The International Journal of Biochemistry & Cell Biology 80 (2016) 19–30

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review article

Metabolic pathways in the periphery and brain: Contribution to mental disorders?

Andrzej Nagalski [1], Kamil Kozinski [1], Marta B. Wisniewska [*,1]

Laboratory of Molecular Neurobiology, Centre of New Technologies, University of Warsaw, 02-097 Warsaw, Poland

ARTICLE INFO

Article history:
Received 16 May 2016
Received in revised form
14 September 2016
Accepted 15 September 2016
Available online 17 September 2016

Keywords:
Serious mental disorders
Diabetes
Genetic risk factors
Metabolism
Insulin

ABSTRACT

The association between mental disorders and diabetes has a long history. Recent large-scale, well-controlled epidemiological studies confirmed a link between diabetes and psychiatric illnesses. The scope of this review is to summarize our current understanding of this relationship from a molecular perspective. We first discuss the potential contribution of diabetes-associated metabolic impairments to the etiology of mental conditions. Then, we focus on possible shared molecular risk factors and mechanisms. Simple comorbidity, shared susceptibility loci, and common pathophysiological processes in diabetes and mental illnesses have changed our traditional way of thinking about mental illness. We conclude that schizophrenia and affective disorders are not limited to an imbalance in dopaminergic and serotoninergic neurotransmission in the brain. They are also systemic disorders that can be considered, to some extent, as metabolic disorders.

1. Introduction

The high prevalence between schizophrenia (SCZ) and diabetes was first observed by Sir Henry Maudsley in 1879. In the 1920s and 1930s, a series of preliminary studies of small groups of patients revealed higher glucose levels, diabetes-like glucose tolerance curves, and frequent insulin resistance in patients with "dementia precox," which SCZ was referred to at the time (Kohen, 2004). Also at that time, insulin-shock therapy was introduced by Manfred Sakel to treat dementia precox by inducing coma and convulsions (Sakel, 1994). Soon afterward, clinicians noticed that some patients required more insulin to achieve seizures (Meduna et al., 1942), further corroborating the link between diabetes and SCZ.

In recent decades, many potential biological risk factors and mechanisms of diabetes and serious mental illnesses (SMIs) have been proposed. This was accompanied by an expansion of the identification of genetic risk factors based on genome-wide association studies (GWASs) and other large cohort analyses. Combining genetic and biological risk factors between diabetes and SMIs led to tentative evidence that both diseases might share a common pathophysiological nexus.

This review examines and discusses the potential factors that are responsible for the observed comorbidity, including the effects of impaired glucose metabolism on brain function, genetic risk factors, and potential pathophysiological mechanisms.

1.1. Serious mental illnesses: schizophrenia, bipolar disorder, and major depression

Schizophrenia, bipolar disorder (BD), and major depression (MD) are three psychiatric disorders that are often described under the term SMIs. These disorders are separate disease entities with multifactorial and poorly understood etiology and heterogeneous symptoms (Insel, 2010; Kato, 2008; Kavanagh et al., 2015; Wong and Licinio, 2001). They are diagnosed according to established criteria, but the current biological and medical view is that they lie on a continuum with overlapping phenotypes. Major depression is characterized by low mood, anhedonia, fatigue, psychomotor retardation, ideas of guilt and unworthiness, and, in cases of psychotic depression, hallucinations. All of these symptoms occur

Abbreviations: ACCORD-MIND, Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes; BBB, blood-brain barrier; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; DISC1, disrupted in schizophrenia 1; GLUT, glucose transporter; GSK3, glycogen synthase kinase 3; GWAS, genome-wide association study; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; INSR, insulin receptor; MAPK, mitogen-activated protein kinase; MD, major depression; MRI, magnetic resonance imaging; NHGRI-EBI, National Human Genome Research Institute-European Bioinformatics Institute; NPY, neuropeptide Y; SCZ, schizophrenia; SMI, serious mental illness; T2D, type 2 diabetes; SNP, single-nucleotide polymorphism; TCF7L2, transcription factor 7-like 2; TNFα, tumor necrosis factor α.

* Corresponding author.
E-mail address: m.wisniewska@uw.edu.pl (M.B. Wisniewska).
[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.biocel.2016.09.012
1357-2725/

in BD and SCZ. In BD, the periods of depression alternate with periods of mania that manifest as heightened energy and mood. Schizophrenia is the most severe disorder of these three. Patients with SCZ suffer from negative and positive symptoms and cognitive impairments. Negative symptoms include anhedonia, flattened affect, and asociality. Positive symptoms include delusions, hallucinations, disorganized thinking and speech, agitation, and catatonia. Lying between these illnesses is schizoaffective disorder, which is a combination of positive symptoms and mood alterations. Serious mental illnesses are generally accepted to be caused by impairments in monoaminergic systems in the brain, and multiple genetic, biological, and social risk factors contribute to the development of these conditions (Green et al., 2015; Kato, 2008; Kavanagh et al., 2015). However, the mechanisms that link these risk factors with etiology and the actual manifestations of SMIs need to be discovered.

1.2. Type 2 diabetes

Diabetes is the most common metabolic disorder, occurring in one out of every 11 adults. It is characterized by chronically elevated glucose levels in the blood as a result of deficits in insulin secretion or insulin action (Tripathy and Chavez, 2010). In healthy people, high blood glucose levels after a meal induce the secretion of insulin by β-cells in the pancreas (Del Prato et al., 2002). Glucose is then absorbed from the blood by insulin-sensitive cells (primarily skeletal muscle cells, adipocytes, and liver cells) to be stored as glycogen or fat. This mechanism is disturbed in people with diabetes, ultimately leading to hyperglycemia, which is harmful to many organs and tissues (Tuomi et al., 2014). There are two main types of this disease. Type 2 diabetes (T2D) is the most common form of diabetes, which results from a reduction of the sensitivity of target organs to the actions of insulin (Tuomi et al., 2014). Such insulin resistance is followed by a failure of pancreatic β-cells to produce and secrete sufficient insulin. Similar to SMIs, T2D is a complex polygenic disorder that is triggered by both genetic and environmental risk factors, the pathophysiology of which is still not fully understood.

1.3. Comorbidity of diabetes and serious mental illnesses

Looking at the association between diabetes and SMIs, meta-analyses have shown that people who suffer from any of these three SMIs develop T2D at least two-times more often than the general population (Anderson et al., 2001; Annamalai and Tek, 2015; Asghar et al., 2007; Knol et al., 2006; Mezuk et al., 2008; Roy and Lloyd, 2012; Vancampfort et al., 2013). The prevalence of T2D in individuals with SMIs may be even higher. An estimated 70% of cases of T2D in people with SMIs are undiagnosed, contrasting with ~25-30% in the general population (Taylor et al., 2005; Voruganti et al., 2007).

Although the prevalence of T2D in SMIs is generally accepted, antipsychotics, mood-stabilizing medications, and an unhealthy lifestyle are often blamed for this comorbidity, rather than a direct link between these disorders. Numerous studies have addressed the problem of obesity, metabolic syndrome, and diabetes as side effects of psychoactive medications (Holt and Peveler, 2009; Rojo et al., 2015). Differentiating between the effects of antipsychotic medications and the medication-independent association between T2D and SMIs is difficult because virtually all psychiatric patients receive pharmaceutical treatment. Two pieces of evidence, however, corroborate the latter possibility (although they do not necessarily exclude the former). First, the bidirectional relationship between depression and T2D has been consistently reported (Chen et al., 2013; Pan et al., 2012; Rotella and Mannucci, 2013) and was recently supported by a significant genetic correlation (Kan et al., 2016). In SCZ (or BD), it is not possible to observe a bidirectional relationship because these diseases affect mostly young people who are unlikely to have established T2D. Nevertheless, several studies reported lower glucose tolerance in first-episode and drug-naive SCZ patients compared with matched controls (Enez Darcin et al., 2015; Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2016; Kirkpatrick et al., 2009; Ryan et al., 2003). For example, in a recent study of a sample of 84 SCZ and 98 matched healthy subjects, the average glucose level in a 2-h glucose tolerance test was approximately 30% higher in SCZ patients (Garcia-Rizo et al., 2016). Second, T2D is more prevalent not only in SCZ patients but also in their families (Foley et al., 2016; van Welie et al., 2013; Yang et al., 2012). To summarize, the association between SMIs and T2D might result from an impairment of glucose metabolism or shared genetic risk factors and pathophysiological mechanisms. This review considers both of these possibilities.

2. Role of glucose in physiological and pathological brain function

Numerous metabolic disorders, such as homocysteine metabolism disorders, urea cycle disorders, lipid storage disorders, and leukodystrophies, are rare but important causes of psychiatric disorders in adolescents and adults (Demily and Sedel, 2014). Therefore, changes in metabolism can have serious consequences on the central nervous system. These effects can range from psychosis, depression, and mania in cases of severe disruptions to periodic or subtle behavioral disturbances in cases of mild disruptions. Glucose metabolism is closely integrated with brain physiology, but unclear is whether dysregulated glucose metabolism can exert these kinds of effects.

2.1. Glucose energy metabolism in the brain

The brain demands high amounts of energy. Although the brain represents only ~2% of the mass of the human body, approximately 20% of the oxygen and 25% of the glucose that are consumed in the body are dedicated to brain function (Belanger et al., 2011). Two main processes contribute to the high energy demands of the brain: (*i*) maintenance and restoration of ion gradients that are dissipated by signaling processes, such as postsynaptic and action potentials, and (*ii*) the synthesis, uptake, and recycling of neurotransmitters (Alle et al., 2009; Harris et al., 2012; Mergenthaler et al., 2013). The overall energy budget of the brain is a result of intense coordination between the main cell types in the brain (i.e., neurons, astrocytes, and oligodendrocytes) and epithelial cells of cerebral blood vessels, which form the blood-brain barrier (BBB).

The obligatory fuel for the brain is glucose. The brain requires a constant supply of glucose because it can store only a small amount of glycogen in astrocytes (Brown et al., 2005; Sickmann et al., 2009; Wender et al., 2000). Glucose is transported across the BBB through the saturable and insulin-independent glucose transporter 1 (GLUT1), which is expressed on vascular endothelial cells (Bondy et al., 1992; Kobayashi et al., 1996). The uptake of glucose by glial cells is also facilitated by GLUT1, whereas neurons use another insulin-independent transporter, GLUT3, which has higher affinity for glucose and higher transport capacity (Bondy et al., 1992). During maturation in childhood or upon prolonged starvation, brain cells can utilize ketone bodies that are produced in the liver (Lutas and Yellen, 2013).

Different cell types in the brain have distinct metabolic profiles, which have been studied particularly for neurons and astrocytes (Belanger et al., 2011; Magistretti and Allaman, 2015) and are beginning to be elucidated for oligodendrocytes (Saab et al., 2013). Neurons sustain a high rate of oxidative metabolism compared