* 2013; 39:33–42. [PubMed: 22282454]
10. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry.* 2012; 69:776–86. [PubMed: 22474070]
11. Caravaggio F, Borlido C, Wilson A, Graff-Guerrero A. Examining endogenous dopamine in treated schizophrenia using [C]-(+)-PHNO positron emission tomography: a pilot study. *Clin Chim Acta.* 2015; 23:00152–7.
12. Laruelle M. Schizophrenia: from dopaminergic to glutamatergic interventions. *Curr Opin Pharmacol.* 2014; 14:97–102. [PubMed: 24524997]
13. Craft S, Stennis Watson G. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol.* 2004; 3:169–78. [PubMed: 14980532]
14. Gerozissis K. Brain insulin: regulation, mechanisms of action and functions. *Cell Mol Neurobiol.* 2003; 23:1–25. [PubMed: 12701881]
15. Plum L, Schubert M, Brüning JC. The role of insulin receptor signaling in the brain. *Trends Endocrinol Metab.* 2005; 16:59–65. [PubMed: 15734146]
16. Schulingkamp R, Pagano T, Hung D, Raffa R. Insulin receptors and insulin action in the brain: review and clinical implications. *Neurosci Biobehav Rev.* 2000; 24:855–72. [PubMed: 11118610]
17. Figlewicz DP. Insulin, food intake, and reward. *Semin Clin Neuropsychiatry.* 2003; 8:82–93. [PubMed: 12728408]

18. Anthony K, Reed LJ, Dunn JT, et al. Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? *Diabetes*. 2006; 55:2986–92. [PubMed: 17065334]
19. Bingham EM, Hopkins D, Smith D, et al. The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. *Diabetes*. 2002; 51:3384–90. [PubMed: 12453890]
20. Pacold S, Blackard W. Central nervous system insulin receptors in normal and diabetic rats. *Endocrinology*. 1979; 105:1452–7. [PubMed: 499083]
21. Pezzino V, Costantino A, Russo P, Gullo D, Papa V. Insulin receptor content in tissues of normal and diabetic rats measured by radioimmunoassay. *J Endocrinol Invest*. 1996; 19:593–7. [PubMed: 8957742]
22. Labouèbe G, Liu S, Dias C, et al. Insulin induces long-term depression of ventral tegmental area dopamine neurons via endocannabinoids. *Nat Neurosci*. 2013; 16:300–8. [PubMed: 23354329]
23. Potter GM, Moshirfar A, Castonguay TW. Insulin affects dopamine overflow in the nucleus accumbens and the striatum. *Physiol Behav*. 1999; 65:811–6. [PubMed: 10073485]
24. Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? *Trends Neurosci*. 2007; 30:375–81. [PubMed: 17604133]
25. 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; 36:2336–46. [PubMed: 22712725]
26. Liu S, Labouèbe G, Karunakaran S, Clee SM, Borgland SL. Effect of insulin on excitatory synaptic transmission onto dopamine neurons of the ventral tegmental area in a mouse model of hyperinsulinemia. *Nutr Diabetes*. 2013; 16:38.
27. Schoffelmeer AN, Drukarch B, De Vries TJ, Hogenboom F, Schetters D, Pattij T. Insulin modulates cocaine-sensitive monoamine transporter function and impulsive behavior. *J Neurosci*. 2011; 31:1284–91. [PubMed: 21273413]
28. Breier A, Su TP, Saunders R, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA*. 1997; 94:2569–74. [PubMed: 9122236]
29. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry*. 1998; 155:761–7. [PubMed: 9619147]
30. Kahn BB. Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance. *Cell*. 1998; 92:593–6. [PubMed: 9506512]
31. Accili D. Insulin receptor knock-out mice. *Trends Endocrinol Metab*. 1997; 8:101–4. [PubMed: 18406794]
32. Joshi RL, Lamothe B, Cordonnier N, et al. Targeted disruption of the insulin receptor gene in the mouse results in neonatal lethality. *EMBO J*. 1996; 15:1542–7. [PubMed: 8612577]
33. Accili D, Drago J, Lee EJ, et al. Early neonatal death in mice homozygous for a null allele of the insulin receptor gene. *Nat Genet*. 1996; 12:106–9. [PubMed: 8528241]
34. Kahn CR, Vicent D, Doria A. Genetics of non-insulin-dependent (type-II) diabetes mellitus. *Annu Rev Med*. 1996; 47:509–31. [PubMed: 8712800]
35. Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes*. 2014; 63:2232–43. [PubMed: 24931034]
36. Plum L, Belgardt BF, Bruning JC. Central insulin action in energy and glucose homeostasis. *J Clin Invest*. 2006; 116:1761–6. [PubMed: 16823473]
37. Brüning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. *Science*. 2000; 289:2122–5. [PubMed: 11000114]
38. Saller CF, Kreamer LD. Glucose concentrations in brain and blood: regulation by dopamine receptor subtypes. *Brain Res*. 1991; 546:235–40. [PubMed: 1829974]
39. Americ SP, Chow SA, Bhatnagar RK, Webb RL, Fischer LJ, Long JP. Evidence that central dopamine receptors modulate sympathetic neuronal activity to the adrenal medulla to alter glucoregulatory mechanisms. *Neuropharmacology*. 1984; 23:137–47. [PubMed: 6371573]

40. Sartorius T, Peter A, Heni M, et al. The brain response to peripheral insulin declines with age: a contribution of the blood-brain barrier? *PLoS ONE*. 2015;10.
41. Heni M, Schopfer P, Peter A, et al. Evidence for altered transport of insulin across the blood-brain barrier in insulin-resistant humans. *Acta Diabetol*. 2014; 51:679–81. [PubMed: 24370925]
42. Woods SC, Porte D Jr. Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *Am J Physiol*. 1977; 233:E331–4. [PubMed: 910946]
43. Steffens AB, Scheurink AJ, Porte D Jr, Woods SC. Penetration of peripheral glucose and insulin into cerebrospinal fluid in rats. *Am J Physiol*. 1988; 255:R200–4. [PubMed: 3044143]
44. Plata-Salaman CR. Insulin in the cerebrospinal fluid. *Neurosci Biobehav Rev*. 1991; 15:243–58. [PubMed: 1852315]
45. Schwartz MW, Bergman RN, Kahn SE, et al. Evidence for entry of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs. Quantitative aspects and implications for transport. *J Clin Invest*. 1991; 88:1272–81. [PubMed: 1918377]
46. Baura GD, Foster DM, Porte D Jr, et al. Saturable transport of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *J Clin Invest*. 1993; 92:1824–30. [PubMed: 8408635]
47. Strubbe JH, Porte D Jr, Woods SC. Insulin responses and glucose levels in plasma and cerebrospinal fluid during fasting and refeeding in the rat. *Physiol Behav*. 1988; 44:205–8. [PubMed: 3070584]
48. Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. *Diabetes*. 2000; 49:1525–33. [PubMed: 10969837]
49. Havrankova J, Roth J, Brownstein MJ. Concentrations of insulin and of insulin receptors in the brain are independent of peripheral insulin levels: studies of obese and streptozotocin-treated rodents. *J Clin Invest*. 1979; 64:636–42. [PubMed: 156737]
50. Ono T, Steffens AB, Sasaki K. Influence of peripheral and intracerebroventricular glucose and insulin infusions on peripheral and cerebrospinal fluid glucose and insulin levels. *Physiol Behav*. 1983; 30:301–6. [PubMed: 6342012]
51. Kono T, Takada M. Dopamine depletion in nigrostriatal neurons in the genetically diabetic rat. *Brain Res*. 1994; 634:155–8. [PubMed: 8156386]
52. Saller CF. Dopaminergic activity is reduced in diabetic rats. *Neurosci Lett*. 1984; 49:301–6. [PubMed: 6493613]
53. Bradberry CW, Karasic DH, Deutch AY, Roth RH. Regionally-specific alterations in mesotelencephalic dopamine synthesis in diabetic rats: association with precursor tyrosine. *J Neural Transm Gen Sect*. 1989; 78:221–9. [PubMed: 2529883]
54. Crandall EA, Fernstrom JD. Effect of experimental diabetes on the levels of aromatic and branched-chain amino acids in rat blood and brain. *Diabetes*. 1983; 32:222–30. [PubMed: 6337901]
55. Bitar M, Koulu M, Rapoport SI, Linnoila M. Diabetes-induced alteration in brain monoamine metabolism in rats. *J Pharmacol Exp Ther*. 1986; 236:432–7. [PubMed: 2418197]
56. Trulson ME, Himmel CD. Decreased brain dopamine synthesis rate and increased [3H]spiroperidol binding in streptozotocin-diabetic rats. *J Neurochem*. 1983; 40:1456–9. [PubMed: 6403671]
57. Kwok RP, Walls EK, Juorio AV. The concentration of dopamine, 5-hydroxytryptamine, and some of their acid metabolites in the brain of genetically diabetic rats. *Neurochem Res*. 1985; 10:611–6. [PubMed: 2409457]
58. Kwok RP, Juorio AV. Concentration of striatal tyramine and dopamine metabolism in diabetic rats and effect of insulin administration. *Neuroendocrinology*. 1986; 43:590–6. [PubMed: 3528901]
59. Chen CC, Yang JC. Effects of short and long-lasting diabetes mellitus on mouse brain monoamines. *Brain Res*. 1991; 552:175–9. [PubMed: 1913176]
60. Lackovic Z, Salkovic M, Kuci Z, Relja M. Effect of long-lasting diabetes mellitus on rat and human brain monoamines. *J Neurochem*. 1990; 54:143–7. [PubMed: 2293606]
61. Lim DK, Lee KM, Ho IK. Changes in the central dopaminergic systems in the streptozotocin-induced diabetic rats. *Arch Pharm Res*. 1994; 17:398–404. [PubMed: 10319147]

62. Cumming P, Wong DF, Dannals RF, et al. The competition between endogenous dopamine and radioligands for specific binding to dopamine receptors. *Ann N Y Acad Sci.* 2002; 965:440–50. [PubMed: 12105119]
63. Laruelle M, D'Souza CD, Baldwin RM, et al. Imaging D2 receptor occupancy by endogenous dopamine in humans. *Neuropsychopharmacology.* 1997; 17:162–74. [PubMed: 9272483]
64. Verhoeff NP, Kapur S, Hussey D, et al. A simple method to measure baseline occupancy of neostriatal dopamine D2 receptors by dopamine in vivo in healthy subjects. *Neuropsychopharmacology.* 2001; 25:213–23. [PubMed: 11425505]
65. Abi-Dargham A, Rodenhiser J, Printz D, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA.* 2000; 97:8104–9. [PubMed: 10884434]
66. Martinez D, Greene K, Broft A, et al. Lower level of endogenous dopamine in patients with cocaine dependence: findings from PET imaging of D(2)/D(3) receptors following acute dopamine depletion. *Am J Psychiatry.* 2009; 166:1170–7. [PubMed: 19723785]
67. Caravaggio F, Borlido C, Hahn M, et al. Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy nonobese humans. *Int J Neuropsychopharmacol.* 2015:25.
68. Dunn JP, Kessler RM, Feurer ID, et al. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. *Diabetes Care.* 2012; 35:1105–11. [PubMed: 22432117]
69. Guo J, Simmons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Mol Psychiatry.* 2014; 19:1078–84. [PubMed: 25199919]
70. Cosgrove KP, Veldhuizen MG, Sandiego CM, Morris ED, Small DM. Opposing relationships of BMI with BOLD and dopamine D2/3 receptor binding potential in the dorsal striatum. *Synapse.* 2015; 69:195–202. [PubMed: 25664726]
71. Caravaggio F, Raitsin S, Gerretsen P, Nakajima S, Wilson A, Graff-Guerrero A. Ventral striatum binding of a dopamine D2/3 receptor agonist but not antagonist predicts normal body mass index. *Biol Psychiatry.* 2015; 77:196–202. [PubMed: 23540907]
72. Lovestone S, Killick R, Di Forti M, Murray R. Schizophrenia as a GSK-3 dysregulation disorder. *Trends Neurosci.* 2007; 30:142–9. [PubMed: 17324475]
73. Bernstein HG, Ernst T, Lendeckel U, et al. Reduced neuronal expression of insulin-degrading enzyme in the dorsolateral prefrontal cortex of patients with haloperidol-treated, chronic schizophrenia. *J Psychiatr Res.* 2009; 43:1095–105. [PubMed: 19394958]
74. Zhao Z, Ksiazak-Reding H, Riggio S, Haroutunian V, Pasinetti GM. Insulin receptor deficits in schizophrenia and in cellular and animal models of insulin receptor dysfunction. *Schizophr Res.* 2006; 84:1–14. [PubMed: 16581231]
75. Schubert M, Gautam D, Surjo D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci USA.* 2004; 101:3100–5. [PubMed: 14981233]
76. Freyberg Z, Ferrando SJ, Javitch JA. Roles of the Akt/GSK-3 and Wnt signaling pathways in schizophrenia and antipsychotic drug action. *Am J Psychiatry.* 2010; 167:388–96. [PubMed: 19917593]
77. Beaulieu JM, Gainetdinov RR, Caron MG. The Akt-GSK-3 signaling cascade in the actions of dopamine. *Trends Pharmacol Sci.* 2007; 28:166–72. [PubMed: 17349698]
78. Kleinridders A, Cai W, Cappellucci L, et al. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc Natl Acad Sci USA.* 2015; 112:3463–8. [PubMed: 25733901]
79. Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. *Br J Psychiatry Suppl.* 2004; 47:S67–71. [PubMed: 15056596]
80. Fernandez-Egea E, Bernardo M, Parellada E, et al. Glucose abnormalities in the siblings of people with schizophrenia. *Schizophr Res.* 2008; 103:110–3. [PubMed: 18514487]
81. Kirkpatrick B, Miller BJ, Garcia-Rizo C, Fernandez-Egea E, Bernardo M. Is abnormal glucose tolerance in antipsychotic-naïve patients with nonaffective psychosis confounded by poor health habits? *Schizophr Bull.* 2012; 38:280–4. [PubMed: 20558532]

82. Kirkpatrick B, Fernandez-Egea E, Garcia-Rizo C, Bernardo M. Differences in glucose tolerance between deficit and nondeficit schizophrenia. *Schizophr Res.* 2009; 107:122–7. [PubMed: 19046857]
83. Chen S, Broqueres-You D, Yang G, et al. Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naïve first-episode patients with schizophrenia. *Psychiatry Res.* 2013; 210:825–9. [PubMed: 24113122]
84. Fan X, Liu E, Pristach C, Goff DC, Henderson DC. Higher fasting serum insulin levels are associated with a better psychopathology profile in acutely ill non-diabetic inpatients with schizophrenia. *Schizophr Res.* 2006; 86:30–5. [PubMed: 16750348]
85. Takayanagi Y, Cascella NG, Sawa A, Eaton WW. Diabetes is associated with lower global cognitive function in schizophrenia. *Schizophr Res.* 2012; 142:183–7. [PubMed: 23031192]
86. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999; 156:1686–96. [PubMed: 10553730]
87. Sharma E, Rao NP, Venkatasubramanian G. Association between antipsychotic-induced metabolic side-effects and clinical improvement: a review on the evidence for “metabolic threshold”. *Asian J Psychiatr.* 2014; 8:12–21. [PubMed: 24655620]
88. Meltzer HY. Treatment-resistant schizophrenia—the role of clozapine. *Curr Med Res Opin.* 1997; 14:1–20. [PubMed: 9524789]
89. West FH, Bond ED, Shurley JT, Meyers CD. Insulin coma therapy in schizophrenia; a fourteen-year follow-up study. *Am J Psychiatry.* 1955; 111:583–9. [PubMed: 13228713]
90. Jones K. Insulin coma therapy in schizophrenia. *J R Soc Med.* 2000; 93:147–9. [PubMed: 10741319]
91. Kohen D. Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry Suppl.* 2004; 47:S64–6. [PubMed: 15056595]
92. Oriot P, Feys JL, Mertens de Wilmars S, et al. Insulin sensitivity, adjusted beta-cell function and adiponectinaemia among lean drug-naïve schizophrenic patients treated with atypical antipsychotic drugs: a nine-month prospective study. *Diabetes Metab.* 2008; 34:490–6. [PubMed: 18693056]
93. Arango C, Giraldez M, Merchan-Naranjo J, et al. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. *J Am Acad Child Adolesc Psychiatry.* 2014; 53:1179–90. [PubMed: 25440308]
94. Seeman P. All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2(high) receptors. *CNS Neurosci Ther.* 2011; 17:118–32. [PubMed: 20560996]
95. Seeman P, Lee T. Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science.* 1975; 188:1217–9. [PubMed: 1145194]
96. Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Arch Gen Psychiatry.* 1988; 45:71–6. [PubMed: 2892477]
97. Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S. The D2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. *Life Sci.* 1995; 57:L103–7.
98. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry.* 2000; 157:514–20. [PubMed: 10739409]
99. Pilowsky LS, Costa DC, Ell PJ, Murray RM, Verhoeff NP, Kerwin RW. Antipsychotic medication, D2 dopamine receptor blockade and clinical response: a 123I IBZM SPET (single photon emission tomography) study. *Psychol Med.* 1993; 23:791–7. [PubMed: 7901865]
100. Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry.* 2001; 50:873–83. [PubMed: 11743942]
101. Demjaha A, Egerton A, Murray RM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry.* 2014; 75(5):e11–3. <http://dx.doi.org/10.1016/j.biopsych.2013.06.011>. Epub 2013 Jul 25. [PubMed: 23890739]

102. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry*. 2012; 169:1203–10. [PubMed: 23034655]
103. Jablensky A. Subtyping schizophrenia: implications for genetic research. *Mol Psychiatry*. 2006; 11:815–36. [PubMed: 16801952]
104. Nakajima S, Takeuchi H, Plitman E, et al. Neuroimaging findings in treatment-resistant schizophrenia: a systematic review: lack of neuroimaging correlates of treatment-resistant schizophrenia. *Schizophr Res*. 2015; 164(1–3):164–75. <http://dx.doi.org/10.1016/j.schres.2015.01.043>. Epub 2015 Feb 13. [PubMed: 25684554]
105. Konner AC, Hess S, Tovar S, et al. Role for insulin signaling in catecholaminergic neurons in control of energy homeostasis. *Cell Metab*. 2011; 13:720–8. [PubMed: 21641553]
106. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003; 160:13–23. [PubMed: 12505794]
107. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis—linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005; 79:59–68. [PubMed: 16005191]
108. Plitman E, Nakajima S, de la Fuente-Sandoval C, et al. Glutamate-mediated excitotoxicity in schizophrenia: a review. *Eur Neuropsychopharmacol*. 2014; 24:1591–605. [PubMed: 25159198]
109. Nakazawa K, Zsiros V, Jiang Z, et al. GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology*. 2012; 62:1574–83. [PubMed: 21277876]
110. Salavati B, Rajji TK, Price R, Sun Y, Graff-Guerrero A, Daskalakis ZJ. Imaging-based neurochemistry in schizophrenia: a systematic review and implications for dysfunctional long-term potentiation. *Schizophr Bull*. 2015; 41:44–56. [PubMed: 25249654]
111. Hanson DR, Gottesman II. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. *BMC Med Genet*. 2005; 6:7. [PubMed: 15707482]

Fig. 1.

Insulin acting on insulin receptors in the ventral tegmental area can inhibit dopamine neurons and dopamine release into the striatum. The figure has been adapted from Palmiter [24] *TRENDS Neurosci.*