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The metabolic syndrome in schizophrenia: is inflammation a contributing cause?

Brian E Leonard1,2, Markus Schwarz1 and Aye Mu Myint1

Abstract
This non-systematic review of the literature summarizes the evidence that inflammation plays a major role in the psychopathology of schizophrenia and in the mechanisms that contribute to physical ill health that is commonly associated with schizophrenia. The impact of prenatal infections on the developing brain, the possible genetic link between the human lymphocyte antigen gene, inflammation, heart disease and diabetes, together with the increase in pro-inflammatory cytokines in the blood and cerebrospinal fluid provide convincing evidence that inflammation is a major factor in the pathology of this disorder. The changes in immune-related markers and specific neurotransmitters associated with the positive symptoms of schizophrenia are described. In addition, the possible mechanism whereby structural changes occur in the brain is associated with the neurotoxic effects of pro-inflammatory cytokines, together with the neurotoxic metabolites from the tryptophan–kynurenine pathway that is activated by pro-inflammatory cytokines, is also discussed. The role of effective antipsychotic drug treatment in attenuating the inflammatory response is described. However, evidence is limited regarding the causal connection between atypical antipsychotic drugs and the changes in glucose and lipid metabolism that could trigger the onset of physical ill health, including diabetes and heart disease. Indeed, there is evidence that there is a metabolic predisposition to diabetes in patients with schizophrenia that is exacerbated by obesity and thereby contributes to cardiovascular disease and other co-morbid illnesses. It is concluded that the effects of inflammatory mediators on the brain causally contribute to the pathology of schizophrenia and the ill health that accompanies the disorder.

Keywords
Antipsychotics, cytokines, diabetes, ill health, kynurenine pathway, schizophrenia

Introduction
It is generally recognized that mental ill health in patients with schizophrenia is frequently accompanied by physical illness. Thus it has been estimated that the life expectancy for patients with schizophrenia is 20% lower than for the general population. Such increased mortality is often the result of cardiac and cerebrovascular disease, complications of diabetes and cancer and conditions that may be complicated by the abuse of alcohol and illicit drugs of abuse (Newcomer and Hennekens, 2007; Sunquist and Li, 2006).

In addition to the increased frequency of hypertension and elevated cholesterol, schizophrenia is also commonly associated with the metabolic syndrome that is expressed by type 2 diabetes and insulin insensitivity (Holt et al., 2005). The question then arises whether the increase in physical ill health is a reflection of an unhealthy lifestyle (associated with a poor quality diet, lack of exercise and obesity) or due to a genetic predisposition that is exacerbated by antipsychotic drugs. Indeed, there is growing evidence that the metabolic diseases which are associated with schizophrenia result from an interaction of heritable factors with adverse environmental influences, including drug treatments (O’Rahilly, 2009). For example, bone mass is reduced in female patients with schizophrenia being treated with antipsychotic drugs. This is evidently associated with the drug-induced hyperprolactinaemia that causes a reduction in 25-hydroxy vitamin D concentrations (Rey-Sanchez et al., 2008). This is an example of the complications that contribute to the physical ill health and to the increased morbidity and mortality of patients with schizophrenia.

Are these connections causal or co-incidental? Until recently, it was unclear if the different dysfunctional systems associated with ill health in patients with schizophrenia were connected with the underlying psychopathology of the disorder. The situation has now been clarified by evidence that inflammation is a common feature of both medical and psychiatric disorders associated with schizophrenia. Thus it is evident that both cellular and humoral immunity are associated with major psychiatric disorders, changes that are largely reversed by effective drug treatment (Allison et al., 2003; Weiden et al., 2004). The possible link between inflammation and the neurochemical changes that are assumed to be causally connected to the pathology of schizophrenia, and how such changes may impact on the health of the patient, will form the basis of this review.

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Materials and methods

Original scientific and review articles within 40 years, 1971–2011, related to the research areas listed below were screened. Altogether, 124 articles which are most related to the theme of this specific review article were selected and reviewed. The areas and number of articles are listed in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Area of research</th>
<th>Number of articles</th>
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<tbody>
<tr>
<td>1. Epidemiology of schizophrenia</td>
<td>1</td>
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<tr>
<td>2. General relation on inflammation, metabolism, cardiovascular disease and psychiatric disorders</td>
<td>11</td>
</tr>
<tr>
<td>3. Schizophrenia and metabolic syndrome</td>
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<td>4. Antipsychotics and metabolic syndrome</td>
<td>6</td>
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<tr>
<td>5. Inflammation/infection and metabolic syndrome</td>
<td>5</td>
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<tr>
<td>6. Central nervous system and metabolic syndrome</td>
<td>3</td>
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<tr>
<td>7. Infection, inflammation and schizophrenia</td>
<td>40</td>
</tr>
<tr>
<td>8. Schizophrenia, cognition, neuroendocrine and neurodegeneration</td>
<td>12</td>
</tr>
<tr>
<td>9. Stress hormones</td>
<td>6</td>
</tr>
<tr>
<td>10. Tryptophan metabolism, immune system and psychiatry</td>
<td>28</td>
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</tbody>
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Since this is non-systematic review, the findings are discussed along the different subtitles under the main theme of this specific review.

Discussion

Based on the result of the articles reviewed, it could be concluded that there is a role of immune system changes in metabolic syndrome in schizophrenia through its interaction with metabolic, neuroendocrine and neurochemicals.

Importance of immune changes in schizophrenia

The discovery that viral infections that occur during critical periods of neuroontogenesis are frequently linked to schizophrenia in later life lends support to the neurodevelopmental hypothesis of schizophrenia as postulated by Murray and Lewis (1987). The results from a Finnish epidemiological survey also demonstrated that infections in the postnatal brain of children were associated with a fivefold increased risk of schizophrenia in adulthood (Mortensen et al., 1987). Other risk factors that help to support the neurodevelopmental hypothesis include obstetric complications that cause hypoxic damage to the developing brain, changes in the brain that are associated with an increase in inflammation (Nawa et al., 2000). Activation of the glutamatergic system by inflammatory mediators may result in excitotoxic damage to the brain (Tkachev et al., 2007).

While it is plausible to postulate that prenatal exposure of the developing brain to adverse environmental factors could affect neurodevelopment, it is uncertain why the symptoms of the disorder are usually manifest in the adolescent or post-adolescent brain. One possibility is that the changes in the endocrine and immune systems that are associated with neurodevelopmental defects sensitize the developing brain and therefore cause more permanent changes in the neurotransmitter networks in the mature brain (Kronfol and Remnick, 2000). The possible link between neurodevelopmental defects and prenatal immune activation is supported by the environmental studies of Winter et al. (2009), who demonstrated that the in utero exposure of rats to the virometabolic drug polyI:C induced immune activation that resulted in enhanced dopamine turnover in the prefrontal cortex, and a decrease in serotonin in several subcortical regions of the rat brain. The authors conclude that in utero inflammation predisposes the offspring to persistent neurotransmitter changes that may dispose to schizophrenia in later life.

Despite the evidence that prenatal infections that are implicated as important causative factors in schizophrenia, to date the precise identification of the infectious agents is uncertain. Nevertheless, antibody titres against viruses have been detected in the sera of patients with schizophrenia (Lillehøj et al., 2000), and definite signs of chronic inflammation in the brain have been identified (Mueller et al., 1991). The term ‘mild, localized, chronic encephalitis’ has been proposed by Bechter and Hodgkiss (1995) to describe the discrete changes that occur in this disorder. It seems possible that the outcome of the inflammatory changes could be responsible for the selective neurodegenerative changes in areas such as the temporal gyrus, the volume of which has been shown to decrease before the occurrence of the first major schizophrenic episode (Chakos et al., 2005; Körschenhausen et al., 1996; Geuze et al., 2005; Steen et al., 2006).

Perhaps the most compelling evidence for the link between schizophrenia and a dysfunctional immune system is provided by some genetic studies. For example, Lindholm and co-workers (1999) and Badenhoop et al. (1996) demonstrated that a locus at chromosome 6p22 was linked to both schizophrenia and to the genes of the human lymphocyte antigen (HLA) system, a system that is involved in combating viruses. There is also a genetic link between schizophrenia and diabetes. Thus the susceptibility of first-degree relatives of schizophrenic patients to diabetes appears to be associated with the HLA locus on chromosome 6 (Lindholm et al., 1999). There are differences in the genetic signal between type 1 (insulin dependent) and type 2 (insulin independent) diabetes and there is evidence that there is a decrease in type 1 diabetes in schizophrenic patients (Juvonen et al., 2007), whereas there is substantial evidence that, independent of antipsychotic treatment, the frequency of type 2 diabetes is increased. This suggests that insulin, as such, may not be directly linked to the pathology of schizophrenia and that type 2 diabetes is the outcome of dysfunctional metabolism initiated by changes in the immune and endocrine systems and in mitochondrial function.

Of the various cytokines, chemokines, prostenoids and gaseous transmitters such as nitric oxide that form the inflammatory cascade, the pro-inflammatory cytokines (such as interleukins -1,-6 (IL-1,-6), interferon gamma (IFNg), and tumour necrosis factor alpha (TNFα)), appear to play a crucial role. The pro- and anti-inflammatory cytokines (such as IL-4, IL-10 and IL-13) are produced by the Th-1 and Th-2 divisions of the cellular immune system. The serum concentration of the pro-inflammatory cytokines is increased in schizophrenia, as indicated by an increase in the IFNg, TNFα and IL-6 concentrations, while the anti-inflammatory cytokine, IL-4, decreased (Kim et al., 2009); effective antipsychotic treatment attenuated these changes. In their systematic review of changes in seven cytokines in patients with schizophrenia, Potvin and co-workers (2008) reported that the IL-1...
receptor antagonist (IL-1ra), soluble IL-2r and IL-6 were increased while IL-2 synthesis was decreased in the serum of schizophrenia patients. More recently, Bresee and Rapaport (2009) confirmed that the sIL-2r levels were increased and that such changes were associated with an increase in both the positive and negative PANSS scores. These results suggest that immune activation is a persistent feature of schizophrenia even in patients who are stabilized on antipsychotic drugs. However, studies have shown that other inflammatory mediators including C-reactive protein, E-selectin and ICAM are raised in the serum of patients with schizophrenia, and those changes were reversed by effective antipsychotic treatment (Meyer et al., 2009). Thus it would appear that inflammation is increased in the serum of patients with schizophrenia, and that some inflammatory mediators are reduced in response to antipsychotic treatment. Clearly the cytokine changes do not fit neatly into an imbalance between the Th-1 and Th-2 arms of the immune system, as has been postulated previously (Mueller et al., 1997a; Schwarz et al., 2001a), in which the anti-inflammatory Th-2 pathway predominated. A possible reason for the differences between those earlier and more recent original findings could reflect the presence of antipsychotic medication in the serum of the patients from those studies, as drug-naïve schizophrenic patients in a recent study show an increase in pro-inflammatory cytokines (Kim et al., 2009) and some atypical antipsychotics reduce Th-1 marker cytokines, such as IFNγ, and increase Th-2 cytokines such as IL-10. In addition, both typical and some atypical antipsychotics cause prolactinemia, and prolactin is known to enhance the activity of both the Th-1 and Th-2 arms of the immune system and to increase auto-antibody synthesis (Kim et al., 2004; Pac et al., 2006). However, even the meta-analysis report which also included the results from medicated patients demonstrated the enhanced pro-inflammatory response instead of clear-cut Th1 or Th2 activity (Potvin et al., 2008). Thus the most plausible conclusion that may be drawn at this time is that there is a chronic, low-grade inflammatory change associated with the active phase of schizophrenia and that effective treatment largely attenuates these changes.

**Changes initiated by inflammation in schizophrenia**

There is substantial evidence that the innate immune system is activated in patients with schizophrenia. Thus the number of monocytes and some types of cytotoxic cells are increased in the blood, as are the monocytes and macrophages in the cerebrospinal fluid (CSF) of those with acute schizophrenia (Mueller et al., 1998). These findings suggest that immune activation occurs both peripherally and centrally. Of the pro-inflammatory cytokines that are raised in the CSF, IL-6 has been shown to increase (Maes et al., 1995); this cytokine plays a major role not only in the inflammatory cytokine cascade but also in activating B cells, thereby enhancing antibody synthesis.

Of the pro-inflammatory cytokines that have been shown to increase in schizophrenia, IL-6 appears to play a central role in the inflammatory process. Thus there is evidence that the rise in the serum concentration of IL-6 is related to both the duration of the disorder and the resistance of patients to antipsychotic treatment (Zalcman et al., 1994). In addition, there is evidence that IL-6 activates both dopaminergic and serotonergic neurons in the frontal cortex (Kim et al., 2000). As these neurotransmitters have been implicated in the psychopathology of schizophrenia, it is postulated that the increase in IL-6 contributes directly to the psychopathology of the disorder. Moreover, IL-6 also has a non-immunological and non-neurochemical role, such as inducing cellular insulin resistance in hepatocytes (Senn et al., 2002). This could be one of the reasons why incidence of type 2 diabetes is increased in patients with schizophrenia.

In addition to IL-6, it is also apparent that IL-1 increases in the frontal cortex while the expression of IL-1 receptor antagonist decreases in this brain region (Katila et al., 1994; Toyooka et al., 2003). The increase in IL-1 in the brain not only contributes to the inflammatory changes but also activates the hypothalamic–pituitary–adrenal (HPA) axis, an effect that is reflected in the increased response of patients with schizophrenia to any stressful stimulus (Sapolsky et al., 1987; Sapolsky, 2003; Whalley et al., 1989), even though there are reports mentioning hypoactive HPA axis (Hempel et al., 2010) or impaired response (van Venrooj et al., 2010). IL-1 also contributes to the defect in short-term memory seen in many patients with schizophrenia. This occurs due to direct action of the cytokine on the suppression of the long-term potentiation mechanism in the hippocampus (Vereke et al., 2000). In addition to IL-6 and IL-1, other cytokines have also been shown to change in the sera of patients with schizophrenia. For example, IL-2 and IL-4 have been shown to decrease while IFNγ and TNFα increase (Kim et al., 2009), whereas another group reported no differences in IL-2 (Rothermundt et al., 2000). In the CSF there is evidence that the concentration of IL-2 is increased in those patients who relapse following treatment with haloperidol (Mueller et al., 1997b), changes that are associated with the recurrence of psychotic symptoms. The results of these studies suggest that there is substantial evidence for an inflammatory challenge in patients with schizophrenia, although in the more chronic patient with prominent negative symptoms and a poor response to antipsychotic treatment the humoral, anti-inflammatory arm, of the immune system may predominate (Maes et al., 1994; Schwarz et al., 2001b).

Both pro- and anti-inflammatory cytokines are produced by astrocytes, microglia and also neurons, and therefore these cells act as a direct source of inflammatory mediators. The microglia appeared to be activated in schizophrenia and thereby provide the main source of pro-inflammatory cytokines. Conversely, the astrocytes have a largely neuroprotective role in the brain and release anti-inflammatory modulators. In addition, the astrocytes release the neuroprotective peptide S-100 beta. This is raised independent of the type of medication (Rothermundt et al., 2004), which has led to the suggestion that the rise in S-100 beta occurs in response to the neurodegenerative impact of inflammation.

**The effect of antipsychotic drugs on the immune response in patients with schizophrenia**

Both in vitro and in vivo studies have demonstrated that effective antipsychotic treatment of patients with schizophrenia modulates the dysfunctional immune system, but the results of the changes in the balance between the Th1 and Th2 systems are controversial. Thus Wilke and co-workers (1996) demonstrated that the reduction in IFNγ in unmedicated schizophrenic patients was normalized following effective treatment, while Mueller et al. (1997b) showed that the relative number of CD4+CD45RO+ cells, that act as one of the main sources of IFN synthesis, increased in response to antipsychotic therapy. In addition, there is evidence that the
symptoms relative to those treated with risperidone alone (Mueller et al., 1999). The same group has reported that soluble ICAM-1 levels are also increased after short-term antipsychotic treatment, even though both the levels before and after treatment are lower than in healthy controls (Schwarz et al., 2000).

As stated above, increased concentrations of IL-6 are the most consistent findings in schizophrenia research, thereby supporting the view that increased inflammation is associated with the active state of the disorder; effective antipsychotic treatment has been shown to attenuate the elevated IL-6 concentration (Maes et al., 1997; Mueller et al., 2000). The hypothesis of a dysfunctional immune system in patients with schizophrenia is also supported by the blunted reaction to vaccination with Salmonella typhii following their medication with antipsychotics (Ozek et al., 1971).

There are several clinical studies that demonstrate the anti-inflammatory effects of antipsychotic drugs (see Drzyzga et al., 2006). Kim and co-workers (2004) studied the changes in the Th1, Th2 and Th3 cytokines in the serum of drug-naïve patients with schizophrenia before and following antipsychotic treatment and reported that effective treatment increased the serum anti-inflammatory IL-4 concentration and reduced that of the pro-inflammatory cytokine, IFNγ. More recently, experimental studies have also shown that haloperidol and some atypical antipsychotics such as risperidone, olanzapine and clozapine suppressed lipopolysaccharide (LPS)-stimulated TNFα and IL-6 concentrations and increased the concentration of the Th-2 anti-inflammatory cytokine IL-10; haloperidol was without effect! (Sugino et al., 2011). While this study clearly demonstrates that atypical antipsychotics shift the balance from the Th-1 (inflammatory) to the Th-2 (anti-inflammatory) cytokines, it may be argued that LPS treatment of rodent is not comparable with the immune activation that occurs in patients with schizophrenia, and that the Th-2 immune response is not comparable between such species. Nevertheless, such experimental studies do serve to support the clinical studies that provide evidence for the anti-inflammatory potential of atypical antipsychotic drugs.

Both in vitro and in vivo studies have shown that effective treatment of schizophrenic patients with antipsychotics attenuates the inflammatory response. If inflammation plays a crucial role in the psychopathology of schizophrenia, then it seems reasonable to postulate that anti-inflammatory drugs should be of therapeutic benefit in the treatment of the disorder (Greg et al., 2009). Prostaglandin E2 is a major inflammatory mediator in the brain and is synthesized from arachidonic acid by cyclo-oxygenase (COX). Of the two types of COX in the brain, COX-2 is induced by pro-inflammatory cytokines. Celecoxib is a well-established COX-2 inhibitor that is widely used for the treatment of arthritis. A major advantage of celecoxib over many other commercially available non-steroidal anti-inflammatory drugs is its greater lipophilicity. Recent clinical studies have shown that in a prospective, double-blind, randomized trial of risperidone, administered alone or in combination with celecoxib, the addition of the COX-2 inhibitor significantly improved both the positive and negative symptoms relative to those treated with risperidone alone (Mueller et al., 2002). Celecoxib has also been reported to augment the action of amisulpride (Mueller et al., 2010). This is an important ‘proof of concept’ study that will undoubtedly stimulate more detailed studies of the effects of different classes of anti-inflammatory drugs in the treatment of schizophrenia.

The association of immune and neurochemical changes in schizophrenia

Activation of the immune system in schizophrenia occurs not only in the blood but also in the brain. Moreover, the peripheral and central changes are connected not only through immune regulators such as the cytokines, but also via the endocrine and metabolic systems. One of the important systems by which the immune system is linked to neurochemical changes in the brain occurs through the tryptophan–kynurenine pathway. Normally, tryptophan is metabolized to kynurenine by tryptophan 2,3-dioxygenase (TDO) in the liver (Satyanarayana and Rao, 1980). The activity of TDO is increased by tryptophan (Saito et al., 1990) and by cortisol (Salter and Pogson, 1985), whereas indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme that is widely distributed in immune cells, lung, kidney and brain, is increased by pro-inflammatory cytokines such as IFNγ (Carlin et al., 1989; Hu et al., 1995; Taylor and Feng, 1991) and inhibited by anti-inflammatory cytokines such as IL-4 (Musso et al., 1994).

Kynurenine may be further catabolized into either a neurodegenerative or a neuroprotective pathway, depending on the inflammatory status. Thus it may be synthesized into the neurotoxic and apoptotic product 3-hydroxykynurenine (3OHK) by kynurenine-3-monoxygenase (KMO), an enzyme which is induced by the pro-inflammatory cytokine IFNγ (Yasu et al., 1986). 3OHK is also the precursor of the NMDA receptor agonist quinolinic acid (QUIN) that is a potent neurotoxin (Bender and McCreanor, 1985; Chiarugi et al., 2001). Under non-inflammatory conditions, this pathway is balanced by the neuroprotective kynurenic acid (Kyna) pathway in which KYNA acts as an antagonist of the NMDA receptor (Perkins and Stone, 1982) (see Figure 1).

The importance of the tryptophan–kynurenine pathway to the psychopathology of schizophrenia has been investigated by Kim and co-workers (2009), who showed that there was an increase in kynurenine formation and increase in 3OHK relative to Kyna (Myint et al., 2011). It was also observed that there is an inverse relationship between the clinical response to treatment and the CSF 3OHK concentrations in patients with schizophrenia (Myint et al., 2011). Whether 3OHK accumulates or is further catabolized to QUIN is still an open question.

In the brain, the tryptophan–kynurenine pathway is located mainly in astrocytes and microglia (Grant and Kapoor, 1998; Grant et al., 2005) and approximately 60% of brain kynurenine is contributed by the periphery (Gal and Sherman, 1980). The astrocytes produce mainly the neuroprotective KYNA, whereas the microglia and macrophages produce mainly the neurotoxic 3OHK and QUIN (Guillemin et al., 2000, Guillemin et al., 2005a). Under non-inflammatory conditions, the astrocytes remove and metabolize any QUIN produced by the neighbouring microglia (Guillemin et al., 2001). QUIN has been shown to induce apoptosis in human astrocyte culture (Guillemin et al., 2005b), whereas the neuroprotective effect of KYNA against the excitotoxic effect of QUIN has also been demonstrated (Kim and Choi, 1987). Thus it is hypothesized that, in schizophrenia, microglia activation induces QUINA secretion that
Osborne, hyperlipidaemia, hyperglycaemia and hypertension that even dementia (Taubes, 2009; see also Pedersen, 2009). Abdominal which could be causally linked to stroke, asthma, some cancers and importances was emphasized in the recent News Focus article in insulin-dependent metabolic disorders (Must et al., 1999). Its the growing numbers of chronic diseases that are associated with metabolic syndrome?
The role of inflammation and neuroendocrine changes in schizophrenia: a causal link to metabolic syndrome?
The term ‘prosperity’s plague’ has been applied to the link between the growing numbers of chronic diseases that are associated with insulin-dependent metabolic disorders (Must et al., 1999). Its importance was emphasized in the recent News Focus article in ‘Science’, which discussed the mechanisms of insulin resistance which could be causally linked to stroke, asthma, some cancers and even dementia (Taubes, 2009; see also Pedersen, 2009). Abdominal obesity, hyperlipidaemia, hyperglycaemia and hypertension that precede coronary heart disease and type 2 diabetes are important co-morbid factors in schizophrenia (Sui et al., 2007; Citrone and Vreeland, 2008), but what are the possible mechanistic links between these conditions?

**Obesity, inflammation and schizophrenia.** Genetic and environmental factors interact to favour weight gain, and it is now widely recognized that excessive weight gain leads to obesity with concurrent physical ill health. The stores of body fat are normally maintained within a narrow range as part of energy homeostasis, a process which is controlled by the hypothalamus, the brain region that monitors appetite, energy balance and peripheral energy stores. The monitoring of metabolic status is due to such signaling molecules as glucose, insulin, free fatty acids and leptin and ghrelin (Muccioli et al., 2002). Obesity, when it occurs, is due to an active adaptation to elevated body fat rather than a passive process in which fat accumulates. Undoubtedly the genetic background of the individual contributes to the adaptive response to body fat. When energy intake exceeds energy output the resultant nutrient excess triggers responses from the vascular endothelial cells, hepatocytes, myocytes, adipocytes, monocytes and macrophages that causes metabolic dysfunction (Wisse et al., 2007; Rieu et al., 2009), as indicated by an increase in reactive oxygen species generated by the oxidation of glucose and fatty acids by the mitochondria. This contributes to oxidative stress that causes tissue damage and stimulates the inflammatory cascade (De Souza et al., 2005). Long-chain fatty acids and co-enzyme Q also accumulate in conditions of oxidative stress and, when this occurs, reflects a decrease in mitochondrial function. Such changes promote inflammation by activating the C-jun N-terminal kinase (Junk) and nuclear factor kappa-B inflammatory pathways. Thus inflammation is a common end point of obesity, irrespective of its cause.

Of the various factors that contribute to the harmful effects of obesity, white abdominal fat has received particular attention in recent years. It is now recognized that white abdominal fat acts as an endocrine organ that not only regulates fat and nutrient homeostasis but also releases a large number of biologically active substances such as the adipokines, of which adiponectin is particularly important in activating the brain, liver, skeletal muscles and the immune system. In this way the adipokines modulate haemostasis, blood pressure, and lipid and glucose metabolism, and thereby play an important role in cardiovascular function. In addition to the adipokines, adipose tissue also releases pro-inflammatory cytokines (IL-6 and TNFα), acute-phase proteins and leptin. Beyond the regulation of food intake, via the hypothalamus and energy homeostasis, leptin augments the stress response by activating the corticotrophin-releasing factor pathway in the brain, and in this way enhances the HPA axis in addition to the central and peripheral sympathetic nervous system (Muenzberg, 2008; Rebuffe-Serive et al., 1985; Kaneda et al., 2002). Leptin contributes to the inflammation by enhancing the synthesis of cytokines TNFα and IL-6, but its synthesis is also increased by these pro-inflammatory cytokines (Jin et al., 2008). In schizophrenia, as in obesity which is frequently associated with the disorder, there is an imbalance between adiponectin and the pro-inflammatory cytokines TNFα and IL-6 in favour of the latter cytokines (Jin et al., 2008). This explains the vicious cycle between obesity and inflammation and

![Kynurenine Pathway – Beyond IDO](image)

**Figure 1.** Activation of the tryptophan-kynurenine pathway following the actions of pro-inflammatory cytokines and cortisol on indoleamine dioxygenase.
the connection between schizophrenia and obesity through the pro-inflammatory state of the disorder.

Abdominal obesity commonly occurs in schizophrenia (Thakore et al., 2002) and is associated with insulin resistance and the risk of type 2 diabetes (Lois et al., 2008). Obesity, dyslipidaemia and diabetes have serious consequences for the general health of patients with schizophrenia, as they are associated with an increased risk of cardiovascular disease and cancer (Allison et al., 2003; Ladwig et al., 2005). However, concerns have been raised in recent years regarding the metabolic side effects of some atypical antipsychotics that may contribute to an increase in obesity, diabetes and heart disease (Weiden et al., 2004). The increased risk to develop the metabolic syndrome following antipsychotic drug treatment is, in part, related to the propensity of these drugs to induce weight gain (Kraus et al., 1999; Kim et al., 2008). Although all antipsychotics, whether of the first or second generation, can induce weight gain, the relative risk to induce clinically relevant weight changes (above 7%) differs between different antipsychotics (Haddad and Sharma, 2007). Newcomer (2005), for example, has concluded that approximately 25% of antipsychotic-associated cases of the metabolic syndrome do not exhibit weight gain or an increase in abdominal adiposity. This area has been recently reviewed by De Hert et al. (2009).

**Inflammation, obesity, diabetes and schizophrenia.**

The link between obesity and type 2 diabetes is provided by a reduction in insulin function, thereby resulting in a reduction in the transport of glucose into target tissues including the brain. It has been shown that phosphatidylinositol-3-hydroxykinase, a key enzyme in the inositol receptor pathway, is inactivated by the inflammatory mediators such as IL-6 and TNFα that are increased in both schizophrenia and obesity (Demuro and Obici, 2006; van Nimwegen et al., 2008). Another mechanism whereby insulin resistance occurs in obese subjects is due to TNFα down-regulating tyrosine kinase activity associated with the insulin receptor function, increasing the expression of the GLUT-4 glucose transporter and thereby reducing glucose transport into target tissues (Halle et al., 1998). In addition to the subsequent occurrence of insulin resistance, TNFα also stimulates hepatic lipolysis that contributes to dyslipidaemia. Thus in schizophrenia, obesity, combined with inflammation, could play a major role in insulin resistance. While it is unlikely that the inhibition of the insulin-sensitive pathways by inflammatory mediators is the only factor of importance in precipitating type 2 diabetes in patients with schizophrenia, it does emphasize the value of the integrative approach in understanding how schizophrenia is frequently associated with physical ill health.

For over 100 years reports have indicated that abnormalities in glucose metabolism, linked to the occurrence of diabetes, are more frequent in those with a serious mental illness (Kohen, 2004). A lifetime prevalence of 15% was reported by the Schizophrenia Patient Outcomes Research Team in the USA from data obtained before the widespread use of atypical antipsychotics (Bushe and Holt, 2004). In an outpatient cohort, the prevalence rate was 18% and it was noteworthy that the prevalence increased with age, the greatest being in the 60–69 year age group (Citrone et al., 2006). In an attempt to determine the impact of antipsychotic use on the incidence of glucose abnormalities in patients with schizophrenia, Bushe and Leonard (2004, 2007) systematically reviewed the prospective glucose data obtained from 22 published randomized controlled trials and reported that there were no consistent significant differences in the glucose parameters in patients treated with antipsychotics. Where significant differences were reported, it was found that the antipsychotics were being used in doses that exceeded the maximum licensed or labelled dose, and the methodology used, and the reporting of the metabolic data, made interpretation and the drawing of conclusions difficult.

More recently, Bushe has extended the review of glucose abnormalities to include patients with bipolar and major depressive disorders in addition to schizophrenia (Bushe, 2009), and concluded that a major problem in causally relating abnormalities in glucose metabolism to antipsychotics stems from the design of the clinical trials, the frequently high drop-out rates and the lack of primary endpoints for evaluating abnormalities in glucose metabolism. Thus, in future, regular glucose monitoring for all patients with schizophrenia should be the routine, and is particularly important in those patients on long-term antipsychotic treatment.

Clearly, as there is an underlying vulnerability for patients with schizophrenia to develop diabetes, diet and lifestyle should always be an important component of treatment. Diabetes is an important risk factor for heart disease in the general population, and in those suffering from schizophrenia there is already a three-fold increase risk of heart disease. The impact of abnormal glucose metabolism, irrespective of the possible cause, on the increased incidence of heart disease in such patients should therefore be a cause for concern.

**Conclusion**

Although physical ill health, commonly associated with schizophrenia, is frequently attributed to an unhealthy lifestyle associated with lack of exercise, poor diet and smoking, it is now apparent that there are underlying inflammatory processes that could contribute to the metabolic abnormalities that predispose patients with schizophrenia to the obesity and diabetes that precede ill health. The causal contribution of antipsychotic drugs to obesity and type 2 diabetes is at present uncertain, but it is evident that some atypical antipsychotics are more problematic than other atypicals, and the first-generation neuroleptics, in this regard.

There is substantial clinical evidence that there is an increase in inflammatory mediators in patients with schizophrenia that initiate changes in glucose and lipid metabolism and thereby contribute to insulin resistance. While there is some evidence that antipsychotic drugs attenuate the inflammatory changes, physical ill health often remains a major problem. Clearly there is a need to increase the research to obtain a better understanding of the metabolic dysfunction in schizophrenic patients, with the aim of developing treatments that are not only effective in ameliorating the psychiatric symptoms but also in improving the physical ill health of these patients. The mechanisms whereby inflammatory mediators initiate the cellular changes which contribute to dysfunctional physical and mental ill health are being elucidated, but the causes of the vulnerability to chronic low-grade inflammation are still speculative. While the evidence that effective treatment of schizophrenia with antipsychotic drugs lends support to the inflammation hypothesis of schizophrenia, the precise mechanisms whereby this occurs requires further research. Clearly, if anti-inflammatory drugs have antipsychotic effects, as the preliminary studies with celecoxib would indicate (Mueller et al., 2002), it remains to be determined whether this is a property which is
unique to celecoxib, or whether it is a property common to all anti-inflammatory drugs that inhibit the cyclooxygenases.

There are many other questions that also arise from the inflammation hypothesis of schizophrenia, and this short review has posed only the more obvious ones.

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Conflict of interest

The authors declare that they have no conflict of interests regarding the content of this review and that this review has been written entirely by them.

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