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REVIEW

CINP

Understanding the role of inflammatory-related pathways in the pathophysiology and treatment of psychiatric disorders: evidence from human peripheral studies and CNS studies

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Abstract

Many lines of evidence now support the hypothesis that inflammation-related pathways are involved in the pathophysiology of psychiatric disorders. Much of the data underpinning this hypothesis has come from the study of inflammation-related proteins in blood of individuals with mood disorders and schizophrenia. Significantly, recent data have emerged to suggest that changes in inflammation-related pathways are present in the CNS of subjects with psychiatric disorders. It is therefore timely to overview how such data, plus data on the role of inflammation-related proteins in CNS function, is contributing to understanding the pathophysiology of mood disorders and schizophrenia. In addition, it has been suggested that antidepressants, mood stabilizers and antipsychotic drugs act on inflammation-related pathways and therefore measuring levels of inflammation-related proteins in blood may be useful in monitoring treatment responsiveness. Despite these important neuropsychopharmacological discoveries, there is no clear understanding as to how inflammatory-related pathways can precipitate the onset of psychiatric symptoms. This review will focus on data suggesting that acute-reactive proteins and cytokines are affected by the pathophysiology of mood disorders and schizophrenia, that levels of blood inflammation-related proteins before and after treatment might be useful in the diagnosis of psychiatric disorders or measuring responsiveness to drug treatment. Finally, it will be postulated how changes in these proteins affect CNS function to cause psychiatric disorders.

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Introduction

Changes in inflammatory-related pathways have long been suggested to have a role in the pathophysiology of mood disorders (Maes *et al*. 1992) and schizophrenia (Sz) (Lin *et al*. 1998). After a great deal of effort to test this important hypothesis, the mechanisms by which inflammatory-related pathways can precipitate the symptoms of psychiatric disorders, presumably by affecting CNS function, is beginning to be understood. This review will therefore consider the evidence, at the molecular level, that supports the hypothesis that inflammatory-related pathways are involved in the pathophysiology of psychiatric disorders. In addition, by extrapolating from this and other evidence, potential mechanisms by which inflammatory-related processes in the CNS could cause the symptoms of psychiatric disorders will be presented.

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The peripheral inflammation/immune system

The peripheral inflammation/immune system has been extensively studied. The immune system consists of two processes, the innate system that recognizes and responds to pathogens but does not give long-lasting immunity and the adaptive immune system which allows a long-lasting recognition of specific

pathogens by the generation of genetically modified cell lines that can produce a directed antibody response (Chaplin, 2003). Central to the innate immune response are the toll-like receptors (Palsson-McDermott & O'Neill, 2007), which are pattern recognition receptors. Members of this family of receptors can detect lipopolysaccharides on Gram-negative bacteria, components on Gram-positive bacteria, double-stranded RNA produced by viruses, bacteria flagella, single-stranded RNA and unmethylated cpG DNA. This family of receptors is expressed by macrophages in which they mediate phagocytic activity and stimulate the release of acute-phase proteins such as C-reactive protein (CRP), fibrinogen, albumin and serum amyloid A protein. Whilst release of acute-phase proteins represent an initial response against infection, another response is the production of cytokines which drive the adaptive immune response by stimulating T and B cells to produce antigen-specific responses (Herrington & Hall, 2008). Most importantly for this review, the acute-phase proteins and cytokines are inextricably linked to inflammation and levels of these proteins are viewed as markers of inflammatory activity (Arai *et al*. 1990). Hence, this review will focus on the evidence involving acute phase proteins and cytokines in the pathophysiology and treatment of psychiatric disorders. From these and other data, some postulates will be formed as to the possible mechanisms by which inflammation-related pathways may be involved in the genesis of symptoms associated with psychiatric disorders.

Peripheral inflammatory markers in psychiatric disorders: diagnostic potential

The majority of data supporting a role for inflammatory pathways in the pathophysiology of psychiatric disorders comes from the measurement of circulating inflammatory markers. A review of these studies shows that there is considerable evidence to suggest there are changes in inflammatory-related proteins (IRPs) in blood from individuals with major depressive disorder (MDD), bipolar disorder (BD) and Sz (Supplementary Table 1). However, as is common in many areas of psychiatric research, the data on whether changes in IRPs occur in blood from subjects with psychiatric disorders is not consistent. This is perhaps not surprising given that IRP levels in blood vary with many factors which include sleep disturbance (Ryan *et al*. 2005), body weight (Wellen & Hotamislioil, 2003), glycaemic state (Huerta & Nadler, 2002), diurnal variation (Miller *et al*. 2003) and even sample storage conditions (Flower *et al*. 2000; Friebe & Volk, 2008). Therefore the lack of standardization across studies measuring IRPs in the blood from subjects with psychiatric disorders could be the simple explanation as to why outcomes are not consistent.

To better understand the usefulness of IRP blood levels as a diagnostic aid it will be necessary to complete well controlled multi-centre trials using well considered standardized blood collection processes. Standardization will need to begin by agreeing on anticoagulant use, blood processing and storage as these factors all seem to influence cytokine stability. In addition, it will be critical to determine if 'apparent' changes in IRPs in a single blood sample are actually reflecting a shift in diurnal secretion of these proteins (Petrovsky *et al*. 1998) rather than a change in the amount of IRPs in blood over prolonged periods. Therefore studies are required to determine the nature of cytokine diurnal secretion in humans and if this is altered in people with psychiatric disorders. In addition, given the relationship between blood IRPs and body weight (Wellen *et al*. 2003), care should be taken to exclude individuals who have experienced significant weight changes prior to blood sampling. To control for diurnal variation (Petrovsky *et al*. 1998) in cytokine secretion, once this is shown not to have phase-shifted, and the effect of glycaemic variation (Huerta & Nadlet, 2002) blood collection should be in the fasting state and at a standardized time of day. Finally, given the potential for variation in blood IRPs during the menstrual cycle (O'Brien *et al*. 2007*a*), this variable should also be controlled for in any study of blood IRPs in psychiatric disorders. It might be that a working group is required to consider all of these parameters and issue guidelines similar to those used in many endocrine protocols examining hormones in blood.

Peripheral inflammatory markers in psychiatric disorders: treatment monitoring and response prediction

Whilst many studies have tested the validity of measuring levels of inflammatory-related markers in the blood of subjects with MDD, BD and Sz (Supplementary Table 1) as a diagnostic aid, some studies have attempted to determine if changing levels of IRPs in blood before and after drug treatment could provide a measure of drug responsiveness. One novel study showed that treatment with paroxetine prior to treatment with cytokine interferon-α2B in subjects with malignant melanoma reduced levels of depression induced by that inflammatory cytokine (Musselman *et al*. 2001). These data would suggest that

antidepressant drugs can interfere with the mechanisms that allow inflammatory-related pathways to generate depressive symptoms. However, it is less clear whether measuring IRPs in blood may be an indicator of treatment responsiveness in psychiatric disorders because recent studies have reported that levels of circulating IRPs are either *changed* [tumour necrosis factor-α (TNF-α) and CRP (Tuglu *et al*. 2003); interleukin-6 (IL-6) (Basterzi *et al*. 2005); IL-12, transforming growth factor-β1 (TNF-β1) (Sutcigil *et al*. 2007); interleukin-2 receptor (IL-2R) (Eller *et al*. 2008); TNF, CRP (Tousoulis *et al*. 2009); IL-6, TNF (Yoshimura *et al*. 2009)] or *not changed* [TNF (Himmerich *et al*. 2004); TNF, IL-8 (Eller *et al*. 2008); TNF, IL-1β, CRP (Piletz *et al*. 2009)] after antidepressant drug treatment. In internally controlled studies, were IRPs were measured before and after treatment, it has been reported that antidepressants decrease levels of pro-inflammatory IRPs (Basterzi *et al*. 2005; Sutcigil *et al*. 2007) and increased levels of anti-inflammatory IRPs (Narayan *et al*. 2008), which is consistent with an overall anti-inflammatory effect. Finally, data from some studies suggests that elevated levels of IRP prior to (Eller *et al*. 2008) or after (O'Brien *et al*. 2007*b*; Yoshimura *et al*. 2009) antidepressant drug treatment may be indicative of treatment resistance. Unfortunately, despite some promising findings on levels of circulating IRPs as a marker of antidepressant responsiveness, it must be acknowledged that many of the current studies have been completed on small patient cohorts using different antidepressants and different treatment regimens. Therefore it is still not possible to conclude that measuring IRPs in blood is useful in monitoring antidepressant drug treatment.

Early evidence that mood stabilizers might influence IRP levels came from the finding that TNF and IL-6 were increased in the blood of individuals treated with lithium (Haack *et al*. 1999). The notion that lithium can affect cytokine levels is supported by *in-vitro* data using human blood cells showing exposure of the cells to lithium can affect cellular expression of IRPs (Rapaport & Manji, 2001). Moreover, in normal control subjects it has been reported that treatment with valproate increases levels of circulating IL-6 (Shiah *et al*. 2005), data that suggest increasing IRPs in blood may be a common feature of all mood stabilizers. However, studies to determine whether treatment with mood stabilizers alter levels of circulating IRPs and whether monitoring levels of these proteins may provide a useful indicator of treatment response are required to test such a hypothesis.

An early indicator that antipsychotic drugs may alter IRP levels in blood came from a report that levels of IL-1α and IL-6, but not IL-1β, IL-2 or TNF, were increased in the blood from Sz subjects taking antipsychotic drugs (Xu *et al*. 1994). By contrast, another study showed that levels of IL-2 were decreased in drug-naive Sz subjects, that levels of IL-3A were decreased in the same individuals after antipsychotic drug treatment and that there was no changes in IL-1β levels either in the untreated or treated state (Bessler *et al*. 1995). These data suggest there must be a complex interaction between disease pathophysiology and drug action. Moreover, a study showing that clozapine treatment (10 wk) decreased levels of blood TNF without changing levels of IL-6 (Monteleone *et al*. 1997) suggests that changes in levels of blood cytokines may be drug specific. This hypothesis is supported by the differing outcomes from studies measuring blood cytokines before and after treatment in Sz subjects that reported IRP levels to be *reduced* [interferon-γ (IFN-γ), IL-2 – mixed treatment (Arolt *et al*. 2000); IFN-γ – risperidone (Cazzullo *et al*. 2002); IL-2 – risperidone and haloperidol (Zhang *et al*. 2004); IL-2, IL-6 – risperidone but not haloperidol (Zhang *et al*. 2005); IL-6, IL-13 – mixed treatment (Pae *et al*. 2006)], *unchanged* [mixed treatment, IL-2, IFN-γ (Rothermundt *et al*. 2000); IL-2, IL-8 – risperidone and haloperidol (Zhang *et al*. 2004); IFN-γ, transforming growth factor-β1 (TGFB1) – mixed treatment (Kim *et al*. 2004); TNF, IL-2, IL-10 (Pae *et al*. 2006)] or *increased* [IL-10 – risperidone (Cazzullo *et al*. 2002); IL-4 (Kim *et al*. 2004); IL-12 – mixed treatment (Crespo-Facorro *et al*. 2008)] after such treatments. Hence it seems clear that the conclusion, reached by the Clinical Antipsychotic Trials of Intervention and Effectiveness study (Meyer *et al*. 2009), that changes in IRP blood levels vary with different antipsychotic drug treatments was correct. Moreover, this conclusion is essentially proven by a longitudinal study showing drug-specific effects of risperidone and haloperidol on IRP levels in blood (Zhang *et al*. 2005). Finally, one study has suggested that neither IRP blood levels on admission nor after a standardized antipsychotic drug treatment regimen gave any insight into the likelihood of treatment responsiveness (Erbagci *et al*. 2001). This is a disappointing outcome as it suggests that IRP blood monitoring may not be useful in assessing drug responsiveness in subjects receiving antipsychotic drugs.

A recent study has suggested that the effects of drug treatment on circulating IRPs are regulated by genetics (Zai *et al*. 2006). If that is correct, variation in the genetic make-up of the cohorts used in the study of the effects of antipsychotic drug treatment on blood IRPs could be one confound that has contributed to some

variation in study outcomes. From a theoretical viewpoint it is significant that there is evidence to suggest treatment with most psychotropic drugs has the potential to influence blood inflammatory markers. This raises the need for studies in drug-naive subjects to determine the true status of blood inflammatory markers in individuals with psychiatric disorders.

The effect of psychotropic drug treatment on inflammatory markers

The notion that measuring levels of circulating blood cytokines can be used as a marker of drug responsiveness is based on the hypothesis that treating with psychotropic drugs must affect the expression of such markers in the periphery and CNS. The ability to modulate inflammatory-related pathways has been a known mechanism of action of antipsychotic drugs for at least 50 years (Pollmacher *et al*. 2000). Significantly, antipsychotic drugs have drug-specific effects on IRP levels which could account for some of the different clinical benefit/side-effect profiles of the different antipsychotic drugs. Of importance are the recent clinical trials suggesting improved clinical benefits when using drugs such as celecoxib (Muller *et al*. 2006; Nery *et al*. 2008) and aspirin (Laan *et al*. 2010) as adjunctive treatments with antipsychotic drugs. These studies suggest that antipsychotic drugs alone are not an optimal way of modulating IRPs in Sz subjects.

Antidepressants have also long been known to affect the production of IRPs (Maes, 2001), however the effects of such treatments appear to be drug-specific and have complex temporal variability (Fazzino *et al*. 2009; Kubera *et al*. 2000). Current data show that antidepressants do not have class-specific effects and thus more research is required to better understand how antidepressants can alter IRP expression. Moreover, the recent finding that there are clinical benefits in using celecoxib as an adjunctive treatment to antidepressant drugs (Akhondzadeh *et al*. 2009) would suggest that, as with antipsychotic drugs, antidepressant drugs alone do not produce optimal effects on IRPs in people with depression.

There is some evidence that the mood stabilizers lithium (Beyaert *et al*. 1991) and valproate (Brouland *et al*. 1989; Ichiyama *et al*. 2000) effect IRP expression. Again, it has been suggested that celecoxib has some benefit as an adjunctive treatment with BD (Nery *et al*. 2008). However, such a combination of treatments has been suggested to run the risk of significant adverse events (Slordal *et al*. 2003) and therefore the use of cox-2 inhibitors in the treatment of BD may need to be pursued with caution.

Given that current data suggest that targeting inflammation-related pathways in psychiatric disorders seems to give therapeutic benefit, it is becoming more critical to understand how these pathways are affected by the pathophysiology of those disorders; in particular it is becoming important to know if these pathways are altered in the CNS.

Peripheral inflammatory markers in psychiatric disorders: CSF studies

Whilst the study of MDD, Sz, BD and various drug treatments give a broad indication that IRPs may be affected by the pathophysiology and treatment of psychiatric disorders, it was the demonstration of increased IL-1β in the blood and CSF of Sz subjects that provided the first indication that blood IRPs may reflect changes in those proteins in the CNS (Barak *et al*. 1995). In the same study, CSF and blood levels of TNF, IL-2 and IL-6 were reported as unaltered in Sz and that soluble IL-2R was increased in the CSF but not blood from subjects with the disorder. In another CSF study, levels of IL-6 were reported as increased in subjects with a delayed, but not poor, response to antipsychotic drugs (Garver *et al*. 2003). Thus, as with the study of blood, the study of CSF has yet to provide a clear indicator as to the likely changes in inflammation-related pathways in Sz subjects.

Changes in inflammatory pathways in psychiatric disorders – findings from the study of the human CNS transcriptome

The availability of technology that allows large-scale measurement of gene expression at the level of the transcriptome and proteome has impacted greatly on current understanding of the pathophysiology of psychiatric disorders (Dean *et al*. 2005). Therefore it is important to consider findings from such studies when trying to understand the pathophysiology of psychiatric disorders.

There have been a number of microarray studies examining changes in the transcriptome in MDD subjects. These have suggested that changes in pathways involved in the fibroblast growth-factor system (Evans *et al*. 2004), oligodendrocytes (Aston *et al*. 2005; Klempan *et al*. 2009), glutamate/neutral amino-acid transport (Choudary *et al*. 2005), GABA neurotransmission (Choudary *et al*. 2005; Klempan *et al*. 2009), catabolism of polyamines (Sequeira *et al*. 2006) and cell proliferation (Tochigi *et al*. 2008) as being affected by the pathophysiology of MDD. Importantly, a

recent microarray study of the dorsolateral prefrontal cortex has now provided strong evidence that a significant number of genes involved in inflammatory-related pathways are altered in MDD (Shelton *et al*. 2010). These data show that the levels of mRNA for both pro- and anti-inflammatory genes (IL-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, IFN-γ, lymphotoxin-α) are increased in the CNS of subjects with the disorder. Significantly, the predominant changes in gene expression appear to involve the interleukins rather than a generalized up-regulation of all genes involved in inflammatory-related pathways. The failure of other microarray studies to detect altered expression of cytokines in the CNS of MDD subjects could be because of the use of tissue from different tissue collections, the use of different microarray platforms or, of more biological relevance, the use of different CNS regions.

Significantly, a meta-analysis of microarray studies using post-mortem tissue from BD subjects did not suggest a significant involvement of inflammatory-related pathways in the pathophysiology of the disorder at the level of gene expression (Elashoff *et al*. 2007). By contrast, microarray studies do support the notion that the pathophysiology of BD affects mitochondrial function (Iwamoto *et al*. 2005; Quiroz *et al*. 2008; Sun *et al*. 2006), apoptosis (Kato *et al*. 2007), signalling pathways (Nakatani *et al*. 2006), ubiquitination (Ryan *et al*. 2006) and synaptic function (Ryan *et al*. 2006).

There have been many microarray studies using post-mortem CNS from Sz subjects and an overview of these findings is beyond the remit of this review. Significantly, two of these studies have reported increased expression of immune pathway genes (Arion *et al*. 2007; Saetre *et al*. 2007) which is relevant to this review as perturbation of the immune processes is often linked to inflammation (Taub & Oppenheim, 1994). In addition, a study focused on the CNS microvasculature has identified perturbation of inflammatory-related pathways in tissue from Sz subjects (Harris *et al*. 2008). These data give rise to the possibility that changes in CNS IRPs may be due to blood IRPs crossing the blood–brain barrier (Banks & Erickson, 2010). In addition, a microarray study that focused on gene expression in the dorsolateral prefrontal cortex of Sz subjects at different durations of illness reported changes in levels of expression of genes involved in inflammation-related pathways, but only in tissue from subjects who had had the disorder for more than 20 years (Narayan *et al*. 2008). This finding argues that changes in inflammation-related pathways could be contributing to the progressive nature of the pathophysiology of Sz (Lieberman *et al*. 2001).

The conclusion that inflammation-related pathways were affected in long-duration Sz was based on a gene ontology analysis of microarray data and showed changed expression of 13 genes involved in such pathways. Gene ontology analysis is an *in-silico* approach to deriving biologically relevant meaning from a large microarray dataset and further manual curation is needed to begin to fully identify functional pathways within each gene ontology category. Thus a closer examination of the microarray data on genes involved in inflammation-related pathways in long-duration Sz, and data from other functional assays examining the expression of these genes, suggests that many of the changes in the expression of genes involved in inflammatory processes could result from the increased expression of TGFB1 in the CNS of subjects with long-duration Sz (Fig. 1). This hypothesis is strongly supported by findings that show that exogenously applied TGFB1, in *in-vitro* studies, causes the same directional changes in the expression of five of the inflammatory-related genes listed in the inflammation gene ontology category constructed using data from gene expression in the cortex from subjects with long-duration Sz (Narayan *et al*. 2008). Thus, it has been shown that TGFB1 increases the expression of chemokine ligand 5 (CCL5) (Happel *et al*. 2008); a finding that reflects the complex nature of inflammatory pathways as TGFB1 is anti-inflammatory (Buisson *et al*. 2003) whereas CCL5 is an inflammatory cytokine (Soria & Ben-Baruch, 2008). Moreover, TGFB1 has been shown to increase the expression of the complement component 1, q subcomponent β chain (C1QB) (Morgan *et al*. 2000); the expression of which is associated with inflammation and is increased in the cortex of subjects with long-duration Sz. TGFB1 also increases prostaglandin-endoperoxide synthase 1 (PTGS1: COX1) expression in astrocytes, but not neurons (Luo *et al*. 1998); PTGS1 expression is increased in long-duration Sz. It should be noted that in the same *in-vitro* study (Luo *et al*. 1998), it was shown that TGFB1 increases prostaglandin-endoperoxide synthase 2 (PTGS2: COX2) expression in astrocytes and neurons but the expression of PTGS2 was decreased in the cortex of subjects with long-duration Sz. However, an inverse relationship between the expression of PTGS2 and prostaglandin E receptor 3 (PTGER3) has been reported in human chondrocytic cells (Abulencia *et al*. 2003) which is similar to the inverse relationship between the expression of those genes in the CNS of subjects with long-duration Sz. Combining the data from the changes in expression of

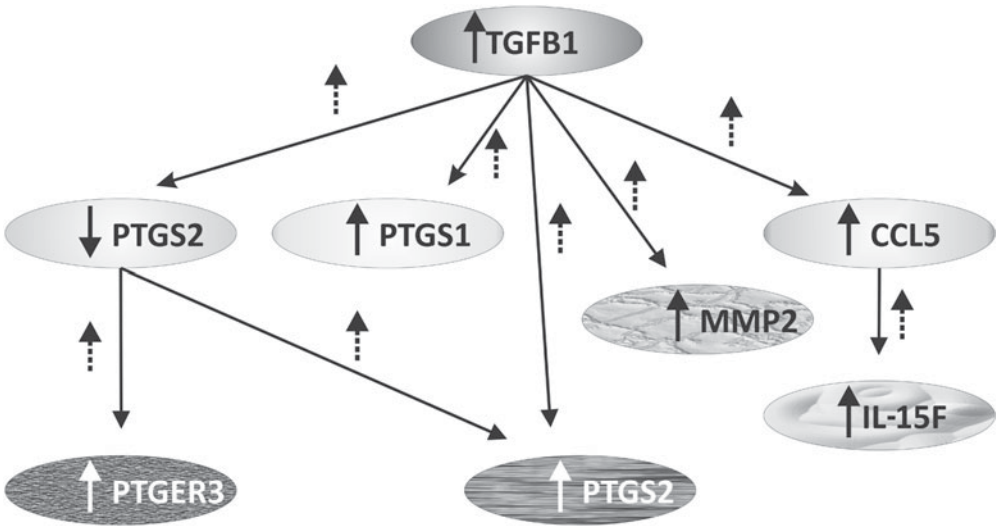

Fig. 1. A schematic showing the genes that were identified as having changed levels of expression in the cortex of subjects with long-duration schizophrenia (direction of changes shown by solid arrows) which are also changed after the addition of exogenous transforming growth-factor β1 (TGFB1) in *in-vitro* experimental models (direction of changes shown by dotted arrows). Significantly, TGFB1 alters both the expression and secretion of matrix metallopeptidase 2 (MMP2) and secreted MMP is a potent pro-inflammatory protein. CCL5, Chemokine ligand 5; C1QB, complement component 1, q subcomponent β chain; PTGS1, prostaglandin-endoperoxide synthase 1; PTGS2, prostaglandin-endoperoxide synthase 2; PTGER3, prostaglandin E receptor 3; IL-1F5, interleukin-1F5.

inflammation-related pathways in long-duration Sz and the effects of exogenous TGFB1 it would seem that TGFB1-related gene expression is probably associated with pro-inflammatory, rather than anti-inflammatory, outcomes in the CNS of individuals with long-standing Sz.

Supporting the hypotheses the TGFB1 is causing pro-inflammatory effects is in the CNS of long-standing Sz are data showing that increases in TGFB1 cause the exocytosis of matrix metallopeptidase 2 (MMP2) (Phillips *et al*. 2003). MMPs are zinc-dependent endopeptidases that are capable of degrading all kinds of extracellular matrix proteins (Jezierska & Motyl, 2009) and therefore have an active role in inflammation. Importantly, it has been shown that levels of gene expression of MPP2 are optimized to levels of exocytosis of that protein (Parekh & Wittrup, 1997); this means it is reasonable to postulate that increased levels of TGFB1 would cause increased exocytosis and expression of MMP2 in the CNS of subjects with long-duration Sz.

The involvement of PTGS1 and PTGS2 in the pathophysiology of Sz is significant because these genes encode proteins that synthesize prostaglandins by metabolizing arachidonic acid. A notable difference between PTGS1 and PTGS2 is that the former is a constitutively active enzyme whereas the latter is induced when required (Pairet & Engelhardt, 1996). In the periphery, PTGS2 inhibition is linked to the anti-inflammatory effects of non-steroidal anti-inflammatory drugs whereas PTGS1 is more involved in the gastric and renal side-effects associated with those drugs. Whilst, the effects of the two enzymes in the CNS are yet to be elucidated, the finding that the expression of both PTGSs is altered in the CNS of Sz subjects suggests changes in prostaglandin-related inflammatory activity (Kelly, 1996) and this could be contributing to the pathophysiology of long-duration Sz. Supporting this proposal is the data showing that the expression of the prostaglandin E receptor 3 (PTGER3) is increased in the cortex of Sz subjects. Significantly, PTGER3 has been shown to potently regulate CNS function (Momiyama *et al*. 1996) and therefore may regulate many of the CNS actions of prostaglandins. For example, PTGER3 is present on serotonergic neurons in the raphe suggesting it acts as an interface between prostaglandins and serotonergic pathways (Momiyama *et al*. 1996). This provides a potential mechanistic link between the changes in prostaglandin activity, as identified by gene expression changes in long-duration Sz (Narayan *et al*. 2008), and the well accepted notion that changes in

serotonergic function are important in the pathophysiology of Sz (Dean, 2003).

There is further evidence for the notion that TGFB1-related pathways are important in the pathophysiology of long-duration Sz. In particular, it has been shown that levels of expression of CCL5 are directly related to levels of the expression of IL-1F5 in a mouse model of biliary atresia (Leonhardt *et al*. 2006) and the expression of both CCL5 and IL-1F5 are increased in long-duration Sz (Narayan *et al*. 2008). Whilst it has yet to be established whether there CCL5 directly controls the expression of IL-1F5, it is significant that IL-1F5 belongs to a family of proteins that have an important role in immune regulation and pro-inflammatory processes (Barksby *et al*. 2007). In addition, TGFB1$^{-/-}$ have been shown to develop lethal immunopathology in multiple organs in conjunction with enhanced T-cell proliferation and activation with increased CD4+ T-cell differentiation into T helper 1 (Th1) and Th2 cells (Li *et al*. 2007). These data suggest that TGFB1-mediated changes in the CNS could involved multiple IRPs and inflammation-related pathways. Finally, TGFB1 has been shown to increase its own expression and to increase the expression of the TGFB1 receptor in the mouse hippocampus (Morgan *et al*. 2000). This means that changes in TGFB1 expression in the CNS could be related to an ongoing gain of function due to looping amplification processes (Gasser, 2009). Importantly, as the data on long-duration Sz do not show a change TGFB1 receptor, it is unlikely such a TGFB1 gain of function is involved in the pathophysiology of long-duration Sz.

Changes in inflammatory pathways in psychiatric disorders – findings from the study of the human CNS proteome

Whilst the majority of microarray studies do not seem to have added significantly to understanding the role of inflammatory-related pathways in the pathology of psychiatric disease, there are findings that raise the possibility of different inflammatory-related pathways contributing to the pathophysiology of MDD and long-duration Sz. However, when considering the implications of findings from the study of the human CNS transcriptome it must be remembered that there is not necessarily a strong correlation between changes in mRNA levels and in protein in the same tissue (Dean *et al*. 2007). This has lead to the use of technologies that can examine changes in the human proteome to attempt to understand the pathophysiology of psychiatric disease (Edgar *et al*. 2000), a technology suggested to be particularly suited to understanding the pathophysiology of disease of the human CNS that involves inflammatory processes (Suk, 2010). It is therefore significant that a recent review of the studies of the human CNS proteome of Sz subjects does not conclude that IRP levels are particularly affected in this disorder, rather pathways involved in brain energy metabolism, brain plasticity and synaptic function appear to be particularly affected (Martins-de-Souza *et al*. 2010). In addition, there appear to be few proteomic studies on BD and these do not suggest that there are significant changes in IRP levels associated with mood disorders (English *et al*. 2009).

In contrast to studies on the human proteome, a single protein study has recently reported increased levels of transmembrane (tmTNF), but not the soluble (sTNF), form of TNF in the dorsolateral prefrontal cortex, but not cingulate cortex of MDD subjects (Dean *et al*. 2010). To appreciate the significance of this finding it is necessary to understand the underlying biochemistry of TNF. In the CNS, TNF is expressed by microglia (Morganti-Kossman *et al*. 1997), astrocytes (Lieberman *et al*. 1989) and a limited population of neurons (Chung *et al*. 2005). All cells synthesizing TNF produce a monomeric type-2 transmembrane protein that is inserted into the cellular membrane as a homo-trimer termed tmTNF-α (McCoy & Tansey, 2008) (Fig. 2). In the membrane, tmTNF has a long leader sequence forming an intracellular domain, a 26-amino-acid transmembrane domain and a 20-amino-acid extracellular domain (Yan *et al*. 2009). The cleavage of tmTNF by TNF-α converting enzyme (ADAM17) gives rise to a soluble TNFα (sTNF) (McCoy *et al*. 2008). Significantly, data from TNF knock-in mice that have non-cleavable tmTNF, and hence cannot produce sTNF, shows that it is sTNF that is critical in activating inflammatory processes (Ruuls *et al*. 2001).

The two forms of TNF can activate two TNF receptors (TNFR1 and TNFR2) in cell membranes, with TNFR2 being preferentially activated by tmTNF and TNFR1 being preferentially activated by sTNF (McCoy *et al*. 2008). Significantly, TNFR1 appears to be expressed by most cells whereas TNFR2 is primarily expressed by immune cells (including microglia), endothelial cells and neurons (Eissner *et al*. 2004; McCoy *et al*. 2008). Notably, TNFR1 contains a cytoplasmic death domain that is critical in activating a complex receptor-signalling pathway (McCoy *et al*. 2008). TNFR1 can also indirectly recruit members of the TNF receptor-associated factor (TRAF) family of proteins to modulate cellular gene expression (Wajant *et al*. 2003). Currently it would appear that acute activation of TNFR1 is a cytoprotective process (Sato *et al*. 2005)

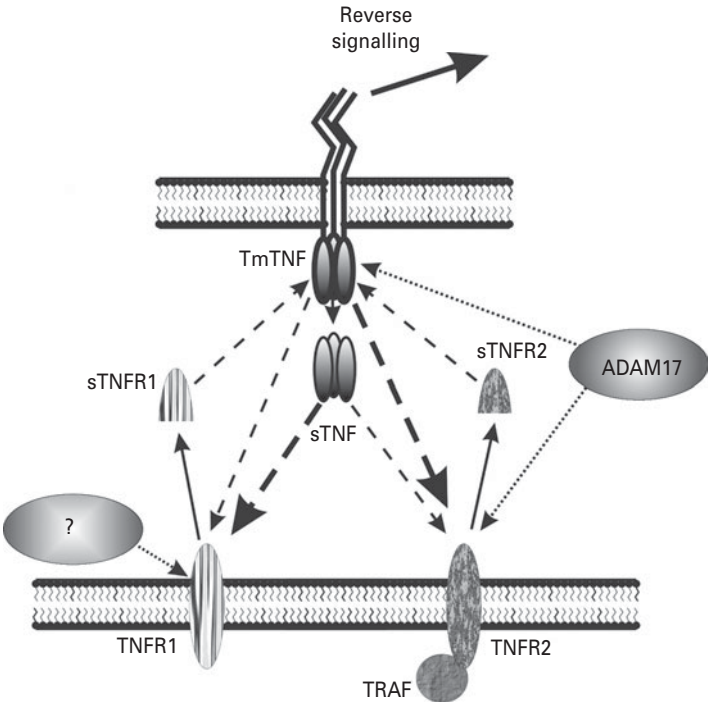

Fig. 2. A schematic showing the processing of tumour necrosis factor (TNF) and its receptors. TNF exists in the membrane as transmembrane TNF (tmTNF) which is a homotrimer of the TNF gene product. tmTNF is cleaved by a TNF cleaving enzyme (ADAM17) to form soluble TNF (sTNF). Both tmTNF and sTNF activate two TNF receptors (TNFR1 and TNFR2). sTNF preferentially activates TNFR1 and tmTNF preferentially activates TNFR2. TNFR2 instigates signalling through TNF receptor-associated factor (TRAF) whereas TNFR1 signals primarily through a death domain. TNFR2 is cleaved by ADAM17 to form a soluble form of TNFR2 whilst TNFR1 is cleaved by an unknown process to form a soluble form of TNFR1. Both forms of soluble TNFRs can bind weakly through tmTNF. Significantly, tmTNF can also signal through its intracellular domain, giving what is termed reverse signalling.

whereas prolonged activation leads to caspase-induced apoptosis (Tobiume *et al*. 2001). TNFR2 signals by a direct recruitment of TRAF proteins and can have protective and inflammatory effects (Wajant *et al*. 2003). In addition, TNFR2 is cleaved by ADAM17 and TNFR1 is cleaved by an unknown enzyme; this cleavage of TNFRs is important in controlling levels of TNFR activation (McDermott *et al*. 1999).

In beginning to interpret the potential outcomes of increased levels of tmTNF in the cortex of MDD subjects, it is clear the elevated levels of this protein could be associated with increased activity of inflammation-related pathways. However, increased TNF-mediated neurodegenerative processes are associated with increased levels of $CD4^+$ and $CD8^+$ T cells as well as astrocytosis, microgliosis and demyelination (Wajant *et al*. 2003). The notion that TNF-mediated neurodegeneration can be involved in the pathophysiology of disorders of human CNS is supported by an extensive literature showing abnormalities in $CD4^+$- and $CD8^+$-mediated outcomes in multiple sclerosis (Friese & Fugger, 2009). Therefore the absence of any evidence for neurodegenerative processes, such as astrocytosis or gliosis (Damadzic *et al*. 2001; Gilmore & Bouldin, 2002; Muller *et al*. 2001), in the CNS of MDD subjects could be an indicator that increased tmTNF is not activating inflammatory-related pathways. It is therefore important to acknowledge that until there is a better understanding of TNF-mediated processes in the human CNS it would be premature to suggested that the increased levels of tmTNF in the cortex of MDD subjects is indicative of increased activity within inflammatory-related pathways.

The potential roles for cytokines in human CNS

Whilst the exact mechanism and outcomes remain to be understood, there is a growing body of data suggesting a role for inflammatory-related pathways in disorders of the human CNS. Current evidence

from studies using human post-mortem CNS would suggest a role for cytokine-related pathways in the CNS of subjects with mood disorders. There is also evidence for a TGFB1-driven contribution to the pathophysiology of Sz. Therefore it is worth considering what is known about the function of these proteins and their associated pathways in the CNS, rather than the periphery.

There is a growing understanding of the complex role of TNF in the CNS. Thus, TNF can have diverse impacts on neurodevelopment processes including dendritic arborization which has been suggested to be the mechanism by which TNF can modulate behaviour and learning processes (Park & Bowers, 2010). It is also becoming clear that changed TNF signalling alone does not induce apoptotic processes, rather a secondary stimulus is required for TNF to induce a cell to move to an apoptotic state (Park *et al*. 2010). This indicates that changes in levels of TNF alone may not be sufficient to activate inflammation-related pathways. In addition, TNF has the capacity to modulate long-term potentiation, with late phase effects being modulated through changes in protein expression (Butler *et al.* 2004). TNF-mediated changes in protein expression can also regulate levels of ion channels and ligand-gated ion channel receptors in the CNS (Park *et al*. 2010). In addition, TNF can further affect neurotransmitter pathways by affecting the activity of serotonergic as well as glutamatergic neurons (Muller & Schwarz, 2007). Importantly, the communication between TNF and neurotransmitters is bidirectional as the activity of TNF can be controlled by neurotransmitters (Pavlov *et al*. 2006). Hence it is clear that TNF has effects on CNS function that go beyond modulating inflammation and some of these affects could be what causes the onset of the symptoms of psychiatric disorders. Therefore a better understanding of the overall affects of TNF is required to unravel the mechanisms by which TNF may be involved in the pathophysiology of disorders such as MDD.

From the current understanding of the roles of tmTNF, it can be postulated that aberrant signalling through three potential mechanisms could be involved in the pathophysiology of mood disorders (Fig. 3).

First would be aberrant signalling because of a derangements in a number of non-cell contact paracrine mechanisms (Fig. 3*a*) involving sTNF signalling through TNFR1 or TNFR2 (Eissner *et al*. 2004; McCoy *et al*. 2008) or sTNFR1 (Wajant *et al*. 2003), sTNFR2 (McDermott *et al*. 1999) acting at tmTNF. As levels of sTNF are not altered in the cortex of subjects with mood disorders over-activation of TNFR1 or TNFR2 by sTNF appears unlikely. The second mechanism could involve changes microglia-mediated cell–cell contact where tmTNF could be brought into contact with TNFR1 or TNFR2 (Fig. 3*b*). This model implies that the increased levels of tmTNF observed in the CNS of subjects with mood disorders are due to increased tmTNF expression by microglia or an increase in the number of microglia. The third model is based on cell–cell contact where tmTNF and TNFR1 or TNFR2 are expressed on adjacent cells (Fig. 3*c*). The latter two models would provide both forward and reverse signalling because of activation of TNFR1 or TNFR2 by tmTNF and TNFR1 or TNFR2 activation of tmTNF. Given that tmTNF is predominantly expressed by astrocytes (Lieberman *et al*. 1989) and TNFR2, the favoured receptor for tmTNF, is expressed by neurons and microglia (Eissner *et al*. 2004; McCoy *et al*. 2008) the latter two models would suggest a potential for astrocyte/microglia or astrocyte/neuron signalling. Thus, there is now a clear need to better understand tmTNF signalling mechanisms as these may have a pathophysiological role in mood disorders.

The interleukins also control many critical CNS processes such as the regulation of sleep (Krueger, 2008). Significantly, different members of the interleukin family are involved in inflammation-related and protective processes which, in part, depend on whether the interleukin is acting outside or inside a cell (Luheshi *et al*. 2009). The overall outcome of any change in interleukin levels in the CNS would therefore depend on the balance between the different family members, e.g. it is known that increased levels of the IL-1 family are associated with increased inflammatory-related pathway activity (Luheshi *et al*. 2009). To make the effects of interleukins even more complex some interleukins, such as IL-18, have a mixed inflammation-related and homeostatic role in the CNS (Alboni *et al*. 2010). Thus, given the potential for widespread changes in expression of interleukins in the CNS of subjects with psychiatric disorders (Shelton *et al*. 2010) it will be necessary to better define the changes in the balance and/or location of interleukins before it can be determined if their overall impact is indicative of an inflammation-related response.

Finally, there is the intriguing finding that TGFB1 pathways may be affected in the CNS of subjects with long-duration Sz. TGFB1 is generally regarded as an anti-inflammatory cytokine in the CNS (Saud *et al*. 2005) but it is argued here that the nature of expression changes in the CNS of long-duration Sz subjects would be pro-inflammatory. Significantly, ageing in humans

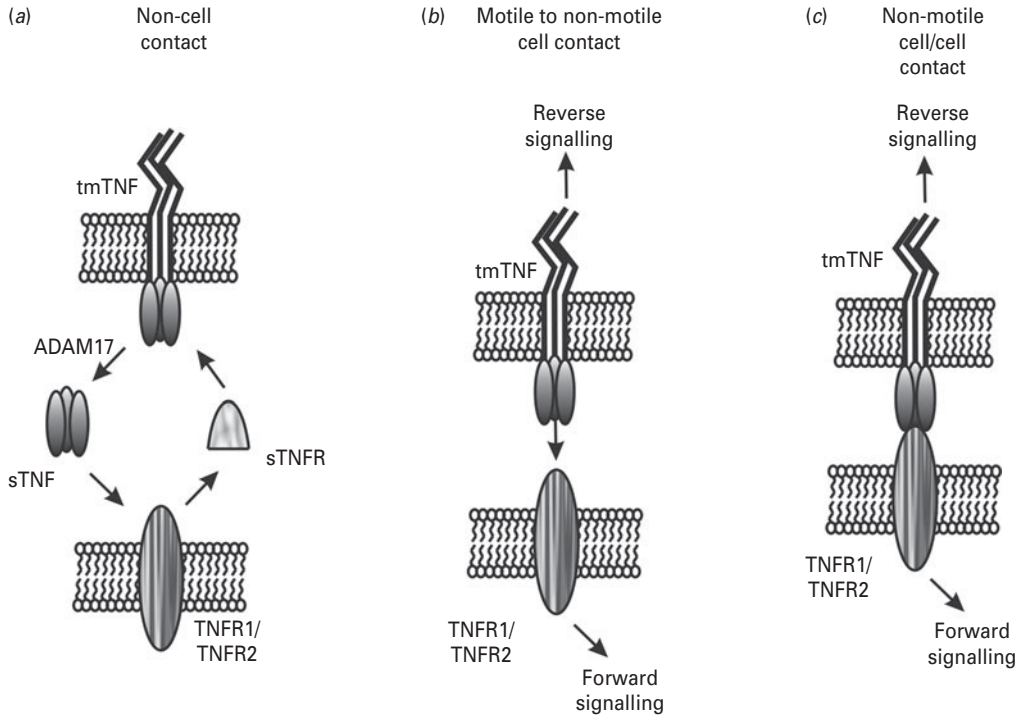

Fig. 3. A schematic showing the potential signalling mechanisms for tumour necrosis factor (TNF) in CNS. The first mechanism invokes an endocrine/paracrine model where solubilized TNF (sTNF) is cleaved from transmembrane TNF (tmTNF) or a TNF receptor (TNFR1 or TNFR2) is cleaved to form a soluble TNF receptor (sTNFR). The sTNF or sTNFR then comes into contact with TNFR1/TNFR2 or tmTNF, respectively, to cause cell signalling, this model does not require cell–cell contact. The second model is a motile–non-motile cell contact whereby tmTNF can come in contact with TNFRs to instigate signalling which could occur when microglia come into contact with other cells in the CNS. The final model shows the potential for the TNF system to have a unique role in cell–cell contact. In this model contact between non-motile cells expressing tmTNF or TNFRs could become established for prolonged periods resulting in both forward and reverse signalling by tmTNF and TNFR1/2, respectively. Conceivably such a mechanism could be used to monitor and/or regulate cell–cell contact.

is associated with altered responsiveness to cytokines due to a fundamental change in the reactive state of microglia (Dilger & Johnson, 2008). Given that such an overall change in cytokine responsiveness is predicted to result in an increase in inflammatory-related pathways, it could be argued that the increase in the activity of TGFB1-related pathways in long-duration Sz (which by definition is in older individuals) represents some form of accelerated age-related inflammatory process. However, like other factors involved in inflammation-related pathways, TGFB1 has many diverse effects such as controlling overall astrocyte gene expression (Hamby *et al*. 2006), inhibiting neurogenesis (Buckwalter *et al*. 2006) and inducing the death of microglia (Kim *et al*. 2004). Thus, again it may be presumptive to assume that changes in TGFB1-driven pathways in the CNS of long-duration Sz subjects are associated with changes in an inflammatory-related status.

Conclusions

Peripheral studies have underpinned the notion that there are changes in inflammatory-related pathways in the CNS of subjects with psychiatric disorders (Lin *et al*. 1998; Maes *et al*. 1992). Importantly, the fold-change in levels of cytokines in blood from subjects with psychiatric diseases (Supplementary Table 1) do not seem to be of the same order of magnitude as those in the blood of subjects with an inflammatory-related disorder such as rheumatoid arthritis (Chen *et al*. 2009). This could suggest that the changes in cytokine-related pathways in individuals with psychiatric disorders are reflective of processes other than activation of peripheral inflammatory pathways. Moreover, many factors influence blood cytokine levels on a day-to-day basis which would argue that a standardized regimen is needed for the collection of blood in which IRPs are to be measured (Corsini & House, 2010) if the

true value of measuring circulating cytokines as a diagnostic aid or a predictor of treatment outcome is to be fully assessed in psychiatric disorders. Such studies are essential as it is important to assess any potential aid that may be helpful in assessing or treating psychiatric disorders.

Several lines of evidence are emerging to support the notion that changes in what have been classically regarded as immune-related pathways (Maes *et al*. 1992) are present in the CNS of subjects with psychiatric disorders. Natural end products of a chronic inflammatory process would be oedema, the presence of activated microglia, apoptosis and/or gliosis. Significantly, there is evidence to suggest that there are increased levels of activated microglia in the CNS of Sz subjects (van Berckel *et al*. 2008; Wierzba-Bobrowicz *et al*. 2005) and that the presence of elevated levels of microglia may be associated with individuals with psychiatric disorders dying by suicide (Steiner *et al*. 2008). Therefore, understanding which inflammation-related pathways are affected in the CNS of subjects with psychiatric diseases should be a high priority. In this regard, there is growing evidence from animal studies that increases in pro-inflammatory pathways can lead to decreased availability of tryptophan with a concomitant increase in levels of kynurenine in the CNS due to increases in the activity of the enzyme indoleamine 2,3-dioxygenase. Whilst a critical analysis of this hypothesis is beyond the remit of this review, such changes in the CNS could result in altered levels of serotonin and other neurotransmitters which could in turn cause the onset of depression (for a comprehensive review see Myint *et al*. 2009). Moreover, the demonstration of changed levels of kynurenate in Sz (Miller *et al*. 2006; Schwarcz *et al*. 2001) and BD (Miller *et al*. 2006) give direct support for a role for changes in kynurenine pathways in the pathophysiology of psychiatric diseases; with these changes possibly being associated with the onset of psychoses rather than depression. More studies on kynurenine pathways in the CNS will be required to better elucidate the symptomological outcomes from changes in these pathways.

It is now acknowledged that a much better understanding of the pathophysiology of psychiatric disease is required as a basis for new drug design (Insel, 2009). This well-argued position underlies the urgency of understanding the role of cytokines and other IRPs in the pathophysiology of psychiatric disorders. Such knowledge will be particularly potent when the mechanisms involved in the genesis of the symptoms are unravelled. This is because the drug etanercept, which targets the TNF-related pathways (Esposito & Cuzzocrea, 2009), has been shown to have antidepressant effects (Tyring *et al*. 2006). This is strong data to support the premise that targeting and modulating inflammatory-related systems can have therapeutic benefits in subjects with psychiatric disorders.

Note

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Statement of Interest

None.

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