Progress in Neuro-Psychopharmacology & Biological Psychiatry xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Immune system and glucose metabolism interaction in schizophrenia: A chicken–egg dilemma

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ARTICLE INFO

Article history:
Received 28 July 2012
Received in revised form 15 September 2012
Accepted 22 September 2012
Available online xxxx

Keywords:
Glucose metabolism
Immune system
Lymphocytes
Microglia
Mononuclear phagocyte system
Schizophrenia

ABSTRACT

Impaired glucose metabolism and the development of metabolic syndrome contribute to a reduction in the average life expectancy of individuals with schizophrenia. It is unclear whether this association simply reflects an unhealthy lifestyle or whether weight gain and impaired glucose tolerance in patients with schizophrenia are directly attributable to the side effects of atypical antipsychotic medications or disease-inherent derangements. In addition, numerous previous studies have highlighted alterations in the immune system of patients with schizophrenia. Increased concentrations of interleukin (IL)-1, IL-6, and transforming growth factor-beta (TGF-β) appear to be state markers, whereas IL-12, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and soluble IL-2 receptor (sIL-2R) appear to be trait markers of schizophrenia. Moreover, the mononuclear phagocyte system (MPS) and microglial activation are involved in the early course of the disease. This review illustrates a "chicken–egg dilemma", as it is currently unclear whether impaired cerebral glucose utilization leads to secondary disturbances in peripheral glucose metabolism, an increased risk of cardiovascular complications, and accompanying pro-inflammatory changes in patients with schizophrenia or whether immune mechanisms may be involved in the initial pathogenesis of schizophrenia, which leads to disturbances in glucose metabolism such as metabolic syndrome. Alternatively, shared underlying factors may be responsible for the co-occurrence of immune system and glucose metabolism disturbances in schizophrenia.

1. Introduction

1.1. The influence of cardiovascular risk factors, diabetes and metabolic syndrome on the life expectancy of schizophrenic patients

The average life expectancy of individuals with schizophrenia is 12 to 15 years lower than that of the general population (van Os and Kapur, 2009). In addition to the higher suicide rate (approximately 5%), increased cardiovascular risk factors, such as types 1/2 diabetes and metabolic syndrome (defined by the American Heart Association as the presence of three or more of the following components: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, prothrombotic state, and pro-inflammatory state (Grundy et al., 2004)) are important factors contributing to the high mortality rate observed for patients with schizophrenia (Mitchell et al., in press). It is unclear whether this association is simply reflective of an unhealthy lifestyle (e.g., smoking, physical inactivity, poor diet, and obesity) or whether weight gain and impaired glucose tolerance in schizophrenic patients is due to the side effects of atypical antipsychotic medications, e.g., clozapine and olanzapine (Buchholz et al., 2008; Newcomer, 2007; Scheen and De Hert, 2007; Stahl et al., 2009).

Abbreviations: 5HT2C receptor, a subtype of 5-hydroxytryptamine receptor that binds the neurotransmitter serotonin; AgRP, agouti-related peptide; AITD, autoimmune thyroid disease; Akt1, a serine–threonine protein kinase; ARC, hypothalamic arcuate nucleus; BMI, Body-Mass-Index; CAPON, C-terminal PDZ domain ligand of neuronal nitric oxide synthase; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CD, cluster of differentiation; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; CSF, cerebrospinal fluid; DCs, dendritic cells; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; GLP-1, glucagon-like peptide-1; GLUT4, insulin-sensitive glucose transporter 4; IFN-γ, interferon-gamma; IGF-1, insulin-like growth factor-1; IL, interleukin; LMNA, gene encoding lamin A/C; MCH, melanin-concentrating hormone; MHC, Major Histocompatibility Complex; MPS, mononuclear phagocyte system; NPY, neuropeptide Y; NTS, nucleus tractus solitarii; PBMCs, peripheral blood mononuclear cells; PolyI:C, polyriboinosinic–polyribocytidilic acid; POMC, pro-opiomelanocortin; PYY, peptide YY; RGS4, regulator of G-protein signaling 4; S100B, a calcium-binding member of a family of proteins that are 100% soluble in ammonium sulfate at neutral pH; sIL-2R, soluble IL-2 receptor; sRAGE, soluble receptor for advanced glycation products; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; TRH, thyrotropin releasing hormone.

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http://dx.doi.org/10.1016/j.pnpbp.2012.09.016

However, impaired fasting glucose tolerance has also been reported in drug-naïve patients with schizophrenia (Chiu et al., 2009; Guest et al., 2010; Kirkpatrick et al., 2009; Ryan et al., 2003; Saddichha et al., 2008; Spelman et al., 2007) and their unaffected siblings (Fernandez-Egea et al., 2008), suggesting disease-inherent abnormalities in glucose metabolism. Moreover, as summarized by McIntyre et al. (2005), schizophrenia-related insulin resistance has already been observed in several studies that were performed in the pre-neuroleptic era. For instance, increased fasting glucose levels or abnormal oral glucose tolerance tests have been documented.

Interestingly, numerous previous studies have highlighted alterations in the immune system of patients with schizophrenia. Recent systematic reviews and meta-analyses have provided evidence of altered cytokine and inflammation-related kynurenine pathway metabolite levels in the peripheral blood of schizophrenic patients (Miller et al., 2011; Myint, 2012; Potvin et al., 2008; Schwarcz et al., 2012). Increased concentrations of interleukin (IL)-1, IL-6, and transforming growth factor-beta (TGF-β) appear to be state markers, whereas IL-12, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and soluble IL-2 receptor (sIL-2R) appear to be trait markers, as these protein levels remained elevated during acute exacerbations and following antipsychotic treatment (Miller et al., 2011). Moreover, it has been proposed that the mononuclear phagocyte system (MPS)/microglial activation is involved in the pathogenesis of early acute disease phases (Busse et al., 2012; Doorduin et al., 2009; Drexhage et al., 2010; Nikkila et al., 1995; Steiner et al., 2006, 2008; van Berckel et al., 2008). Recently, it has been identified that central nervous system (auto)antibodies directed against neurotransmitter receptors, such as NMDA glutamate receptors or acetylcholine receptors, are produced in a subpopulation of patients with a clinical diagnosis of schizophrenia (Borda et al., 2002; Steiner et al., in press; Tanaka et al., 2003; Tsutsui et al., 2012). This finding could help to bridge the gap between current immune and neurotransmitter hypotheses of schizophrenia (Steiner et al., 2012a).

This review illustrates the potential interactions between the immune system and glucose metabolism disturbances in schizophrenia. We present three different perspectives to explain these findings: 1) impaired cerebral glucose utilization is an important starting point in the pathogenesis of schizophrenia and leads to secondary changes in peripheral glucose metabolism, an increased risk of cardiovascular complications, and accompanying pro-inflammatory changes; 2) immune mechanisms may be involved from the beginning in the pathogenesis of schizophrenia, leading to disturbances in glucose metabolism, giving rise to metabolic syndrome as a resulting secondary phenomenon; and 3) shared underlying factors may be responsible for the co-occurrence of immune system and glucose metabolism disturbances in schizophrenia.

1.2. Physiologic regulation of adipose tissue mass, food intake, and energy expenditure

The various afferent inputs used by the brain to adjust food intake and energy metabolism can be broadly subdivided into two groups, which are as follows: orexigenic (appetite stimulating) and anorexigenic (appetite suppressing) factors (see Table 1).

Of the afferent signals reflecting the size of body adipose mass, insulin and leptin are the best studied and understood, and both hormones appear to be required for the control of food intake, body weight, and metabolic homeostasis (Porte et al., 2005). Although leptin is secreted primarily from adipocytes and insulin is released from the endocrine pancreas, both hormones circulate at levels proportionate to body fat mass and exert relatively long-term inhibitory effects on food intake. This signal is transduced via the inhibition of neuropeptide Y (NPY) as well as Agouti-related peptide (AgRP) neurons, and the activation of pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART) neurons of the hypothalamic arcuate nucleus (ARC) (Porte et al., 2005).

Table 1
Important orexigenic (appetite stimulating) and anorexigenic (appetite suppressing) factors that regulate food intake and energy metabolism. These factors are produced in the pancreas (insulin), adipose tissue (leptin), gastrointestinal tract (ghrelin, cholecystokinin/CCK, glucagon-like peptide-1/GLP-1, and peptide YY/PYY) and in the brain (neuropeptide Y/NPY, Agouti-related peptide/AgRP, orexin-A, melanin concentrating hormone/MCH, pro-opiomelanocortin/POMC, cocaine- and amphetamine-regulated transcript/CART, thyrotropin releasing hormone/TRH, corticotropin releasing hormone/CRH, and oxytocin).

Orexigenic factors	Anorexigenic factors
	Insulin
	Leptin
Ghrelin	CCK
	GLP-1
	PYY
NPY	POMC
AgRP	CART
Orexin-A	TRH
MCH	CRH
	Oxytocin

Satiety signals responding to recently ingested nutrients are more varied and function primarily on a meal-to-meal basis to control gastric emptying and the timing of meal initiation and termination. Unlike adiposity signals, these meal-related signals collectively regulate the amount of energy consumed during individual meals but are not generated in proportion to body energy stores. These short-term signals, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), Ghrelin and peptide YY (PYY), originate from the gastrointestinal tract during a meal and reach the nucleus tractus solitarii (NTS) in the caudal brainstem via the vagus nerve (Grill and Kaplan, 2002; Valassi et al., 2008). Ghrelin, an acylated peptide secreted by cells in the gastric mucosa, has orexigenic effects, stimulates food intake and is implicated in meal initiation (Cummings and Foster, 2003). In contrast, PYY, a close relative of NPY, is secreted primarily from the distal small intestine and colon and appears to inhibit feeding (anorexigenic effect) (Batterham et al., 2002). Afferent fibers project from the NTS to the ARC, where satiety signals are integrated with adiposity signals, namely leptin and insulin, and with several hypothalamic and supra-hypothalamic inputs.

As previously mentioned, ARC neurons secrete orexigenic substances, such as NPY and AgRP, and anorexigenic peptides, such as POMC and CART. Other brain areas involved in the control of food intake are located downstream from the ARC. These areas include the paraventricular nucleus, which produces anorexigenic peptides such as thyrotropin releasing hormone (TRH), corticotropin-releasing hormone (CRH) and oxytocin; the lateral hypothalamus; and the perifornical area, which secrets the orexigenic substances orexin-A and melanin-concentrating hormone (MCH) (Valassi et al., 2008).

Evidence suggests that many of these hormones and hypothalamic systems also regulate energy expenditure. The importance of insulin for thermogenesis was originally inferred from pharmacological studies in rats that demonstrated increased body temperature and energy expenditure, as well as reduced food intake when insulin was injected into the hypothalamic ventromedial and paraventricular nuclei (McGowan et al., 1992; Menendez and Atrens, 1991). These pharmacological studies suggest that the action of insulin in the hypothalamus simultaneously reduces food intake while increasing sympathetic nervous system outflow to brown adipose tissue to produce heat from fatty acid oxidation and increase energy expenditure.

Please cite this article as: Steiner J, et al, Immune system and glucose metabolism interaction in schizophrenia: A chicken–egg dilemma, Prog Neuro-Psychopharmacol Biol Psychiatry (2012), http://dx.doi.org/10.1016/j.pnpbp.2012.09.016