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REVIEW

Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment?

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Abstract
Rationale Current psychotropic medications have been shown to modulate immune activation. However, the effects of individual psychotropic agents on the immune system and how these might contribute to their efficacy remain largely unclear.
Objective This paper aims to review previous literature on the effects of antidepressants and antipsychotics on the immune system, with a systematic review of in vitro findings, and discuss the relevance of these effects for the response to treatment and future drug development.
Results Inflammatory markers have been associated with fluctuations in clinical status and with treatment response both in depression and psychosis. The in vitro literature on antidepressants shows that some antidepressants, such as clomipramine and fluoxetine, more consistently decrease pro-inflammatory cytokines (interleukin (IL)-6, interferon (IFN)-γ, tumour necrosis factor (TNF)-α), whilst others (mirtazapine and venlafaxine) tend to increase their levels. However, any overall conclusion is challenged by several inconsistent findings, which appear partly dependent on different methodological approaches used. The in vitro studies on antipsychotics are even less clear-cut showing pro- and anti-inflammatory activity for the same antipsychotic agent (haloperidol, clozapine, risperidone) across different studies. We also noted inconsistencies between in vivo and in vitro literature, which could partly be attributed to the interaction in vivo with various biological systems or lifestyle factors that can modulate the immune system.
Conclusions Inflammatory markers seem to hold potential for developing more individualised treatment strategies in the future. In this context, further research disentangling the differential immunomodulatory effects of different drugs could be used for tailoring treatment to specific individuals, according to their immune endophenotypes.

Keywords Inflammation · Antipsychotic · Antidepressant · Cytokine · Immune system · Medication · Psychosis · Depression

Introduction

Over the years, increasing evidence has shown a continuous and bidirectional crosstalk between the immune system and the nervous system. Experimental models and longitudinal data suggest that dysregulation of the inflammatory system can respectively elicit and precede a constellation of psychiatric symptoms and psychiatric disorders (Baumeister et al. 2014b). In this context, the possible immune-modulatory effect of psychotropic medications has lately attracted considerable interest in psychiatric research (Mondelli and Howes 2014).

Determining friend from foe, innocuous from dangerous and inert from toxic, the immune system is specialised in responding to millions of environmental stimuli we are in

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contact with every day. Inflammation is the process of recruiting, accumulating and activating blood-based leukocytes, including phagocytes such as neutrophils and monocytes, which bind and ingest microbial organisms and produce reactive oxygen and nitrogen species to destroy them. In the brain and wider central nervous system (CNS), microglia are the resident macrophages that facilitate neuroinflammatory states. Crucially, inflammatory immune cells produce a variety of cytokines, whilst some cytokines promote inflammation, others, particularly in later stages of the inflammatory response, reduce it as a method of negative feedback.

Interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α are some of the main cytokines described as pro-inflammatory; these cytokines are primarily produced by macrophages, neutrophils and/or dendritic cells and confer both local and systemic effects, including stimulation of immune cells, induction of pyrexia and hepatic release of acute phase proteins such as C-reactive protein (CRP), as well as maladaptive effects such as septic shock, cardiovascular alterations and insulin resistance. Whilst they are generally crucial and adaptive in the acute response, chronic elevations of pro-inflammatory cytokines may damage host tissue and have been implicated in a number of autoimmune disorders such as rheumatoid arthritis or myopathies. Of note, several inflammatory markers have somewhat ambiguous function in that they can both promote and inhibit inflammation (Zakharova and Ziegler 2005; Scheller et al. 2011).

Acute and chronic inflammation can impact directly as well as indirectly on CNS activity. Pro-inflammatory cytokines can, in fact, directly enhance the production and release of radical oxygen and nitrogen species via macrophage and neutrophil activation (Dedon and Tannenbaum 2004). For example, it has recently been shown that TNF-α increases oxidative stress in rodent hippocampal cell cultures through the activation of microglia cells (Grinberg et al. 2013). On the other hand, cytokines can indirectly affect the CNS by modulating the activity of several monoaminergic systems, which are currently the primary targets of psychotropic medications. Indeed, an increase in cytokine levels reduces serotonin bioavailability, partially through activation of competitive tryptophan metabolic pathways, but also through up-regulation of transporter and uptake activities (Felger and Lotrich 2013; Baumeister et al. 2014b). Cytokines can also inhibit dopamine synthesis, reduce dopaminergic signaling in the basal ganglia and up-regulate cellular reuptake whilst inhibiting vesicular reuptake, which may lead to increased cytosolic dopamine concentrations inducing auto-oxidative stress (Felger and Lotrich 2013; Baumeister et al. 2014b). More recently, different studies have also shown a link between inflammation and glutamatergic system. In particular, cytokines augment glutamate release from astrocytes whilst inhibiting the expression of glutamate transporters, which may result in an increased concentration of extracellular glutamate potentially causing excitotoxic effects (Ida et al. 2008; Miller et al. 2013). High cytokine levels have also been linked with an increased activity of key enzymes in the kynurenine pathway, resulting in elevated concentrations of kynurenine metabolites (Zunszain et al. 2011). Of note, the activation of this pathway mediates the inhibitory effects of IL-1β on neurogenesis and may result in excitotoxic effects due to the production of quinolinic acid, an *N*-methyl-D-asparte (NMDA) receptor agonist (Zunszain et al. 2012). Finally, cytokines can alter the negative feedback of the neuroendocrine stress system, the hypothalamic–pituitary–adrenal axis (HPA axis) (Pace et al. 2007), which can also affect CNS function and has been implicated in several psychiatric conditions, including depression and psychosis (Borges et al. 2013; Baumeister et al. 2014a).

Finally, cytokines are potent modulators of neurogenesis and neuroplasticity. Several studies in foetal human and rodent hippocampal neural progenitor cells have reported decreased neurogenesis yet increased gliogenesis when exposed to IL-1β or TNF-α (Johansson et al. 2008; Zunszain et al. 2012; Crampton et al. 2012; Chen et al. 2013a, b; Borsini et al. 2015). Cytokines can modulate expression of crucial factors involved in the process of neuroplasticity. For example, administration of IL-1β has been shown to down-regulate expression of brain-derived neurotrophic factor (BDNF) in the rat hippocampus (Barrientos et al. 2004); moreover, pro-inflammatory cytokines and BDNF can act on common intracellular pathways relevant to neuroplasticity, like the mitogen-activated protein (MAP) kinase cascade and the phosphatidylinositol-3 kinase/Akt signaling, and downstream regulators of apoptosis such as Bad and bcl-2 (Manji and Chen 2002). In this context, our laboratory has also shown a mediatory role of IL-6 in the association between stress and low BDNF levels in first episode psychosis patients (Mondelli et al. 2011).

An established evidence base shows that psychiatric disorders are associated with alterations of the immune system (Zajkowska and Mondelli 2014; Potvin et al. 2008; Dowlati et al. 2010; Miller et al. 2011; Baumeister et al. 2014b), with increasing evidence suggesting that only some of the inflammatory abnormalities are stable and could be considered as trait markers, whereas other markers change along fluctuations in clinical states or are linked to specific symptoms.

In the context of studies conducted in patients with schizophrenia, two meta-analyses (Potvin et al. 2008; Miller et al. 2011) consistently showed abnormalities in cytokine levels in these patients, albeit with some variations between the two papers when considering the clinical status. Specifically, the more recent evidence suggests that IL-6 may be a state marker of schizophrenia, as it is elevated only in currently symptomatic patients, but not in stable outpatients, whose levels do not differ from healthy controls. Additionally, some studies have found IL-6 to be correlated with duration of illness or being a potential biomarker for early psychotic symptoms (Ganguli et al. 1994; Stojanovic et al. 2014). In contrast, other

inflammatory markers, including TNF-α and interferon (IFN)-γ, appear to be elevated throughout acute and remission phases and have therefore been suggested as possible trait markers (Miller et al. 2011).

Similarly, a meta-analysis on inflammatory changes in depression in clinical as well as community-based samples found elevations of IL-1β, IL-6 and CRP with a stronger effect in clinically depressed samples (Howren et al. 2009). Noteworthy, their study included samples comorbid for coronary artery disease or cancer. A more recent meta-analysis by Valkanova et al. (2013) on longitudinal studies confirmed association between elevations of CRP and IL-6 levels and subsequent depressive symptoms. More recently, it was reported that the levels of several cytokines, including IL-1RA, IL-6, IL-8 and IFN-γ, normalise in depressed patients after recovery, supporting the presence of increased inflammatory state during the acute phase of depression (Dahl et al. 2014). Further evidence has demonstrated individual cytokine alterations also within the cerebrospinal fluid of patients with depression and psychosis (Martinez et al. 2012; Schwieler et al. 2015), suggesting that peripheral inflammation corresponds to central inflammation. There are several pathways via which peripheral inflammatory activity can induce inflammatory signaling in the brain. As outlined by Dantzer et al. (2008), these include (a) cytokines and pathogen-associated molecular patterns (PAMPs) stimulating afferent nerves projecting to the CNS and (b) activity of cytokines and PAMPs in circumventricular areas.

Further, there is direct evidence for a causal relationship of inflammatory activity on neuropsychiatric symptoms, stemming out of the literature on interferon-α treatment in disorders such as hepatitis C. Long-term effects with on-going treatment include fatigue and depressive symptoms prevalent in up to 80 and 60 % of treated individuals, respectively, as well as a risk of acute side effects that can include confusional states, psychotic symptoms and speech impediments (Raison et al. 2005).

Of note, there is evidence which suggests that pro-inflammatory phenotypes are associated with worse clinical outcome and adverse course of illness, as recent meta-analyses have shown that childhood trauma contributes to pro-inflammatory phenotypes as well as to more recurring and persistent depression (Nanni et al. 2012; Baumeister et al. 2015). Indeed, the exposure to specific environmental factors can mold the adaptive and innate immune memory for prolonged periods of time unfolding negative effects over time (MacGillivray and Kollmann 2014). This is particularly interesting when considering environmental risk factors involved in the onset or relapse of psychiatric disorders that are also associated with pro-inflammatory phenotypes. For example, psychosocial stress and childhood adversity, well-known precipitants of psychiatric disorders, have been recognised to stimulate the release of a variety of inflammatory markers (Hepgul et al. 2012; Di Nicola et al. 2013; Miller et al. 2009; Baumeister et al. 2015). Of note, preclinical studies have shown that early-life stress tends to have a programming effect on neuroimmune functions, leading to a pro-inflammatory state in adulthood, which in turn can contribute to development of neuropathological behaviours (Giovanoli et al. 2013; Viviani et al. 2013).

Given the substantial evidence suggesting the relevance of inflammation to psychiatric disorders, it is not surprising that recent research has also revealed that psychotropic treatments often impact on immune function in vivo (Hiles et al. 2012; Tourjman et al. 2013; Table 3). It has been observed that specific inflammatory phenotypes are associated with clinical status (acute episode/relapse/remission) as well as with specific psychiatric symptoms (Tsai et al. 2001; Dickerson et al. 2007, 2013; Potvin et al. 2008; Munkholm et al. 2013; Serafini et al. 2013). In recent years, the associations between specific inflammatory phenotypes and clinical status (e.g. treatment response) as well as brain structural abnormalities (e.g. reduction in regional cortical thickness) of patients with either psychosis or depression have emerged, opening up the possibility to use the inflammatory biomarkers as a clinical predictors (O'Brien et al. 2007; Cannon et al. 2014; Mondelli et al. 2015). This raises the important question as to whether inflammatory modulation of current treatments acts as a potential pathway for conveyance of therapeutic effects, as well as whether inflammatory modulation is a viable potential target for novel treatment options. Despite significant enthusiasm, evidence is not unequivocal, and potential mechanisms remain somewhat elusive.

Below, we will review current knowledge of the impact of psychotropic medications on inflammatory parameters, with a systematic review of in vitro human studies, which will be contrasted with findings from several in vivo meta-analyses. We will address the question as to whether apparent changes in inflammatory markers following psychotropic medications mediate therapeutic effects or simply mark the sequel of successful treatment response and whether such effects are dependent on systemic effects in the whole organism. In this context, we will discuss the role of inflammatory markers in predicting efficacy of treatments, the potential use of anti-inflammatory agents as treatment options in psychiatry and the relevance of psychoneuroimmunological research for the development of future treatment strategies.

The in vitro effects of psychotropic medications on immune function

Emerging evidence has suggested that psychopharmacological agents, including antidepressants and antipsychotics, bring about changes in some, but crucially not all, inflammatory markers observed in psychiatric patients. Moreover, there is a need to establish whether these changes occur due to direct

cellular effects or through systemic changes associated with pharmacological effects. In order to assess direct cellular immunomodulatory effects of antipsychotic and antidepressant agents, a systematic review of the in vitro literature was conducted. In April 2015, Scopus, Medline, Embase and PsycINFO were searched for the terms "antipsychotic", "neuroleptic" and "antidepressant", cross-referenced with "cytokine", "interleukin", "chemokine", "CRP", "TNF", "inflammat*" and cross-referenced with "cell*" and "vitro". For studies to be included, they had to be conducted in human blood or blood-based cell, assessing the effect of in vitro incubation with psychotropic agents on any cytokine. Using such a strategy allows for comparison with the several meta-analyses already published on the effects of such agents on peripheral cytokine levels in vivo. We identified 17 eligible studies using antidepressants (Table 1; Xia et al. 1996; Maes et al. 1999; Lin et al. 2000; Kubera et al. 2001; Kubera et al. 2002; Rudolf et al. 2002; Szuster-Ciesielska et al. 2003; Kubera et al. 2004; Maes et al. 2005; Diamond et al. 2006; Carvalho et al. 2008; Carvalho et al. 2010; Himmerich et al. 2010; Krause et al. 2012; Munzer et al. 2013; Tsai et al. 2014; Waiskopf et al. 2014) and 12 eligible studies employing antipsychotics (Table 2; Bleeker et al. 1997; Leykin et al. 1997; Hinze-Selch et al. 1998; Moots et al. 1999; Song et al. 2000; Rudolf et al. 2002; Szuster-Ciesielska et al. 2004; Carvalho et al. 2010; Chen et al. 2011; Himmerich et al. 2011; Chen et al. 2013b; Krause et al. 2013).

The in vitro immunomodulatory effects of antidepressant agents

In the identified studies, a total of 19 different antidepressant medications were investigated, including six tricyclic antidepressants (TCAs; clomipramine, amitriptyline, imipramine, desipramine, nortriptyline, trimipramine), five selective serotonin reuptake inhibitors (SSRIs; fluoxetine, sertraline, escitalopram, citalopram, paroxetine), two noradrenergic and specific serotonergic antidepressants (NaSSA; mirtazapine, mianserin), two serotonin noradrenaline reuptake inhibitors (SNRI; venlafaxine, *o*-desmethylvenlafaxine), one monoamine oxidase inhibitor (MAOI; moclobemide), one serotonin antagonist and reuptake inhibitor (SARI; trazodone) and one noradrenaline reuptake inhibitor (NRI; reboxetine) (Table 1). Investigated inflammatory markers included IFN-γ (11 studies), IL-10 (nine studies), TNF-α (eight studies), IL-6 (seven studies), IL-2 (four studies), IL-1β (three studies), IL-4 (two studies), IL-12 (two studies), IL-1RA (one study), IL-8 (one study), IL-17 (one study), TNF-β (one study), transforming growth factor (TGF)-β (one study), IL-22 (one study) and interferon-inducible protein (IP)-10 (one study). The majority of studies were carried out in whole blood samples, and the most commonly used immunostimulant for co-incubation was lipopolysaccharide (LPS). Four studies had obtained samples from patients with major depressive disorder, two samples of which were classified as treatment-resistant.

Although several studies reported that antidepressants inhibited cytokine levels, this was not unequivocal. Rather, the evidence suggests more complex interaction effects where antidepressants can attenuate, but also enhance, inflammatory activity. All three studies investigating the effects of clomipramine on stimulated IFN-γ levels found significant attenuating effects. Conversely however, one study found that imipramine inhibited stimulated IFN-γ levels but increased unstimulated levels. Thus, co-incubation with immunostimulants may moderate any immunomodulatory effects of psychotropics, suggesting that antidepressant might have different immunomodulatory (inhibitory or stimulatory) effects depending on the pre-existing levels of inflammation. Moreover, several studies showed dose-dependent relationships. For example, it appears that desipramine at low doses stimulates IL-10 and IFN-γ whilst inhibiting the same markers at high doses. Further, agents belonging to the same class may still show opposing effects. As such, two studies found attenuating effects of the TCA clomipramine on IL-6, yet another study found that the TCA imipramine stimulates IL-6. Indeed, in the same study, the TCAs clomipramine and desipramine had opposing effects on LPS-stimulated IL-1β levels. Even within agents, such contradictory findings were reported, with, e.g. fluoxetine being reported to increase IL-6 in one study but decrease IL-6 in another. Conversely however, all studies investigating the effects of fluoxetine on TNF-α report at least trend-level inhibiting effects.

In conclusion, although immunomodulation is evident, there appears to be no clear unidirectional attenuation of inflammatory activity, although such effects do occur. However, there are cases where antidepressants, depending on co-incubation, sample type, dose, class or individual pharmacodynamics, may stimulate inflammation.

The in vitro immunomodulatory effects of antipsychotic agents

In the identified studies, a total of six different antipsychotic medications were investigated, including two typical antipsychotics (chlorpromazine, haloperidol) and four atypical antipsychotics (clozapine, *n*-desmethylclozapine, quetiapine, risperidone). Investigated inflammatory markers included IFN-γ (six studies), IL-10 (five studies), IL-2 (five studies), TNF-α (five studies), IL-6 (five studies), IL-4 (five studies), IL-1β (three studies), IL-1RA (two studies), IL-12 (two studies), IL-8 (one study), IL-17 (one study), sIL-2R (one study), TNF-β (one study), and TGF-β (one study). The majority of studies were carried out in whole blood samples, and the most commonly used immunostimulant for co-incubation was LPS. Three of the included studies had obtained samples from patients with schizophrenia.

Table 1 In vitro effects of antidepressants

Study	Year	Sample	Donor	Psychotropic	Stimulant	Marker	Significant attenuating effects	Significant augmenting effects	Additional notes
Carvalho et al.	2008	Whole blood	15 tr-MDD 28 HC	Clomipramine	LPS	IL-6	Clomipramine (ST)–IL-6 Clomipramine (UN)–IL-6	–	
Carvalho et al.	2010	Whole blood	33 HC	Clomipramine Amitriptyline Sertraline Paroxetine Venlafaxine	LPS	IL-6	Amitriptyline (ST)–IL-6 Clomipramine (ST)–IL-6	–	
Diamond et al.	2006	Whole blood	8 HC	Reboxetine Fluoxetine Desipramine Clomipramine Trimipramine	LPS Con A	IL-1β TNF-α IFN-γ IL-10 IL-12	Clomipramine (Con A)–IFN-γ Clomipramine (LPS)–IL-1β Desipramine (Con A)–IFN-γ (hd), IL-10 (hd) Fluoxetine (Con A)–IFN-γ Reboxetine (Con A)–IFN-γ Trimipramine (Con A)–IFN-γ	Desipramine (Con A)–IFN-γ (ld), IL-10 (ld) Desipramine (LPS)–IL-1β Reboxetine (Con A) IL-10 (ld) Trimipramine (LPS)–IL-12	
Himmerich et al.	2010	Whole blood	6 HC	Venlafaxine *O*-desmethyl-venlafaxine Amitriptyline Nortriptyline Imipramine Desipramine	TSST-1	IFN-γ	Amitriptyline (ST)–IFN-γ Desipramine (ST)–IFN-γ Imitriptyline (ST)–IFN-γ Nortriptyline (ST)–IFN-γ	–	
Krause et al.	2012	Whole blood	21 MDD 38 HC	Venlafaxine Reboxetine Imipramine Fluoxetine	LPS	IFN-γ IL-10	–	Imipramine (ST)–IL-10 (MDD)	Decreased IL-10 levels in MDD patients normalised to those in healthy controls following imipramine treatment
Kubera et al.	2001	Whole blood	5 HC	Imipramine	PHA LPS	IFN-γ IL-10	–	–	
Kubera et al.	2002	Whole blood	17 HC	Fluoxetine Imipramine	PHA LPS	IFN-γ IL-10 TNF-α	Fluoxetine (ST)–IFN-γ TNF-α Imipramine (ST)–IFN-γ	–	
Kubera et al.	2004	Whole blood	7 tr-MDD 19 HC	Fluoxetine Imipramine Venlafaxine	PHA LPS	IL-6 TNF-α	Fluoxetine (ST)–TNF-α (trend-level)	Fluoxetine (ST + 5-HTP)–IL-6 Imipramine (ST)–IL-6 Venlafaxine (ST)–IL-6	Fluoxetine stimulated IL-6 release when co-incubated with 5-HTP but not on its own
Lin et al.	2000	Whole blood	9 HC	Moclobemide	PHA LPS	IL-6 TNF-α IL-8 IFN-γ IL-10 IL-1RA	Moclobemide (UN)–TNF-α, IL-8	Moclobemide (ST)–IL-10	
Maes et al.	1999	Whole blood	9 HC	Clomipramine Sertraline Trazodone	PHA LPS	IFN-γ IL-10	Clomipramine (ST)–IFN-γ Sertraline (ST)–IFN-γ Trazodone (ST)–IFN-γ	Clomipramine (ST)–IL-10 Sertraline (ST)–IL-10	
Maes et al.	2005	Whole blood	17 HC	Fluoxetine	PHA LPS	IFN-γ IL-10 TNF-α	Fluoxetine (ST)–IFN-γ, TNF-α, IFN-γ/IL-10 ratio	–	
Munzer et al.	2013	Whole blood	15 MDD	Citalopram Escitalopram Mirtazapine	None	IL-1β IL-2 IL-4 IL-6	Escitalopram (UN)–IL-17 (hd)	Citalopram (UN)–IL-1β, IL-6, IL-22, TNF-α (hd) Mirtazapine (UN)–IL-1β, TNF-α (hd), IL-22 (hd)	

Table 1 (continued)

Study	Year	Sample	Donor	Psychotropic	Stimulant	Marker	Significant attenuating effects	Significant augmenting effects	Additional notes
						IL-17 IL-22 TNF-α			
Rudolf et al.	2002	Whole blood	7 HC	Amitriptyline	PHA	IL-2 IFN-γ	–	–	
Szuster-Ciesielska et al.	2003	PBMC	16 HC	Imipramine Mianserin	PHA LPS	IL-2 IFN-γ IL-10 IL-4 IL-12 TNF-β TGF-β	Imipramine (ST)–IL-2, IFN-γ, IL-4, TNF-β Mianserin (ST)–IL-2, IFN-γ, IL-4, TNF-β	Imipramine (ST)–IL-10, TGF-β Imipramine (UN)–IL-10, IFN-γ Mianserin (ST)–IL-10, TGF-β Mianserin (UN)–IFN-γ, IL-10	
Tsai et al.	2014	Monocytes	nr	R-fluoxetine S-fluoxetine Imipramine Moclobemide Venlafaxine Bupropion Mirtazapine	LPS	IP-10	Buproprion (ST)–IP-10 (all doses) R-fluoxetine (ST)–IP-10 (hd) S-fluoxetine (ST)–IP-10 (hd)	–	
Waiskopf et al.	2014	PBMC	nr	Fluoxetine	LPS	TNF-α IL-6	Fluoxetine (ST)–IL-6, TNF-α	–	
Xia et al.	1996	Monocytes T cells	nr	Imipramine Clomipramine Citalopram	LPS PHA	IL-1β IL-6 TNF-α IL-2 IFN-γ	Citalopram (PHA)–IL-2 (48 h) Citalopram (LPS)–IL-1β (10 h), TNF-α (4 h, 10 h) Clomipramine (PHA)–IL-2 (24 h, 48 h), IFN-γ (24 h, 48 h) Clomipramine (LPS)–IL-1β (10 h), TNF-α (4 h, 10 h) Imipramine (PHA)–IL-2 (24 h, 48 h) IFN-γ (48 h) Imipramine (LPS)–IL-1β (10 h), TNF-α (4 h, 10 h)	–	T cells were stimulated with PHA, and cytokine release was measured at 24 and 48 h, whilst monocytes were stimulated with LPS and cytokine release was measured at 4 and 10 h. In monocytes stimulated with LPS, no significant effect of any of the agents was found on IL-6 secretion at either 4 or 10 h of incubation, although the authors report a trend-level effect at 10 h without specifying the agent (which show similar levels on a provided bar chart). Similarly, all agents suppressed TNF-α production at 4 and 10 h, although no significance levels are reported for this effect

ld low dose, *md* medium dose, *hd* high dose, *LPS* lipopolysaccharide, *TSST-1* toxic shock syndrome toxin 1, *PHA* phytohaemagglutinin, *PMA* phorbol myristate acetate, *SZ* schizophrenia, *HC* healthy control, *tr-MDD* treatment-resistant MDD, *MDD* major depressive disorder, *ST* stimulated, *UN* unstimulated, *IL* interleukin, *IFN* interferon, *TNF* tumour necrosis factor, *TGF* transforming growth factor, *IP* IFN-γ-inducible protein, *PBMC* peripheral blood mononuclear cells

As can be seen in Table 2, the evidence on typical antipsychotics is generally inconclusive. Whilst two studies found that haloperidol inhibits IFN-γ, two other studies found augmenting effects, and a fifth study found no effects. Most consistently perhaps, IL-4 and IL-2 were inhibited by haloperidol in three and two studies, respectively, although again this was not replicated in all other studies. There was also no consistent effect on IL-10, with significant augmentation by haloperidol in only one of four studies. Similarly, significant attenuation of IL-6 by haloperidol was reported in none of four studies. Chlorpromazine was investigated in three studies, one of which showed no significant effects, whilst the other two reported findings diametrically opposed. In particular, one study showed an attenuation of IL-2, IL-4 and TNF-α levels, whilst an increase of these markers was shown in the other study. Both studies were carried out in healthy controls; however, the study reporting augmentation was conducted in whole blood cells stimulated with toxic shock syndrome toxin (TSST)-1, whilst the other study was carried out in peripheral blood mononuclear cells (PBMCs) stimulated with LPS and phytohaemagglutinin (PHA). It remains unclear whether these methodological differences may account for the inconsistent findings.

Quetiapine and risperidone showed similarly inconclusive patterns of immunomodulation. Risperidone was investigated in a total of four studies. Whilst one study found inhibitory effect on IL-6, the decrease in IL-6 levels was not replicated in another study. IFN-γ modulation showed somewhat inconsistent findings, with attenuation in two studies, one of which however also showed augmentational effects depending on the immunostimulation methodology. This effect was also shown for quetiapine. Notably, both quetiapine and risperidone were reported to decrease TNF-α. Similarly, the results for clozapine appear contradictory and elusive. Clozapine attenuated IL-6 in three out of four studies, although in one those studies a low dose led to increased levels of the same marker. Clozapine stimulated IL-10 in two studies but showed no significant effects in two other studies. Similarly, IFN-γ modulation appeared dependent on the immunostimulant agent, as well as on the doses.

Similar to what was reported for antidepressants, the systematic review focussing on antipsychotics showed no clear evidence on a unidirectional effect. Rather, it appears that immunomodulation occurs with idiosyncratic patterns depending on methodology. Several factors may play a role in this, including the cell type, the donor group, whether cells are stimulated and what immunostimulant agent is used, as well as doses and time frames of incubation protocols.

Differences between in vitro and in vivo effects of psychotropic medications on immune function

Dissecting the immunomodulatory effects of antidepressant agents

Two recent meta-analyses have investigated in depth the in vivo effects of antidepressant on immune function (Table 3). In particular, Hiles et al. (2012) have previously described significant decreases of IL-6 and CRP as a consequence of antidepressant treatment, but no changes for IL-10, albeit considerable and significant heterogeneity for all of these findings was reported. The effect of antidepressants on inflammatory markers was particularly pronounced for IL-6 in outpatients rather than in inpatients and in male rather than female patients (Hiles et al. 2012). In contrast, in a similar meta-analysis, Hannestad et al. (2011) failed to show significant effects of antidepressant treatments on serum levels of TNF-α and IL-6, despite significant improvements in depression severity; in contrast, they found significant decreases in IL-1β.

Despite the heuristic value of considering different classes of psychotropic drugs as uniform agents and explore their effect on the overall inflammatory process, this may veil their real role and actual mechanism of action. Indeed, psychotropic drugs with different pharmacodynamic profiles seem to have diverging effects on immune function, with some having been counter-intuitively associated with increased levels of inflammatory cytokines. Differential effects in immunomodulation appear to be evident when looking at the effects of specific antidepressants also when looking at in vivo studies. For example, Hannestad et al. (2011) report that, when considering only treatment with SSRIs, a consistent reduction of IL-6 levels was found, although with low statistical power. In contrast, one study found that the noradrenaline reuptake inhibitor duloxetine appears to be associated with increases in IL-6 in depressed patients (Fornaro et al. 2011). Notably, these effects are opposed to those observed in the in vitro literature, where there is evidence of an increase in IL-6 levels following incubation with the SSRI fluoxetine in one study whilst relatively consistent evidence for a decrease of TNF-α following treatment with fluoxetine.

Whilst this evidence of immunomodulation of psychotropic drugs is emerging, the biomedical mechanisms remain partially elusive and, in line to the varying impact of different medications, may differ fundamentally between classes of drugs and individual agents. Evidence on the presence of several neurotransmitters, including dopamine, serotonin and norepinephrine in the immune cells (i.e. lymphocytes, monocytes/macrophages, granulocytes, astrocytes and microglia), may explain a direct effect of these drugs on the immune system, as well as the inconsistencies between the in vivo and in vitro findings (Drzyzga et al. 2006). Whilst any such effects are necessarily conferred initially through

Table 2 In vitro effects of antipsychotics

Study	Year	Sample	Donor	Psychotropic	Stimulant	Marker	Significant attenuating effects	Significant augmenting effects	Additional notes
Bleeker et al.	1997	Whole blood PBMC	7 HC	Chlorpromazine	LPS	IL-1β IL-1RA IL-10 TNF-α	–	–	
Carvalho et al.	2010	Whole blood	33 HC	Haloperidol Risperidone	LPS	IL-6	–	–	
Chen et al.	2011	PBMC T cells	HC	Haloperidol Risperidone Clozapine	Th1/Th2 cell differentiation PMA Ionomycin	IFN-γ IL-4	Clozapine (Th1-stim)–IFN-γ Clozapine (PBMC)–IFN-γ Haloperidol (Th2-stim)–IL-4 Haloperidol (PBMC)–IL-4 Risperidone (Th1-stim)–IFN-γ Risperidone (PBMC)–IFN-γ	Haloperidol (Th1-stim)–IFN-γ Haloperidol (PBMC)–IFN-γ	Both Th1 and Th2 differentiation-directed stimulations were investigated in T cells. In PBMCs, 10 days of treatment as well as 28 days were investigated, with augmenting effects of haloperidol on IFN-γ only occurring at the latter
Chen et al.	2013	Monocyte-derived macrophages	HC	Haloperidol Risperidone Clozapine	LPS	IL-6 IL-8 IL-10 IL-12 TNF-α	Clozapine (ST)–IL-6, IL-8, IL-12, TNF-α (dose-dependent; all markers) Risperidone (ST)–IL-6, IL-8, IL-12, TNF-α (dose-dependent; all markers)	Clozapine (ST)–IL-10 (dose-dependent; all markers) Risperidone (ST)–IL-10 (dose-dependent; all markers)	
Himmerich et al.	2011	Whole blood	10 HC	Chlorpromazine Clozapine Haloperidol *N*-desmethylclozapine Quetiapine	TSST-1	IL-1β IL-2 IL-4 IL-6 IL-17 TNF-α	*N*-desmethylclozapine (ST)–IL-2 (md, hd), TNF-α (md) Quetiapine (ST)–IL-2 (md), TNF-α (md)	Chlorpromazine (ST)–IL-2 (ld, md), IL-4 (ld, md), IL-17 (hd), TNF-α (ld, hd) Clozapine (ST)–IL-4 (ld-hd), IL-17 (ld, hd) *N*-desmethylclozapine (ST)–IL-4 (ld), IL-17 (ld, hd) Quetiapine (ST)–IL-17 (ld, hd) Haloperidol (ST)–IL-17 (ld, hd)	Doses ranged from 0.25-fold to 2-fold of the maximum clinical dose
Hinze-Selch et al.	1998	PBMC	17 SZ	Clozapine	Pokeweed mitogen	TNF-α IL-6 IL-2 sIL-2R	Clozapine (ST)–IL-6 (hd), sIL-2R (hd; varied between time points)	Clozapine (ST)–IL-6 (ld), sIL-2R (ld)	The study was carried out over 6 weeks of clozapine treatment in vivo, with PBMCs being obtained at several time points for in vitro experimentation
Krause et al.	2013	PBMC	12 SZ 24 HC	Haloperidol Clozapine Quetiapine Risperidone	LPS Poly I:C	IL-4 IL-10 IFN-γ	Quetiapine (poly I:C) -IFN-γ (SZ) Risperidone (poly I:C) -IFN-γ (SZ)	Clozapine (poly I:C)-IFN-γ (SZ) Haloperidol (poly I:C) -IFN-γ (SZ; trend-level) Quetiapine (LPS)-IFN-γ (SZ) Risperidone (LPS)–IFN-γ (SZ)	Under LPS stimulation, SZ patients showed lower IFN-γ production than HCs Under poly I:C stimulation, SZ was associated with a trend towards higher IFN-γ production
Leykin et al.	1997	Lymphocytes	21 SZ 14 HC	Clozapine Haloperidol	PHA	IL-2 IFN-γ IL-4	Clozapine (ST)–IL-2, IL-4, IFN-γ Haloperidol (ST)–IL-2, IL-4, IFN-γ	–	
Moots et al.	1999	Whole blood	1 HC	Haloperidol	LPS	IL-1β TNF-α	Haloperidol (ST)–IL-1β, TNF-α	–	
Rudolf et al.	2002	Whole blood	7 HC	Clozapine Haloperidol	PHA	IL-2 IFN-γ	–	Clozapine (ST)–IL-2, IFN-γ Haloperidol (ST)–IL-2, IFN-γ	
Song et al.	2000	Whole blood	9 HC	Clozapine Haloperidol	LPS PHA	IL-1RA IL-6 IFN-γ	Clozapine (ST)–IL-6 (ld), IL-1RA (ld), IFN-γ (ld), IL-10 (ld)	Clozapine (ST)–IL-1RA (md, hd), IFN-γ (md) Clozapine (UN)–IL-1RA (md, hd)	

Table 2 (continued)

Study	Year	Sample	Donor	Psychotropic	Stimulant	Marker	Significant attenuating effects	Significant augmenting effects	Additional notes
						IL-10	Clozapine (UN)–IL-6 (ld), IL-1RA (ld)	Haloperidol (ST)–IL-1RA (ld, md, hd) Haloperidol (UN)–IL-1RA (ld, md, hd)	
Szuster-Ciesielska et al.	2004	PBMC	16 HC	Chlorpromazine Clozapine Haloperidol	LPS PHA	IL-2 IFN-γ IL-10 IL-4 IL-12 TNF-β TGF-β	Chlorpromazine (ST)–IL-2, IFN-γ, TNF-β, IL-4 Clozapine (ST)–TNF-β Haloperidol (ST)–IL-2, IFN-γ, TNF-β, IL-4	Chlorpromazine (ST)–IL-10, TGF-β Chlorpromazine (UN)–IL-10 Clozapine (ST)–IFN-γ, IL-10, TGF-β Clozapine (UN)–IL-10 Haloperidol (ST)–IL-10, TGF-β Haloperidol (UN)–IL-10	

ld low dose, *md* medium dose, *hd* high dose, *LPS* lipopolysaccharide, *TSST-1* toxic shock syndrome toxin 1, *PHA* phytohaemagglutinin, *PMA* phorbol myristate acetate, *SZ* schizophrenia, *HC* healthy control, *tr-MDD* treatment-resistant MDD, *MDD* major depressive disorder, *ST* stimulated, *UN* unstimulated, *IL* interleukin, *IFN* interferon, *TNF* tumour necrosis factor, *TGF* transforming growth factor, *IP* IFN-γ-inducible protein, *PBMC* peripheral blood mononuclear cells

monoaminergic modulation, a host of downstream systems may mediate the immunomodulatory effects, and these effects may differ depending on target tissue, timing as well as dispositional factors, such as genetic or epigenetic loading. Moreover, we cannot exclude the role of other factors such as dose and duration of treatment, as well as the interaction with other biological systems, which are concomitantly affected by psychotropic medications.

Dissecting the immunomodulatory effects of antipsychotic agents

Similarly to what we found in the literature for antidepressants, recent studies have reviewed the in vivo effects of antipsychotics on immune system (Table 3). Miller et al. (2011) performed a meta-analysis on studies reporting cytokine levels in patients with psychosis before and after antipsychotic treatment and reported significant increases in sIL-2R and IL-12 and a decrease in IL-1β and IL-6 following antipsychotic treatment. Interestingly, antipsychotic treatment appears to significantly and concurrently correlate with both decreases in IL-6 and improvements in symptom scores. Similarly, a recent meta-analysis by Tourjman et al. (2013) confirmed that antipsychotic treatment increases plasma levels of IL-12 and sIL-2R but decreases IL-1β and IFN-γ with moderate effect sizes. However, the study found no effects on IL-2, IL-4, IL-6, IL-10, IL-1RA, sIL-6R, TGF-β or TNF-α, as well as no evidence for moderating effects of duration of treatment. Tourjman et al. (2013) further noted in their discussion that clozapine and olanzapine appear to increase, rather than decrease, levels of IL-6 in individual studies. Similarly, Pollmächer et al. (1996) reported that clozapine increases TNF-α, soluble TNF receptors and sIL-2R. Paradoxically, the in vitro literature suggests that IL-6 attenuation is one of the somewhat more consistent effects of clozapine. Similarly, the in vitro studies reported no evidence for modulation of TNF-α other than in one out of three studies.

These inconsistencies between in vivo and in vitro studies could partly be attributed to the interaction in vivo of various biological systems that can modulate the immune system. For example, since cytokines are also produced by adipocytes, some of the increase in inflammatory markers following clozapine treatment could be related to the metabolic adverse effects and weight gain which largely characterise the side effects profile of this drug (O'Connell et al. 2014). A recent study of 190 patients with treatment-resistant schizophrenia receiving clozapine found significant elevations of serum hs-CRP and IL-1RA, but not IL-6, when compared with healthy controls, with IL-1RA, hs-CRP and IL-6 significantly correlating with body mass index within patients, albeit with gender differences (Klemettilä et al. 2014). Notably, as many antipsychotics induce metabolic syndrome, a condition associated with increased inflammation, it is difficult to

Table 3 In vivo effects of antidepressants and antipsychotics

Class	Meta-analysis	IL-1β	IL-1RA	IL-2	sIL-2R	IL-4	IL-5	IL-6	sIL-6R	IL-8	IL-10	IL-12	TNF-α	CRP	TGF-β	IFN-γ
Antidepressants	Hannestad et al. (2011)	↓	–	–	–	–	–	= / ↓ (SSRI only)	–	–	–	–	=	–	–	–
	Hiles et al. (2012)	–	–	–	–	–	–	↓	–	–	=	–	–	↓	–	–
Antipsychotics	Miller et al. (2011)	↓	=	=	↑	–	–	↓	–	=	=	↑	=	–	↓	=
	Tourjman et al. (2013)	↓	=	=	↑	=	–	=	=	–	=	↑	=	–	=	↓

↓ decrease, ↑ increase, = no change, – the parameter was not assessed

disentangle whether these increases in inflammatory markers are a direct consequence of the treatment rather than of their metabolic side effects. In this context, a recent longitudinal study looked at the effects of risperidone on pro-inflammatory cytokines in first episode schizophrenia, showing an initial decrease in IL-1β and IL-6 levels in the first few weeks of treatment, followed by a gradual increase of these cytokines after 3–6 months of treatment, during which patients also experienced progressive weight gain and increases in TNF-α levels (Song et al. 2014). Interestingly, higher baseline levels of IL-1β, but not IL-6 or TNF-α, were predictive of weight gain.

Inflammatory markers in the prediction of treatment response and inflammation as a therapeutic target

Beyond the findings that psychotropic medications can modulate immune function in mental illnesses, there is reason to suspect that, in turn, immune function of psychiatric patients plays a role in their treatment response. Miller et al. (2011) found that sIL-2R but not IL-6 levels are significantly higher in patients with treatment-resistant psychosis. More recently, our group has also shown increased levels of IL-6 and IFN-γ to be associated with poor treatment response in first episode psychosis patients (Mondelli et al. 2015). Similarly, Cattaneo et al. (2013) showed increased baseline gene expression of IL-1β and TNF-α in depressed patients, who subsequently (12 weeks) did not respond to antidepressant treatment. Consistent with these findings, previous studies found higher levels of IL-6 and TNF-α in prospective treatment-resistant depression patients when treated with antidepressants (O'Brien et al. 2007; Lanquillon et al. 2000; Eller et al. 2008). More recently, inflammatory state has been suggested also to predict transition to psychosis. Stojanovic et al. (2014) showed increased levels of IL-6 in subjects with at-risk mental state who then developed psychosis when compared with those who did not.

Based on the above findings, cytokines could help stratifying population samples for clinical trials testing new therapeutic agents. In particular, it has recently been reported that baseline IL-6 levels may predict treatment response to ketamine in treatment-resistant depressed patients, with higher IL-6 levels amongst responders (Yang et al. 2015). Some of the most interesting findings in this area were recently reported by Raison et al. (2013): in a study in treatment-resistant depressed patients, they showed that whilst the adjunct use of the TNF-α antagonist (infliximab) with antidepressants showed no overall significant effect on depression scores, the therapeutic effects became significant when considering only individuals with high levels of baseline CRP.

A recent meta-analysis of studies using anti-inflammatory agents (e.g. cyclooxygenase inhibitors, minocycline) as add-on treatment in psychosis showed differential effects of various types of anti-inflammatory agents, with an overall modest effect for aspirin, *N*-acetylcysteine and estrogens, whilst other agents, such as celecoxib and minocycline, showed no or limited effects (Sommer et al. 2014). Furthermore, it seems that adjunctive treatment with non-steroidal anti-inflammatory drugs has a greater effect on symptom severity in patients at their first episode of psychosis (Nitta et al. 2013). Similarly, Köhler et al. (2014) conducted a systematic review and meta-analysis of anti-inflammatory treatments in depressive disorders, concluding that such treatment strategies, particularly celecoxib, appear warranted in both clinical and subclinical depression, both in terms of efficacy and adverse effects. However, they also comment that the high risk of bias within studies, as well as the considerable heterogeneity, may undermine their findings. Notably, a recent systematic review suggested that evidence for the use of anti-inflammatory agents in the treatment of bipolar disorder currently remains largely inconclusive (Ayorech et al. 2014). Indeed, the findings reported so far suggest that considering abnormal levels of inflammatory markers when planning therapeutic choices might increase the potential benefit of treatments.

It is well known that the immune system is highly integrated with the metabolic system and that patients with depression and psychosis have higher prevalence of metabolic abnormalities and physical health problems. In this context, it has been recently suggested that increased baseline inflammation might predispose not only to worse treatment response but also to development of more severe metabolic abnormalities in psychiatric patients (Russell et al. 2015). Therefore, the use of anti-inflammatory agents, specifically in individuals with high

baseline levels of inflammation, may not only be efficacious for the treatment of psychiatric symptoms but also offer a potential target for preventing adverse metabolic effects.

Future research directions and remaining issues

Notably, the fact that very different classes of drugs with different molecular targets can modulate inflammatory function in idiosyncratic patterns suggests that immunomodulatory effects of these agents may play a mediatory role in conveyance of pharmacotherapeutic effects. On the other side, other factors relevant to patients with psychiatric disorders are increasingly recognised to influence immune function. There is reason to believe that reductions in inflammatory signaling can also occur in the context of other "non-pharmacological" interventions, as supported by the finding that several psychosocial interventions impact on inflammatory function. Previous studies have provided evidence that mindfulness-based and cognitive-behavioural interventions can decrease both peripheral as well as stimulated pro-inflammatory cytokines, including IL-6 and TNF-α, along with decrease in stress, anxiety and depression scores (Zautra et al. 2008; Lengacher et al. 2012; Rosenkranz et al. 2013). Similarly, evidence suggests that unhealthy dietary patterns contribute to pro-inflammatory as well as psychopathological phenotypes (Lucas et al. 2014; André et al. 2014), whilst exercise, calorie restriction or supplementation with omega-3 polyunsaturated fatty acids can decrease inflammation and improve mental well-being (Kiecolt-Glaser et al. 2011; Numao et al. 2012; MacDonald et al. 2014; Cairns et al. 2014). This literature review underlines the importance of appreciating the wider host of factors that can interact with inflammatory function when considering the possible therapeutic effects of psychotropic drugs via inflammatory modulation (Fig. 1). A crucial point emerging from studies published so far is that the argument that inflammatory signaling can cause and maintain ill mental health, whilst its modulation can alleviate mental disorder ultimately and simplifies a complex of intricate bio-psychological processes in which psychotropic drugs may play a significant and intriguing yet possibly limited role.

Conclusions and further remarks

The literature published so far has provided strong evidence of the role of inflammation in psychiatric disorders and suggests a general effect of fluctuations in clinical status and symptom severity on the inflammatory function. Over the years, this has raised increasing interest in the possible effect of currently used psychotropic medications in modulating immune system and in the use of immunomodulatory drugs in psychiatry. Although the evidence of overall effect of main psychotropic drugs (such as antipsychotics and antidepressants) appear to decrease/normalise some of the increased inflammatory markers present in these patients, different types of psychotropic medications show specific, and at times opposite, immunomodulatory effects. Especially in the in vitro literature, there is no clear discernible pattern of immunomodulation, strongly suggesting that any such effects occur in complex in vivo interactions. The differences across various drugs could be partly ascribed to their different pharmacodynamic profiles as well as research methodologies in both in vivo and in vitro studies. Other factors such as duration of treatment, effect of metabolic changes, concurrent dietary or psychosocial interventions could also play a role in explaining

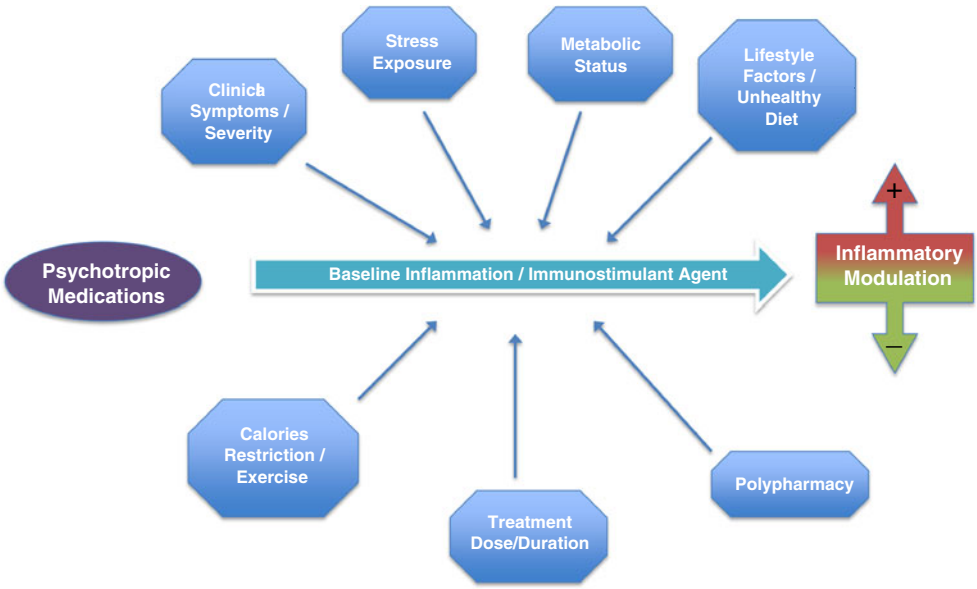

Fig. 1 Factors that may impact on the effects of psychotropic medications on inflammatory modulation

differential effects in the in vivo studies. Inflammatory markers seem to hold potential for stratification of patients for future treatment strategies. In this context, the differential immunomodulatory effects of different drugs, and the factors predicting inflammatory modulation, could be used in the future for tailoring treatment to specific individuals, according to their immune endophenotypes.

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