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Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia

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ABSTRACT

Schizophrenia is a debilitating psychiatric illness that remains poorly understood. While the bulk of symptomatology has classically been associated with disrupted brain functioning, accumulating evidence demonstrates that schizophrenia is characterized by systemic inflammation and disturbances in metabolism. Indeed, metabolic disease is a major determinant of the high mortality rate associated with schizophrenia. Antipsychotic drugs (APDs) have revolutionized management of psychosis, making it possible to rapidly control psychotic symptoms. This has ultimately reduced relapse rates of psychotic episodes and improved overall quality of life for people with schizophrenia. However, long-term APD use has also been associated with significant metabolic disturbances including weight gain, dysglycemia, and worsening of the underlying cardiometabolic disease intrinsic to schizophrenia. While the mechanisms for these intrinsic and medication-induced metabolic effects remain unclear, inflammation appears to play a key role. Here, we review the evidence for roles of inflammatory mechanisms in the disease features of schizophrenia and how these mechanisms interact with APD treatment. We also discuss the effects of common inflammatory mediators on metabolic disease. Then, we review the evidence of intrinsic and APD-mediated effects on systemic inflammation in schizophrenia. Finally, we speculate about possible treatment strategies. Developing an improved understanding of inflammatory processes in schizophrenia may therefore introduce new, more effective options for treating not only schizophrenia but also primary metabolic disorders.

1. Introduction

Schizophrenia is a multi-system disease that alters the functioning of the central nervous, immune, cardiovascular, and endocrine systems. There is an approximate 20-year reduction in life expectancy associated with schizophrenia, with most of the associated morbidity and mortality attributable to increased rates of type 2 diabetes mellitus (T2DM), cardiovascular disease, and respiratory diseases [1]. Yet, the pathogenesis of schizophrenia remains poorly understood. Genetic studies have provided various associations but have mostly formulated schizophrenia as a polygenic and multifactorial illness with much unknown about the etiology and mechanisms of pathogenesis [2,3].

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In addition to brain dysfunction, many systemic disturbances also occur in schizophrenia. Metabolic dysfunction and cardiovascular disease, including in the form of metabolic syndrome, have long been associated with the illness [4]. Metabolic syndrome is of high clinical relevance in schizophrenia given the impact of the metabolic disturbances on morbidity and mortality in schizophrenia. However, factors contributing to increased prevalence of metabolic syndrome in schizophrenia include a range of behavioral components, many of which correlate with low socioeconomic status, such as smoking, poor dietary habits and low physical activity. Medical components including underlying inflammatory disease in schizophrenia, inadequate management of metabolic disease by care providers, and use of antipsychotic drugs (APDs) are also involved. Critically, virtually all APDs, including first-generation APDs (FGAs) and newer second-generation APDs (SGAs), have been strongly associated with metabolic abnormalities [5,6].

Immunologic dysregulation is increasingly recognized as an important feature of both metabolic disease and schizophrenia and multiple lines of evidence support an etiologic role for inflammation in schizophrenia. Genetic studies have linked schizophrenia to immune and inflammatory genes, and epidemiologic studies have demonstrated associations with autoimmune disease and maternal *in utero* infections [2,7,8]. Nevertheless, the relationships between metabolic disease and schizophrenia are complex. While metabolic disease often co-occurs with schizophrenia, the majority of individuals with metabolic disease do not develop schizophrenia, and not all individuals with schizophrenia develop metabolic disease. This apparent dichotomy may be explained in part by evidence that the pathogenesis of schizophrenia is multi-factorial. Moreover, some of the relationships between metabolic and immunological disturbances may be distinct to the multiple biological subtypes of schizophrenia that are likely to exist. Undoubtedly, much remains to be determined with regards to the role of inflammation in causing schizophrenia as well as in the progression of the illness. While acknowledging the heterogeneity of schizophrenia, it is, however, our view that existing evidence necessitates exploration of inflammatory targets for advancing the treatment of both psychiatric and metabolic aspects of schizophrenia. Improved identification of connections between metabolic disturbances and immunologic dysfunction may also shed light on the mechanisms by which schizophrenia and APDs produce metabolic disturbances separately and in combination.

Here, we discuss new and emerging evidence that immune dysfunction may be integral to the metabolic abnormalities both intrinsic to schizophrenia and those which are exacerbated by APDs. We review evidence of immunometabolic disturbances in schizophrenia and the impact of APDs on those disturbances. Based on these data, we speculate that APDs likely exert a mixture of favorable and unfavorable changes on immunologic abnormalities in schizophrenia that may ultimately promote inflammation with repeated use. Improved understanding of the interactions between schizophrenia pathogenesis, inflammation and metabolism sheds further light on schizophrenia as a multisystemic illness and enables novel treatment strategies aimed at mitigating undesirable metabolic effects of APD therapies.

2. Intrinsic metabolic disturbances in schizophrenia

2.1. Glucose metabolism and insulin

In the pre-APD era, it was already recognized that glucose metabolism is altered in schizophrenia, with multiple studies reporting higher prevalence of diabetes in patients with schizophrenia [9–11]. Furthermore, severity of disease correlated with increased fasting and post-prandial blood glucose levels [12]. More recent work confirmed these findings, showing that glucose homeostasis is altered in first-episode psychosis (FEP) [13]. Furthermore, FEP patients have increased fasting plasma glucose and insulin levels, glucose intolerance, and insulin resistance compared with healthy controls [14]. Although fasting plasma glucose levels are elevated, levels are maintained within the normal range, suggesting compensatory increases in insulin secretion [13]. Furthermore, hemoglobin A1c (HgbA1c) levels are not altered in FEP subjects [14]. Importantly, a recent meta-analysis has confirmed the presence of elevated insulin and decreased leptin, which suppresses appetite, in APD-naïve FEP patients [15]. Moreover, individuals at high-risk of developing schizophrenia more commonly show glucose intolerance compared to healthy controls [16]. However, glucose intolerance does not predict which high-risk individuals go on to develop schizophrenia. Thus, while glucose intolerance and insulin resistance are intrinsic parts of schizophrenia, we contend that they may not have a directly causal relationship with the illness [16]. Nevertheless, metabolic disturbances continue to worsen over the course of schizophrenia [17]. Consistent with this, in the two-year period after initiating treatment, FEP patients demonstrate significant increases in HgbA1c [18], further suggesting intrinsic derangements of fundamental mechanisms of metabolic regulation.

2.2. Lipid metabolism

Similar to disturbances in carbohydrate metabolism, lipid metabolism is also altered in schizophrenia. Approximately 40 % of patients with schizophrenia and associated psychotic disorders have abnormal lipid profiles [17]. APD-naïve patients have lower total cholesterol, LDL and HDL compared to healthy controls [14,19]. In contrast, FEP patients followed over a two-year period after initiating APD treatment demonstrated significant increases in blood triglycerides and total cholesterol, co-incident with reduction in HDL compared to baseline [18]. These data collectively suggest that: 1) subjects with psychotic disorders likely possess lipid abnormalities intrinsic to illness that are present at the time of diagnosis of schizophrenia; and 2) APDs likely exacerbate these underlying dyslipidemias.

2.3. Metabolic syndrome

Higher rates of metabolic syndrome, whose features include hypertension, obesity, and diabetes, have been observed in chronic schizophrenia patients. Quantitatively, patients with chronic schizophrenia are at a four-fold increased risk of abdominal obesity and two-fold increased risk of diabetes and metabolic syndrome when compared with cohort-matched general population controls [20]. Although evidence supports APDs contributing to cardiometabolic risk, there is mounting data pointing to an intrinsic increased risk of metabolic syndrome in APD-free and drug-naïve patients with schizophrenia as well as in their siblings [21].

2.4. Adipokines

Adipokines are cytokines secreted by adipose tissue that affect metabolism and communicate with tissues including the brain, liver, muscle, and adipose tissue, as well as the immune system. Arguably, the most important function of leptin, an adipokine produced by small intestine cells and adipocytes, is inhibition of feeding which is achieved through its action on the hypothalamic arcuate nucleus. Studies of adipokines in APD-naïve FEP patients have repeatably demonstrated decreased blood levels of leptin compared to healthy individuals, with lower leptin levels generally associated with increased hunger [15]. Adiponectin, on the other hand, is the most abundant peptide produced by adipose tissue and is suggested to play a role in preventing insulin resistance and cardiovascular disease [22]. Adiponectin has not been consistently demonstrated to have altered levels in APD-naïve FEP patients [15]. Lastly, ghrelin, which is produced in the stomach and hypothalamus and is important in stimulating appetite and food intake, remains unaffected in APD-naïve FEP patients compared to healthy individuals [15].

2.5. Chronic low-grade inflammation

Several lines of evidence described below support a causal role for inflammation in schizophrenia pathogenesis. This includes consistently elevated blood and CSF cytokines, immune cell and tissue immunologic disturbances as well as genetic studies linking inflammatory and immune genes to schizophrenia. Importantly, the chronic, low-grade inflammation present in people with schizophrenia mirrors what is observed in primary metabolic diseases like T2DM and metabolic syndrome with regard to cytokine alterations, as discussed below. Furthermore, evidence strongly supports immune dysfunction as central to the pathogenesis of metabolic disease. Therefore, we propose that the inflammatory state in schizophrenia may be a key determinant of metabolic dysfunction in people with schizophrenia.

3. Immune dysregulation and metabolic disturbance

The observation that insulin resistance increases during septic infections provided the initial evidence for cross-talk between inflammation and metabolism [23]. Insulin resistance has since been found to accompany immunologic activation states including chronic infections and autoimmune disease [24]. Moreover, adipose tissue has been identified as a major source of inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, and IL-10 implicated in obesity [23]. Indeed, obesity exhibits a unique inflammatory state that is unlike classical acute inflammation as it neither produces overt physical signs of inflammation nor readily resolves [25]. This chronic, low-grade inflammatory state in metabolic disease results in part from nutrient excess, which initiates immune cell activation and perpetuates the inflammatory response [26]. Similar cytokine alterations have been observed in a variety of diseases including cardiovascular disease, Alzheimer's disease, T2DM, metabolic syndrome, cancer, osteoporosis, anemia, chronic kidney disease, and depression [27,28].

3.1. Metabolic effects of cytokines and adipokines

Many cytokines are dysregulated in primary metabolic diseases such as T2DM and metabolic syndrome – diseases characterized by chronic, low-grade inflammation accompanied by insulin resistance. Such inflammatory states are considered to result from complex interactions between enlarged adipocytes and immune cells that infiltrate fatty tissue [29]. These interactions yield abnormalities in various cytokines and other mediators such as adipokines [30] as detailed below and in Table 1.

3.1.1. IL-1β and IL-1Rα

The interleukin-1 (IL-1) pathway is an important regulator of energy homeostasis and weight gain. In the pancreas, IL-1β production is stimulated by high levels of glucose and fatty acids which in turn alters local B cell function and results in insulin deficiency and progression to type 2 diabetes mellitus [31]. Consistent with this, diminished IL-1 signaling is metabolically protective. Mice deficient in the IL-1 receptor (IL-1R) are less vulnerable to high-fat diet-induced insulin resistance, glucose intolerance and inflammatory cytokine production by adipose tissue macrophages [32]. Likewise, treatment of patients with T2DM with IL-1Rα, which counteracts IL-1β activity by blocking IL-1R signaling, improves chronically elevated blood glucose and insulin production, as well as reduces levels of other inflammatory markers including IL-6 and C-reactive protein (CRP) [33]. Similar results have been obtained with IL-1β blocking antibodies in patients with T2DM [34].

3.1.2. IL-2 and sIL-2R

Studies on T cell-related cytokines in metabolic disease have been relatively sparse despite T cells being some of the most prolific producers of cytokines in the body. Increased levels of cytokines produced by key subsets of T cells including type 1 helper T cells (*i.e.*, IL-12), as well as the type 2 helper T cells (*i.e.*, IL-4, IL-5, IL-13) have been associated with metabolic syndrome [35].

3.1.3. IL-6

IL-6 is a pleiotropic cytokine with both pro- and anti-inflammatory functions, as well as important regulatory effects on metabolism in muscle and adipose tissue [36,37]. While dramatically increased levels of IL-6 are found in sepsis and associated with a massive inflammatory response, more moderate elevations of blood IL-6 levels are found in chronic, low-grade inflammatory conditions. Animal studies have demonstrated protective effects of IL-6 signaling against obesity, glucose intolerance, and insulin resistance [38]. In clinical practice, results are more complex. Anti-IL-6R drug tocilizumab reduces HgbA1c in T2DM but leads to weight gain and altered lipid metabolism [39–42].

3.1.4. IL-10

IL-10 is a potent anti-inflammatory cytokine secreted by immune cells in adipose tissue [43]. Thus, by reducing inflammation, IL-10 may improve derangements in metabolism. Indeed, mice treated with recombinant IL-10 are protected against insulin resistance and glucose intolerance [44]. Furthermore, mice overexpressing IL-10 in skeletal muscle were protected against obesity-associated insulin resistance, glucose intolerance, and inflammation [45]. Clinically, decreased blood IL-10 levels have been found in obese individuals with insulin resistance and glucose intolerance compared to healthy controls [46]. This is consistent with reports that low IL-10 levels are associated with metabolic syndrome [47].

3.1.5. TGF-β

A genome-wide association study has provided support for the transforming growth factor-β (TGF-β) pathway involvement in T2DM [48]. Increased TGF-β1 release has been reported in adipose tissue of obese individuals and is enhanced by insulin [49], suggesting that the

Table 1
Metabolic effects of common inflammatory mediators, selected studies.

Mediator	Glucose Intolerance	Insulin Resistance	Weight Gain	Inflammation	First author, year	Study Details
IL-1Rα	↓	–	–	↓	Larsen, 2007	T2DM patients treated with IL-1Rα
IL-1β	↑	–		↑	Cavelti-Weder, 2012	T2DM patients treated with αIL-1β mAB
IL-6	↓	↓	↓		Matthews, 2010	IL-6-deficient mice on high-fat diet
IL-6R	↑				Ogata, 2011	T2DM patients treated with αIL-6R
IL-10	↓	↓			Pennyline, 1994	NOD mice treated with hIL-10
IL-10	↓	↓	–	↓	Hong, 2009	Mice overexpressing IL-10 in skeletal muscle on high-fat diet
TGF-β	↑	↑	↑	↑	Yadav, 2011	Mice Smad3-deficient or treated with αTGF-β mAb on high-fat diet
TNF-α	–	–		↑	Wascher, 2011	Metabolic syndrome patients treated with αTNF-α mAb
TNF-α	↑	↑	–		Uysal, 1997	TNF-deficient mice on high-fat diet
CRP	↑	↑	–	↑	Kaneko, 2011	Mice overexpressing human CRP

chronic hyperinsulinemia of T2DM or metabolic syndrome may further potentiate TGF-β1-driven inflammation. Consistent with this, mice either deficient in Smad3 (a molecule critical for TGF-β signaling) or administered TGF-β1 blocking antibody are protected from high fat diet-induced obesity, glucose intolerance and insulin resistance [50].

3.1.6. TNF-α

The connection between cytokines and metabolic disease was discovered when mice deficient in tumor necrosis factor-α (TNF-α) were protected from obesity-induced insulin resistance, despite weight gain [51]. These results may be due in part to TNF-α's modulation of intracellular signaling by the insulin receptor [52]. However, despite strong associations of TNF-α levels and insulin resistance, clinical trials of TNF-α blocking therapy have been unsuccessful in improving altered glucose homeostasis and insulin sensitivity [53,54]. This suggests a supporting rather than central role for TNF-α in driving metabolic dysregulation.

3.1.7. IFN-γ

Interferon (IFN)-γ is known to inhibit adipocyte differentiation and counteract the effects of insulin resulting in adipocyte insulin resistance [55]. Additionally, IFN-γ stimulates classical macrophage activation or M1 macrophage polarization in adipose tissue. This classical macrophage activation state is considered central to obese adipose tissue inflammation [56]. In obese mice lacking IFN-γ, adipose tissue inflammatory cell accumulation is reduced and glucose tolerance is improved relative to control obese mice [57]. Therefore, IFN-γ plays a central role in metabolism and adipose tissue inflammation, although clinical evidence is lacking at this time.

3.1.8. Adipokines

Adipokines are mainly produced by adipocytes and unbalanced adipokine levels are observed in individuals with obesity [58]. White adipose tissue, especially when accumulated in the abdominal area, is a major source of adipokines in the blood [22]. Leptin and adiponectin, two of the most important adipokines, have functions in fat metabolism and energy homeostasis. High leptin levels and leptin resistance have been reported in individuals with obesity, which lead to increased food intake. On the other hand, decreased levels of adiponectin have been reported in obese individuals compared to healthy controls [59]. Since adiponectin has insulin-sensitizing properties and prevents atherosclerosis [59,60], these diminished levels may accelerate and/or exacerbate cardiometabolic disease in affected individuals.

4. Crosstalk between inflammation and metabolic disturbances in schizophrenia

Some of the earliest reported experimental evidence of the immune system's impact on behavior has been credited to Dr. Vassily K. Khoroshko, who, over a century ago, immunized dogs against brain homogenates and noted behavioral changes [61,62]. This work was foundational in developing the understanding that an immune response against endogenous antigens can generate psychiatric and neurological disorders [63]. Furthermore, these initial studies are consistent with growing evidence that immunologic abnormalities may play an important role in the pathophysiology of schizophrenia [64,65]. Indeed, recent work shows that chronic, low-grade elevation of immune markers is present in people with schizophrenia [66,67]. Evidence from genome-wide association studies has repeatably demonstrated that associations with the major histocompatibility complex (MHC) region, which have frequently been linked to autoimmune diseases, are also linked to schizophrenia [68]. Furthermore, the strongest genetic link identified to date in patients with schizophrenia is to complement component C4, implicating the innate arm of the immune system in schizophrenia pathogenesis [69].

4.1. Cytokine alterations intrinsic to schizophrenia

4.1.1. Blood levels of cytokines

While classically considered immunologic molecules, cytokines exhibit pleiotropic and redundant effects across multiple organ systems, which vary according to the timing, magnitude and context of cytokine signals [70]. Therefore, it is challenging to interpret pathologic significance on the basis of observational studies measuring cytokine levels alone. Nevertheless, elevated levels of cytokines in specific disease states indicate alterations in homeostatic immune mechanisms, which can reveal important mediators warranting additional investigation. A large body of evidence supports alteration of cytokine levels in schizophrenia. A recent meta-analysis of FEP cases reported elevated blood levels of IL-1β, sIL-2R, IL-6, TNF-α, TGF-β, and CRP [71]. These results were largely consistent with a prior meta-analysis on blood cytokine levels in FEP, with the exception that IL-12 was previously reported to be significantly elevated [72]. Separate meta-analyses reported that levels of other cytokines were also altered in FEP including IL-1Rα, IL-4, IL-8, IL-10, IL-12 and IFN-γ, however these findings were less consistent across studies [73,74]. Similarly, blood levels of IL-17 have been found to be changed in acute psychotic episodes. However, these results were also highly variable, with some work showing IL-17 is either increased, decreased or unchanged from controls [75–79]. There is also evidence that IL-23, which stimulates development of IL-17-producing Th17 cells, is highly elevated during FEP and schizophrenia relapses, and the IL-23 elevations persist during treatment [80]. Together, these data linking changes in blood cytokine levels to FEP are largely independent of whatever potential confounds may arise in response to chronic medication treatment. Consistent with this, blood cytokine levels in APD--naïve patients mirror the findings above [72,74].

Although some data have associated decreased blood levels of the anti-inflammatory cytokine IL-10 at presentation in acute psychotic episodes, others found IL-10 to be increased or not different from controls [73,81–83]. Importantly, the cytokine elevations described above can occur without generalized systemic inflammation, as indicated by the absence of elevations in C-reactive protein (CRP), a marker of systemic inflammation [84]. These data are summarized in Table 2.

Chemotactic cytokines or chemokines are also altered in schizophrenia. A recent study demonstrated elevated blood levels of CCL2, CCL4, CCL11, CCL17 and CCL22 in a population of subjects with schizophrenia or schizoaffective disorder [85]. A recent meta-analysis supported the association of elevated levels of CCL2 and CCL3 in both FEP and schizophrenia relapse patients hospitalized for acute psychotic episodes, while CCL4, CCL11 and IL-8 were elevated in schizophrenia relapses but not in FEP [86].

4.1.2. CSF levels of cytokines

Studies of cytokine levels in the cerebrospinal fluid (CSF) from patients with schizophrenia have revealed significant increases in IL-1, IL-6, and IL-8, with a greater increase in IL-6 in the first 5 years after diagnosis compared to subsequent periods [87,88], consistent with similar alterations in the blood (Table 2) [71,72]. In contrast, CSF levels of IL-1α, IL-1β, and IL-2 are not significantly different from those of healthy controls.

Table 2
Cytokines altered in first-episode psychosis.

	Mediator(s)	First author, year
Blood	IL-1β, sIL-2R, IL-6, TNF-α, TGF-β, CRP	Pillinger, 2019
	IL-1β, sIL-2R, IL-6, TNF-α	Upthegrove, 2014
	IL-1Rα, IL-1β, sIL-2R, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, TGF-β, IFN-γ	Goldsmith, 2014
	IL-23	Borovcanin, 2015
CSF	IL-1β, IL-6, IL-8	Gallego, 2018
	IL-6, IL-8	Orlovska-Waast, 2019

4.1.2.1. Genetic evidence for cytokine involvement in schizophrenia. In a recent meta-analysis by Hudson and Miller, schizophrenia risk was associated with polymorphisms affecting the expression of IL-1β, IL-6, and sIL-6R [89]. IL-10 polymorphisms associated with reduced IL-10 expression were also linked to increased likelihood of developing schizophrenia. Similarly, genetic variants corresponding to lower IL-6 activity associate with increased likelihood of developing schizophrenia and metabolic syndrome, further suggesting the interconnectedness of schizophrenia, metabolic dysregulation and inflammation [90,91]. Such findings support a protective role for CRP and IL-6 against the development of schizophrenia [92]. Lastly, TNF-α and TNFR2 promoter polymorphisms have been associated with increased risk of schizophrenia and worsened symptom severity in men [93,94].

4.2. Immune cell alterations in schizophrenia

4.2.1. Microglia

Recent work has increasingly linked microglia, the predominant immune cell population in the brain, to the pathogenesis of schizophrenia [95]. As noted above, the strongest genetic link to schizophrenia is with complement C4, a protein that interacts with microglia as part of physiological synaptic pruning during development [69]. However, it remains to be determined whether C4 contributes to schizophrenia pathogenesis exclusively during synaptic pruning in development, or whether exogenous inflammatory stimuli inappropriately activate C4-dependent processes outside of the normal developmental period. Indeed, microglia are maintained in an active state of surveillance of the brain milieu under normal physiological conditions [96]. Injury or exposure to pro-inflammatory signals such as IFN-γ and TNF-α may activate microglia, causing them to release pro-inflammatory cytokines along with other factors such as cyclooxygenase (COX)-2, nitric oxide and reactive oxygen species (ROS) [97,98].

Initial brain tissue analysis from subjects with schizophrenia supported both increased overall numbers of microglia as well as increases in activated microglia [99,100]. In contrast, subsequent systematic review of postmortem brain tissue studies in schizophrenia was inconclusive, showing that half of the 22 studies reported increased microglia numbers in brain regions including frontal cortex, dorsolateral prefrontal cortex and hippocampus [101]. The remaining studies showed either reduced numbers of microglia in the temporal lobe or no difference from controls [101]. Evidence supporting altered expression of microglia activation markers in schizophrenia is limited. Expression of the microglia activation marker, major histocompatibility complex class II (MHC class II), which is involved in antigen presentation, has been demonstrated in the frontal cortex and hippocampus of subsets of individuals with schizophrenia who had completed suicide and in late-onset schizophrenia patients [99,102,103]. Other microglial markers such as CD68 are unchanged in schizophrenia [104,105].

Microglial hyperactivity may also play important contributing roles in reducing gray matter thickness and diminishing numbers of dendritic spines in schizophrenia – observations repeatedly described in schizophrenia patients (both FEP and chronic) [106–108]. A recent study demonstrated synaptic pruning by microglia derived from patient-derived induced pluripotent stem cells (iPSCs) [109]. Specifically, induced microglial cells (iMGs) reengineered from peripheral monocytes of schizophrenia patients eliminated synapse structures across a range of neural subtypes including telencephalic cortical neurons. This microglial phenomenon is especially important in the brain of at-risk adolescent patients since the brain undergoes major elimination of synapses during late adolescence and early adulthood, a critical period for onset of psychosis [109].

4.2.2. Lymphocytes

In a recent meta-analysis by Jackson and Miller, no changes in levels of lymphocytes were found in either FEP or in chronic schizophrenia subjects compared to healthy controls [110]. Prior work found increased percentages of $CD4^+$ T cells and natural killer (NK) cells in the blood during acute psychotic episodes, as well as increased $CD4^+$ T cells in FEP patients [111]. Furthermore, an increased ratio of $CD4^+/CD8^+$ T cells was determined to be state-dependent, worsening during acute psychotic episodes and resolving with treatment [111]. Increases in both pro-inflammatory Th17 cells and anti-inflammatory regulatory T cells (Tregs) have also been reported in schizophrenia patients, which was inferred to represent a higher T cell "inflammatory set point" [112]. A recent study also indicated that despite increased abundance of Tregs in patients with schizophrenia, functional measures demonstrated reduced Treg activity [113].

Mirroring the pattern of altered blood cytokine levels above, mRNA expression of cytokine receptors (*e.g.*, IL-1R1, TNFR1, and TNFR2) are elevated in blood lymphocytes of subjects with schizophrenia [114]. Additional evidence supporting a role for T cells in schizophrenia pathogenesis includes higher incidence of genetic polymorphisms in genes encoding factors involved in T cell activation or survival including CTLA-4, TGF-β and CD28 in schizophrenia patients [115–118]. Together, there is growing support for low levels of T cell activation that may contribute to disease development in schizophrenia.

4.2.3. NK cells

NK cells are a major lymphocyte subset that, to date, has received less attention in schizophrenia research. Studies have been mixed on whether NK cell numbers in the blood are altered, but most studies have shown no difference from healthy controls [119,120]. DeLisi et al. reported NK cell cytotoxic activity is deficient in schizophrenia, despite normal NK cell numbers [121]. In contrast, other studies showed increased NK cell cytotoxic activity in patients with schizophrenia [122]. Clearly more work is needed to clarify these discrepancies.

4.2.4. Neutrophils

A recent meta-analysis found elevated blood levels of monocytes and neutrophils, as well as total white blood cells in both chronic schizophrenia and in FEP with similar effect sizes [110]. Other reports have consistently documented increased neutrophils counts in patients with schizophrenia [123,124]. Given the consistency of this finding across studies, it has been proposed that the neutrophil-to-lymphocyte ratio be considered as a supportive diagnostic metric [125,126]. During remission of symptoms, the elevated neutrophil-to-lymphocyte ratio decreases relative to periods of relapse [123,127]. Furthermore, clinical scores of positive symptoms in psychosis correlate well with neutrophil counts [123,128]. Functionally, expression of neutrophil gelatinase-associated lipocalin is increased in serum and blood cells from patients with schizophrenia relative to healthy controls [123,129]. Nevertheless, it remains unclear whether the elevation of neutrophils is etiologically related to symptoms of schizophrenia.

4.2.5. Monocytes and macrophages

Blood monocytes are consistently elevated in schizophrenia [110, 123,130]. Data from the CATIE trial have demonstrated a correlation between higher monocyte counts and symptom severity scores in young, non-obese patients [131]. As with the neutrophil-to-lymphocyte ratio, the monocyte-to-lymphocyte ratio is also elevated in schizophrenia [132]. During remission of schizophrenia symptoms, the elevated monocyte-to-lymphocyte ratio decreases relative to relapse [127]. Within blood monocytes, inflammatory gene expression (*i.e.*, transcription/MAPK regulating factors) also rises, suggesting a higher inflammatory setpoint [133]. Significantly, some studies have also described ultrastructural changes and increased IL-1β production in monocytes from unmedicated patients with acute psychosis [134,135]. These data also provide evidence of impaired activation of monocytes in schizophrenia. Indeed, in a case-controlled study of 80 matched pairs of patients, elevated levels of sCD14 and reduced levels of lipopolysaccharide binding protein, typically products of monocytes, correlated with patients later diagnosed with schizophrenia [136].

Macrophages are tissue-resident phagocytes that derive from monocytes or repopulate locally [137]. To date, relatively few studies have focused on monocytes and macrophages in brain tissue of patients with schizophrenia. However, a recent study demonstrated monocytes infiltrating into the prefrontal cortex, as well as macrophages, which are typically retained in the perivascular space, in the brain parenchyma of individuals with schizophrenia with increased peripheral inflammation [138]. Infiltrating macrophages share many markers with microglia and, therefore, are difficult to distinguish from microglia in histologic studies. Given the importance of macrophages in primary metabolic disease and obese adipose tissue inflammation [56], we speculate that these cells not only contribute to the low-grade inflammation in schizophrenia, but likely play important roles in the pathogenesis of the metabolic disease associated with the illness.

4.2.6. Eosinophils

Eosinophils have received relatively little attention in schizophrenia research compared to other cell types. A recent study reported a consistent reduction in blood eosinophils in FEP patients compared to controls that resolves with treatment [123]. On the other hand, a recent meta-analysis reported no difference in levels of blood eosinophils in FEP patients relative to controls [110]. Additional work is needed to discern what roles, if any, eosinophils play in the etiology or treatment of schizophrenia.

4.2.7. Astrocytes

Astrocytes are important mediators of inflammation in the brain. For example, pro-inflammatory stimulation causes astrocytes to release additional pro-inflammatory cytokines such as IL-1β, CCL5, and TNF-α [139]. Study of astrocytes and other glial cells in schizophrenia has been mainly limited to structural imaging studies, measurement of peripheral markers and tissue examination. FEP patients exhibit elevated blood levels of S100 calcium-binding protein B (S100B), a protein expressed predominantly in astrocytes and oligodendrocytes [140]. Blood levels of S100B typically reflect astrocyte damage and BBB permeability, given the role of astrocytes in maintaining the BBB. Moreover, these higher S100B levels correlate with structural changes in the white matter [140]. Acute psychotic episodes are also associated with elevated S100B levels [141], and chronic increases in S100B are associated with more severe negative symptoms [142]. These lines of evidence therefore suggest possible involvement of astrocytes and glial cells in the pathogenesis of schizophrenia.

4.3. Tissue level alterations

4.3.1. Pathway analysis

Transcriptomic analysis of postmortem prefrontal cortex of individuals with schizophrenia revealed pathways associated with innate immune and inflammatory signaling (*e.g.*, TNF-α, NF-kB, p38 MAPK, IL-6 via STAT3, IL-2 via STAT5, IFN-γ, TLR signaling cascades), protozoal infection, as well as autoimmune conditions such as lupus [143]. Consistent with this, another human postmortem brain study employing next-generation sequencing and pathway analysis similarly implicated inflammatory response pathways and identified elevations in IL-1β, IL-6 and IL-8 signals [144]. Moreover, a study assessing the serum protein profile in FEP revealed proteins and small molecules associated with acute or chronic inflammatory conditions and endothelial cell dysfunction [77]. Notably, signals associated with cardiovascular disease and T2DM were also identified, further linking immune system signaling to metabolic abnormalities intrinsic to psychotic illnesses [77].

4.4. Blood brain barrier alterations in schizophrenia

The blood brain barrier (BBB) and choroid plexus jointly regulate passage of cells and molecules including immune modulators into the central nervous system (CNS), normally protecting the brain from changes in body's acute immune responses. Under physiological conditions, capillaries at the BBB come in close contact with neurons to deliver nutrients and regulate a vast array of cellular functions. The endothelial cells of the blood vessel walls are sealed by tight junctions with pericytes and astrocytes on either side acting as additional barriers [145,146]. Several factors can lead to the BBB becoming leaky: reactive astrogliosis, increased expression of leukocyte adhesion molecules, changes in ion channel expression across cell membranes, and leakiness of tight junctions [147,148]. Consequently, only small numbers of leukocytes are allowed into the brain due in part to the low level of expression of adhesion molecules (*e.g.*, ICAM-1, VCAM-1, E-selectin) [149]. However, during an inflammatory response, leukocyte adhesion molecules are upregulated to facilitate leukocyte recruitment across the BBB and into the CNS parenchyma [149]. Indeed, various immune cells are present in the choroid plexus including special $CD4^+$ T cells, macrophages, and dendritic cells [150]. In addition, the choroid plexus is an access point for macrophages to traffic into and out of the CSF in the ventricular space [150]. Intriguingly, peripheral inflammation causes acute inflammatory changes in the choroid plexus, where the BBB is absent, to allow access by peripheral immune cells [151,152]. Peripheral blood cytokines can modulate BBB permeability and expression of leukocyte adhesion molecules [153]. Additionally, several mechanisms of cytokine-mediated communication across the BBB have been described including afferent signaling via the vagus nerve, release from infiltrating immune cells, direct passage through the BBB, self-stimulating release from CNS cytokine reservoirs and stimulation via circumventricular organs [153].

Measuring the ratio of CSF:serum albumin (QAlb) is the gold standard method of studying BBB permeability. As albumin levels under normal conditions are 200 times lower in the CSF than in the plasma, higher levels of QAlb are indicative of an impaired BBB. Many studies have reported increased QAlb levels in schizophrenia patients; however, these studies usually report on a small number of patients without sufficient evidence to infer the effects of APDs [154–157]. Moreover, soluble intracellular adhesion molecule-1 (sICAM1) is proposed to be a reliable indicator of an inflammatory response which can impair the BBB integrity, and high levels of sICAM1 have been associated with elevated CSF albumin levels in subjects with schizophrenia [156]. Elevated CSF albumin and IgG levels are also linked to higher risk of developing negative symptoms in schizophrenia patients [157].

Due to the relatively small number of studies specifically focused on FEP and/or APD-naïve patients, it is difficult to determine whether BBB impairment is a primary contributor to schizophrenia pathophysiology or occurs as a secondary consequence of schizophrenia and/or APD treatment. However, a study conducted by Severance and colleagues found that blood-CSF permeability, CSF:serum albumin ratio, and intrathecal IgG levels were significantly increased in FEP patients compared to healthy controls, supporting the possibility of BBB disruption intrinsic to schizophrenia [156].

Evidence of disrupted cerebral microvasculature can also be indicative of an impaired BBB including abnormal expression of cell adhesion molecules and ion transport channels as has been described in schizophrenia [158]. Disruptions in the population of astroglial cells in both grey and white matter, as well as a reduction in oligodendrocyte number and decreased number of astrocytes associated with the BBB–particularly in the prefrontal cortex (PFC), cingulate cortex, and hippocampus have been reported in studies measuring the levels of GFAP in postmortem brain samples of individuals with schizophrenia [159–161]. Lastly, increased glutamate levels and NMDA glutamate receptor hypofunction may also be implicated in BBB hyperpermeability [162]. Indeed, increased glutamate levels in the thalamus, basal ganglia, and medial temporal cortex have been reported in schizophrenia [163]. This is particularly important given that glutamate can originate from the metabolic and the vesicular pools, both of which may contribute to disease pathology [164].

4.5. In utero and early life contributions to schizophrenia pathogenesis

Analogous to a compromised or leaky BBB, there is increasing evidence suggesting that compromised integrity of the placental barrier may similarly contribute to the altered immune profile and low-grade inflammation associated with development of schizophrenia later in life [165]. To this last point, it has been shown that maternal immune activation (MIA) and the ensuing inflammatory responses produce leakiness of the placental barrier, leading to immune cell passage through the placenta which triggers inflammation in the developing fetal brain [165–167] Linking maternal inflammation to risk of schizophrenia, it has been demonstrated that increased maternal levels of CRP (a marker of systemic inflammation) are associated with an elevated risk of schizophrenia in the offspring [168]. Furthermore, there is a long-standing literature linking schizophrenia to maternal exposure to infectious illnesses which may in turn precipitate MIA [169]. Increased incidence of schizophrenia has been reported following influenza and rubella epidemics [169,170]. In addition, prospective studies investigating birth cohorts found maternal/prenatal infection with rubella [171], influenza [172,173], toxoplasmosis [174], or herpes simplex virus 2 [175,176] to be associated with increased schizophrenia and psychosis risk. Some work also suggests that preventing maternal infection can potentially mitigate schizophrenia risk in the offspring [170,173]. These infectious sources for MIA are especially relevant today given the uncertainties concerning long-term effects of maternal SARS-CoV-2 infection on schizophrenia risk in the midst of the present global pandemic [177].

In utero as well as early life exposures to emotional and/or psychological stress have also been linked to pro-inflammatory states and increased schizophrenia risk [165,178,179]. Early life stressors (*i.e.*, emotional or physical abuse) can also alter immune system function, increase systemic and neuroinflammation, and lead to alterations in brain wiring that may ultimately culminate in higher risk of developing schizophrenia [169,180,181]. Indeed, early life stress modifies microglial function (*i.e.*, phagocytic activity) during brain maturation across multiple brain regions including the hippocampus, striatum, medial prefrontal cortex, and anterior cingulate cortex [165,182–184]. We speculate that these stress-induced changes to microglia may modify synaptic pruning to induce the circuit-level abnormalities that are implicated in triggering a first episode of schizophrenia [109,185,186]. Conversely, environmental enrichment may mitigate or even reverse some of the neuroinflammatory consequences of prenatal or early life stress [165,187–189], suggesting that psychosocial interventions may be used to mitigate risk in people at risk for developing schizophrenia.

Overall, the above findings suggest that inflammation resulting from maternal and/or childhood environmental stressors contributes to schizophrenia risk. Nevertheless, the majority of maternal infections or exposures to early life stress or traumas do not result in schizophrenia in the offspring [169]. This suggests that relationships between MIA, emotional and environmental stressors in early life and schizophrenia risk are complex and heterogeneous [169,190]. Consequently, a multiple hit model has been increasingly proposed where exposures to *in utero* or early life stressors can produce inflammatory states that "prime" the brain to become more sensitive to additional environmental and intrinsic insults acquired later in life [190]. The combination of genetic vulnerabilities and accumulated pre- and postnatal environmental stressors could therefore act as triggers to push vulnerable individuals past the threshold necessary to develop schizophrenia [168,169,191,192].

4.6. Gut-brain axis alterations and schizophrenia

There is growing evidence of a dysfunctional gut-brain axis that may serve as a nexus of the pathological processes associated with schizophrenia, inflammation and dysmetabolism. One of the central aspects of these disturbances involves alterations of the gut microbiome. While the number of studies remains limited, it has been suggested that dysbiosis is a factor in the pathogenesis of schizophrenia [193]. Indeed, the gut microbiome can mediate CNS function and behavior via gut-brain axis and is disturbed in schizophrenia [193–195]. Both unmedicated and medicated patients with schizophrenia have diminished microbiome diversity versus control subjects [194]. Furthermore, fecal transplants from subjects with schizophrenia to germ-free mice resulted in marked brain neurochemical changes (*i.e.*, altered hippocampal glutamine/glutamate and GABA levels) along with behavioral changes associated with hypoglutamatergic function compared to mice receiving fecal transplants from healthy controls [194]. These microbiome alterations have been associated with disruptions in intestinal wall integrity which can lead to bacterial translocation to stimulate immune responses that ultimately result in chronic inflammatory states associated with schizophrenia [196,197]. Importantly, the gut microbiome can influence BBB permeability. It has been shown that the changes in the microbiome composition in patients that lead to chronic inflammation in schizophrenia can also erode BBB integrity and lead to increased BBB leakiness [147,198]. This in turn may foster increased infiltration of the brain with immune cells from the peripheral circulation such as activated microglia that can further exacerbate disease pathology as described above [147,199].

4.7. Similarities in inflammatory features of schizophrenia and metabolic syndrome

FEP patients exhibit intrinsic immunologic alterations that occur simultaneously with subtle metabolic disturbances including altered carbohydrate and lipid metabolism. Nearly all of the cytokines altered in FEP and schizophrenia are similarly affected in metabolic disease, including IL-1Rα, IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α, TGF-β and CRP [200–203]. Thus, we propose that immunologic disturbances may play critical roles in the intrinsic and APD-induced metabolic disease in schizophrenia (Fig. 1).

5. APD effects on immune features of schizophrenia

5.1. Cytokines

5.1.1. Blood

Several meta-analyses have assessed the acute impact of APD treatment on blood cytokine levels (summarized in Table 3). Elevations in IL-1β, IL-6 and TGF-β in people with schizophrenia resolve with APD treatment [72]. In FEP, APD treatment increases sIL-2R and IL-12, while decreasing IL-1β and IFN-γ with the atypical APD clozapine particularly raising sIL-2R levels [204,205]. Moreover, a recent meta-analysis on FEP patients started on APDs reported that IL-1β, IL-2, IL-6, and IFN-γ are reduced with APD treatment, while TNF-α and IL-17 do not resolve to baseline [206,207]. However, another study in patients with juvenile psychosis who were treated with haloperidol or clozapine found increased IL-1β levels in the blood which correlated with response to treatment, while non-responders did not show this IL-1β increase [208]. Overall, these findings suggest that APDs selectively reduce inflammation associated with psychosis.

The chronic effects of APD treatment on blood cytokine levels have been less well studied. Available data supports an acute reduction of proinflammatory cytokine levels including IL-1β and IL-6, that is followed by a return to the baseline elevated levels in schizophrenia by 6 months of treatment with APDs [209]. Additional studies have reported that long-term APD treatment increase proinflammatory cytokine levels [204], which may further potentiate ongoing inflammatory and metabolic abnormalities intrinsic to schizophrenia. Cumulatively, the combination of intrinsic and long-term APD-induced changes in chronic schizophrenia likely leads to marked increases in insulin resistance, weight gain as well as heightened risk of T2DM (Fig. 1C).

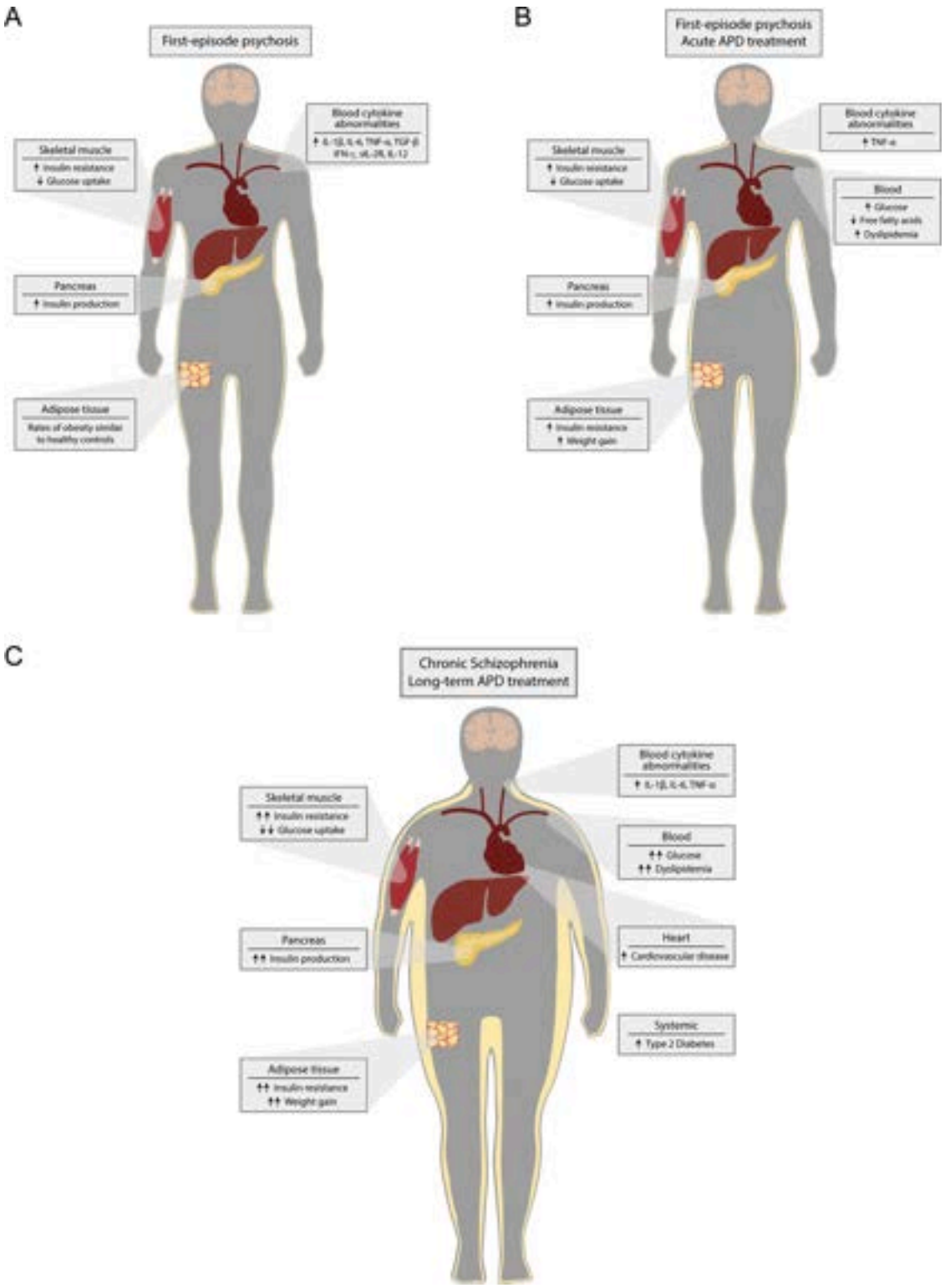

Fig. 1. Inflammation and metabolic dysfunction across time and treatment in psychosis. We present a summary comparing inflammatory and metabolic alterations in individuals experiencing: first-episode psychosis (FEP) who are unmedicated (Panel A), FEP acutely treated with antipsychotic drugs (APDs) (Panel B), or chronic schizophrenia treated with long-term APD therapy (Panel C). We propose that: (1) the metabolic disturbances that arise in unmedicated FEP are due to a combination of metabolic dysfunction in several peripheral organs including skeletal muscle, pancreas, and adipose tissue; and (2) dysregulated inflammatory cytokine modulators in the blood fuel a systemic inflammatory state that further exacerbates the metabolic abnormalities intrinsic to early psychotic illness. Acute APD treatment further exacerbates the metabolic abnormalities intrinsic to FEP, particularly leading to increased insulin resistance in adipose tissue and weight gain, as well as elevated TNF-α levels. Over time, the ongoing inflammatory and metabolic abnormalities intrinsic to schizophrenia and long-term APD therapy APDs lead to even greater longer-term weight gain and insulin resistance and increase risk for type 2 diabetes in chronic schizophrenia. Together, combined immune and peripheral metabolic dysfunction has synergistic effects that culminate in the development of increased weight gain, insulin resistance, dysglycemia and metabolic syndrome, even in the absence of APD therapy.

Table 3
Cytokines altered by APD treatment.

Mediator(s)	Change	First author, year
IL-1β, IL-6, TGF-β	↓	Miller, 2011
sIL-2R, IL-12	↑	Tourjman, 2013
IL-1β, IFN-γ	↓	
IL-2, IL-6	↓	Capuzzi, 2017
IL-1β, IFN-γ	↓	Romeo, 2018

5.1.2. CSF

Studies examining levels of CSF inflammatory markers and the impact of APDs have not identified consistent effects [210]. Though elevated levels of IL-1α and IL-8 relative to the serum have been reported in schizophrenia patients, studies have been limited [211].

5.2. Adipokines

Adipokines exhibit important effects on metabolism and their production is modulated by APDs. APDs, especially SGAs, increase leptin levels in patients and this correlates with significant increases in BMI beginning as early as 2 weeks following treatment initiation [212–214]. Additionally, leptin enhances the hypothalamic pituitary axis (HPA) stress response and promotes production of pro-inflammatory cytokines (IL-6 and TNF-α), which in turn reinforces the production of leptin [22]. While intrinsic metabolic and immune disturbances exist in schizophrenia, weight gain induced by APDs and lifestyle factors also increase leptin production. On the other hand, adiponectin exhibits anti-inflammatory effects, including reducing the inflammatory response by macrophages [215]. Decreased adiponectin has been reported in both obesity and individuals with schizophrenia taking SGAs [216,217]. Adiponectin-knockout mice demonstrate elevated expression of TNF-α and IL-6 and systemic delivery of adiponectin decreases pro-inflammatory cytokine levels, increases anti-inflammatory cytokine levels (such as IL-10) and decreases cell adhesion molecule expression [218].

5.3. Immune cell populations

5.3.1. Microglia

As discussed above, intermittent activation of microglia may be associated with schizophrenia. Efforts have also focused on characterizing APDs' effects on microglial activation, which vary based on tissue, cell type and drug class (*e.g.*, FGAs versus SGAs). Nitric oxide and TNF-α production from activated microglia are inhibited by APDs perospirone and quetiapine, while ziprasidone enhances TNF-α production [219]. Furthermore, in both primary microglia and a microglia-derived cell line, treatment with the APD spiperone inhibited microglial activation and ultimately prevented or diminished production of pro-inflammatory cytokines and nitric oxide [220]. Analysis of the pathways affected by APDs and their impact on microglia raises the possibility that APDs alter microglial function via inhibition of intracellular calcium signaling [221].

5.3.2. Lymphocytes

APDs have been shown to exert mostly suppressive effects on T cell pro-inflammatory activity. For example, blood Th17 cell number decreased in response to 4 weeks of risperidone treatment in patients with schizophrenia and correlated with symptomatic improvement [76]. Furthermore, APD treatment normalizes the increased CD4/CD8 T cell ratios observed during acute psychotic episodes [110,111]. To control for potential confounds related to intrinsic effects of psychotic illness, studies in healthy adults demonstrate inhibition of Th1 polarization and IFN-γ production as well as enhancement of Th2 polarization with clozapine, while IFN-γ production is weakly enhanced by haloperidol [222]. Though blood cytokine levels have indicated that the Th1/Th2 ratio is increased in schizophrenia, this ratio decreases with APD treatment [223]. In a recent study, STAT3 gene expression was downregulated in peripheral blood mononuclear cells along with significant reductions in plasma levels of IL-1β, IL-6, and IL-17A in APD-treated patients [79].

5.3.3. Granulocytes

Elevated neutrophil counts have been consistently reported during acute psychotic episodes and resolve with APD treatment [123,124,127]. On the other hand, SGAs, especially clozapine, can induce agranulocytosis, suggesting a profound interaction *in vivo* between these cells and APDs. To date, however, the precise mechanisms remain unknown [224–226]. A shift towards more immature neutrophils has also been observed after the initiation of therapy with various APDs including both FGAs and SGAs [227,228]. In particular, clozapine inhibits IL-8-induced neutrophil chemotaxis [229]. In contrast, clozapine and haloperidol increase activation markers and microbicidal activity in neutrophils isolated from healthy donors [230], suggesting that APDs may act on abnormalities in neutrophil function intrinsic to illness.

5.3.4. Monocytes

There is evidence demonstrating elevated blood monocyte counts in schizophrenia during acute psychotic episodes, which subsequently improves with APD treatment, although to a lesser degree compared to neutrophils [123,124,127]. These APD effects on monocytes are likely both direct and indirect. Evidence suggests indirect suppression of monocyte activation via APD-induced reduction in IL-1, IL-6 and TNF-α levels [135]. Similarly, APD treatment has been correlated with elevated monocyte production of IL-1β [208]. Prior *in vitro* work also suggests that APDs, including olanzapine and aripiprazole, act directly on monocytes to reduce production and release of pro-inflammatory cytokines IL-1β and TNF-α [231].

5.3.5. Dendritic cells

Previous work investigated whether APDs including risperidone and haloperidol were cytotoxic to human dendritic cells co-cultured with T-cells. These studies showed increased levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α, as well as decreased levels of IL-12, IP-10 and IFN-γ in cells treated with risperidone, while haloperidol had no effect [232].

5.3.6. Astrocytes and other glial cells

Though existing studies remain limited, no significant differences in blood levels of astrocyte marker S100B have been observed between different APDs [233]. In contrast, work assessing the impacts of haloperidol or risperidone on cytokine production in primary rat glial cell cultures showed that the APDs increased IL-10 production in the absence of inflammatory stimulation [234]. When cells were exposed to inflammatory conditions, the APDs inhibited production of TNF-α and IL-1β [234]. Further work is required to better characterize these APD-induced effects on astrocyte and glial function.

5.3.7. Adipocytes

Adipocytes, which store fat, are central to the development of metabolic disease and weight gain. APDs have been reported to induce adipocytes to express proinflammatory genes including TNF-α, IL-1β, IL-8 and MCP-1 via activation of the inflammatory gene transcription factor NFκB [235]. However, the direct effects of APDs on adipocytes have not been substantiated in patients with schizophrenia or in adipose tissue of people treated with APDs. Therefore, this is an active area of research that requires further exploration to understand the relevance of these observations to APD-induced metabolic disease.

5.4. Impact of APDs on the metabolic disturbances via cytokine modulation

While it remains possible that the immunologic and metabolic abnormalities in schizophrenia are at least partially driven by APD treatment, immunologic and metabolic abnormalities are already evident in APD-naïve patients, suggesting that these alterations are intrinsic to the illness. It is therefore noteworthy that many of the metabolic parameters affected by APDs overlap with those intrinsic to schizophrenia, suggesting a common underlying pathway. Although data are relatively limited, it is also important to note that the acute effects of APDs on cytokine levels do not appear to persist, as discussed above. Rather, as metabolic effects including weight gain and insulin resistance becomes more pronounced, the initial APD-induced cytokine reductions reverse and begin to resemble the cytokine alterations often observed in primary metabolic disease [204,209].

Given that APDs modulate cytokine levels, which in turn influence systemic metabolism, APD-induced cytokine changes may be predicted to cause weight gain. The most consistent APD-induced changes in cytokine levels, reductions of IL-1β and IL-6, are in fact both expected to cause weight gain based on data from mouse models [32,38]. Conversely, in a rat hypothalamic neuronal cell line, olanzapine was found to increase IL-6, while aripiprazole decreased IL-10 [236], suggesting acute upregulation of hypothalamic inflammatory pathways. However, clinical data are less clear.

It is difficult to determine how the reduction of both IL-1β and IL-6 by APDs affect glucose intolerance and insulin resistance, given that these cytokines exhibit variable and even opposing effects depending on the nature of the signal (*e.g.*, acute versus chronic elevation of IL-6) [38,40,41]. Moreover, it remains unknown how APDs' effects on systemic inflammation relate to APDs' therapeutic effects in psychotic disorders, requiring further direct examination.

6. Immunometabolic parameters and disease features in schizophrenia

6.1. Cytokine levels and clinical features of schizophrenia

Cytokine levels correlate with clinical features of schizophrenia (Table 4). Cytokines including IL-1β, IL-6 and TGF-β are consistently elevated during acute psychotic episodes and resolve with treatment [72]. Other cytokines, IL-12, IFN-γ, TNF-α, and sIL-2R, remain elevated after remission of symptoms [72]. Conversely, an analysis of the Danish Neonatal Screening Biobank examining fetal dried blood spots showed no evidence of abnormal inflammatory markers at birth for individuals who later developed schizophrenia [237]. However, development of illness in patients at high-risk has been associated with alterations in IL-1β, IL-7, IL-8, matrix metalloproteinase (MMP)-8, cortisol, albumin and salivary cortisol, but not CRP or IL-6 levels [238]. Importantly, lack of treatment response to APDs is correlated with pronounced elevations of IL-2 and IL-6 [239–241] (see Table 4).

Table 4
Inflammatory markers and disease features in schizophrenia, selected studies.

Mediator(s)	Disease feature	First author, year
IL-1β, IL-7, IL-8, MMP-8, cortisol, albumin	Increased likelihood to progress to schizophrenia in high-clinical risk patients	Khoury, 2018
IL-1β, IL-6, TGF-β	Acute psychotic episode	Miller, 2011
IL-12, IFN-γ, TNF-α, sIL-2R	Remain elevated after remission of acute psychosis	Miller, 2011
IL-2, CCL11	Weak correlation with negative symptom severity	Noto, 2015a
TNF-α, IL-6	Prominent negative symptoms or depression	Goldsmith, 2018; Noto, 2015b; Lee, 2017; Stojanovic, 2014
IL-1β	Negative symptom severity	Dai, 2020
sIL-2R, IL-6	General schizophrenia severity	Dahan, 2018
IL-6	Treatment refractory schizophrenia	Lin, 1998
IL-2, IL-6	Treatment refractory schizophrenia	Zhang, 2005
IL-2, IL-6, IL-8, IFN-γ,sTNFR1	Reduced treatment responsiveness	Momtazmanesh, 2019

6.2. Schizophrenia symptom domains and immune alterations

Elevation of particular cytokines correlates with severity of certain schizophrenia symptom classes. One of the most frequently reported clinical correlations has been the association of elevated levels of TNF-α, IL-1β, and IL-6 with the negative symptoms and depressive symptoms in schizophrenia [242–246]. With regard to cognitive deficits that characterize schizophrenia, a recent systematic review determined that elevated CRP levels correlated strongly with worsened cognitive functioning. Worse cognitive functioning was also correlated with elevated TNF-α levels, albeit with less consistent evidence [247]. Other work has shown overall symptom severity correlates with increased levels of both sIL-2R and IL-6 [248]. Blood cytokine abnormalities therefore correlate with many clinical features of schizophrenia as well as treatment responsiveness. Therefore, we speculate that targeting inflammation may provide novel therapeutic targets in patients with a preponderance of negative symptoms. Additionally, recent work has shown that metabolic syndrome is significantly associated with cognitive impairments in patients with schizophrenia, contributing to functional decline throughout the illness [249,250]. Overall, these findings suggest close relationships between metabolic comorbidity, immune alterations and worsened negative symptoms as well as cognitive functioning in patients with schizophrenia.

To date, evidence supports an association of APD-induced weight gain with symptomatic improvement [251]. The strongest associations with APD treatment responsiveness and weight gain have been found with clozapine and olanzapine [252]. With regard to other metabolic alterations including serum lipids, leptin, insulin and triglyceride levels have all been associated with clinical improvement [251]. However, post-hoc analysis of the landmark CATIE trial did not find these same associations, even in the assessment of individual drugs [252], suggesting additional work is required to investigate these relationships.

We also ask how inflammation may influence the above relationships between schizophrenia, treatment response and metabolic dysfunction? While increased IL-6 levels correlate with APD treatment resistance in schizophrenia, these elevations of IL-6 prior to initiation of APD therapy are also associated with APD-induced weight gain [253]. Furthermore, once APD treatment is initiated, changes in cytokine levels during APD treatment also correlate with weight gain [254], supporting the idea that APD effects on inflammation may contribute to metabolic dysregulation. Therefore, we speculate that the effects of APDs on inflammation may be two-fold—on one hand improving cognitive and negative symptoms, while on the other abrogating the protection against weight gain and metabolic dysfunction driven by low grade inflammation. Overall, current evidence supports the association of APD-induced metabolic effects with both changes in the inflammatory state and symptomatic improvement. Consequently, we speculate that APDs, by reducing the positive symptoms of schizophrenia, diminish the stress of patient experiences during psychotic episodes and thus may limit stress-induced inflammation that would otherwise drive detrimental systemic metabolic alterations. However, in the longer term, by driving development of weight gain and insulin resistance via the mechanisms discussed above, these drugs increase overall inflammation that further exacerbates symptomatic and metabolic domains of schizophrenia.

7. Targeting inflammation in treatment of schizophrenia

Many similarities exist between the inflammatory states observed in

schizophrenia and primary metabolic diseases. Indeed, many of the inflammatory mediators elevated in schizophrenia have been directly linked to alterations in metabolism as discussed above. To date, treatment strategies targeting cytokine abnormalities in isolated metabolic disease have been tested clinically, albeit mostly in the context of rheumatoid disease [42,255,256]. Accordingly, we speculate that targeting mediators of inflammation in schizophrenia may similarly improve the metabolic profiles and even the psychiatric pathophysiology of affected individuals.

Of the inflammatory mediators identified, those observed in treatment-refractory disease may be the most high-yield targets including IL-2, IL-6, IL-8 and IFN-γ. It may be that for certain individuals, treatment resistance is driven by reduced capacity of APDs to affect production of particular inflammatory mediators. This hypothesis is substantiated by the observation that prior to diagnosis with schizophrenia, patients at high clinical risk and their first-degree relatives exhibit inflammatory differences from controls [257,258]. Consistent with this, aspirin and celecoxib, drugs which reduce inflammation, can have beneficial effects beyond the effects provided by APDs alone [259]. Aspirin and celecoxib have shown efficacy as adjunctive treatments to APDs when administered to patients with FEP, resulting in greater reduction than placebo in positive and negative symptom scores [259]. Minocycline is an antibiotic with high brain penetrance that exhibits anti-inflammatory properties. Studies investigating the adjunctive benefits of minocycline with APDs have demonstrated significant anti-inflammatory effect and additional improvement of negative and general symptom severity with addition of minocycline [260,261].

Nevertheless, little is known about targeting inflammation in schizophrenia, and few studies targeting altered cytokines in schizophrenia have been published to date. In a randomized control trial with the IL-6R-blocking antibody Tocilizumab, no benefit was found for psychiatric and cognitive symptoms in APD-treated schizophrenia patients with refractory symptoms [262]. Metabolic effects were not assessed in this study. The lack of therapeutic effect may be due to the relative exclusion of Tocilizumab from the brain; although, it may also suggest that IL-6 is not central to schizophrenia pathogenesis. As described above, data from rheumatoid arthritis have shown improvement in metabolic parameters with Tocilizumab. This metabolic improvement resulting from treatment with Tocilizumab may be a secondary effect, resulting from improvement of the primary pathologic mechanism central to rheumatoid arthritis [42,255,256]. In schizophrenia, it remains to be determined whether targeting specific proinflammatory cytokines could differentially affect metabolic and psychiatric disease. If predominant metabolic or psychiatric effects are revealed for individual cytokines, it may be possible to approach treating specific features of schizophrenia according to patients' particular disease features more precisely. Furthermore, patient differences in the profiles of altered inflammatory mediators may explain at least some of the heterogeneity within schizophrenia. It may be that disease features such as elevated IL-6 represent a distinct but overlapping clinical entity. Future work may be able to both define these distinct clinical entities and therefore create more tailored treatment approaches.

Lastly, it is undeniable that lifestyle and environmental factors are also important components that should be considered in treatment of schizophrenia as well as the associated immunologic and metabolic disturbances. Lack of exercise, poor diet, smoking, as well as the possible effects of APD treatment on increased food craving and food preference are all more prevalent in patients with schizophrenia and known to increase insulin resistance, central fat accumulation, and systemic inflammation [263–266]. Developing a better understanding of the interplay between these extrinsic factors with the intrinsic and drug-induced determinants of schizophrenia's psychiatric and metabolic symptoms will be essential in the coming years.

8. Conclusions

In summary, the underlying immune and metabolic alterations in schizophrenia constitute an important underlying component of illness that often precedes clinical diagnosis. We speculate that the underlying pathogenesis of schizophrenia brings about compensatory immunologic and metabolic changes that represent the body's attempt to restore homeostasis. Some immune abnormalities intrinsic to schizophrenia are normalized by APDs, while others are not. On the other hand, the metabolic disturbances intrinsic to schizophrenia are generally exacerbated by APDs to differing degrees. Though the precise nature of the relationships between the psychiatric, inflammatory and metabolic disturbances remains unclear, it is clear that alterations within the three domains are interlinked. There are several possibilities including a common etiology that simultaneously disrupts each system in parallel. Alternatively, dysfunction in one system may drive the disruption of the others [71]. Increasing evidence of connections between the immune system and regulation of metabolism makes it likely the immune and metabolic alterations in schizophrenia are connected via common pathways that are central to schizophrenia pathogenesis. For example, disturbances in the gut-brain axis produced both by schizophrenia and APDs alter peripheral and central modulation of inflammation and lead changes in BBB permissiveness to immune cells – features with major implications on both brain and metabolic function [195]. Such interconnections between immune, metabolic and neuronal function provide critical new mechanistic insights into schizophrenia pathogenesis. Indeed, there is evidence that altered neuronal activity in psychiatric disorders leads to local inflammation and that reduction of CNS inflammatory activity may translate to improvement of psychiatric symptoms [267,268]. We can also speculate that disease-associated changes in neuronal circuit activity increase overall metabolic demands of neurons, and such factors may collectively contribute to or even drive inflammatory changes that further exacerbate psychiatric pathology. Consistent with this, several small studies examining the therapeutic impact of targeting inflammatory processes have shown early promising results as adjunctive schizophrenia treatments [267]. Presently, however, APDs remain the recommended standard of care in treating the psychotic symptoms of schizophrenia. Though these medications may produce metabolic disturbances as described above, ultimately, they improve clinical psychiatric outcomes and quality of life, making the benefits of APD treatment outweigh the risks in the longer term [269]. Nevertheless, further studies investigating new avenues of treatment including adjunctive anti-inflammatory therapies are warranted and, if successful, may lead to a new standard of care. Consequently, greater exploration of the immunometabolic disturbances in schizophrenia will yield new insights into pathogenesis of schizophrenia that are essential for development of such novel therapeutic strategies to target root causes of the illness.

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Author statement

TRP, RA, SW, SMA, RWL, JSB, MKH, and ZF wrote the manuscript. All the authors reviewed and confirmed the manuscript.

Declaration of Competing Interest

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