Chapter 1
Insulin Resistance in Schizophrenia

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Abstract Schizophrenia and diabetes have been known to be linked disorders for decades. One reason is due to the fact that a major side effect of antipsychotic medication treatment is metabolic syndrome, which increases the risk of the patients developing type 2 diabetes and cardiovascular disorders. However, signs of metabolic syndrome in schizophrenia patients were identified more than 100 years ago, even before the development of antipsychotic drugs. This suggests that schizophrenia itself predisposes towards diabetes and, in turn, insulin resistance may be a risk factor for the development of schizophrenia. This review summarizes the findings surrounding this issue and places them into context with regards to increasing our understanding of the aetiology of schizophrenia and in support of biomarker and drug discovery efforts.

Keywords Schizophrenia · Psychosis · Insulin resistance · Antipsychotic · Antidiabetic · Biomarker

1.1 Introduction

Schizophrenia is a debilitating psychiatric disorder ranked as number 15 on the list of years lived with disability (YLD) [1]. It is characterised by disturbances in perception, cognition and behaviour, resulting in impaired functioning in social settings such as interpersonal relationships, parenting and self-care [2]. It is considered to be a polygenic disorder triggered by one or more environmental risk factors, although these have not been fully elucidated due to the complex nature and heterogeneity of the disorder [3]. Individuals suffering from schizophrenia are more likely to develop co-morbidities such as obesity, type 2 diabetes and metabolic syndrome [4]. These can have a negative impact on life-expectancy as patients with chronic

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schziophrenia have a greater than two-fold higher risk of death, mostly from cardiovascular and metabolic diseases, compared to the general population [5]. This translates to a shortened life expectancy of approximately 14.5 years [6].

The weight gain associated with antipsychotic drug treatment has long been recognized as a health concern [7]. There have been numerous reports on patients who received antipsychotic drugs as far back as their inception in the 1950s and decades later it became evident that the second generation antipsychotic drugs, such as clozapine and olanzapine, were linked with disrupted glucoregulation and the onset of type 2 diabetes. As weight gain and metabolic syndrome are common responses to antipsychotic drug treatment, patients with schizophrenia have a high risk of adverse cardiovascular and cerebrovascular responses, which accounts for part of the high mortality rate [5]. For these reasons, all antipsychotic drugs now have a warning on their labels that their use may be associated with metabolic risks [8].

Although the prevalence of metabolic syndrome is higher in schizophrenia patients treated with antipsychotics, a high rate of this syndrome has been reported to occur in first episode patients who had not yet received these medications [9, 10]. A link between schizophrenia and abnormal glucose metabolism was reported as far back as the late nineteenth century through a study which revealed an increased prevalence of diabetes in families with a history of insanity [11]. Furthermore, some patients with schizophrenia require relatively high doses of insulin, suggesting a degree of insulin resistance [12]. More recently, investigations beginning in the 2000s showed that there was an increased frequency of impaired glucose tolerance, insulin resistance and hyperinsulinaemia in antipsychotic naive first episode patients [13–17].

This review discusses the findings surrounding metabolic syndrome in both antipsychotic-naive first episode and antipsychotic-treated schizophrenia patients with a view to increasing our understanding of the aetiology and progression of schizophrenia. It will also describe the implications on identification of potential novel biomarkers for improved stratification of patients, identification of novel drug targets and treatment strategies. This will enable a personalised medicine approach so that individuals suffering from schizophrenia may be offered earlier and more targeted treatment options for the best possible treatment outcomes.

1.2 Insulin Resistance and Metabolic Syndrome Associated with Antipsychotic Treatment

Since the discovery of clozapine in the 1970s and the subsequent development of other second generation antipsychotics, there has been a noticed improvement and significant recovery of some schizophrenia patients in terms of cognition and psychotic symptoms, along with their increased integration into society [18]. However, these benefits have been overshadowed by potential side effects, such as the risk of agranulocytosis, weight gain and related complications. Schizophrenia patients

have a decreased life expectancy due to increased incidence of co-morbidities such as metabolic syndrome [5, 6] and many of these effects are known to be induced by antipsychotic treatment [19, 20]. These drugs are used to treat individuals with first onset or refractory schizophrenia [21] and two of these, olanzapine and clozapine, are thought to be the most efficacious [22, 23]. However, these two drugs are also the most likely to lead to weight gain and disrupted glucose and lipid metabolism [21, 24]. A meta-analysis published in 2013 on the prevalence of metabolic syndrome in schizophrenia patients found that the overall rate of this syndrome was 32.5% with the highest rates observed for those receiving clozapine at 51.9%, compared to 20.2% for patients who were not receiving medication [25]. A 10-year naturalistic study of schizophrenia and schizoaffective disorder patients who had received clozapine found that 43% developed diabetes with an average weight gain of 13.5 kg [20]. Furthermore, there was a cardiovascular disease-related mortality rate of 9% and this was significantly correlated with body mass index (BMI). However, a more recent meta analysis found a mortality rate from any cause of only 0.6% in schizophrenia patients who had received clozapine for more than 1 year [26]. The reasons for this discrepancy are not clear.

Clozapine binds to the 5-hydroxytryptamine $(HT)_{2A/2C}$ receptor subtypes and has high affinity for several dopaminergic receptors. Unlike most first generation antipsychotics, clozapine only shows weak antagonism at the dopamine D_2 receptor, which was widely assumed to be a key modulator of neuroleptic activity [27]. Most second generation antipsychotics have multiple molecular targets, including adrenergic, histaminergic, serotonergic and muscarinic receptors, with the noted lower antagonistic effects on dopamine D_2 receptors compared to the first generation antipsychotic drugs [28]. The weight gain associated with these drugs has been linked to antagonism of the histaminergic H_1 receptor as meta-analyses have shown a significant correlation between risk of weight gain and histamine H_1 receptor affinity [29, 30]. In turn, this can increase the risk of insulin resistance which can lead to increased risk of type 2 diabetes and cardiovascular disease [31, 32]. Other studies have reported elevations in circulating leptin levels in patients receiving antipsychotics [33]. The secretion of this hormone is a normal response to increased fat deposition. However, the normal associated suppression of food intake by this hormone does not occur in patients receiving antipsychotic drugs. This suggests that the signalling mechanisms that regulate food intake in the hypothalamus may be disrupted by antipsychotic drug action.

There are several factors associated with antipsychotic treatment that appear to have an influence on weight gain, including dosage and duration of treatment, past and current medications, age and gender, stress, smoking, presence of other diseases, genetic predisposition, diet and physical activity [34]. A randomized double-blind prospective study of olanzapine, risperidone and haloperidol treatment found significant weight gain induced by by the treatment in drug-naive patients with first-episode schizophrenia and identified risk factors for this side effect including a lower BMI and use of olanzapine [35]. A recent study found that the greatest influential factor was the choice of antipsychotic drug [36]. A study from 2015 supports the hierarchical ranking of second generation antipsychotics found in previous studies [37]. This

Table 1.1 Molecules identified by Schwarz et al. [39] linked with the increased BMI following treatment of schizophrenia patients for 6 weeks with second generation antipsychotics

Protein	Function
Apolipoprotein C III	Lipid transport
Apolipoprotein H	Lipid transport
Epidermal growth factor	Growth factor
Follicle stimulating hormone	Hormone
Interleukin-18	Inflammation
Interleukin-25	Inflammation
Interleukin-6 receptor	Inflammation
Matrix metalloproteinase I	Inflammation
Placenta growth factor	Growth factor
Thyroid stimulating hormone	Hormone

study found that clozapine and olanzapine had the highest risk, followed by amisulpride, asenapine, iloperidone, paliperidone, quetiapine, risperidone and sertindole as having a medium risk, and aripiprazole, lurasidone and ziprasidone with the lowest risk. This was consistent with an earlier retrospective study which analyzed the weight gain propensity of different antipsychotics. Treatment with clozapine and olanzapine resulted in the most weight gain, while risperidone was intermediate and sertindole was the lowest [38]. In line with the above studies, the respective affinities of these antipsychotics for the histamine H_1 receptor appeared to be the most robust correlated factor with the weight gain.

Along with the above attributes, a number of molecular predictors of weight gain have been identified. Schwarz et al. used a multiplex immunoassay approach to test whether or not serum molecules measured before initiation of treatment could be associated with the subsequent weight gain following a 6-week treatment with antipsychotics [39]. They found that the baseline levels of 10 serum molecules associated with lipid transport, inflammation, growth factor and hormone signalling were significantly correlated with the change in BMI (Table 1.1). In addition to weight gain, they found a significant increase in triglyceride levels and insulin:glucose ratios, consistent with known metabolic side effects of second generation antipsychotic treatments [21, 24, 40, 41]. Another study found that lower baseline levels of leptin predicted the greatest increase in BMI in female schizophrenia patients treated with olanzapine for up to 1 year [42]. This effect was not observed in the case of male schizophrenia patients.

1.3 Insulin Resistance in First Onset Antipsychotic Naive Schizophrenia Patients

Although insulin resistance and other metabolic symptoms can be associated with treatment with second generation antipsychotics, there is substantial evidence which has demonstrated that these effects were seen in schizophrenia patients even before

the original development and availability of antipsychotics [12] and recent studies conducted within the last two decades have confirmed that first onset schizophrenia patients can exhibit metabolic abnormalities including impaired glucose tolerance and insulin resistance even before these individuals were administered antipsychotics [13, 14]. In a study published in 2003, Ryan and Colleagues found that 4 out of 26 hospitalized first onset schizophrenia patients had impaired fasting glucose tolerance before the administration of antipsychotics compared to none of the healthy volunteers [13]. They also found that the schizophrenia patients had significantly higher fasting plasma levels of glucose, insulin and cortisol and they also had an elevated homeostatic model assessment of insulin resistance (HOMA-IR) reading, compared with the controls. In a cross sectional study carried out in 2007, Spelman et al. found that 4 out of 38 non-obese individuals who fulfilled the criteria for first episode drug-naive schizophrenia had impaired fasting glucose tolerance compared with 8 out of 44 of the unaffected relatives of these patients and none out of the 38 healthy controls [14]. Hyperinsulinaemia or insulin resistance have also been found in antipsychotic-free chronic schizophrenia subjects [33, 43], consistent with a study of schizophrenic patrients from the 1966 Northern Finland Birth Cohort which identified insulin resistance in 45% and 33% of the total and non-medicated schizophrenia patients, respectively [44]. Another investigation found impaired glucose tolerance in drug-naïve schizophrenia patients compared to matched controls and separate study found that a similar group of patients had hepatic insulin resistance through the use of a hyperinsulinaemic clamp method [45].

The finding of a high prevalence of impaired glucose tolerance in the non-affected relatives supports the likelihood of a shared environmental or genetic background in these effects, as described in recent reviews [9, 46–49]. The above findings were not supported by a study published in 2008, which found that first episode patients with schizophrenia did not differ from healthy controls in their baseline measurements of glucose, lipids or prevalence of diabetes [50]. In contrast, the results of a study of 160 individuals with schizophrenia who presented to the Early Psychosis Intervention Programme in Singapore showed significantly lower BMI, low density lipoprotein (LDL) and cholesterol, with higher prevalence of diabetes compared to controls [51]. More recent studies found a cardiometabolic risk factor signature in drug-naive adolescents and young adults with first onset psychosis [52].

A study published in 2010 in Molecular Psychiatry showed for the first time that first onset schizophrenia patients who had not received antipsychotics at the time of their admission had high circulating levels of insulin-related molecules [16]. To obtain sufficient numbers of antipsychotic naive patients, subjects were recruited from four independent clinical centres over 2006–2008 along with matched controls. Although glucose levels were not significantly altered, the first onset patients (n = 66) showed increased levels of insulin, proinsulin, des 31,32 proinsulin and C-peptide compared to the levels seen in controls (n = 78). All of these molecules are derived from the pathway involved in proinsulin to insulin conversion and are therefore packaged into the same secretory granules for storage and release along with the mature insulin molecule [53]. For this reason, this study and a follow up investigation showed that first onset antipysychotic naive schizophrenia patients

also had high circulating levels of the secretory granule protein chromogranin A, compared to controls [16, 17]. This indicated that the insulin-producing cells (β cells) in pancreatic islets may be under increased secretory demand in at least some schizophrenia patients. The increased levels of insulin and elevated HOMO-IR have now been confirmed in recent studies from different research groups [11, 54, 55]. In one of these studies, Steiner et al. tested whether or not insulin resistance in first onset schizophrenia patients can be distinguished from stress and medication effects [54]. They found that insulin resistance, serum cortisol, and urinary stress hormones metanephrine and normetanephrine were increased in patients compared to controls but no significant correlations were found between HOMO-IR and the levels of the stress hormones, smoking or clinical symptoms. However, HOMA-IR showed a strong correlation with BMI. Taken together, these findings supported the case that the effects on signalling are related to schizophrenia as opposed to being a side-effect of antipsychotic treatment, hormonal stress axis activation or lifestyle factors.

1.4 Effects of Insulin Resistance in Schizophrenia on Other Neuroendocrine Systems

In addition to disturbances in insulin-related pathways, there have been a number of reports related to altered hypothalamic pituitary adrenal (HPA) and hypothalamic pituitary gonadal (HPG) axes in first onset and chronic schizophrenia subjects [56–58].

1.4.1 Growth Hormone

Insulin and growth hormone share many elements of the same signalling pathways such as the growth hormone receptor/Janus kinase 2/signal transducer and activator of transcription (GHR/JAK2/STAT), GHR/JAK2/SHC-transforming protein 1 (SHC)/ mitogen-activated protein kinase (MAPK) and growth hormone/insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathways [59]. This suggests that there may be some elements of potential cross-talk. For example, one study found that insulin has a direct, inhibitory effect on basal and stimulated growth hormone secretion by GH3 cells [60]. Consistent with this finding, a number of studies have found changes in growth hormone levels in schizophrenia patients. A multiplex immunoassay profiling study found decreased levels of growth hormone in serum from first and recent onset schizophrenia patients compared to controls [17]. Likewise, a combined two-dimensional difference gel electrophoresis (2D-DIGE) and combination of liquid chromatography tandem mass spectrometry analysis found decreased levels of growth hormone A-chain in

postmortem pituitary glands from schizophrenia patients, compared with the levels of growth hormone A-chain in postmortem pituitaries from controls [61]. A case report found that 2 males and 1 female diagnosed with schizophrenia developed acromegaly due to a growth hormone-secreting pituitary macroadenoma [62]. This may be consistent with the above findings considering a possible desensitization of growth hormone signalling pathways related to neuronal functions, due to consistently elevated levels of this hormone. The association of acromegaly with schizophrenia has been well documented [63–68]. In addition, a sleep study of schizophrenia patients found prolonged sleep onset latency, increased time awake and decreased stage 2 sleep, with elevated growth hormone release following growth hormone releasing hormone stimulation, compared to controls [69].

1.4.2 Cortisol

In 2003, Ryan et al. showed that some first-episode, antipsychotic-naive schizophrenia patients have higher circulating levels of insulin and cortisol compared to healthy control subjects [13]. This was confirmed in a multiplex immunoassay study carried out in 2011 which found elevated serum insulin and cortisol levels (along with other hormones) in first onset schizophrenia patients [17]. Other studies have described that psychiatric disorders such as depression can be associated with insulin resistance and changes in the diurnal cortisol curve [70]. In addition, a comparison of ultra high-risk (UHR) and antipsychotic-naïve first-episode schizophrenia patients with matched controls using the Perceived Stress Scale and the Recent Life Events Questionnaire and measurements of day-time saliva cortisol levels found that symptom severity was correlated with altered cortisol levels in the UHR patients [71]. This finding suggested that altered cortisol levels play a role only in the early phases of the disease. The exact mechanism regulating the relationship between insulin and cortisol secretion remains to be determined. A meta-analysis carried out by Pillinger et al. assessed insulin resistance and found an elevated homeostatic model assessment of insulin resistance (HOMA-IR) in drug-naïve first-episode schizophrenia patients compared to controls but they highlighted activation of the stress axis and lifestyle factors as potential confounding factors [11]. However, we found recently that insulin resistance and altered glucose metabolism in first-episode schizophrenia patients were related to schizophrenia, as opposed to being a consequence of antipsychotic treatment, body composition or stress axis activation [54].

1.4.3 Gonadal Steroids

A number of studies have shown that several steroid hormones of the HPG axis can affect the onset and progression of schizophrenia. For example, estrogen has been found to be neuroprotective [72] and this may explain the typically later onset of

schizophrenia with less extreme symptoms in females compared to males [73, 74]. A number of studies have now shown that estrogen supplementation can lead to an abatement of symptoms in both males and females with schizophrenia although further research is required to develop newer and safer drugs which target this pathway [75]. A study of first onset schizophrenia males revealed significantly lower serum levels of estradiol, estrone, total testosterone and free testosterone, compared to controls [76]. These findings were consistent with those of a later study which showed that testosterone levels in male schizophrenia patients were negatively associated with Positive and Negative Syndrome Scale (PANSS ratings) scores with no correlation found for female patients [77].

1.4.4 Other Hormones

In addition to the changes described in circulating insulin, growth hormone and cortisol levels described above, we found that the serum concentrations of chromogranin A, pancreatic polypeptide, progesterone and prolactin were increased in first onset schizophrenia patients (Fig. 1.1) [17]. As many hormones are influenced by ultradian or circadian rhythms, the secretion of these molecules is likely to be coordinated through an oscillatory feedforward–feedback relationship between the islets of Langerhans and other components of the HPA and HPG systems [78]. For example, higher serum prolactin levels have been shown to be associated with insulin resistance in men [79] and hypoglycaemia has been linked to a decrease in the amplitude of growth hormone pulsatility [80]. In addition, studies of high fat diet-induced obese rats showed both hyperinsulinemia and increased progesterone levels [81]. The changes found in chromogranin A may also be of interest since this molecule is found in many neuroendocrine cell types, where it undergoes limited proteolytic processing to produce smaller functional peptides including vasostatin, which has been shown to inhibit vasoconstriction in blood vessels [82], catestatin, which inhibits secretion from catecholaminergic adrenal chromaffin cells [83], and pancreastatin, which inhibits insulin secretion [84, 85]. The other hormone found to be altered in the schizophrenia patients in the multiplex immunoassay study was pancreatic polypeptide [17]. Previous studies have shown that this islet hormone is involved in regulation of energy balance [86]. These findings all demonstrate potential links to the metabolic disturbances found in both first onset and chronic schizophrenia patients.

1.5 Conclusions

It is clear that schizophrenia patients suffer from metabolic abnormalities along with the psychiatric symptoms. This in true in the case of both first onset patients prior to treatment and in more chronic patients who have received medications over

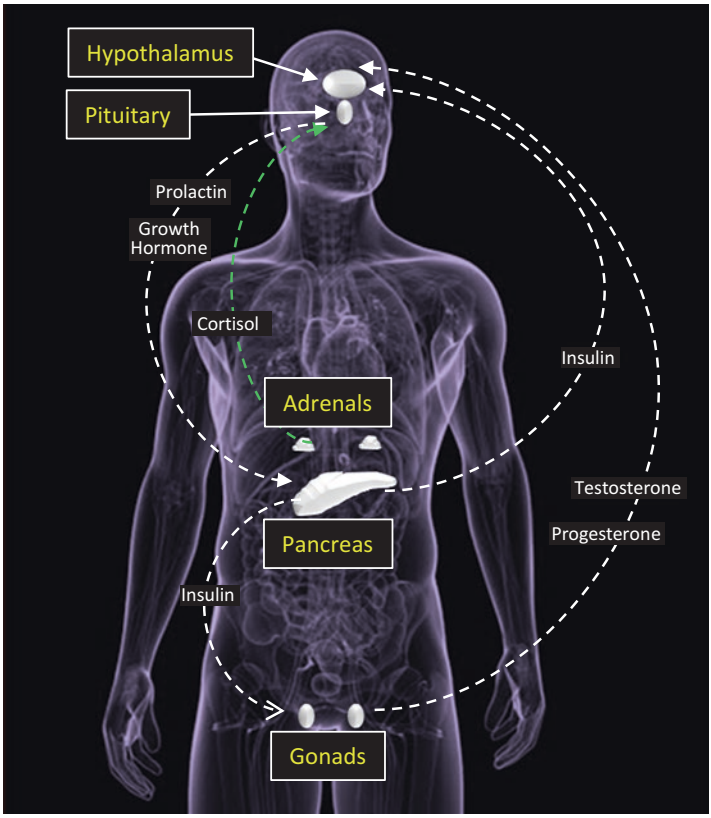

Fig. 1.1 Diagram showing the hormonal pathways known to be affected in schizophrenia

both short- and long-term periods. There is some evidence for the effectiveness of physical activity interventions for people with schizophrenia although the greatest barrier appears to be the poor rates of compliance [87]. One possible way of increasing compliance is through the incorporation of an achievable goal into the exercise program such as shown in a study which used the incentive of training for a 5 kilometer race [88]. In this study, 11 out of the 17 patients participated in all of the training sessions and 14 participated in the actual event. A study carried out in 2016 found a compliance rate of greater than 80% with other health benefits through the use of active-play video games to improve aerobic fitness [89]. One study of 24 schizophrenia patients who participated in an individually tailored 90 min outdoor cycling session per week for 3 months found a high level of adherence with short-term benefits on self-esteem, positive relationship, global function and quality of life [90]. However, long-term benefits were maintained only in the case of positive relationship change. These findings suggest that physical exercise can be effective to improve physical and mental health of individuals with schizophrenia. However, further strategies at increasing compliance are essential.

Given the likelihood of improved compliance, the use of oral medications for control of the metabolic symptoms has received increasing attention. With antipsychotic use, there have been a number of studies which have used a combination therapy with metformin for the management of weight gain [91–93]. Metformin is a biguanide compound which has been widely used in the treatment and management of type 2 diabetes mellitus [94]. Metformin treatment results in mild weight loss and reduces fasting glucose, insulin and triglyceride levels via suppression of hepatic gluconeogenesis and increased peripheral insulin sensitivity while increasing high-density lipoprotein [94–96]. Although there is substantial evidence of weight loss associated with metformin of obese and overweight people who are already taking antipsychotics such as clozapine, there have been no published studies which have investigated the effect of metformin in attenuating weight gain if given at the time of antipsychotic initiation. With this in mind, a 24-week double-blind placebo-controlled trial is planned to study the effects of metformin given at the time of clozapine treatment commencement in 86 people with primary outcome measurements of endpoint compared to initial body weight between the metformin and placebo groups [97]. The researchers also plan to examine potential biomarkers associated with weight change among the trial subjects.

One investigation reviewed the effects of hormones or drugs that target the HPA and gonadal axes as potential candidates for improving cognition in psychiatric disorders [58]. This identified 12 studies that considered the effects of HPA axis drugs and 14 that targeted the HPG axis. Trials reporting positive results were found for treatments of bipolar disorder, major depressive disorder and schizophrenia. In the case of schizophrenia this included the drug dehydroepiandrosterone, a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids [98, 99], raloxifene, a drug used in the treatment of osteoporosis in post-menopausal women [100], and pregnenolone, which is a precursor in the biosynthesis of most steroind hormone [101]. The authors also identified at least two positive replication studies for the effects of raloxifene and pregnenolone.

It is concluded that psychiatric disorders such as schizophrenia are linked with metabolic disorders such as insulin resistance and perturbations of the HPA and HPG axes. These disturbances can occur at first onset in drug-naive patients as well as in chronic patients who have been treated with psychiatric medications for varying periods. However, these problems have lent themselves to further studies in search of biomarkers and novel drug targets. This search may eventually lead to the development of tools for improved patient stratification and targeted treatment of patients suffering from schizophrenia in line with personalized medicine approaches [102–105]. It is anticipated that this will lead to improvements in the lives of individuals with schizophrenia as well as their families, along with reduced costs for societies and healthcare services throughout the world.

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