Role of inflammation in the pathogenesis of schizophrenia: a review of the evidence, proposed mechanisms and implications for treatment.

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The role of inflammation in the pathogenesis of schizophrenia: a review of the evidence, proposed mechanisms and implications for treatment

Running title
Inflammation in schizophrenia pathogenesis

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Abstract

Aim: Over the past several decades, there has been a growing research interest in the role of inflammation in the pathogenesis of schizophrenia. This review aims to summarise evidence in support of this relationship, to discuss biological mechanisms that might explain it, and to explore the translational impact by examining evidence from trials of anti-inflammatory and immunomodulatory agents in the treatment of schizophrenia.

Methods: This narrative review of the literature summarises evidence from observational studies, clinical trials and meta-analyses to evaluate the role of inflammation in the pathogenesis of schizophrenia and to discuss associated implications for treatment.

Results: Epidemiological evidence and animal models support a hypothesis of maternal immune activation during pregnancy, which increases the risk of schizophrenia in the offspring. Several biomarker studies have found associations between classical pro-inflammatory cytokines and schizophrenia. The precise

biological mechanisms by which inflammatory processes might contribute to the pathogenesis of schizophrenia remain unclear, but likely include the actions of microglia and the complement system. Importantly, several trials provide evidence that certain anti-inflammatory and immunomodulatory agents show beneficial effects in the treatment of schizophrenia. Nevertheless, there is a need for further precision-focused basic science and translational research.

Conclusions: Increasing our understanding of the role of inflammation in schizophrenia will enable novel opportunities for therapeutic and preventative interventions that are informed by the underlying pathogenesis of this complex disorder.

Keywords

Schizophrenia; inflammation; immune system; aetiology; treatment

Introduction

Schizophrenia is a complex disorder affecting perception, cognition, emotion and motivation with a global lifetime prevalence of 1% (World Health Organisation, 2001). The precise pathogenesis of schizophrenia is a subject of active clinical research. Over the past several decades, there has been much interest in the relationship between inflammation, the immune system and schizophrenia with potential implications for novel avenues of treatment. The aims of this narrative review are three-fold: firstly, to summarise evidence that implicates inflammation in the pathogenesis of schizophrenia; secondly, to discuss biological mechanisms by which inflammatory processes might give rise to psychosis (with a specific focus on the complement system); and thirdly, to examine evidence from clinical trials of anti-inflammatory and immunomodulatory agents in the treatment of schizophrenia.

1 Evidence for the role of inflammation in the pathogenesis of schizophrenia

Inflammation is a complex biological cascade activated by a noxious stimulus. The process of inflammation will generally signal and activate the immune system to defend against such threats, with the aims of minimising tissue damage and preventing systemic spread. In the acute context, for example physical trauma or local infection, inflammation results in the classical, familiar symptoms of heat, redness, swelling and pain (Scott, Khan, Cook, & Duronio, 2004). When the activating stimulus is successfully withdrawn or treated, the acute inflammatory response appropriately subsides. In contrast, in the context of schizophrenia there is evidence for a chronic, low-grade activation of inflammation and the immune system, which is the subject of this review.

Measurement of inflammation and immune activation requires the use of markers such as cytokines (key signalling proteins that modulate inflammation and the immune response), many of which have been studied as potential biomarkers of schizophrenia. For example, raised serum interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), both classical pro-inflammatory cytokines, are raised in acute psychotic relapses in patients with schizophrenia, and IL-6 levels are found to reduce after anti-psychotic treatment of acute illness (Goldsmith, Rapaport, & Miller, 2016). Meta-analyses have demonstrated increased pro-inflammatory cytokines in patients with established schizophrenia (Brian J. Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). Similar findings have been noted in medication-naïve patients with first-episode psychosis (Upthegrove, Manzanares-Teson, & Barnes, 2014) as well as in people at clinical high risk of psychosis (Khoury & Nasrallah, 2018) suggesting that increased inflammation occurs early in the course of the disorder and is not simply a result of medication use. However, studies measuring inflammatory biomarkers in psychosis have often been cross-sectional in nature with the limitation that the temporal relationship between exposure (inflammation) and outcome (psychosis) cannot be directly inferred. Several longitudinal studies have attempted to address this. For example, elevated serum C-reactive protein (CRP) at age 15 has been associated with increased risk of developing schizophrenia by age 27 (Metcalf et al., 2017). Higher serum levels of IL-6 at age 9 have been associated with a twofold greater risk of psychotic disorder at age 18 (Golam M. Khandaker, Pearson, Zammit, Lewis, & Jones, 2014). Further longitudinal studies are required, but these findings suggest that the increase in inflammatory tone does occur at an early phase, preceding the onset of overt psychotic symptoms.

Biomarker investigations add to the evidence for inflammation and immune dysregulation in psychosis, but may also have translational utility in terms of diagnostic or prognostic value. For example, Perkins et al (2014) identified a panel of 15 analytes (which included several immunomodulatory cytokines) that together distinguished between people at high risk of psychosis who did or did not transit to disorder. Similarly, raised IL12p40 has been associated with increased risk of transition from the at risk mental state to psychotic disorder (Focking et al., 2016). In addition to their association with disorder, inflammatory cytokines may serve as markers or predictors of treatment response. Treatment resistant patients have been found to demonstrate elevated levels of TNF receptor 1 (Noto et al., 2013), IL-2 (Tan et al., 2015), IL-6 (Lin, Kenis, Bignotti, Tura, De Jong, Bosmans, Pioli, Altamura, Scharpé, et al., 1998), IL-8 and IL-10 (Maes, 2002). In patients with first-episode psychosis, raised plasma levels of IL-6 and interferon-γ were found at baseline and after 12 weeks of conventional antipsychotic treatment in non-responders compared to responders (Mondelli et al., 2015). Such findings are important in that they may help to define a subset of patients who do not respond optimally to traditional treatments, but who may benefit from therapies that target other biological pathways such as anti-inflammatory or immunomodulative agents.

Oxidative stress

Intimately related to inflammation is the concept of oxidative stress. This occurs when there is an imbalance between production of free radicals such as reactive oxygen species (ROS) and antioxidant defence mechanisms (Betteridge, 2000) which can result in cell and molecular damage. ROS may be released from damaged tissue, serving as activators of inflammation and immune processes (Lugrin, Rosenblatt-Velin, Parapanov, & Liaudet, 2014). Immune cells such as macrophages and microglia

produce and use ROS to kill pathogens (Bordt & Polster, 2014; Zhai et al., 2012). Thus, oxidative stress may be an inducer as well as a product of inflammation. Given the evidence for low-grade inflammatory activation in schizophrenia, it follows that several studies have also demonstrated evidence for an association with oxidative stress; see (Koga, Serritella, Sawa, & Sedlak, 2016) for a review of this area. A meta-analysis of 44 studies found reduced total antioxidant status in first-episode psychosis and acute relapses of schizophrenia (Flatow, Buckley, & Miller, 2013). Catalase and superoxide dismutase (both antioxidant defence enzymes) were reduced in first-episode psychosis, although catalase was significantly increased in stable outpatients, suggesting it may be a state as opposed to trait marker (Flatow et al., 2013). A recent meta-analysis of first-episode psychosis studies found complementary findings of reduced total antioxidant status in first-episode psychosis patients compared to controls (Fraguas et al., 2018). However, a further meta-analysis of early-onset (before age 18) first-episode psychosis found no significant differences between patients and controls for six markers of oxidative stress, including total antioxidant status (Fraguas, Diaz-Caneja, Rodriguez-Quiroga, & Arango, 2017). This contradictory result might suggest that oxidative stress is time-dependent, although significant study heterogeneity and lack of control for confounding are pertinent considerations. Nevertheless, whether oxidative stress is causal to or a product of inflammation in schizophrenia, it represents a potentially amenable treatment target via therapies with antioxidant properties, such as N-acetylcysteine (M. Berk, Malhi, Gray, & Dean, 2013) and polyunsaturated fatty acids (Pandya, Howell, & Pillai, 2013) as discussed in more detail in Section 3 below.

Origins of inflammation

Having presented evidence that inflammation is associated with schizophrenia, what are the origins of this relationship? The answer to this question remains unclear but is almost certainly multi-factorial.

Firstly, patients with schizophrenia may be genetically predisposed to inflammatory activation. Genome-wide association studies have shown that the major histocompatibility complex on chromosome 6p, known for its key role in immunity, is an important region for single nucleotide polymorphisms in patients with the disorder ("Biological insights from 108 schizophrenia-associated genetic loci," 2014; Consortium, 2014; Purcell et al., 2009). In particular, variation of the complement component 4A (C4A) gene has been linked with schizophrenia risk (Sekar et al., 2016). The complement system is a network of proteins involved in the innate immune response and evidence for its possible role in schizophrenia pathogenesis will be examined in more detail later in this review. Several single nucleotide polymorphisms (SNPs), many with postulated roles in inflammation and immunity, have been identified in schizophrenia (Birnbaum & Weinberger, 2019). However, the effect size for any individual SNP is small, and pathway analyses have been inconsistent in their degree of immune system involvement (Network & Pathway Analysis Subgroup of Psychiatric Genomics, 2015; Wang et al., 2018).

Secondly, prenatal exposure to the influenza virus, as well as to other pathogens (such as *Toxoplasma gondii* and herpes simplex virus type 2) has been associated in several studies with an increased risk of schizophrenia in the offspring (Brown & Derkits, 2010; G. M. Khandaker, Zimbron, Lewis, & Jones, 2012). Maternal immune activation may represent a common pathway, likely in concert with other factors, by which prenatal exposure to infection might increase the risk of neuropsychiatric disorders later in life (Estes & McAllister, 2016). Supporting evidence for this

hypothesis is derived from animal models (Cotter et al., 1993; Farrelly et al., 2015; Giovanoli et al., 2013). For example, in mice, maternal exposure to lipopolysaccharide (which induces an immune-like response) caused offspring to demonstrate behavioural features such as increased anxiety and reduced social interaction (Hava, Vered, Yael, Mordechai, & Mahoud, 2006).

Thirdly, there is a well-established association between psychological trauma in childhood and increased risk of psychosis (Varese et al., 2012). Childhood trauma is significantly correlated with severity of positive psychotic symptoms in people with psychotic disorders (Bailey et al., 2018). Evidence of increased inflammation has been found in adults with a history of childhood trauma. For example, a meta-analysis found significantly higher levels of CRP, TNF-α and IL-6 in adults who experienced abuse as children (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2015). Inflammation appears to be common to both trauma and psychosis, and may represent an underlying biological mechanism that at least partially explains this association. This hypothesis has been studied in mice who were exposed to prenatal immune activation and, subsequently, stress during puberty (Giovanoli et al., 2013). Mice exposed to both environmental factors demonstrated increased markers of neuroinflammation including increased microglial activation in the peripubertal period. It is postulated that prenatal immune activation 'primes' the offspring to increased deleterious effects of stress in puberty (Giovanoli et al., 2013). Howes & McCutcheon (2017) outline the 'two-hit' neurodevelopmental model for schizophrenia whereby perinatal immune activation causes priming of microglia that become excessively activated in response to stress in childhood or adolescence. This leads to abnormal synaptic pruning during this critical neurodevelopmental phase that, in the setting of a general pro-inflammatory state,

contributes to cortical pathology and the characteristic features of schizophrenia (which typically have their onset in the second or third decades of life).

Fourthly, recent research has considered the influence of the gastrointestinal (GI) tract and the microbiome in the pathogenesis of schizophrenia (Severance, Yolken, & Eaton, 2016). For example, coeliac disease, an autoimmune disorder affecting the gastrointestinal tract, has been associated with increased risk of schizophrenia diagnosis (Eaton et al., 2006). Even in patients without apparent GI co-morbidities, it is theorised that increased gut permeability (driven by factors such as stress, infections or brain signalling via the vagus nerve) allows antigens to enter and interact with the systemic circulation, giving rise to an inflammatory response (Kelly et al., 2015). Changes in the microbiome, the ecosystem of bacteria residing in the gut, have been postulated to be relevant to psychiatric disorders such as depression (Dash, Clarke, Berk, & Jacka, 2015). There is evidence for microbiome disruption from elevated plasma markers of bacterial translocation in schizophrenia patients compared to controls (Severance et al., 2013) although more studies examining the microbiome directly are required.

Other proposed origins of inflammation in schizophrenia include obstetric complications (Mittal, Ellman, & Cannon, 2008), prenatal (Q. Shen et al., 2008) and postnatal malnutrition (Radhakrishnan, Kaser, & Guloksuz, 2017) and substance use (Costello, Copeland, Shanahan, Worthman, & Angold, 2013; B. J. Miller, Buckley, & McEvoy, 2018). In reality, a constellation of genetic and environmental factors, each of varying individual risk, likely operate in tandem to increase the risk of disorder in susceptible individuals, and this process may be at least partly mediated by inflammatory mechanisms. We will now consider these possible mechanisms in more detail.

2 Biological mechanisms linking inflammation and psychosis

Whilst an association between inflammation and schizophrenia has been well-established, the underlying mechanisms by which inflammatory processes may eventually give rise to psychotic symptoms are not fully understood. One proposed mechanism relates to the effect of cytokines upon the kynurenine pathway. Pro-inflammatory cytokines, such as IL-6, activate indoleamine-2,3-deoxygenase which shifts tryptophan metabolism into kynurenine (Haroon, Raison, & Miller, 2011). This is subsequently converted to kynurenic acid, an endogenous central nervous system (CNS) N-methyl D-aspartate (NMDA) receptor antagonist (Schwarcz & Pellicciari, 2002). NMDA receptor hypofunction has been implicated for some time in schizophrenia pathology (Carlsson & Carlsson, 1990).

Other proposed mechanisms involve toll-like receptors (TLRs), found on cells of the innate immune system, which recognise molecular patterns unique to pathogens (Medzhitov, 2001). It is theorised that pathogenic molecules from maternal infections may be the source of activation of some TLRs, although this remains to be determined conclusively (Venkatasubramanian & Debnath, 2013). Activation of TLRs leads to downstream signalling pathways and production of pro-inflammatory molecules, including cytokines (Takeuchi & Akira, 2010). Over-activity of pathways involving TLRs 2, 4, 8 and 9 has been associated with psychosis (McKernan, Dennison, Gaszner, Cryan, & Dinan, 2011). TLR-induced release of IL-1β, IL-6, IL-8 and TNF-α were found to be significantly higher in patients with schizophrenia and bipolar disorder treated with specific TLR agonists compared to healthy controls (McKernan et al., 2011). Furthermore, TLR-4 was found to be overexpressed in post-mortem brains of schizophrenic patients (MacDowell et al., 2017).

The blood-brain barrier

It cannot necessarily be directly inferred from evidence of increased peripheral inflammatory biomarkers that inflammation is concurrently increased in the CNS. Nevertheless, evidence of increased central inflammation in schizophrenia comes from studies of cerebrospinal fluid (CSF). A recent meta-analysis found significant increases in IL-6 and IL-8, among several other inflammatory measures, in CSF samples from patients with schizophrenia compared to healthy controls (Orlovska-Waast et al., 2018). The temporal and pathogenetic relationships between peripheral and central inflammation in schizophrenia remain unclear. Cytokines are relatively large molecules that do not easily permeate across an intact blood-brain barrier (BBB). However, Capuron & Miller (2011) summarise three pathways by which peripheral cytokines might influence the CNS. Firstly, pro-inflammatory cytokines might access the brain via the circumventricular organs (a humoral pathway). Secondly, cytokines in the periphery may stimulate the vagus nerve leading to activation of the nucleus of the tractus solitarius (a neural pathway). Finally, cytokines can stimulate microglia to recruit monocytes (a cellular pathway).

Notwithstanding these theoretical shortcuts around the BBB, dysfunction of the BBB itself may occur in psychosis. Peripheral biomarkers of BBB dysfunction have been found to be elevated in the setting of schizophrenia. In a meta-analysis of case-control studies, blood levels of S100B (classically considered a marker of brain damage and BBB dysfunction) were raised by 76% in patients with schizophrenia compared to controls (Aleksovska et al., 2014). Peripheral levels of markers of endothelial cell adhesion such as intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1 are aberrant in schizophrenia (Nguyen et al., 2017) and these changes may be stage-dependent (Stefanović et al., 2016). Pollak et al (2018) summarise further evidence for BBB dysfunction from studies of CSF, post-mortem studies and

neuroimaging. Taken together, there is evidence of increased BBB permeability in psychosis and this provides a plausible mechanism by which pro-inflammatory cytokines from the periphery could cross the BBB and directly influence inflammation in the CNS. However, once inside the CNS, how do cytokines exert their effects? The answer may relate to microglia, the resident immune cells in the CNS.

Microglia

There is evidence for activation of microglia in schizophrenia; in a meta-analysis of post-mortem studies, microglial density was significantly increased in the brains of schizophrenia patients compared to controls (van Kesteren et al., 2017). Neuroimaging by positron emission tomography has also demonstrated microglial activation, both in patients with established schizophrenia as well as people at high risk of the disorder (Bloomfield et al., 2016). Microglia play an important role in synaptic pruning (Hong, Dissing-Olesen, & Stevens, 2016) and their over-activation, induced by a heightened inflammatory state, might help to explain the evidence of synaptic loss associated with schizophrenia (Osimo, Beck, Reis Marques, & Howes, 2018). It is important to note that alterations in microglial function (and inflammation more generally) are not specific to the pathology of schizophrenia and have been demonstrated in other psychiatric disorders including depression, bipolar disorder and autism (Goldsmith et al., 2016; Réus et al., 2015) tentatively suggesting some commonality in the underlying pathogenetic mechanisms of these differing clinical phenotypes.

Thus far, immune and inflammatory processes have been discussed as being generally upregulated in schizophrenia. Further precision in our understanding may be gained by focusing on specific aspects of these processes. The complement system is an example of a specific component of the immune system for which evidence is

accumulating to implicate its involvement in the pathogenesis of schizophrenia, to which our attention now turns.

The complement system in schizophrenia

The complement system is a group of plasma proteins representing a key component of the innate immune system, and an adjunct to adaptive immune processes. The system functions as a cascade activated by foreign or damaged cells or debris along one of three pathways (the classical, alternative and lectin pathways) that converge on a terminal pathway involving formation of a membrane attack complex. Complement system proteins have a range of functions in immunity and defence from infection, including opsonisation, promotion of phagocyte function as well as B cell activation, maintenance and elimination (Sarma & Ward, 2010). When control of the system becomes dysregulated, or the response is inappropriately directed toward self-antigens, the complement system may contribute to disease. Complement system dysregulation has been associated with several neurological disorders that have psychiatric manifestations, such as systemic lupus erythematosus (Popescu & H. Kao, 2011), multiple sclerosis (Ingram, Hakobyan, Robertson, & Morgan, 2009; Michailidou et al., 2016) and epilepsy (Maja Kopczynska et al., 2018). The complement system is also relevant to the pathogenesis of neurodegenerative conditions such as Alzheimer's disease (VanItallie, 2017), where mouse models have shown that complement proteins and microglial cells contribute to synaptic loss (S. Hong et al., 2016).

There are several lines of evidence linking the complement system to the pathophysiology of schizophrenia (Nimgaonkar, Prasad, Chowdari, Severance, & Yolken, 2017). As previously mentioned, Sekar et al have shown that on a genetic level, alleles of the genes encoding complement component 4A (C4A) and C4B are associated with schizophrenia (Sekar et al., 2016). Moreover, they demonstrated that this

correlated with increased levels of C4A mRNA in post-mortem brain tissue from schizophrenic patients and that the C4 proteins were expressed at synapses. Studies have shown complement proteins C1q and C3 to be expressed at synapses in the rodent brain and, together with microglia, these proteins mediate synaptic elimination in post-natal neurodevelopment (Stephan, Barres, & Stevens, 2012; Stevens et al., 2007). It is therefore plausible that aberration of the complement system at least partially explains the observation of reduced synaptic density in schizophrenia (Osimo et al., 2018) although further confirmatory evidence in humans is required to advance this hypothesis.

From a serological perspective, individual complement proteins, including C1, C1q, C2, C3, C4 and C5, from the sera of schizophrenic patients have shown increased haemolytic activity compared to controls (Shcherbakova et al., 1999). However, another study showed increased haemolytic activity of C1, C3 and C4 but decreased activity of C2 compared to controls and no mean difference in total complement haemolytic activity between disease and control samples (Hakobyan, Boyajyan, & Sim, 2005). Studies have also measured complement proteins directly using techniques such as nephelometry and enzyme-linked immunosorbent assay (ELISA). Several such studies have demonstrated increased levels of complement proteins such as C3 and C4 (Ali et al., 2017; Maes et al., 1997; Santos Soria, Moura Gubert, Cereser, Gama, & Kapczinski, 2012) although contradictory results have also been reported (W. Hong et al., 2016; Mayilyan, Dodds, Boyajyan, Soghoyan, & Sim, 2008; Schwarz et al., 2012). Studies measuring complement system proteins serologically have used heterogenous methods and patients at various stages of disorder or clinical status (for example acute psychosis compared to remission), which may account for some of these inconsistencies. Indeed, a recent study found differences in levels of complement

proteins depending on the stage of disorder; mean C4, for example, was increased in chronic schizophrenia patients compared to controls, but this finding did not hold in first-episode psychosis (FEP) patients (Laskaris et al., 2019). Further, the effects of medication and other confounders (such as BMI) have often not been adequately controlled, calling for further studies that focus on earlier stages of disorder.

In a recent study Kopczynska and colleagues measured 11 complement proteins by ELISA in serum samples from FEP patients compared to controls (M. Kopczynska et al., 2017). When measured individually, only one (the terminal complement complex) was found to be significantly greater in patients. However, a logistic regression model implicated several complement analytes (including, among others, C3, C4 and C5) and the model demonstrated moderate performance in distinguishing cases and controls. In a recent study that used discovery-based proteomic techniques to measure proteins in blood samples taken at age 11 from young people who went on to develop the extended psychosis phenotype at age 18, several proteins were significantly altered in this group compared to controls who did not (English et al., 2018). The complement and coagulation systems were most significantly implicated. Of interest in relation to the stress-diathesis model of schizophrenia, exposure to stress has been associated with upregulation of the complement pathway in animal models (Melanie Focking et al., 2018) suggesting a novel possible biological mechanism for the known relationship between stress exposure and risk of psychosis as previously discussed. These findings suggest that dysregulation of the complement system occurs early and may be predictive of increased risk for disorder in later life. Indeed, increased levels of C1q have been found in mothers whose children developed psychosis compared to mothers whose offspring had no psychiatric disorder, suggesting that prenatal exposure may be relevant (Severance, Gressitt, Buka, Cannon, & Yolken, 2014). Akin to certain

other markers of inflammation, preliminary evidence suggests that dysregulation of specific complement proteins may also be associated with poor response to antipsychotic drug treatment (M. Focking et al., 2018).

3 Anti-inflammatory drugs and immunotherapies in schizophrenia

Given the growing understanding of the role of inflammation in psychosis, it follows that some patients might benefit from therapies that target inflammatory processes. There are several different classes of anti-inflammatory agents with varying mechanisms of action used to treat a range of infectious and immunological diseases. Below, we review evidence from trials and meta-analyses for the most-studied classes of these drugs. Some have shown promise in treatment of schizophrenia, particularly as adjuncts to standard therapies, but none are yet part of standard clinical practice.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of drugs that target inflammation by inhibition of the enzyme cyclo-oxygenase (COX) which produces pro-inflammatory prostaglandins. Aspirin (acetylsalicylic acid) was the first such drug to be widely used and has more recently been tested as an adjunct in the treatment of schizophrenia. In a double-blind trial of 70 patients with established schizophrenia, participants were randomised to receive aspirin or placebo in addition to standard antipsychotic therapy. Treatment with aspirin showed small but significant reductions in total and positive symptom scores on the Positive and Negative Syndrome

Scale (PANSS) (4.86 and 1.57 points respectively) at three months (Laan et al., 2010). Another trial found patients randomised to aspirin showed significant reductions in general psychopathology but not total, positive or negative PANSS scores at four months (Weiser et al., 2012). In a meta-analysis the combined effect size for both trials was small (0.3) but significant (Sommer et al., 2013).

Traditional NSAIDs inhibit, to varying degrees, both isoforms of the COX enzyme (COX-1 and COX-2) (Cashman, 1996). It is thought that their troublesome gastrointestinal side-effects are primarily mediated by COX-1 inhibition, while their anti-inflammatory actions relate to inhibition of COX-2. Celecoxib is a selective COX-2 inhibitor developed as an anti-inflammatory agent with theoretical minimisation of the problematic effects of COX-1 inhibition. In their recent meta-analysis, Zheng et al (2017) identified eight double-blinded randomised trials of celecoxib as adjunctive treatment in the setting of schizophrenia (626 patients in total). The combined effect size for change in total PANNS score was not significant. However, in subgroup analyses, a small but significant effect was observed for the three included trials with predominantly first-episode psychosis patients (standardised mean difference: -0.47). The authors concluded that celecoxib may have a role as an adjunct in the early phase of psychosis (Zheng et al., 2017). Although celecoxib theoretically minimises the side-effects of NSAIDs on the gastrointestinal tract, there is evidence of increased cardiovascular risk associated with its use (Caldwell, Aldington, Weatherall, Shirtcliffe, & Beasley, 2006) which may limit its therapeutic potential in patients with schizophrenia, who are already at greater risk of cardiovascular disease (Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014).

N-acetyl cysteine

N-acetyl cysteine (NAC) is a precursor of glutathione which, in line with findings of oxidative stress, has been found to be deficient in schizophrenia (Do et al., 2000). NAC has antioxidant properties as well as anti-inflammatory actions arising from inhibition of TNF-α, IL-1β and IL-6 (Palacio, Markert, & Martínez, 2011). In their meta-analysis, Sommer et al (2013) found that NAC was one of three agents (the other two were aspirin and estrogen) for which a significant beneficial effect was found (weighted effect size: 0.45). This was, however, based on results from only one trial (Michael Berk et al., 2008). A more recent trial of adjunctive NAC compared to placebo in 84 patients with chronic schizophrenia found significant improvements in PANSS positive, negative and general psychopathology scores in those randomised to NAC (Sepehrmanesh, Heidary, Akasheh, Akbari, & Heidary, 2018). A 12-month trial demonstrated improvements for NAC compared to placebo for PANSS total, negative and disorganised thought scores (Breier et al., 2018). Regarding cognitive effects, a trial of 58 patients with psychosis randomised to NAC or placebo found significantly higher working memory performance (Rapado-Castro et al., 2016) although these cognitive effects were not replicated in the trial by Breier et al (2018).

Minocycline

Minocycline is a tetracycline antibiotic with anti-inflammatory and neuroprotective properties (Garrido-Mesa, Zarzuelo, & Gálvez, 2013). It has also been shown to inhibit microglial activation (Kim et al., 2004) suggesting a potential benefit in the pathogenesis of schizophrenia. Xiang et al (2017) conducted a meta-analysis of eight randomised controlled trials of minocycline in schizophrenia (548 patients). Compared to placebo, adjunctive minocycline treatment demonstrated significant improvement in total PANSS or Brief Psychiatric Rating Scale score (standardised mean difference: -0.64). No impact was noted on general functioning, but positive,

negative and general symptom scores significantly improved (Xiang et al., 2017). However, a recent well-conducted randomised controlled trial of 12-month adjunctive minocycline versus placebo in first-episode schizophrenia-spectrum disorder patients (Deakin et al., 2018) found no difference in positive, negative or total PANSS score, or on inflammatory biomarkers (IL-6 and CRP), raising doubts about the efficacy of this treatment.

Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids with several biological effects, including antioxidant and anti-inflammatory properties. In a meta-analysis of 68 randomised trials, supplementation with omega-3 fatty acids significantly reduced TNF-α, IL-6 and CRP levels in healthy subjects as well as those with chronic autoimmune and non-autoimmune diseases (Li, Huang, Zheng, Wu, & Li, 2014). Promising results have been described for omega-3 fatty acids as interventions to reduce symptoms in depressive disorder (Mocking et al., 2016). In schizophrenia, a meta-analysis of double-blind placebo-controlled randomised trials of omega-3 fatty acids as augmentative agents found no beneficial effect on psychotic symptoms (Fusar-Poli & Berger, 2012). However, it is possible that any beneficial effects are most (or perhaps only) apparent in the early stages of disorder. For example, a randomised controlled trial of supplementation for six months with omega-3 fatty acids (in addition to standard antipsychotic treatments) in patients with first-episode psychosis found significant benefits compared to placebo in total PANSS score, general psychopathology, depressive symptoms and level of functioning (Pawełczyk et al., (2016). It is also notable that in a trial of omega-3 fatty acid supplementation versus placebo in people at high risk of psychosis, there were fewer transitions to psychosis in the group who received the intervention (Amminger et al., 2010). However, this finding

was not replicated in a recent, larger trial (McGorry et al., 2017) and thus overall the evidence remains inconclusive. Further, if omega-3 fatty acids do have beneficial effects in the early stages of psychosis, it is unclear whether these effects are mediated by their anti-inflammatory functions or via other properties such as modulation of membrane proteins and cellular signal transduction (Fenton, Hibbeln, & Knable, 2000).

Statins

Statins are widely used in cardiovascular disease for their cholesterol-lowering properties via inhibition of 3-hydroxy-3-methylglutaryl co-enzyme A reductase. However, it is increasingly acknowledged that statins also exert several anti-inflammatory effects; for example, by inhibition of the pro-inflammatory actions of endothelial and T cells (Bu, Griffin, & Lichtman, 2011). Their use as adjunctive treatments in schizophrenia was examined in a meta-analysis of six trials (H. Shen et al., 2018). Statins were significantly superior to placebo with regard to improvements in PANSS positive (standardised mean difference -0.31) and negative scales (standardised mean difference -0.31). In consideration of the increased cardiovascular risk already associated with schizophrenia, statins might appear an attractive adjunct to standard therapy. It remains unclear however whether any improvement associated with their use is driven by their proposed anti-inflammatory actions, either alone or in combination with other effects.

Immunomodulatory therapies

There are relatively few trials investigating the use of immunosuppressant drugs in psychosis. A small trial assessed the efficacy and safety profile of azathioprine in treatment-resistant schizophrenia patients with elevated platelet-auto-antibodies (Levine et al., 1997). Of the 11 patients, seven evidenced reduction in platelet auto-antibodies (previously described by the same team as being implicated in schizophrenia

pathophysiology) while two showed improvement in symptoms. However, leucopenia was described as a noteworthy side effect.

Monoclonal antibodies are immune proteins that target specific antigens such as cytokines or their receptors. The role of tocilizumab, an IL-6 receptor antagonist, was studied in a small trial (Brian J. Miller, Dias, Lemos, & Buckley, 2016). Tocilizumab was administered in two infusions to the five patients who completed the trial over this eight-week study. There was a significant improvement in cognition after treatment as evidenced by higher scores in verbal fluency and digit symbol coding (a measure of processing speed). Moreover, another strength is that compared to other classes of anti-inflammatory drugs, cytokine therapies more precisely target the immune system as opposed to other metabolic pathways (Brian J. Miller & Buckley, 2016). However, the small sample size and uncontrolled nature of this trial are significant limitations. A more recent trial randomised 36 participants with stable schizophrenia to 3 monthly adjunctive tocilizumab or placebo infusions, but found no impact on symptoms or functioning at 12 weeks (Girgis et al., 2017). While further trials are awaited, challenges to the clinical use of monoclonal antibodies for treatment of schizophrenia include the lack of direct action upon the brain, as well as the potentially dangerous side effects of immunosuppression.

Taken together, evidence suggests that anti-inflammatory agents have a potential role in the treatment of schizophrenia particularly as adjuncts to standard therapies, although effect sizes are generally small to moderate. The studies conducted to date have however often been of low sample size and frequently focus on short-term outcomes. Longer and larger studies will be of use in further delineating the role of anti-inflammatory treatment in schizophrenia. It may also be useful in future studies to stratify patients according to their inflammatory status at baseline, since a subset of

patients with higher inflammatory tone may be more likely to respond to anti-inflammatory treatments (G. M. Khandaker, Dantzer, & Jones, 2017). Countering this view, a recent meta-analysis examined the variability and distribution of peripheral cytokines in patients with first-episode psychosis compared to controls (Pillinger et al., 2018) and found that the variability of key pro-inflammatory cytokines in first-episode patients was reduced relative to controls. If an immune subtype indeed exists, then we might have expected the variability to be increased in patients rather than reduced. On the other hand, studies have successfully identified subpopulations of patients with immune activation that differ with respect to clinical characteristics such as phenotypic presentation (Fillman et al., 2016) and treatment resistance (Lin, Kenis, Bignotti, Tura, De Jong, Bosmans, Pioli, Altamura, Scharpe, et al., 1998; Maes et al., 2002), suggesting utility in this approach. In future, use of precision immunotherapies specifically targeted towards certain aspects of the immune system or inflammatory pathways, such as the complement system, may yield improved outcomes while limiting the off-target effects of more conventional anti-inflammatory agents.

Complement system therapeutics

As we have previously outlined, the complement system is a specific component of the immune system which may be a potential therapeutic target given the growing evidence for its role in schizophrenia. Development of drugs that target the complement system is an active area of research. Eculizumab, a monoclonal antibody to C5, is already used in the treatment of paroxysmal nocturnal haemoglobulinuria and atypical haemolytic uraemic syndrome (Tomlinson & Thurman, 2018). Other agents are currently under active investigation at preclinical and clinical phases, including for disorders such as myasthenia gravis (Howard, 2017), glaucoma (Williams et al., 2016) and rheumatic diseases (Thurman, Frazer-

Abel, & Holers, 2017). Within the field of neuropsychiatry, a recent preclinical study using a mouse model showed activation of C3 after traumatic brain injury was associated with activation of microglia and reduced synaptic density; inhibition of the complement system led to improved cognitive and functional recovery (Alawieh, Langley, Weber, Adkins, & Tomlinson, 2018). Considering the dysregulation observed in several complement proteins (including C1, complement factor H and complement factor I) before the development of the extended psychosis phenotype (English et al., 2018), agents which inhibit these proteins may have therapeutic or disease prevention effects. Some already exist; the C1 esterase inhibitor conestat alfa (Cruz, 2015), for example, is used in the treatment of hereditary angioedema. Re-purposing of such agents may provide impact in the treatment and prevention of psychiatric disorder. Challenges in the development of drugs targeting the complement system include potential side effects such as increased risk of infection (Harris, 2017) and, importantly for psychiatric disorders, ensuring enough drug reaches and remains active within the brain (Morgan, 2017). To date there have been no studies investigating the role of complement therapies specifically for schizophrenia. However, the evidence outlined above builds a convincing case for exploratory preclinical studies in this area.

Conclusions

Epidemiological, serological and neuroimaging studies suggest there is evidence of increased inflammation in patients with schizophrenia (see the Table for a summary of the major points in this review). These inflammatory changes may occur at an early stage, preceding the onset of clinical symptoms. It is possible that immune activation in the perinatal period sets the stage for neurodevelopmental changes (such

as increased synaptic pruning, mediated by microglia) which increase the risk of schizophrenia later in life, and these effects may be compounded by the pro-inflammatory impact of childhood trauma. Improving our understanding of the aetiology of schizophrenia is undoubtedly a worthwhile endeavour, but the maximal translational benefit for patients will relate to potential impact upon the treatment of this complex disorder. To date, mixed clinical effects have been noted in clinical trials of anti-inflammatory agents in schizophrenia. A more focused approach using drugs that target specific immune and inflammatory pathways, and perhaps targeting patients with heightened inflammatory tone at baseline, may yield improved outcomes in this regard. Critically, this will depend on an increased understanding of the precise mechanisms of inflammatory and immune dysfunction in schizophrenia, for which further research is required to advance theory into clinical practice.

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Conflict of interest statement

The authors declare no conflicts of interest relevant to this work.

Table: Evidence, mechanisms and treatment of inflammation in schizophrenia: a summary

Evidence for the role of inflammation in the pathogenesis of schizophrenia	• Schizophrenia is associated with chronic low-grade activation of inflammation and the immune system • This is evidenced by biomarker study findings such as increased levels of pro-inflammatory cytokines in first-episode psychosis and established schizophrenia • Oxidative stress occurs with inflammation and has also been associated with schizophrenia • The origins of inflammatory and immune activation in schizophrenia are complex but may include: 1. Genetic predisposition 2. Prenatal exposure to infections 3. Psychological trauma 4. Gastrointestinal tract and microbiome 5. Other environmental exposures such as obstetric complications, malnutrition and substance use
Biological mechanisms linking inflammation and psychosis	• Not fully understood. Kynurenine pathway activation may be implicated via NMDA antagonism • Toll-like receptors activate pro-inflammatory molecules and may be over-activated in psychosis • Blood-brain barrier dysfunction in schizophrenia may allow peripheral inflammatory signals to influence activity of microglial cells • Microglial activation may explain excess in synaptic pruning associated with schizophrenia, possibly in association with activation of the complement system
Anti-inflammatory drugs and immunotherapies in schizophrenia	• Non-steroidal anti-inflammatory drugs such as aspirin have a small but significant effect as adjuncts to antipsychotics in schizophrenia • Cyclo-oxygenase 2 inhibitors such as celecoxib have shown little effect in schizophrenia, though may show promise in first-episode patients • N-acetylcysteine, an anti-inflammatory and antioxidant agent, has shown benefit as adjunctive therapy • Minocycline showed promise in previous meta-analyses although a recent large trial evidenced no benefit • Omega-3 fatty acids have anti-inflammatory properties and may reduce transition from high-risk state to psychosis, although this remains contested • Statins have shown superior benefits to placebo in several trials as adjunctive treatments • Several small trials of immunomodulatory therapies such as tocilizumab have been attempted, but further evidence is required • Ongoing research may open avenues for novel treatment targets, such as therapies targeting the complement system.

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