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

Johann Steiner a,b,k, Hans-Gert Bernstein a, Kolja Schiltz a,b, Ulf J. Müller a, Sabine Westphal c, Hemmo A. Drexhage d, Bernhard Bogerts a,b

a Department of Psychiatry, University of Magdeburg, Magdeburg, Germany
b Center for Behavioral Brain Sciences, Magdeburg, Germany
k Institute of Clinical Chemistry/Lipid Outpatient Clinic, University of Magdeburg, Magdeburg, Germany
c Institute of Immunology, Erasmus Medical Center, Rotterdam, The Netherlands

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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.

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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 type 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).
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).

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 secretes 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; Mendez 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.

### Table 1

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<tr>
<th>Orexigenic factors</th>
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<td>Ghrelin</td>
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<td>NPY</td>
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2. The “selfish-brain” theory and its implications for schizophrenia: impaired cerebral glucose utilization in schizophrenia leads to secondary peripheral metabolic changes and increased cardiovascular risk, including pro-inflammatory changes

2.1. Physiology of the cerebral glucose metabolism

The brain has the highest metabolic activity of all organs. Its uptake rates during physical rest are approximately 15% of the heart minute volume, 20% of the body’s oxygen supply, and 50% of the body’s glucose supply, while the brain-to-body mass ratio is only approximately 2–3% (Magistretti et al., 1995). Other important glucose “consumers” include skeletal and heart muscles (particularly during physical activity), as well as red blood cells. Due to its high need, continuous cerebral glucose supply is important for intact brain function, as the brain has very limited energy storage compounds (i.e., it has a small glycogen reservoir). Alternatively, lactate, which is produced by anaerobic glycolysis during physical activity in muscle cells, and ketone bodies, which are produced from the degradation of fatty acids during fasting, can be used as energy for neurons (Magistretti et al., 1995).

Active insulin transportation at the blood–brain barrier links the brain’s glucose metabolism with pancreatic insulin production (Banks, 2006). Insulin and insulin receptors are not only expressed in the hypothalamus, as previously assumed, but are also distributed throughout the central nervous system (Frolich et al., 1998; Wang et al., 2009). Findings by Steen et al. (2005) showed that patients with Alzheimer’s disease have impairments in insulin signal transduction cascade, including insulin, insulin receptors, and Akt1, particularly in the brain. The term “type 3 diabetes” was coined to describe disturbances in insulin signaling with a strong focus on the brain (Steen et al., 2005). Similar mechanisms may be relevant in schizophrenia (see below). Physiologically, insulin facilitates cellular glucose uptake into brain tissue, while systemically it regulates body weight, energy disposal, food intake and locomotion (Bruning et al., 2000). Thus, impaired cerebral insulin receptor signaling may cause disturbances in the uptake of glucose into brain tissue, resulting in cellular glucose deprivation.

2.2. Disturbances of cerebral glucose metabolism in schizophrenia

Several researchers have aimed to assess the glucose metabolism in the brain of patients with schizophrenia. For example, glucose metabolism has been studied via biochemical analyses of post-mortem tissues, measurements of glucose levels in the cerebrospinal fluid (CSF), or in vivo imaging studies. Cerebral insulin signaling is quite affected by schizophrenia (see the above-mentioned notion of “type 3 diabetes”), as evidenced by the decreased expression of cerebral insulin receptors (β-subunit), the reduced activity of the signal transduction protein Akt1, and the diminished neuronal expression of insulin-degrading enzyme in the dorsolateral prefrontal cortex (Bernstein et al., 2009; Emamian et al., 2004; Zhao et al., 2006). These changes may cause disturbances in neural glucose uptake and utilization, as suggested by measurements of elevated CSF glucose levels (Holmes et al., 2006). In vivo fluorodeoxyglucose positron emission tomography (FDG-PET) and functional magnetic resonance imaging (fMRI) studies also demonstrate impaired cerebral glucose utilization in brain areas that are important in the pathogenesis of schizophrenia, resulting in the “metabolic disconnection” of the dorsolateral prefrontal cortex and mediiodorsal thalamus with the limbic system (Buchbaum et al., 2007; Mitelman et al., 2005). The mediotemporal region and the hippocampus in particular appear to be of specific importance for the cognitive impairments noted in schizophrenia. Studies addressing neuronal activation using fMRI have demonstrated that schizophrenic subjects show impaired patterns of hippocampal activity in novelty detection, declarative learning, and memory tasks (Ragland et al., 2006; Weiss et al., 2004; Zierhut et al., 2010). Notably, it has been demonstrated that hippocampus-dependent memory performance can be improved by the administration of glucose in rodents and humans (Gold et al., 1986; Sunram-Lea et al., 2002). In humans, it has been shown that this effect is more pronounced when the task is cognitively demanding (Sunram-Lea et al., 2002) or when the cognitive resources that can be applied for it are limited, as is the case in the elderly and in schizophrenic patients (Fucetola et al., 1999; Newcomer et al., 1999). Nevertheless, the defective glucose utilization noted in functional studies may result from either defective cellular mechanisms of glucose utilization or it may be a secondary effect of lower neuronal activation.

2.3. The “selfish brain” theory and schizophrenia

An interpretation of the aforementioned findings in the context of the “selfish brain” theory is intriguing. This theory describes the tendency of the human brain to cover its own, comparably high energy requirements with the utmost priority when regulating energy fluxes within an organism. In this respect, the brain is thought to behave selfishly (Peters et al., 2004, 2007). Given the assumption of disrupted cerebral energy supply in schizophrenia due to cerebral insulin resistance, the “selfish brain” theory may provide a novel explanation for the preferred intake of high carbohydrate, high fat foods and diminished physical activity and exercise in schizophrenic patients as a way to improve the brain’s energy supply. Thus, one could speculate that increased blood glucose levels following treatment with atypical antipsychotic drugs are not an “unwanted side effect” after all but might be therapeutic to improve cerebral glucose supply.

2.3.1. Adaptive behavioral changes and atypical antipsychotic drugs may induce counter-regulatory mechanisms to overcome impaired cerebral glucose metabolism: a short-term perspective

According to the “selfish brain” theory, impaired glucose supply to the cerebral cortex, which could be caused by cerebral disturbances in insulin signaling, may lead to counter-regulatory adaptive mechanisms, such as the above-mentioned changes in food intake and physical activity. The most effective drugs, clozapine and olanzapine (Ebenbichler et al., 2003; Lieberman et al., 2005; Newcomer, 2007), may improve energy supplies via several different mechanisms, which are as follows: 1) appetite stimulation, possibly via serotonergic mechanisms (5HT2C-antagonism), could lead to increased food intake; 2) the antihistaminic properties of these drugs cause sedation, daytime sleepiness or prolonged nighttime sleep and result in an overall reduction in physical activity, which subsequently decreases energy expenditure; 3) previous animal experiments suggest that antipsychotic drugs may ameliorate the action of insulin on brain tissue, e.g., via the increased phosphorylation of Akt1 (Emamian et al., 2004; Sutton and Rushlow, 2011)—this mechanism could improve cerebral glucose uptake and utilization; and 4) clozapine increases the span of mitochondrial respiration that can be used for ATP synthesis (unpublished data, J. Steiner) via a decrease in leak respiration,1 which contributes to thermogenesis (Mozo et al., 2005; Rolfe and Brown, 1997). This mechanism may promote reduced energy expenditure. Consistent with this assumption, reduced body temperature has been observed in clozapine- and olanzapine-treated patients (olanzapine is pharmacologically similar to clozapine) and may contribute to the side-effect of increased weight gain, while the increased efficacy of mitochondrial respiration may be beneficial with respect to supplying the brain with energy (Evers et al., 2010; Salmi et al., 1994; Stefanidis et al., 2009). In summary, several

1 Under certain conditions, protons can re-enter the mitochondrial matrix without contributing to ATP synthesis. This process is known as a proton leak, or mitochondrial uncoupling, and is due to the facilitated diffusion of protons into the matrix. The process results in the production of heat and is mediated by a proton channel called thermogenin, or uncoupling protein 1 (UCP1).
mechanisms may lead to improved cerebral glucose supply, including the more efficient utilization of glucose.

2.3.2. Adaptive behavioral changes and atypical antipsychotic drugs may induce metabolic syndrome, type 2 diabetes and a systemic pro-inflammatory state: a long-term perspective

According to the “selfish brain” theory, the above-mentioned adaptive behavioral changes and the effects of atypical antipsychotic drugs on food intake and energy expenditure are “selfish”, as the brain’s energy supply is improved. However, the long-term systemic side effects of atypical antipsychotics include obesity, metabolic syndrome, and the development of type 2 diabetes. Indeed, the most effective drugs, clozapine and olanzapine, are those with the highest diabetogenic risk and lead to a mean weight gain of approximately 10 kg within the first year of treatment (Ebenbichler et al., 2003; Lieberman et al., 2005; Newcomer, 2007).

In the long term, the risk of developing overweight and particularly visceral obesity is increased in schizophrenia due to disease-inherent and drug-induced mechanisms (see above). Visceral obesity is a chronic, low-grade inflammatory disease that predisposes people to metabolic syndrome, type 2 diabetes and its cardiovascular complications. Adipose tissue is not a passive storehouse for fat; rather, it is an endocrine organ that synthesizes and releases a variety of bioactive molecules, some of which are produced by local inflammatory cells, including macrophages (Bories et al., 2012). MPS cells located in the visceral fat are an important site for IL-1β, IL-6, and TNF-α secretion, and they provide a potential link between abdominal obesity and systemic inflammation (Fontana et al., 2007; Meshkani and Adeli, 2009; Xu et al., 2003). In particular, IL-6 seems to induce insulin resistance and an increased production of C-reactive protein (CRP) in the liver (Meshkani and Adeli, 2009; Xu et al., 2003). TNF-α may also induce insulin resistance by suppressing the expression of the insulin-sensitive glucose transporter 4 (GLUT4) in peripheral tissues (Hauner et al., 1995; Lofgren et al., 2000). Shim et al. (2006) observed a higher white blood cell count, including increased numbers of monocytes in the blood of patients with metabolic syndrome and type 2 diabetes. MPS activation along with increased levels of IL-1β, IL-6, and CRP have also been detected in schizophrenia; however, many of these studies did not control for the important confounding factor of visceral obesity (Drexhage et al., 2010; Miller et al., 2011; Potvin et al., 2008; Sicras-Mainar et al., in press). Thus, it remains unclear whether such cytokine changes reflect schizophrenia-specific pathophysiological changes or whether these changes are related to visceral obesity and the development of metabolic syndrome. While elevated levels of CRP have been considered to be cardiovascular risk markers in schizophrenia (Sicras-Mainar et al., in press), Beumer et al. (in press) recently performed a study that focused on the potential link between pro-inflammatory cytokines, schizophrenia and obesity. Compared to healthy controls, IL-1β and IL-6 levels were increased in the schizophrenia cohort, even when considering Body-Mass-Index (BMI) as a potential confounder. However, unfortunately, BMI values were only available in some of the tested healthy controls, and waist circumference data were not presented in this study. The authors concluded that increased MPS activation is a key component in the pathophysiology of schizophrenia. Additional studies are necessary to validate this finding.

Several studies have observed increased levels of S100B in the peripheral blood and cerebrospinal fluid of schizophrenic patients. This finding has been attributed primarily to astrocyte damage or dysfunction (Rothermundt et al., 2001, 2004; Schroeter and Steiner, 2009). However, meanwhile, it is known that peripheral S100B blood levels correlate with body mass and the development of insulin resistance in schizophrenic patients (Steiner et al., 2010a,b). Accordingly, we observed a negative correlation between body mass and the “counter player” and competitive inhibitor of S100B, namely, the soluble receptor for advanced glycation products (sRAGE) (Donato, 2007; Steiner et al., 2009). Notably, S100B is widely expressed in adipocytes (Gonzalves et al., 2010; Netto et al., 2006) and may provide a link between disturbances in glucose metabolism and pro-inflammatory changes, as S100B is capable of activating the MPS, including microglial cells (Adami et al., 2004; Bianchi et al., 2007; Steiner et al., 2011, 2012b).

The historic use of insulin coma therapy, which was introduced in 1933 by Manfred Sakel, has been widely used for the treatment of major psychiatric disorders, including schizophrenia (Crammer, 2000). The mechanism of action has not yet been elucidated; however, this therapy could be helpful in overcoming cerebral insulin resistance by improving the cellular glucose supply for nervous tissue. Similarly, studies are currently underway to determine if other drugs may be helpful in improving insulin signaling using less harmful interventions. Several studies have shown that treatment with the antidiabetic drug metformin reduces the risk of systemic metabolic side effects in olanzapine-treated patients (Bushe et al., 2009). Moreover, the “gliazones”, a group of insulin sensitizing drugs, have been tested in this context and have shown promising results (Baptista et al., 2009; Edlinger et al., 2007; Henderson et al., 2009). These and other compounds may improve the efficacy of treatment and reduce the systemic cardiovascular side effects of atypical antipsychotic drugs when used in future combination therapies.

3. Immune mechanisms may be involved as primary factors in the pathogenesis of schizophrenia, leading to disturbances in glucose metabolism as a secondary phenomenon

In contrast to the above-mentioned view that immune system changes and metabolic dysfunction represent a secondary phenomenon in schizophrenia as a result of disturbances in cerebral glucose utilization, recently published animal experiments point to a different perspective. In this section, we summarize data from animal experiments that suggest a role for prenatal immune activation in the triggering of schizophrenia-related MPS/microglial activation and the development of metabolic syndrome. Stimulated by the work of Barker et al. (Dover, 2009), the concept of “early-life priming of adult disease” is now widely accepted. This concept refers to the phenomenon that environmental acting during sensitive embryonic developmental periods can induce lifelong changes in physiologic, metabolic, and behavioral functions, as well as in psychiatric disorders (Bale et al., 2010; Luo et al., 2010).

3.1. Prenatal immune activation is associated with an increased risk of developing schizophrenia

Accordingly, the neurodevelopmental hypothesis of schizophrenia postulates that the occurrence of disturbances in brain maturation in the second trimester may result in limbic dysfunction and structural changes, such as decreased hippocampal and cortical volume due to neuropil reduction (Weinberger, 1987). Genetic vulnerability is believed to interact with inflammatory and immunological reactions that interfere with brain development during pregnancy. In several studies, the children of mothers who suffered from influenza, cytomegalovirus, or herpes virus infections during pregnancy appeared to have an increased risk of developing schizophrenia (Brown, 2008; Torrey et al., 2006; Yolken and Torrey, 1995). Polyriboinosinic–polycytidylic acid (PolyI:C) is an analog of double-stranded RNA that stimulates cytokine-associated acute phase response, as it is a virus-like mimic (Fatemi et al., 2002, 2008). Its administration in mice during vulnerable periods of pregnancy induces changes in brain morphology, physiology and neurochemistry, as well as inducing behavioral changes that are partly reminiscent of human schizophrenia after puberty in the offspring of female mice (Meyer and Feldon, 2005; Winter et al., 2009). This induced immune activation results in enhanced dopamine turnover in the prefrontal cortex and a decrease in serotonin levels in several subcortical regions of the rat brain. The authors concluded
that in utero inflammation predisposes the offspring to persistent neurotransmitter changes and thus to the development of schizophrenia later in life. Of note, many of these changes may be prevented by treating rats with risperidone during adolescence (Piontkewitz et al., 2012).

Post-mortem and PET analysis showed an increased number of activated microglial cells in patients with schizophrenia (Bayer et al., 1999; Busse et al., 2012; Doorduin et al., 2009; Radewicz et al., 2000; Steiner et al., 2008; van Berckel et al., 2008). Therefore, it has been hypothesized that these cells contribute to disease pathogenesis and may actively be involved in the gray matter loss observed in schizophrenia. Juckel et al. analyzed the number and shape of microglia in the offspring of mice exposed to Poly:C during pregnancy and observed higher microglial densities in the hippocampus and striatum, but not in the frontal cortex at postnatal day 30, which is similar to adolescence in humans (Juckel et al., 2011). The microglia of the offspring of Poly:C-treated mothers were morphologically characterized by reduced arborization, which is indicative of a state of higher activation compared to the offspring of vehicle-treated mice (Juckel et al., 2011). This study supports the hypothesis of “early-life priming of adult disease” in schizophrenia, in which maternal infection during embryogenesis contributes to MPS/microglial activation during adulthood.

4. Prenatal immune activation is associated with an increased risk of developing schizophrenia-related metabolic alterations and an increased pro-inflammatory cytokine production

Furthermore, U. Meyer’s group used the same animal model to test whether schizophrenia-related metabolic alterations and increased pro-inflammatory cytokine production can be primed by prenatal exposure to Poly:C (Pacheco-Lopez et al., in press). They used high-resolution computed tomography of fat distribution and indirect plasma cytokine and cortisol measurements. Prenatal immune activation caused altered glycemic regulation and abnormal ingestive behavior, which led to adult onset of excess visceral and subcutaneous fat deposition. These effects were accompanied by age-dependent changes in the peripheral secretion of pro-inflammatory cytokines that may actively be involved in the gray matter loss observed in schizophrenia. These effects were accompanied by age-dependent changes in the peripheral secretion of pro-inflammatory cytokines (IL-6 and TNF-α) and T cell-related (IL-2 and IFN-γ) cytokines and stress-axis activation.

Thus, schizophrenia-related metabolic abnormalities and increased pro-inflammatory cytokine production may be primed by prenatal virus-like immune activation. However, the exact mechanisms are still unclear. It will be quite difficult to substantiate these findings in schizophrenia patients, as such studies in humans are primarily restricted to an epidemiological approach due to ethical restrictions.

5. Shared underlying factors may be responsible for the co-occurrence of immune system and glucose metabolism disturbances in schizophrenia

5.1. Clustering of schizophrenia, thyroid autoimmune disease and type 1 diabetes: an aberrant immune activation set point for local mononuclear phagocytes and microglial cells

Autoimmune thyroid disease (AITD) and autoimmune type 1 diabetes co-occur frequently and the co-occurrence of AITD and type 1 diabetes is known as subtype 3A of a syndrome called autoimmune polyendocrine syndrome (Betterle and Zanchetta, 2003). While AITD may present as a schizophrenia-like disorder, i.e., as Hashimoto’s encephalitis (Lin and Liao, 2009), a large Danish national study showed that patients with schizophrenia had a 45% higher chance of developing an autoimmune disease, including thyroid autoimmune disease (Eaton et al., 2010). Moreover, these autoimmune diseases were more prevalent in first-degree relatives of patients with schizophrenia.

The finding of a relatively high familial co-occurrence of psychiatric disorders and endocrine and other organ-specific autoimmune diseases refutes the concept that psychiatric disorders and endocrine autoimmune disease are the cause or consequence of each other and imply the existence of shared immune pathogenic factors for schizophrenia and endocrine autoimmune diseases. One of these shared factors is thought to be an intrinsically high activation set point for the MPS. Microglia are the representatives of the MPS in the brain, while dendritic cells and macrophages are the representatives of this system in endocrine organs and monocytes are the representatives of this system in the circulation.

There is mounting evidence that dendritic cells and macrophages in the thyroid and pancreatic islets of patients with AITD and autoimmune diabetes exist in an aberrant pro-inflammatory state. This abnormal set point of cells most likely plays a role in breaking T cell tolerance and inducing an aberrant autoimmune response towards thyroglobulin and β cells. An intrinsic defect in T regulatory cell function adds to this problem, leading to a further imbalance between T effector and T regulatory forces (unpublished data, H.A. Drexhage).

Under steady state conditions, immature forms of dendritic cells (iDCs), due to their strong endocytic capability, also take up compounds present in the vicinity, such as thyroglobulin when in the thyroid and insulins in the pancreatic islets. After the uptake of these “auto-antigens”, the iDCs mature partly under the influence of local cytokines (such as TGF-β) to semi-mature DCs and travel via the lymphatics to the draining lymph nodes (known there as interdigitating cells) while carrying the auto-antigens. In the draining lymph nodes, the superb antigen-presenting capability of the semi-mature DCs becomes evident, and they begin to trigger and expand in particular subsets of auto-reactive natural T regulatory cells (Sakaguchi et al., 2008; Steinman et al., 2003). In triggering this subpopulation of CD4+ T cells, DCs build up a strong non-reactivity (=tolerance) towards self under steady-state conditions.

Tissue macrophages in the brain, known as microglia, have similar regulatory functions as dendritic cells and macrophages in endocrine tissues. Animal studies have shown that microglia do not differentiate from circulating monocytes, as originally thought, but differ instead from primitive myeloid progenitors that emigrate from the yolk sac into the brain parenchyma (Alliot et al., 1999; Ginhoux et al., 2010). Microglia participates in various aspects of brain development, including developmental cell death, axon remodeling, synaptogenesis, and synaptic pruning (Pont-Lezica et al., 2011; Schlegelmilch et al., 2011; Tremblay and Majewska, 2011).

A switch to a high immune activation set point of steady-state glandular dendritic cells and microglia may alter their role in the regulation of growth and the function of neighboring parenchymal cells, while reduced auto-antigen tolerance could trigger the co-occurrence of schizophrenia, thyroid autoimmune disease and type 1 diabetes (unpublished data, H.A. Drexhage). As stated before, histologic and PET studies observed signs of microglial activation in schizophrenia (Bayer et al., 1999; Busse et al., 2012; Doorduin et al., 2009; Radewicz et al., 2000; Steiner et al., 2006, 2008; van Berckel et al., 2008) and an accumulation of monocytes and macrophages in the cerebrospinal fluid of patients with schizophrenia during acute psychotic episodes. These findings support the MPS activation hypothesis in schizophrenia (Nikkilä et al., 1999). Consistent with the idea of an impaired auto-antigen tolerance, more T cells have been observed in the cerebrospinal fluid and in the hippocampal brain tissue of schizophrenia patients during later disease stages (Busse et al., 2012; Maxeiner et al., 2009). With regard to the peripheral circulation, there is evidence for increased numbers of pro-inflammatory IL-17-producing cells (and, to a lesser extent, IL-4-producing cells), predominantly in younger and active schizophrenia cases (unpublished data, H.A. Drexhage). Similarly, the activation of dendritic cells, macrophages and various subsets of T cells have been observed in the thyroid and pancreatic islets of patients affected by AITD and autoimmune type 1 diabetes.
diabetes (unpublished data, H.A. Drexhage). Elimination of the dendritic cells and T cells from the thyroid or pancreatic islets in animal models of endocrine autoimmune disease, e.g., via knock-outs or treatment with clodronate or T cell-depleting therapies, results in a halting of the autoimmune process. Therefore, it may be assumed that these immune cells are the local force of the autoimmune reaction. It has also been assumed that it is not a numerical deficit, but a defect in the function of T regulator cells (possibly an intrinsically reduced IL-2 signaling), which fails to keep the locally activated dendritic cells, T effector cells and macrophages in check (unpublished data, H.A. Drexhage).

5.2. Shared genetic predisposition for schizophrenia and a dysfunctional immune system

Perhaps the most compelling evidence for the link between schizophrenia and a dysfunctional immune system is provided by genetic studies (Leonard et al., 2012). For example, Badenhoop et al. (1996), Lindholm et al. (1999) and Stefansson et al. (2009) demonstrated that a gene locus on chromosome 6p22 was linked to both schizophrenia and to the genes of the major histocompatibility complex (MHC) system, a system that is involved in one of the most important functions of the immune system, i.e. antigen presentation. There is also a genetic link between schizophrenia and type 1 diabetes (Lindholm et al., 1999).

5.3. Shared genetic predisposition for schizophrenia and type 2 diabetes

It is now well established that individuals with schizophrenia are at an increased risk for the development of type 2 diabetes, with estimates suggesting a prevalence of between 15% and 20% in this population (Gough and O'Donovan, 2005). While shared environmental risk factors (see above) may explain the link between the two disorders, a shared genetic link is an alternative explanation.

Many chromosomal regions that have been associated with schizophrenia show an overlapping linkage with type 2 diabetes (Gough and O'Donovan, 2005). The most promising region of interest in both schizophrenia and type 2 diabetes is located on chromosome 1q21–25. These genes include LMNA (which encodes lamin A/C) (Hegele et al., 2000), mutations of which can cause lipodystrophy and diabetes. The insulin receptor-related gene (IRR) also maps to this region (Hirayama et al., 1999) and encodes a protein involved in insulin signaling. Association analysis of chromosome 1q21–22 fine mapping has identified the CAPON (C-terminal PDZ domain ligand of neuronal nitric oxide synthase) gene (Bruzowitzcz et al., 2004). The encoded protein functions as an adapter protein targeting neuronal nitric oxide synthase. The regulator of G-protein signaling 4 (RGS4) gene is another good positional candidate in this region for schizophrenia (Chowdari et al., 2002). This gene is a negative regulator of G protein–coupled receptors, and evidence also suggests that RGS4 may modulate activity at certain serotonergic and metabotropic glutamatergic receptors (Gough and O’Donovan, 2005).

5.4. Disturbances in Akt1 signaling in schizophrenia: possible consequences for the brain and for the immune system

The serine–threonine protein kinase Akt1 is important for the signal transduction of a variety of growth factors and insulin. It has been suggested that cerebral and peripheral insulin signaling in schizophrenia may be disrupted by an altered expression and phosphorylation of Akt1 (Emamian et al., 2004; van Beveren et al., 2012; Zhao et al., 2006).

Akt1 plays an important role in intact prefrontal cortex function (Lai et al., 2006). Moreover, insulin and insulin-like growth factor-1 (IGF-1) stimulate the maturation of oligodendrocytes in culture (van der Pal et al., 1988). Accordingly, Akt1 signaling plays an important role in myelination processes (Narayanan et al., 2009) and is involved in synaptic plasticity and myelination. Thus, the reduced expression and phosphorylation of Akt1 in the dorsolateral prefrontal cortex may contribute to the impaired connectivity of different brain regions, which has been observed in schizophrenia. Indeed, an approximately 75% reduction in Akt1 content and activity in the postmortem brain tissue of schizophrenic patients was observed by Zhao et al. (2006). This finding is consistent with a previous study by Emamian et al. (2004), which reported a significant association between schizophrenia and an Akt1 haplotype that is associated with lower Akt1 protein levels and a greater sensitivity to the sensorimotor gating-disruptive effect of amphetamine. These data support the proposal that alterations in Akt1 signaling contribute to the pathogenesis of schizophrenia and identify Akt1 as a potential schizophrenia susceptibility gene. Consistent with this proposal, Emamian et al. (2004) and Sutton et al. (Sutton and Rushlow, 2011) also showed improved phosphorylation of Akt1 in the brains of rodents after treatment with clozapine or haloperidol, which could compensate for the impaired functioning of this signaling pathway in schizophrenia. Interestingly, Emamian et al. (2004) found similar alterations in Akt1 signaling in the lymphocytes of schizophrenic patients. This finding was replicated by van Beveren et al. (2012) in peripheral blood mononuclear cells (PBMCs) of patients with schizophrenia. Based on these findings, we speculate that Akt1 may provide a potential link for the immune system pathology and glucose metabolism alterations noted in patients with schizophrenia. The consequences of impaired Akt1 on the immune system of patients with schizophrenia are currently unknown. Recent studies on the physiological role of Akt1 suggests that it not only regulates neutrophil and monocyte migration into inflamed tissues (Di Lorenzo et al., 2009), thymic development (Fayard et al., 2007; Juntilla et al., 2007), and peripheral B-cell maturation and survival (Calamito et al., 2010), but that Akt1 also plays an important role in the differentiation of cells in the MPS and the regulation of their inflammatory/tolerogenic state (Van den Bossche et al., 2012).

6. Summary and conclusion

Impaired glucose metabolism and the development of metabolic syndrome contribute to a reduction in the average life expectancy of individuals with schizophrenia. It has been questioned whether this association is simply reflective of an unhealthy lifestyle or whether weight gain and impaired glucose tolerance in patients with schizophrenia are attributable to the side effects of atypical antipsychotic medications or disease-inherent abnormalities. In addition, numerous previous studies have highlighted the alterations in immune system functioning among patients with schizophrenia. Increased concentrations of IL-1, IL-6, and TGF-β appear to be state markers, whereas IL-12, IFN-γ, TNF-α, and sIL-2R appear to be trait markers of the disease. Moreover, mononuclear phagocyte system (MPS)/microglial activation are involved in the pathogenesis of the early acute phases of the disease.

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 schizophrenia. Based on the currently available data, it is more likely that immune system dysfunction and aberrations in glucose metabolism interact as co-occurring factors in patients with schizophrenia. Longitudinal studies focusing on immune- and glucose metabolism-related parameters are needed to clarify the time course of the above-mentioned alterations. Repeated PET scans, indirect calorimetry, the analysis of peripheral blood and CSF, and provocation maneuvers, such as oral glucose tolerance tests, may be helpful in revealing pathophysiological changes that are involved in the pathogenesis of schizophrenia. In this context, future analyses should also focus on prodromal patients and first-degree relatives to allow for the discrimination of risk from changes that are associated with full-blown psychosis.
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