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REVIEW

Schizophrenia: Metabolic aspects of aetiology, diagnosis and future treatment strategies

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Summary Despite decades of research, the pathophysiology and aetiology of schizophrenia remains incompletely understood. The disorder is frequently accompanied by metabolic symptoms including dyslipidaemia, hyperinsulinaemia, type 2 diabetes and obesity. These symptoms are a common side effect of currently available antipsychotic medications. However, reports of metabolic dysfunction in schizophrenia predate the antipsychotic era and have also been observed in first onset patients prior to antipsychotic treatment. Here, we review the evidence for abnormalities in metabolism in schizophrenia patients, both in the central nervous system and periphery. Molecular analysis of *post mortem* brain tissue has pointed towards alterations in glucose metabolism and insulin signalling pathways, and blood-based molecular profiling analyses have demonstrated hyperinsulinaemia and abnormalities in secretion of insulin and co-released factors at first presentation of symptoms. Nonetheless, such features are not observed for all subjects with the disorder and not all individuals with such abnormalities suffer the symptoms of schizophrenia. One interpretation of these data is the presence of an underlying metabolic vulnerability in a subset of individuals which interacts with environmental or genetic factors to produce the overt symptoms of the disorder. Further investigation of metabolic aspects of schizophrenia may prove critical for diagnosis, improvement of existing treatment based on patient stratification/personalised medicine strategies and development of novel antipsychotic agents.

Contents

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1. Introduction

Schizophrenia is a psychiatric disorder ranked among the world's top ten causes of long-term disability, characterised by perceptual, cognitive and behavioural disturbances, culminating in impaired functioning in various social settings such as interpersonal relationships, parenting and self-care. It is now considered to be a polygenic disorder with a variety of environmental risk factors, although the aetiology and pathophysiology have not been fully elucidated.

At the neuropathological level, schizophrenia has no single diagnostic feature. In general, it appears to be characterised by synaptic deficits, alterations in glutamate and dopamine neurotransmission and hypofrontality. In addition to central nervous system effects, peripheral abnormalities have been reported including an impaired skin flush response to niacin administration (Nilsson et al., 2006), increased nailfold plexus visibility and other minor physical abnormalities (Compton and Walker, 2009), and various immune system abnormalities. Therefore, emerging theories on the aetiology must take into account the systemic nature of the disorder.

Schizophrenia patients have a shortened lifespan and excessive mortality resulting from causes in addition to suicide and accidental death. Approximately 60% of deaths in schizophrenia can be attributed to effects of physical illness (Brown, 1997) or metabolic syndrome. Schizophrenia subjects demonstrate several hallmark features of these conditions including hypertension, increased risk of cardiovascular disease, dyslipidaemia, high levels of visceral fat deposition, insulin resistance, impaired glucose tolerance and type 2 diabetes mellitus (Bushe and Holt, 2004). The higher prevalence of metabolic syndrome associated with mental disorders is generally dependent on factors such as the average body mass index (BMI), age and ethnicity of the population in question (Bermudes et al., 2006). However, assessment of metabolic syndrome in schizophrenia patients has been complicated due to the fact that commonly used second generation antipsychotics such as olanzapine and clozapine can induce metabolic conditions such as weight gain and type 2 diabetes mellitus. These side-effects contribute to a high rate of treatment discontinuation, and have been extensively discussed in the literature before (Koller and Doraiswamy, 2002; Meyer et al., 2008). However, there are numerous reports of insulin resistance and impaired glucose tolerance in schizophrenic subjects in the scientific literature which predate the widespread use of antipsychotics (Bushe and Holt, 2004). In addition, recent studies have shown that metabolic abnormalities can occur in first episode antipsychotic-naïve patients, suggesting that such abnormalities play a role in the pathophysiology and onset of the disease (Ryan et al., 2003; Guest et al., 2010). Metabolic dysfunction has not only been reported in schizophrenia but also in cases of bipolar disorder, major depressive disorder and Alzheimer's disease. These disorders are heterogeneous with overlapping symptoms and are currently differentiated only by clinical assessment. A better understanding of the role of metabolic perturbations in schizophrenia and the relationship of these with psychiatric symptoms could result in improved diagnostic and treatment strategies based on a personalised medicine approach.

Although the brain constitutes only 2% of body mass, it has been estimated that it can consume up to 65% of total daily glucose ingestion supplied via the periphery (Peters and Langemann, 2009). Glucose homeostasis is controlled ultimately by central nervous system (CNS) mechanisms mediated by insulin and leptin signalling and through the effects of other components of the diffuse neuroendocrine system. Thus peripheral and CNS metabolic events are linked at a fundamental level.

Here, we review (i) recent evidence for peripheral disturbance in glucose metabolism in schizophrenia, with particular focus on studies in drug-naive or drug-free patients, (ii) recent findings from our laboratory concerning production of insulin and other molecules related to insulin secretion and insulin action in schizophrenia, and (iii) evidence for

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