Advances in Bioscience and Biotechnology, 2012, 3, 551-565 **ABB**
doi:10.4236/abb.2012.324072 Published Online August 2012 (http://www.SciRP.org/journal/abb/)

In vivo immunomodulatory effects of antipsychotics on inflammatory mediators: A review

Valérie Tourjman[1,2], Marie-Ève Koué[3], Edouard Kouassi[1,4,5*], Stéphane Potvin[1,2*]

[1]Centre de Recherche Fernand-Seguin, Hôpital Louis-H Lafontaine, Montreal, Canada
[2]Department of Psychiatry, Faculty of Medicine, University of Montreal, Montreal, Canada
[3]Department of Biochemistry, Faculty of Medicine, University of Montreal, Montreal, Canada
[4]Maisonneuve-Rosemont Hospital Research Center, Montreal, Canada
[5]Department of Medicine, Faculty of Medicine, University of Montreal, Montreal, Canada
Email: *edouard.kouassi@umontreal.ca, *stephane.potvin@umontreal.ca

Received 1 July 2012; revised 2 August 2012; accepted 16 August 2012

ABSTRACT

Background: Substantial evidence demonstrates the presence of an inflammatory syndrome in schizophrenia, which is manifested by increased peripheral levels of interleukin-6 (IL-6), soluble interleukin-2 receptor (sIL-2R), and interleukin-1 receptor antagonist (IL-1RA). Unfortunately, the immunomodulatory effects of antipsychotics on peripheral cytokine levels remain poorly understood. Objectives: The objectives of the current systematic review are to determine if antipsychotics have anti-inflammatory effects in patients with schizophrenia-spectrum disorders and to examine the relationships between antipsychotic-induced cytokine changes and drug response or common side effects. Method: A systematic search was performed in the electronic databases PubMed and EMBASE. Results: We identified 39 studies measureing the effects of 8 antipsychotics on 13 inflammatory mediators and 4 cytokine receptors. This literature suggests that antipsychotics (especially clozapine) consistently decrease peripheral interleukin-2 (IL-2) levels and increase sIL-2R and soluble tumor-necrosis factor (sTNF-R) receptor levels. Changes in IL-2/sIL-2R levels seem to correlate with changes in positive symptoms. Preliminary results suggest that antipsychotics decrease interferon-γ (IFN-γ) and transforming growth factor-β (TGF-β) levels, and increase interleukin-4 (IL-4) levels. Antipsychotic-induced changes in IL-6, C-reactive protein (CRP) and tumor-necrosis factor-α (TNF-α) have been linked with common antipsychotic side effects (metabolic, fever). Discussion: Despite significant clinical heterogeneity across studies, this review has evidenced that antipsychotics can produce both anti- and pro-inflammatory effects that may partially contribute to drug response and drug-induced side effects. In the future, a better understanding of the molecular mechanisms of action of antipsychotics on inflammatory mediators will help to identify novel therapeutic strategies as well as novel biomarkers of treatment response and of drug-induced side effects in schizophrenia.

Keywords: Antipsychotics; Cytokines; Schizophrenia; Weight Gain; Inflammatory Markers

1. INTRODUCTION

Antipsychotic medications have been the mainstay of schizophrenia treatment since the early 1950s. Mostly efficacious for positive symptoms, antipsychotic treatment can lead to disabling extrapyramidal symptoms (EPS), such as Parkinsonism, dystonia, and dyskinesia. These therapeutic and side effects of antipsychotic drugs are most probably related to striatal blockade of D_2-dopamine receptors, although dopaminergic blockade does not fully account for the variance in antipsychotic response and antipsychotic-induced EPS [1]. Moreover, antipsychotics can induce side effects that are related to their effects on non-dopaminergic mechanisms, such as blurred vision, orthostatic hypotension and weight gain [2]. The efficacy of antipsychotics is disappointing, and remission remains an elusive target. In the *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) study, 55% of subjects failed to attain remission at any point [3]. In the same study, the rate of remission was highest with clozapine and second highest with quetiapine, suggesting that dopaminergic receptor affinity alone is an insufficient explanation of antipsychotic efficacy [3]. It is quite likely that non-dopaminergic mechanisms may be relevant to better understand the clinical effects of antipsychotics. Over the years, it has been shown that antipsychotic drugs produce complex immunomodulatory effects that have yet to be fully character-

*Corresponding authors.

rized and understood [4-6]. Importantly, it has been proposed that these effects on immune parameters may account for the therapeutic effects of antipsychotics as well as some of their side effects, including weight gain, agranulocytosis and fever [7,8].

The interest in antipsychotic-induced immunomodulatory effects is timely, since substantial evidence now indicates that schizophrenia is associated with cytokine alterations [9-11]. Recently, our group has performed a meta-analysis of 62 cross-sectional studies measuring peripheral levels of 10 different cytokines and cytokine receptors in a total sample size of 2298 schizophrenia patients and 1858 healthy volunteers. Using this evidence-based procedure, our group has demonstrated the presence of an inflammatory syndrome in schizophrenia, which is illustrated by increased plasma or whole blood levels of IL-6, IL-1RA and sIL-2R, relative to healthy controls [12]. The increases in all these cytokines were independent from antipsychotics, except for sIL-2R, which correlated positively with medication. In contrast, the meta-analysis did not substantiate interleukin-1β (IL-1β), interleukin-4 (IL-4), interleukin-10 (IL-10), IFN-γ, and TNF-α alterations [12]. Preliminary results have shown that peripheral interleukin-8 (IL-8), inteleukin-12 (IL-12) and interleukin-18 (IL-18) levels are also significantly elevated in schizophrenia [13], but these results need to be replicated.

The notion that antipsychotics may have immunosuppressive properties emerged in the literature soon after chlorpromazine was introduced into clinical practice in the 1950s [14]. On mechanistic grounds, animal studies produced preliminary evidence that the immunosuppressive effects of antipsychotics may be due to the inhibition of pro-inflammatory cytokines (IL-1β, IL-2, IL-6, TNF-α) and/or enhanced production of anti-inflammatory cytokines (IL-1RA, IL-4, IL-10) [15-17]. Over the years, numerous prospective pharmacological trials have examined the effects of antipsychotics on plasma/serum cytokine levels in schizophrenia. Thus far, one of the most consistent finding has been the increase in sIL-2R associated with clozapine treatment, a finding that has been replicated with olanzapine, quetiapine and risperidone treatment [8,9,18,19]. Unfortunately, the study of the influence of antipsychotics on other cytokines has sometimes produced results that are either inconsistent or even contradictory (e.g. IL-6, TNF-α) [4]. Potential sources of heterogeneity include the type of antipsychotic tested (first- versus second-generation), treatment duration (4 - 52 weeks), drug status of patients at baseline (treated with antipsychotics, drug-free or drug-naïve), patient type (first-episode versus chronic) and methodological differences in cytokine assessments (*in vivo* versus *in vitro*). The clinical significance of antipsychotic-induced cytokine changes also remains to be determined. Some preliminary results have shown associations between antipsychotic-induced cytokine changes and drug response [9,20]. On the other hand, the cytokine changes associated with antipsychotic treatment may be secondary to some of their common side effects, especially weight gain, since adipocytes secrete inflammatory cytokines, such as IL-6, IL-1RA and TNF-α [21].

In view of the current state of knowledge, the objectives of the current systematic review are: 1) to determine if antipsychotics have anti-inflammatory effects in patients with schizophrenia-spectrum disorders; 2) to identify the most consistent effects of antipsychotics on peripheral cytokine levels; 3) to identify sources of heterogeneity in published results; 4) to examine the relationships between antipsychotic-induced cytokine changes and drug response; and 5) to examine the relationships between antipsychotic-induced cytokine changes and common side effects, such as weight gain.

2. METHODS

A systematic search was performed in the electronic databases PubMed and EMBASE using the key words "antipsychotic" and "inflammation" or "cytokine" or "interleukin" or "inflammatory markers" or "CRP" or "IFN" or "TGF" or "TNF", while excluding animal studies. This search identified studies before January 1st, 2012. Additionally, studies were identified by cross-referencing.

Studies were included in the review if peripheral cytokine levels were prospectively measured *in vivo* in patients with schizophrenia-spectrum disorders before and after treatment with antipsychotics. Studies were excluded if: 1) the study design was cross-sectional [12]; 2) the sample of patients comprised patients with psy- chiatric disorders other than schizophrenia-spectrum disorders [22]; 3) cytokine levels were measured using cerebrospinal fluid [23]; 4) cytokine levels were mea- sured using *in vitro* assessments [22]. These exclusion criteria were applied in order to reduce the heterogeneity of study methodology and to enhance our ability to compare the results of studies included in the review. In particular, *in vitro* studies tend to vary widely in the parameters measured [24]. It is important to underline that despite these filters, we considered that study populations, treatment interventions and durations were too variable for a meta-analysis to be valid, at this time.

3. RESULTS

A total of 39 studies were identified that fulfilled our inclusion criteria [8,9,13,18-21,25-56]. These studies measured the effects of 8 antipsychotics (aripiprazole, clozapine, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone) on 13 inflammatory

mediators [CRP, IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, interleukin-13 (IL-13), IL-18, TGF-β, TNF-α and 4 cytokine receptors (IL-6R, sIL-2R, Leukemia Inhibitory Factor receptor (LIF-R), sTNF-R) (**Table 1**). As expected, studies varied in terms of duration of treatment, diagnostic criteria, patient population (chronic, first-episode, in-/out-patients, etc), socio-demographic variables (age, sex), medication at baseline (drug-naïve, drug-free, wash-out, on FGAs, on SGAs, etc.), and adjuvants allowed (**Table 1**).

3.1. Global Findings

Irrespective of drug status (drug-free or not) or patient type (first-episode or not), antipsychotics produced their most consistent effects on peripheral IL-2, sIL-2R and sTNF-R levels in schizophrenia patients (**Table 2**). Indeed, a decrease in IL-2 levels was observed in most cases. In a complementary fashion, antipsychotic treatment produced elevations in peripheral levels of sIL-2R in a majority of cases (**Table 2**). Despite contradictory results regarding the effects of antipsychotics on TNFα, an increase in sTNF-R2 levels was described in all cases and an increase in sTNF-R1 levels in most cases (**Table 2**). Apart from these changes, there are consistent results showing that antipsychotic treatment is associated with a lack of change in peripheral IL-6, IL-1RA and CRP levels (**Table 2**).

Preliminary results tentatively suggest that antipsychotic treatment may decrease peripheral IFN-γ and TGF-β, and increase IL-4 levels (**Table 2**). In the case of IL-12, contradictory results have been reported thus far (**Table 2**). As for IL-1β, IL-8, IL-10, IL-13, IL-18, LIF-R, sIL-6R, these cytokines or cytokine receptors have not been studied in a sufficient number of studies thus far to reach firm conclusions (**Table 2**).

3.2. The Effects of Specific Antipsychotics

Clozapine is the antipsychotic that has been the most studied thus far with regards to its effects on peripheral cytokines. As shown in **Table 3**, clozapine has been shown to consistently (5 studies out of 5) increase peripheral sIL-2R levels in schizophrenia-spectrum disorders. Three studies showed an increase in sTNF-R1 and sTNF-R2 levels during treatment, and 3 studies out of 5 showed that clozapine therapy was associated with an increase in peripheral TNF-α levels (**Table 3**). Conversely, clozapine does not seem to influence peripheral IL-6 levels in most cases. As for olanzapine, treatment with this SGA has also been associated with a lack of change in both IL-6 (3/3 negative results) and CRP levels (5/6 negative results) (**Table 3**). However, the CATIE study, which included 202 patients treated with olanzapine, showed that 3-month treatment with this SGA induced a significant increase in CRP levels [48]. Quetiapine produced a similar CRP elevation in the CATIE trial (n = 180) [48]. Finally, studies of mixed SGAs produced inconclusive effects on IL-6 (**Table 3**).

3.3. Correlations of Immune and Clinical Changes

Although an understanding of the clinical correlates of cytokine changes during antipsychotic treatment in schizophrenia-spectrum disorders is essential to better understand the functional effects of antipsychotic-induced immune effects, only a few studies have addressed this issue as yet. Thus far, the most consistent association reported in the literature has been between IL-2/sIL-2R and the positive symptoms of schizophrenia. Indeed, an 8-week trial of clozapine or risperidone confirmed a positive correlation between the reductions of IL-2 levels and positive symptoms (as measured with the *Positive and Negative Syndrome Scale*, PANSS) in schizophrenia [43]. Similarly, during an 8-week trial with haloperidol, a positive correlation emerged between changes in IL-2 levels and changes in peripheral homovanilic acid (HVA, dopamine metabolite), the latter being positively correlated with changes in positive symptoms (as measured with the *Scale for the Assessment of Positive Symptoms*) [40]. Finally, in a 12-week trial with quetiapine, increases in sIL-2R levels were correlated with a decrease in PANSS-positive symptoms [9]. Preliminary associations have also been reported between changes in IL-2 levels and changes in PANSS-negative [54] and PANSS-total symptoms [8].

In the case of other cytokines, preliminary associations have been reported between changes in cytokine levels and changes in clinical symptoms. Thus far, correlations have been described between IL-1β levels and PANSS-total symptoms [55]; and between IL-1RA levels and PANSS-negative symptoms [54]. Similarly, associations between changes in IL-6 levels and changes in PANSS-total symptoms [20], PANSS-positive symptoms [43] and global symptoms (as measured with the *Brief Psychiatric Rating Scale*) [31] have been described. Furthermore, cytokines seem to be associated with adverse events caused by antipsychotics. For example, IL-6 is associated with clozapine-induced fever [8] and TNF-α levels with insulin resistance index [21].

4. DISCUSSION

This review highlights the complexity of the interaction of the immune system and antipsychotic medication. Despite significant clinical heterogeneity across studies, the data cumulated here suggest that antipsychotic treatment leads to increases in sIL-2R, sTNF-R and IL-4, and decreases in IL-2, IFN-γ and TGF-β levels in schizophrenia.

Table 1. Pharmacological trials measuring the effects of antipsychotics on peripheral C-reactive protein and cytokine levels in schizophrenia-spectrum disorders.

Author(s)	Subjects	Dx criteria	Drugs at baseline others: both	Length (weeks)	Phase of illness	Treatment during study	Changes in time
Akandji *et al*., 2009 [25]	207 SCZ (36); 165 HC (38)	DSM-IV	44 FGAs; 12 SGAs; 151 both	52	Chronic, stable	Mixed AP	↔ CRP
Akiyama, 1999 [26]	26 SCZ (34.4) (11/15); 27 HC (34.8) (11/17)	DSM-IV	14 drug-naïve; 12 drug-free (mean = 13.8 months)	8	≥2 active symptoms; 12 AP cessation (relapse)	Mixed AP: FGAs & SGAs; bzd	↔ IL-6, IL-1RA, sIL-2R
Baptista *et al*., 2007a [21]	40 SCZ; 37 compl. (22/15)	DSM-IV	Levo 100 mg Hs; fluph decanoate	14	Severe, chronic, inpatients	RCT: OLZ 10 mg + metformin or placebo	↓ TNF-*α* ↔ CRP
Baptista *et al*., 2007b [27]	60 SCZ (34/26)	DSM-IV	Fluph decanoate 25 mg/mo; levo 50 - 200 mg HS	8, 16	Chronic, severe, hospitalized	OLZ 10 - 20 mg	↑ CRP (wk 8) ↔ CRP (wk 16)
Baptista *et al*., 2007c [28]	76 SCZ; 4 bipolar; 72 compl. (42/30)	DSM-IV	On olanzapine (>4 months), mean = 10.3 mg	12	In-/out-patients	RCT: 36 on metformin, 36 on placebo	↔ CRP
Crespo-Facorro *et al*., 2008 [13]	56 SCZ (36/20); 40 SCZ, 12 SF, 4 other; 28 HC (12/16)	DSM-IV	Drug-naive	6	Frist-episode; outpatients; moderate-severe symptoms	OLZ, 20, 5 - 20 mg; RIS, 16, 3 - 9 mg; HAL, 20, 3 - 9 mg; anti-cholinergic	↑ IL-12 (RIS)
Diaz *et al*., 2010 [29]	OLZ, 36 (27.3) (22/14); RIS, 39 (27.4) (24/15); HAL, 36 (27.7) (24/12)	NA	Drug-naive	3 months; 1 year	First-episode	RCT: OLZ, 5 - 20 mg (n = 36); RIS, 3 - 6 mg (n = 39); HAL, 3 - 9 mg (n = 36)	↑ CRP (HAL, at 3 months); ↔ CRP (all AP, at 12 months)
Fernandez-Egea, 2011 [30]	30 SCZ (27.5) (66.7% m); 16 compl.; 21 SCZ, 4 SF, 3 other	DSM-IV	Drug-naïve; no AP in 30 days before; 1 week lifetime AP	16	First-episode; hospitalized	OLZ 22.9mg (10 - 40); up to 3 mg lorazepam HS	↔ IL-6
Frommberger *et al*., 1997 [31]	32 SCZ (age = 33); 12 HC (age = 31); 12 depression	DSM-III-R	11 drug-free (6 months)	8	Acute/remission (inpatients)	Mixed FGAs: hal, flup, per	↓ IL-6
Graham *et al*., 2008 [32]	45 SCZ (23.3) (67% of m); 16 compl.; 41 HC (25.4)		15 drug-naïve; 30 on SGAs (2 - 6 weeks exposure)	24	First-episode; 7 inpatients	Mixed SGAs: 9 ris, 4 olz, 2 qtp, 1 ari	↔ IL-6
Henderson *et al*., 2009 [33]	15 SCZ; 14 compl.	DSM-IV	Stable on olz for 1 month	10	Outpatients; BMI ≥ 30 Kg/m^2 or ≥ 27 + other risk factors	Cross-over of ARI or placebo added to OLZ	↔ CRP
Hinz-Selch *et al*., 2000 [34]	23 SCZ (11/12)	DSM-IIR	5 drug-free (6 months); AP stopped before or within the 1st week of clz	6	Inpatients, residual symptoms, or FGA intolerance	11 CLZ & fluvoxamine; 12 CLZ	↑ sIL-2R, TNF-α, TNF-R1/2
Hori *et al*., 2007 [35]	32 SCZ (35) (18/14); 55 HC (31) (30/25)	DSM-IV	NA	4, 8	In/outpatients	OLZ 5 - 20 mg	↔ TNF-*α*, IL-6, ↓ IL-2
Igue *et al*., 2011 [9]	29 SCZ (30.2) (25/4); 16 SCZ, 11 SA, 2 SF; 28 HC (28.2) (22/6)	DSM-IV	Treated with AP at baseline; >50% on olz	12	Outpatients; moderate symptoms; SUD	QTP (2 - 800 mg)	↔ IL-6, IL-1Ra; ↑ sIL-2R
Kim *et al*., 2009 [36]	71 SCZ (23) (32/39); 53 compl.; 174 HC (32.49) (78/96)	DSM-IV	38 drug-naïve 33 drug-free (4 months)	6	Acute psychotic symptoms, inpatients	Mixed SGAs: ris, n = 20; ami, n = 19; olz, n = 10; ari, n = 4	=↔ INF-y, IL-4, IL-2, TGF; ↓ IL-6, TNF-*α*
Kim *et al*., 2004 [37]	89 SCZ (32.8) (35/54); 66 compl.; 88 HC; (31.3) (34/54)	DSM-IV	43 drug-naïve, 45 drug-free (4 months)	8	First-episode, hospitalized, active psychotic symptoms	Mixed SGAs: 33 ris, 12 olz, 11 qtp, 6 nemo,4 clz	↓ IFN-y, TGF (ris, qtp, olz) ↑IL-4 (ris, qet, olz)

Continued

Kim *et al.*, 2002 [38]	43 SCZ (33.6) (12/31); 29 compl.; 85 HC (32.5) (28/57); 34 depression; 25 bipolar	DSM-IV	Drug-free (4 months)	8	First-episode; active psychotic symptoms; hospitalized	Mixed AP: ris 17, olz 5, nemo 4,cloz-2, hal 1	↓ IL-12
Kim *et al.*, 2001 [39]	25 SCZ (28.4) (11/8); 19 compl.	DSM-IV	Drug free for 6 months	4	Acute psychotic state (inpatients)	RIS (4.3 ± 1.2 mg, at wk4)	↔ IL-6, IL-1β, IL-2, IFN-γ ↑ IL-12
Kim *et al.*, 2000 [40]	25 SCZ (30.1) (25/0); 25 HC (30.1) (25/0)	DSM-IV	Drug-free for 6 months (15 drug-naïve)	8	Newly admitted acute psychotic state	HAL mean = 14.9 mg; benztropine	↓IL-2 ↔ IL-6, IL-1β
Kluge *et al.*, 2009 [8]	30 SCZ (36.7) (12/18)	DSM-IV	Wash-out (length not specified); prior AP: ris or hal	6	Inpatients; BPRS > 24	CLZ 266.7 mg; OLZ 21.2 mg; diazepam 40 mg (first 2 weeks)	↑TNF-α, sTNF-R2, sIL-2R (CLZ, OLZ); ↑sTNF-R1, IL-6 (CLZ)
Lin *et al.*, 2011 [41]	34 SCZ (34.7) (16/18); 30 HC (27.7)	DSM-IV	Drug-free (1 week)	4	Acute psychosis, chronic patients	Mixed SGAs: 12-clz, 19-ris, 1-olz, 2 ris depot	↔ IL-6, TNFα, TGF
Loffler *et al.*, 2010 [42]	10 SCZ; 15 clz poly-pharmacy; 25 psychiatric patients poly-medicated	DSM-IV	Drug-free 2 weeks; bzd	8	Chronic, inpatients	CLZ, 225 - 475 mg, n = 8; hal 2 - 6 mg, n = 2 (6 days)	↑ CRP
Lü *et al.*, 2004 [43]	58 SCZ	NA	NA	8	First-episode	CLZ-24, RIS-34	↓ IL-2 ↔ IL-18 (RIS/CLZ) ↓ IL-6, TNF-α (RIS)
Maes *et al.*, 2002 [44]	31 SCZ; 14 respond. (40) (8/6); 17 non-respond. (40.4) (8/9); 7 HC (40.4) (4/3)	DSM-IV	2-week wash-out for non-responders; responders on hal (5), clz (4), ris (4), perph (1)	16		Mixed SGAs: clz 358.3 (n = 12), ris 3.7 mg (n = 5)	↔ IL-8, IL-10 ↑ LIF-R
Maes *et al.*, 2000 [45]	31 SCZ; 17 non-respond. (8/9); 14 respond.; 7 HC (4/4)	DSM-IV	15-day washout	16	Treatment resistant	Mixed SGAs: cloz 12, ris 5	↔IL-6, sIL-6R, IL-1RA
Maes *et al.*, 1997 [46]	17SCZ (38.2) (11/6); 23 HC (36.3) (13/10)	DSM-IIIR	Drug-free (median = 10 days); prior treatment: hal, perph, thior	5 (mean= 12 days)	Chronic /sub-chronic	CLZ, 353 mg	↑ IL-6, IL-1RA (treatment > 10 days)
Maes *et al.*, 1995 [47]	14 SCZ (27.8) (3/11); 21 HC (33) (8/13); 10 mania	DSM-III-R	Drug-free (median: 25.5 days)	8	(sub)-chronic	Mixed FGAs: hal, perph, thior	↔ sIL-2R; ↓IL-6, sIL-6R
Maes *et al.*, 1994 [18]	14 SCZ (37) (10/4); 26 HC (38) (13/13)	DSM-IIIR	8-day washout	Mean = 73 days	Hospitalized	CLZ 354mg	↑ sIL-2R ↔ IL-6, sIL-6R
Meyer *et al.*, 2009 [48]	789 SCZ (41.2) (74.5% of m)	DSM-IV	On antipsychotics; adjuvants allowed	3 months	Chronic	OLZ n = 202, QTP 180, RIS 178, ZIPRA 86, PERPH 143	↑ CRP (OLZ & QTP only)
Monteleone *et al.*, 1997 [49]	17 SCZ, (25.4) (7/10) ; 17 HC	CIDI	3-week wash-out; 1 drug-naïve patient	10	Chronic	CLZ, n = 13, 312 mg (2 ris 6 mg, 2 hal 6 mg)	↓TNF-α ↔ IL-6
Muller *et al.*, 2004 [50]	25 SCZ (25f)	NA	NA	5	Chronic; acute exacerbation; 1st hospitalization, = 16	RIS + Celecoxib (n = 11) nor RIS + Placebo (n = 14)	↔ sIL-2R, TNF-R1
Muller *et al.*, 1997 [51]	39 SCZ (31) (22/17); 42 HC (29) (24/18)	DSM-IIIR	Drug-free (4 weeks); 16 drug-naïve	16	First-episode; inpatients	Mixed AP (FGAs & SGAs)	↓ s-IL-6R; ↑ sIL-2R

Continued

Pae *et al*., 2006 [20]	35 SCZ (37.7) (21/14)	DSM-IV	2-month wash-out; 17 drug-naïve	8	First-episode, chronic, inpatients	Mixed SGAs: olz-19, ris-14, qtp-2	↔IL-12, IL-10, TNF-*α*; ↓ IL-6, IL-13
Pollmacher *et al*., 1996 [19]	25 SCZ (29.5) (14/11); 23 SCZ, SA, 1 SF	1DSM-III-R	11 drug-free (6 months)	6	Inpatients, non-response or intolerable side effects	CLZ	↑ sIL-2R, TNF-*α*, sTNF-R1/2; ↔ IL-1RA, IL-6
Pollmacher *et al*., 1995 [52]	18 SCZ; 10 clz (31.8) (7/3); HC (35.1) (6/2)	DSM-III-R	6 drug-free (≥4 wks); HAL group = drug- free (1 year)	6	Non-response	CLZ 343 mg, n = 10; HAL 5.5 mg, n = 8	↑ sIL-2R (clz) ↔ sIL-2R (hal)
Sarandol *et al*., 2007 [53]	40 SCZ (34.9) (18/22); 36 compl.; 35 HC (33.5) (17/18)	DSM-IV	9 drug naive, 31 drug free (3 weeks)	6	First-episode	Mixed AP: 7-risp, 5-olz, 5-cloz, 3-qtp, 2-ami, 11-hal, 7 im risp	↔ TNF-*α*, CRP
Sirota *et al*., 2005 [54]	32 SCZ (40.2) (24/6); 22 HC (39.9) (16/6)	DSM-IV	6 drug-naïve, 26 drug-free (<2 months)	8		Mixed FGAs: hal, 20; perph, 10; levo, 2; biperiden; bzd	↔ sIL-2R; ↑ Il-1RA
Song *et al*., 2009 [55]	83 SCZ (27.3) (43/40); 65 HC (28.4) (35/30)	DSM-IV	Drug-naive	4	First-episode	RIS 2 - 4 mg; adjuvants allowed	↓IL-1*β* ↔ TNF-*α*
Zhang *et al*., 2009 [56]	78 SCZ (43.7) (27% f); 30 HC (40.4) (23% f)	DSM-IIR	Drug-free for 2 weeks	12	Chronic	RIS n = 41 6 mg, HAL n = 37 20 mg	↓ IL-2 ↔ IL-6

AP = antipsychotic; ARI = aripiprazole; BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; bzd = benzodiazepines; CLZ = clozapine; compl. = completers; CRP = C-reactive protein; Dx = diagnosis; f = female; FGAs = first-generation antipsychotics; flup = flupenthixol; fluph = fluphenazine; HAL = haloperidol; HC= healthy controls; IFN = interferon; IL = interleukin; im = intramuscular; levo = levomepromazine; LIF-R = leukemia inhibitory factor receptor; m = male; NA = data non-available; nemo = nemonapride; non-respond. = non-responders; OLZ = olanzapine; per = perazine; perph = perphenazine; RCT = randomized-controlled trial; resp. = responders; SA = schizo-affective disorder; SCZ = schizophrenia-spectrum patients; SF = schizophreniform disorder; SGAs = second-generation antipsychotics; SUD = substance use disorders; QTP = quetiapine; RIS= risperidone; TfR = transferring receptor; TGF = transforming growth factor; thior = thioridazine; TNF = tumor necrosis factor; ZIPRA = ziprasidone.

Table 2. Compilation of results, irrespective of drug status.

CRP/Cytokine/Cytokine receptor	Type of change during treatment		
	↓	↔	↑
CRP	0	11	4
IFN-*γ*	3	2	0
IL-1*β*	1	2	0
IL-1RA	0	4	2
IL-2	6	2	0
sIL-2R	0	5	8
IL-4	0	1	3
IL-6	5	16	2
sIL-6R	2	2	0
IL-8	0	1	0
IL-10	0	2	0
IL-12	1	3	2
IL-13	1	0	0
IL-18	0	2	0
LIF-R	0	0	1
TNF-*α*	4	6	4
TNF-R1	0	2	3
TNF-R2	0	0	4
TGF-*β*	3	2	0

CRP = C-reactive protein; IFN = interferon; IL = interleukin; LIF-R = leukemia inhibitory factor receptor; TNF = tumor necrosis factor; TGF = transforming growth factor.

Table 3. The effects of specific antipsychotics on peripheral C-reactive protein, cytokines and cytokine receptor.

Cytokines	Clozapine	Olanzapine	Quetiapine	Risperidone	Mixed SGAs	Haloperidol	Mixed FGAs	Mixed AP: FGAs & SGAs
CRP	↑ [42]	↔ [21,27,28, 29,33] ↑ [48]	↑ [48]	↔ [29,48]	-	↑ [29]	-	↔ [25,53]
IL-1β	-	-	-	↓ [55] ↔ [39]	-	↔ [40]	-	-
IL-1RA	↔ [19] ↑ [46]	-	↔ [9]	-	↔ [45]	-	↑ [54]	↔ [26]
IL-2	↓ [43]	↓ [35]	-	↓ [43,56] ↔ [39]	↔ [36]	↓ [40,56]	-	-
IL-4	-	↑ [37]	↑ [37]	↑ [37]	↔ [36]	-	-	-
IL-6	↔ [18,19,43, 49] ↑ [8,46]	↔ [8,30,35]	↔ [9]	↓ [43] ↔ [39,56]	↓ [20,36] ↔ [32,41,45]	↔ [40,56]	↓ [31,47]	↔ [26]
IL-8	-	-	-	-	↔[44]	-	-	-
IL-10	-	-	-	-	↔ [20,44]	-	-	-
IL-12	-	↔ [13]	-	↑ [13,39]	↔ [20]	↔ [13]	-	↓ [38]
IL-13	-	-	-	-	↓ [20]	-	-	-
IL-18	↔ [43]	-	-	↔ [43]	-	-	-	-
IFN-γ	-	↓ [37]	↓ [37]	↓ [37] ↔ [39]	↔ [36]	-	-	-
TNF-α	↓ [49] ↔ [43] ↑ [8,19,34]	↓ [21] ↔ [35] ↑ [8]	-	↓ [43] ↔ [55]	↓ [36] ↔ [20,41]	-	-	↔ [53]
TGF-β	-	↓ [37]	↓ [37]	↓ [37]	↔ [36,41]	-	-	-
TNF-R1	↑ [8,19,34]	↔ [8]	-	↔ [50]	-	-	-	-
TNF-R2	↑ [8,19,34]	↑ [8]	-	-	-	-	-	-
sIL-2R	↑ [8,18,19,34, 52]	↑ [8]	↑ [9]	↔ [50]	-	↔ [52]	↔ [47,54]	↔ [26] ↑ [51]
sIL-6R	↔ [18]	-	-	-	↔ [45]	-	↓ [47]	↓ [51]
LIF-R	-	-	-	-	↑ [44]	-	-	-

CRP = C-reactive protein; FGAs = first-generation antipsychotics; IFN = interferon; IL = interleukin; TFN = tumor necrosis factor; LIF = leukemia inhibitory factor; SGAs = second-generation antipsychotics.

4.1. IL-2/sIL-2R

A recent meta-analysis revealed that peripheral sIL-2R levels were consistently increased in schizophrenia subjects [12]. In the current review, two studies document increased IL-2 in schizophrenia patients compared to healthy controls [35,40], and one reports lower levels [36]. On the other hand, sIL-2R was found to be higher in schizophrenia patients, relative to controls, in 4 studies [9,18,26,35]. In Maes *et al.*'s study [18], this finding was restricted to younger schizophrenia patients, suggesting that age may be a confounding factor in some cases. Only Müller *et al*. [51] found sIL-2R to be lower in schizophrenia patients. Treatment, however, had consistent effects decreasing IL-2 and increasing sIL-2R in most cases. IL-2 and its soluble receptor seem related to clinical symptoms. Hence, Akiyama *et al*. [26] found a correlation between positive (week 4) and negative (week 1 and 4) symptoms and sIL-2R, while Kim *et al*. [40] found a relationship between IL-2 levels and positive symptoms at baseline and endpoint. Decreases in positive symptoms are associated with increases in sIL-2R with treatment [9]. Zhang *et al*. [56], however, found an inverse relationship between IL-2 and baseline PANSS positive symptoms in a group of patients with chronic schizophrenia. Age may be another factor to consider, as sIL-2R levels are inversely correlated with age of onset [26], suggesting a greater reactivity of the immune system in younger patients. Although the data on IL-2 and its soluble receptor are not yet conclusive, these findings suggest that schizophrenia is accompanied by an inflammatory state that is at least in part corrected

by antipsychotic medication. On the opposite side, some studies have found an association between serum sIL-2R levels and tardive dyskinesia in neuroleptic medicated patients, pointing to potential detrimental effects of sIL-2R [57]. This is supported by recent animal studies showing that peripheral injections of sIL-2R induce behavioral disturbances, while inducing increased neuronal activity localized to cortex and striatum where injected sIL-2R is accumulated [58]. Further clinical and mechanistic studies are required to clarify whether antipsychotic-induced sIL-2R increases play positive or negative roles in psychopathology and/or drug-associated side effects.

4.2. TNF-*α*/sTNF-R

Similarly, the soluble receptors of TNF-*α* attenuate its pro-inflammatory activity [59]. Decreased TNF-*α* levels are seen after treatment with mixed antipsychotics [36] and risperidone [43], while contradictory effects have been reported in the case of olanzapine [8,21]. Noteworthy, Baptista *et al*. [21] noted that the decrease in TNF-α was more prominent in men. As for clozapine, despite some contradictory evidence, most studies described that this antipsychotic elevated TNF-*α* levels in schizophrenia [8,19,49]. In addition, an increase in the soluble receptor of TNF-*α* was seen with clozapine [8,34], and olanzapine [8]. For the moment, the exact significance of these effects of clozapine and olanzapine remains incompletely understood. On the one hand, the effects of clozapine on TNF-*α* may underlie its propensity to produce weight gain, since TNF-*α* is a pro-inflammatory cytokine considered to be an important inhibitor of insulin action [60], and a potent regulator of lipid metabolism [61]. In support of this explanation, Baptista *et al*. [21] described a relationship between changes in TNF-*α* levels and insulin resistance index, and Kluge *et al*. [8] observed a correlation between baseline body mass index and TNF-*α* levels in schizophrenia. On the other hand, the increases in sTNF-R1 levels produced by clozapine and olanzapine may underlie the well-known efficacy of these antipsychotic agents, since sTNF-R1 has been associated with hippocampal neurogenesis [62], and since the hippocampus is a brain structure critically involved in the pathophysiology of schizophrenia [63]. Certainly, future studies ought to investigate whether sTNF-R1 increases are restricted to treatment with these two agents.

4.3. IFN-*γ*

IFN-*γ* is a pro-inflammatory cytokine and a decrease in its levels would contribute to an attenuation of inflammation [64]. Various groups measured IFN-*γ*, noting such a decrease in some [8,37] but not all cases [39] after treatment with several different antipsychotic agents. This decrease is thus consistent with an anti-inflammatory effect of antipsychotic agents.

4.4. IL-4 and TGF-*β*

IL-4 and TGF-*β* are both considered to be anti-inflammatory cytokines [65,66]. While the increase of IL-4 seen by Kim *et al*. (2004) [37] would be in line with a general anti-inflammatory effect of antipsychotic treatment, the reduction of TGF-*β*, noted by the same team, would counteract this effect. However, TGF-*β*, in the context of either IL-4 or IL-6, may drive the differentiation of T-cells in a pro-inflammatory direction [67]. Thus, the decrease of TGF-*β* in the context of increased IL-4 may indeed be anti-inflammatory.

4.5. IL-6

A pro-inflammatory cytokine, IL-6 is usually unchanged [18,49] and sometimes increased [46] during treatment with clozapine, while it is unchanged [26,32,35,56] or decreased during treatment with any other antipsychotic [20,31,37,43] (for more information, refer to **Table 3**). Not all studies had healthy controls, or used the same measures of illness severity. However, in some cases, in accordance with previous reports [12], baseline IL-6 levels seem to be increased compared to healthy controls [9,20,26,31,36,41]. Maes *et al*. [18] found an increase of IL-6 levels compared to controls at baseline but only in younger schizophrenia patients. In contrast, Müller *et al*. [51] found no difference between schizophrenia patients and healthy controls in IL-6 levels at baseline. Clinical characteristics seem to be correlated to IL-6 levels in some cases. Thus, Monteleone *et al*. [49] found a correlation between IL-6 levels and illness duration, and Pae *et al*. [20] found that baseline IL-6 levels were correlated to the general and total PANSS score, while changes in IL-6 correlated with changes in the general and total PANSS score. Although changes in IL-6 during antipsychotic treatment are generally inconsistent, there may be a possibility that clozapine, an effective agent with significant side effects, is associated with a pro-inflammatory effect, at least with regards to IL-6. More precisely, changes in peripheral IL-6, a major endogenous pyrogen, have been associated with clozapine-induced fever [8].

4.6. CRP

CRP is the best characterized systemic and nonspecific biomarker of inflammation. CRP changes in response to antipsychotic treatment vary. In a drug-naïve sample, CRP increased with haloperidol but not risperidone or olanzapine at 3 months, however, these differences were not maintained at 12 months [29]. There was a trend towards a decrease in CRP after treatment with aripiprazole as an add-on treatment to olanzapine [33]. With

clozapine, CRP increased as of week one of treatment [42]. Three other studies revealed a lack of effect of olanzapine on CRP levels in schizophrenia [21,27,28], but 2 of the studies had adjuvants (aripiprazole, metformin) that were added to olanzapine in a randomized, double-blind, placebo-controlled fashion. In contrast, in the CATIE study [48], which included the largest sample of patients in which CRP was studied, and measured the effects of olanzapine, perphenazine, quetiapine, risperidone and ziprasidone, CRP increased with olanzapine and quetiapine, which both produce significant weight gain [68]. Interestingly, the increases in CRP levels correlated with indices of metabolic syndrome. However, the CATIE trial was complicated by the fact that many subjects were previously treated with olanzapine and risperidone. As yet, the reasons for the discrepancy in results between the CATIE study and other trials included in the current review are not fully elucidated and may be related to differences in inclusion criteria. Nevertheless, the CATIE results suggest that CRP elevations may be involved in antipsychotic-induced weight gain or metabolic disorders in schizophrenia, either as a cause or consequence. In non-psychiatric patients, an emerging literature has linked high CRP levels to increased cardiovascular risk in metabolic syndrome patients [69].

4.7. IL-1/IL-1RA

Produced by several inflammatory cells including monocytes/macrophages and neutrophils, and by adipose tissues, IL-1RA is an anti-inflammatory cytokine that inhibits the biological activity of IL-1-α and IL-1β at the IL-1 receptor. In schizophrenia, there is reliable evidence from cross-sectional studies showing that peripheral IL-1RA levels are increased, relative to controls, and that such IL-1RA elevations are present in both schizophrenia patients on- and off-antipsychotic treatment [9,12,26]. Interestingly, the current review showed that IL-1RA levels do not seem to be influenced by most antipsychotics (**Tables 2-3**). Altogether, the results of cross-sectional and follow-up studies suggest that IL-1RA alterations may be independent of antipsychotic medication in schizophrenia. Physiologically, the elevated levels of peripheral IL-1RA observed in schizophrenia may reflect an attempt to restore homeostasis balance in response to an inflammatory syndrome, illustrated by elevations of sIL-2R and IL-6. Unfortunately, the clinical significance of IL-1RA alterations in schizophrenia remains undetermined. IL-1RA and negative symptoms have been shown to decline in parallel fashion [54]. Moreover, a signifycant positive correlation was found, at baseline, between peripheral IL-1RA levels and body mass index in schizophrenia [9], a result consistent with the fact that adipocytes are a major source of IL-1RA production [70].

4.8. Study Limitations and Future Directions

Despite the complex nature of the topic addressed here, the current review revealed a relatively consistent set of patterns regarding the influence of antipsychotics on some cytokines and their receptors that may help define priorities for future research in the field. The fact that antipsychotics seem to possess some anti-inflammatory properties, as illustrated by decreases in IL-2 and IFN-γ as well as increases in sIL-2R, IL-4 and sTNF-R, should encourage the pursuit of further studies examining the potential therapeutic effects of anti-inflammatory drugs in schizophrenia. For instance, preliminary small-scaled randomized controlled trials have shown that celecoxib, a non-steroidal anti-inflammatory drug and selective cyclo-oxygenase-2 inhibitor, may provide partial relief of symptoms in schizophrenia [71]. In contrast, there is a lack of literature regarding the effects of antipsychotics on a large set of cytokines and cytokine receptors, including IL-1β, sIL-6R, IL-8, IL-10, IL-12, IL-13, IL-18 and LIF-R, to name only a few examples. Yet, some of these immune markers have been shown to be altered in schizophrenia, including IL-8 and IL-12 [39,72]. Regarding the potential distinctive profile of typical versus atypical antipsychotics, data are also critically missing. As reviewed here, the small number of in vivo studies which measured the effects of typical antipsychotics on peripheral cytokines suggests that, much like atypicals, typical antipsychotics elevate sIL2-R and decrease IL-2 levels in schizophrenia [51,56]. Conversely, their potential effects on *in vivo* TNF-α, IL-6 and IFN-γ levels are relatively unknown. For the moment, the available literature does not suggest that the changes in peripheral IL-2 and sIL-2R levels produced by antipsychotics in schizophrenia are hallmarks of atypicality.

The molecular mechanisms whereby antipsychotics regulate inflammatory mediator levels are unknown. One potential mechanism includes neurotransmitter receptors that are the targets of antipsychotics on neurons, and that are also expressed in several immune cells where they contribute to regulate the physiology of immune cells as well as the bi-direct communication between the brain and the immune system [73,74]. That antipsychotics consistently increase soluble cytokine receptors, namely sIL-2R, sTNF-RI and sTNF-RII is particularly intriguing. Although multiple mechanisms have been reported [75], these soluble receptors are all generated mainly by proteolytic cleavage and shedding of the corresponding cell-surface cytokine receptors. Various enzymes are involved including the TNF-α converting enzyme (TACE) for generation of sTNF-RI and sTNF-RII, neutrophil elastase (NE) for sTNF-RI, sTNF-RII and sIL-2R, and proteinase 3 (PR3) for sIL-2R. Whether antipsychotics regulate soluble cytokine receptors by regulating the activity of these enzymes, or via other mechanisms remains

to be elucidated. Changes in cytokines in these studies were sometimes affected by age, as in Maes *et al.*'s 1994 study [18]. Another factor was sex. For example, TNF-α decreased more in men and CRP declined only in men [21]. Weight, as in Kluge *et al.*'s 2009 study [8], could also affect cytokine concentrations. Duration of illness was sometimes correlated with baseline IL-6 values [31, 49]. In the three studies where the authors clearly indicated that patients were on stable medication, antipsychotic treatment had no effect on the sole inflammatory marker measured, CRP [25,28,33]. Clearly, this should not be over interpreted; yet it seems likely that findings may be altered by the duration of treatment in various ways. It is highly likely that the variability of findings regarding cytokines and antipsychotic treatment derives, at least in part from the difficulty in conducting studies which control all of these confounding factors.

4.9. Towards a Unifying Model

From the data presented here emerges the understanding that there may be a complex interplay between the characteristics of the immune response such as its variation with age or sex, the direct and indirect effect of illness, and the effect of treatment, as depicted in **Figure 1**. The stress resulting from the illness and its complications must undoubtedly influence both the illness and the inflammatory process. Globally, IL-6 may represent the system's response to the stress of an acute psychotic episode [76]. The nuclear factor-kappaB (NF-KB) may

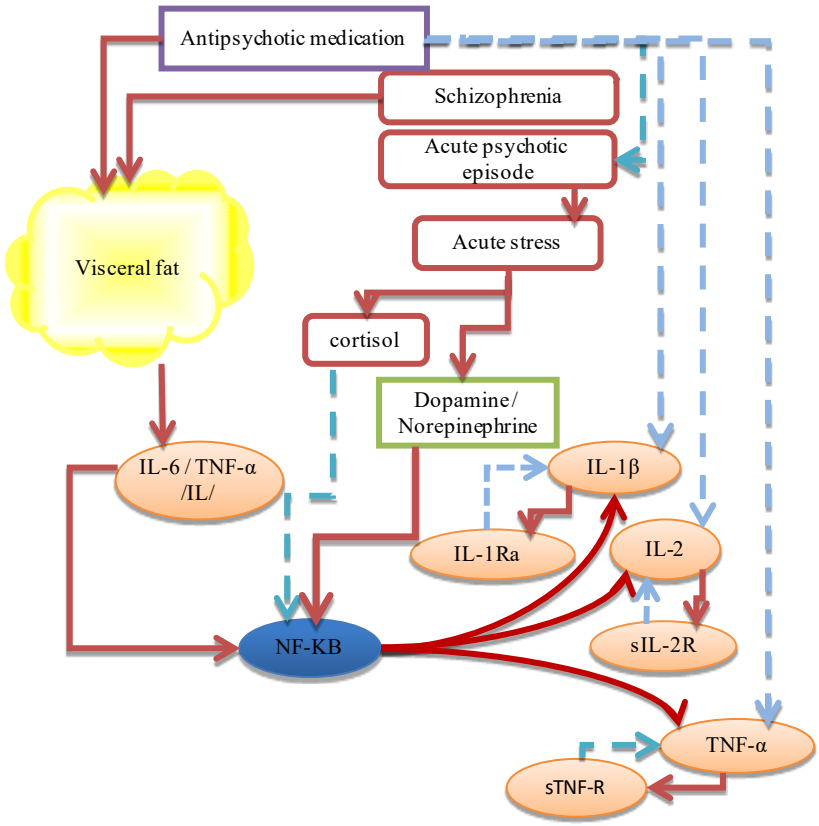

Figure 1. Simplified interaction of the acute and chronic stress of schizophrenia, the immune system, and antipsychotic treatment. Red arrows indicate a promoting and blue an inhibitory influence. Acute stress induces an initial increase of dopamine and norepinephrine leading to increased expression of cytokines (IFN-*γ*, IL-2, IL-6, TNF-*α* and others which are not shown here) through mechanisms involving activetion of the transcript factor NF-KB pathway. Acute stress also leads to a delayed increase of cortisol which functions to break the inflammatory reaction. Chronic stress is associated with a reduced cortisol levels and thus a reduced ability to break the inflammatory reaction. Schizophrenia, chronic stress, and many antipsychotic medications are associated with increased visceral fat which is associated with increases in some pro-inflammatory cytokines. Antipsychotic medications are associated with decreases of pro-inflammatory cytokines such as IFN-*γ* and IL-2, as well as increases in soluble receptors of IL-2 and TNF-*α*, which act to attenuate their inflammatory activity [77,82,83].

play a pivotal role in the transmission of the stress signal into up-regulation of several inflammatory cytokine genes [77]. This response may thus be modulated by psychosocial and biological factors which modulate the stress response. This may explain the variability of results in studies examining IL-6 levels in particular and inflammatory markers in general. Zhang *et al*. [78] found increases in cortisol, IL-6 and IL-2 in chronic schizophrenia, relative to controls. These elevations of cortisol and IL-2 declined after treatment with either risperidone or haloperidol, suggesting an involvement of both the hypothalamo-pituitary-adrenal (HPA) axis and the inflammatory system in schizophrenia. The psychological experience of illness and thus the resultant stress may be changed both by a decrease of symptoms and familiarity with the illness leading to a modification of both the HPA axis and the inflammatory system over time. In addition, the response of the system to stress may be altered through adaptation by repeated exposures to stress [79] and thus produce a different effect on the inflammatory response to psychosis. With some treatments, such as clozapine, which is more often associated with increased IL-6 levels, this evolution over time may be complicated by a tendency to contribute to the development of a metabolic syndrome which may have a direct effect on the inflammatory system and its response to stress [80,81].

Although direct effects of interleukins on cerebral neurotransmission have been described, these have not been sufficiently clarified to hypothesize on their contribution to the interaction of the inflammatory reaction in schizophrenia [84]. Administration of central IL-1β, and TNF-α produces a reduction in rat hypothalamic dopamine. The administration of IL-2 was associated with increased HVA, a metabolite of dopamine, in the hypothalamus and hippocampus, indicating increased dopaminergic activity. IL-2 was associated with increased HVA in the hippocampus, and IL-6 with increased HVA in the hypothalamus [85]. Given the reported relationships between changes in IL-2/sIL-2R levels and positive symptoms of schizophrenia during treatment with antipsychotics, as well as the association between changes in IL-2 levels and changes in peripheral HVA described by Kim *et al*. [40], the biological interactions between dopamine and IL-2/sIL-2R will need to be studied more carefully in the future.

5. CONCLUSION

Interpretation of the data regarding the relationship between cytokines and antipsychotic treatment remains speculative given the paucity of data and the wide divergence of clinical contexts and study variables. Nevertheless, certain patterns emerge from the data which suggest a common trend. This review highlights the potential anti-inflammatory effects associated with antipsychotic treatment but also demonstrates a substantial heterogeneity in the results of the studies investigating this issue. All available data suggest that schizophrenia is associated with inflammation, further supporting previous observations. It is already clear that the relationship is not simple and may be mediated by a complex interplay between multiple factors which are in constant flux as the illness evolves. The numerous attempts to clarify this interplay result in contradictory data as a consequence of the difficulty of controlling dimensions such as age, sex, weight, phase of illness, duration of illness, severity of illness, treatment status, medical comorbidities, substance abuse as well as psychological stress which may all affect the inflammatory reaction. This review also suggests that it is overly simplistic to attribute the therapeutic effects of antipsychotic medication to the anti-inflammatory effect. In fact, those antipsychotic medications which are the most consistently accompanied with pro-inflammatory effects (on TNF-α, IL-6 and CRP), clozapine and olanzapine, are also those which are widely recognised to have the greatest therapeutic effect. Further investigations will need to carefully measure not only biological parameters, such as CRP, the interleukins, TNF-α, and cortisol, but also psychological parameters such as the individual's reaction to stress in general and his illness in particular as well as the stress to which the individual is subjected, which may modulate an individual's inflammatory reaction. In the future, a better understanding of the immunomodulatory effects of antipsychotics and their molecular mechanisms of action on neuro-immune and inflammatory mediators will help to identify novel therapeutic strategies as well as novel biomarkers of treatment response and of drug-induced side effects in schizophrenia.

6. ACKNOWLEDGEMENTS

SP is holder of a Junior 1 salary award from the Fonds de Recherche en Santé du Québec. The authors thank Simon Zhornitsky, PhD, and Simon Fortin-Fournier, MSc, for their technical help.

REFERENCES

[1] Seeman, P. (2002) A typical anti-psychotics: Mechanism of action. *Canadian Journal of Psychiatry*, **47**, 27-38.

[2] Rogers, D.P. and Goldsmith, C.A. (2009) Treatment of schizophrenia in the 21st century: Beyond the neurotransmitter hypothesis. *Expert Review of Neurotherapeutics*, **9**, 47-54. doi:10.1586/14737175.9.1.47

[3] Levin, S.Z., Rabinowitz, J., Ascher-Svanum, H., Faries, D.E. and Lawson, A.H. (2011) Extent of attaining and maintaining symptom remission by antipsychotic medication in the treatment of chronic schizophrenia: Evidence from the CATIE study. *Schizophrenia Research*, **133**, 42-46. doi:10.1016/j.schres.2011.09.018

[4] Drzyzga, L., Obuchowicz, E., Marcinowska, A. and Herman, Z.S. (2006) Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain*, *Behavior*, *and Immunity*, **20**, 532-545. doi:10.1016/j.bbi.2006.02.002

[5] Miller, B.J., Buckley, P., Seabolt, W., Mellor, A. and Kirkpatrick B. (2011) Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry*, **70**, 663-671. doi:10.1016/j.biopsych.2011.04.013

[6] Kato, T.A., Monji, A., Mizoguchi, Y., Hashioka, S., Horikawa, H., Seki, Y., Kasai, M., Utsumi, H. and Kanba, S. (2011) Anti-inflammatory properties of antipsychotics via microglia modulations: Are antipsychotics a "fire extinguisher" in the brain of schizophrenia? *Mini-Reviews in Medicinal Chemistry*, **11**, 565-574.

[7] Baptista, T. and Beaulieu, P. (2002) Are leptin and cytokines involved in body weight gain during treatment with antipsychotic drugs? *Canadian Journal of Psychiatry*, **47**, 742-749.

[8] Kluge, M., Schuld, A., Schacht, A., Himmerich, H., Dalal, M.A., Wehmeier, P.M., Hinze-Selch, D., Kraus, T., Dittmann, R.W. and Pollmächer, T. (2009) Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. *Psychoneuroendocrinology*, **34**, 118-128. doi:10.1016/j.psyneuen.2008.08.016

[9] Igue, R., Potvin, S., Bah, R., Stip, E., Bouchard, R.H., Lipp, O., Gendron, A. and Kouassi. E. (2011) Soluble interleukin-2 receptor levels correlated with positive symptoms during quetiapine treatment in schizophrenia-spectrum disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatryis*, **35**, 1695-1698. doi:10.1016/j.pnpbp.2011.05.011

[10] Monji, A., Kato, T.A., Mizoguchi, Y., Horikawa, H., Seki, Y., Kasai, M., Yamauchi, Y., Yamada, S. and Kanba, S. (2011) Neuroinflammation in schizophrenia especially focused on the role of microglia. *Progress in Neuro-Psychopharmacology & Biological Psychiatryis*, Epub ahead of Print. doi:10.1016/j.pnpbp.2011.12.002

[11] Müller, N., Myint, A.M. and Schwarz, M.J. (2011) Kynurenine pathway in schizophrenia: Pathophysiological and therapeutic aspects. *Current Pharmaceutical Design*, **17**, 130-136. doi:10.2174/138161211795049552

[12] Potvin, S., Stip, E., Sepehry, A.A., Gendron, A., Bah, R. and Kouassi, E. (2008) Inflammatory cytokine alterations in schizophrenia: A systematic quantitative review. *Biological Psychiatry*, **63**, 801-808. doi:10.1016/j.biopsych.2007.09.024

[13] Crespo-Facorro, B., Carrasco-Marín, E., Pérez-Iglesias, R., Pelayo-Terán, J.M., Fernandez-Prieto, L., Leyva-Cobián, F. and Vázquez-Barquero, J.L. (2008) Interleukin-12 plasma levels in drug-naïve patients with a first episode of psychosis: Effects of antipsychotic drugs. *Psychiatry Research*, **158**, 206-216. doi:10.1016/j.psychres.2006.08.005

[14] Cortese, M. (1959) Research on the influence of chlorpromazine on immune processes. *Rivista dell'Istituto Sieroterapico Italiano*, **34**, 198-193.

[15] Mengozzi, M., Fantuzzi, G., Faggioni, R., Marchant, A., Goldman, M., Orencole, S., Clark, B.D., Sironi, M., Benigni, F. and Ghezzi, P. (1994) Chlorpromazine specifically inhibits peripheral and brain TNF production, and up-regulates IL-10 production, in mice. *Immunology*, **82**, 207-210.

[16] Song, C., Lin, A., Kenis, G., Bosman, E. and Maes, M. (2000) The immunosuppressive effects of clozapine and haloperidol: Enchanced production of the interleukin-1 receptor antagonist. *Schizophrenia Research*, **42**, 157-164. doi:10.1016/S0920-9964(99)00116-4

[17] Sugino, H., Futamura, T., Mitsumoto, Y., Maeda, K. and Marunaka, Y. (2009) Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipolysaccharide-treated mice. *Progress in Neuro-Psychopharmacology & Biological Psychiatryis*, **33**, 303-307. doi:10.1016/j.pnpbp.2008.12.006

[18] Maes, M., Meltzer, H.Y. and Bosman, E. (1994) Immune-inflammatory makers in schizophrenia: Comparison to normal controls and affects of clozapine. *Acta Psychiatrica Scandinavica*, **89**, 349-351. doi:10.1111/j.1600-0447.1994.tb01527.x

[19] Pollmächer, T., Hinze-Selch, D. and Mullington, J. (1996) Effect of clozapine on plasma cytokine and soluble cytokine receptor Levels. *Journal of Clinical Psychopharmacology*, **16**, 403-409. doi:10.1097/00004714-199610000-00011

[20] Pae, C.U., Yoon, C.H., Kim, T.S., Kim, J.J., Park, S.H., Lee, C.U., Lee, S.J., Lee, C. and Paik, I.H. (2006) Antipsychotic treatment may alter T-helper (TH) 2 arm cytokines. *International Immunopharmacology*, **6**, 666-671. doi:10.1016/j.intimp.2005.10.004

[21] Baptista, T., Sandia, I., Lacruz, A., Rangel, N., De Mendoza, S., Beaulieu, S., Contreras, Q., Galeazzi, T. and Vargas, D. (2007) Insulin counter-regulatory factors, fibrinogen and C-reactive protein during olanzapine administration: Effects of the antidiabetic metformin. *International Clinical Psychopharmacology*, **22**, 69-76. doi:10.1097/YIC.0b013e32801182e6

[22] Pollmächer, T., Hinze-Selch, D., Fenzel, T., Kraus, T., Schuld, A. and Mullington, J. (1997) Plasma levels of cytokines and soluble cytokine receptors during treatment with haloperidol. *American Journal of Psychiatry*, **154**, 1763-1765.

[23] McAllister, C.G., Van Kammen, D.P., Rehn, T.J., Miller, A.L., Kelley, M.E., Yao, J. and Peters, J.L. (1995) Increases in CSF levels of interleukin-2 in schizophrenia: effects of recurrence of psychosis and medication status. *American Journal of Psychiatry*, **152**, 1291-1297.

[24] Hinze-Selch, D. and Pollmacher, T. (2001) *In vitro* cytokine secretion in individuals with schizophrenia: Results, confounding factors, and implications for future research. *Brain*, *Behavior*, *and Immunity*, **15**, 282-318. doi:10.1006/brbi.2001.0645

[25] Akandji, A.O., Ohaeri, J.U., Al-Ahammri, S. and Fatania, H.R. (2009) Association of blood levels of C-reactive protein with clinical phenotypes in Arab schizophrenic patients. *Psychiatry Research*, **169**, 56-61. doi:10.1016/j.psychres.2008.06.010

[26] Akiyama, K. (1999) Serum levels of soluble IL-2 recep-

tor a, IL-6 and IL-1 receptor antagonist in schizophrenia before and during neuroleptic administration. *Schizophrenia Research*, **37**, 97-106. doi:10.1016/S0920-9964(98)00140-6

[27] Baptista, T., Davila, A., El Fakih, Y., Uzcategui, E., Rangel, N.N., Olivares, Y., Galeazzi, T., Vargas, D., Pena, R., Marquina, D., Villarroel, V., Teneud, L. and Beaulieu, S. (2007) Similar frequency of abnormal correlation between sérum leptin levels and BMI before and after olanzapine treatment in schizophrenia. *International Clinical Psychopharmacology*, **22**, 205-211. doi:10.1097/YIC.0b013e328080ca44

[28] Baptista, T., Rangel, N., Fernandez, V., Carrizo, E., El Fakih, Y., Uzcategui, E., Galeazzi, T., Gutierrez, M.A., Servigna, M., Davila, A., Uzcategui, M., Serrano, A., Connell, L., Beaulieu, S. and de Baptista, E.A. (2007) Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: A multicentric, double-blind, placebo-controlled trial. *Schizophrenia Research*, **93**, 99-108. doi:10.1016/j.schres.2007.03.029

[29] Diaz, F.J., Perez-Iglesias, R., Mata, I., Martinez-Garcia, O., Vasquez-Barquero, J.L., De Leon, J. and Crespo-Facorro, B. (2010) Possible effects of some antipsychotic drugs on C-reactive protein in a drug-naïve psychotic sample. *Schizophrenia Research*, **121**, 207-212. doi:10.1016/j.schres.2010.06.002

[30] Fernandez-Egea,E., Miller, B., Garcia-Rizo, C., Bernardo, M. and Kirkpatrick, B. (2011) Metabolic Effects of Olanzapine in patients With Newly Diagnosed Psychosis. *Journal of Clinical Psychopharmacology*, **31**, 154-159. doi:10.1097/JCP.0b013e31820fcea3

[31] Frommberger, U.H., Bauer, J., Haselbauer, P., Fräulin, A., Riemann, D. and Berger M. (1997) Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: Comparison between the acute state and after remission. *European Archives of Psychiatry and Clinical Neuroscience*, **247**, 228-233. doi:10.1007/BF02900219

[32] Graham, K.A., Cho, H., Brownley, K.A. and Joyce, B.H. (2008) Early treatment-related changes in diabetes and cardiovascular disease risk markers in first episode psychosis subjects. *Schizophrenia Research*, **101**, 287-294. doi:10.1016/j.schres.2007.12.476

[33] Henderson, D.C., Fan, X., Copeland, P.M., Sharma, B., Borba, C.P., Boxill, R., Freudenreich, O., Cather, C., Evins, A.E. and Goff, D.C. (2009) Aripiprazole added to overweight and obese olanzapine-Treated schizophrenia patients. *Journal of Clinical Psychopharmacology*, **29**, 165-169. doi:10.1097/JCP.0b013e31819a8dbe

[34] Hinze-Selch, D., Deuschle, M., Weber, B., Heuser, I. and Pollmächer, T. (2000) Effect of coadministration of clozapine and fluvoxamine versus clozapine monotherapy on blood cell counts, plasma levels of cytokines and body weight. *Psychopharmacology*, **149**, 163-169. doi:10.1007/s002139900351

[35] Hori, H., Yoshimura, R., Yamada, Y., Ikenouchi, A., Mitoma, M., Ida, Y. and Nakamura, J. (2007) Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. *International Clinical Psychopharmacology*, **22**, 21-27. doi:10.1097/YIC.0b013e3280103593

[36] Kim, Y.K., Myint, A.M., Verkerk, R., Scharpe, S, Steinbusch, H. and Leonard, B. (2009) Cytokine changes and tryptophan metabolites in medication-naïve and medication-free schizophrenic patients. *Neuropsychobiology*, **59**, 123-129. doi:10.1159/000213565

[37] Kim, Y.K., Myint, A.M., Lee, B.H., Han, C.S., Lee, H.J., Kim, D.J. and Leonard. B.E. (2004) Th1, Th2, and Th3 cytokine alteration in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **28**, 1129-1134. doi:10.1016/j.pnpbp.2004.05.047

[38] Kim, Y.K., Suh, I.B., Kim, H., Han, C.S., Choi, S.H. and Licinio, J. (2002) The plasma levels of interleukin-12 in schizophrenia, major depression, and bipolar mania: Effects of psychotropic drugs. *Molecular Psychiatry*, **7**, 1107-1114. doi:10.1038/sj.mp.4001084

[39] Kim, D.J., Kim, W., Yoon, S.J., Go, H.J., Choi, B.M., Jun, T.Y. and Kim, Y.K. (2001) Effect of risperidone on serum cytokines. *International Journal of Neuroscience*, **111**, 11-19. doi:10.3109/00207450108986549

[40] Kim, Y.K., Kim, L. and Lee, M.S. (2000) Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics, *Schizophrenia Research*, **44**, 165-175. doi:10.1016/S0920-9964(99)00171-1

[41] Lin, C.C., Chang, C.M., Cahng, P.Y. and Huang, T.L. (2011) *Chang Gung Medical Journal*, **34**, 375-381.

[42] Löffler, S., Löffler-Ensgraber, M., Fehsel, K. and Klimke, A. (2010) Clozapine therapy raises serum concentrations of high sensitive C-reactive protein in schizophrenic patients. *International Clinical Psychopharmacology*, **25**, 101-106. doi:10.1097/YIC.0b013e32833643fd

[43] Lü, L.X., Guo, S.Q., Chen, W., Li, Q., Cheng, J. and Guo, J.H. (2004) Effect of clozapine and risperidone on serum cytokine levels in patients with first-episode paranoid schizophrenia. *Di Yi Jun Yi Da Xue Xue Bao*, **24**, 1251-1254.

[44] Maes, M., Chiavetto, L.B., Bignotti, S., Battisa Tura, G.J., Pioli, R., Boin, F., Kenis, G., Bosmans, E., De Jongh, R. and Altamura, C.A. (2002) Increased serum interleukin-8 and interleukin-10 in schizophrenic patients resistant to treatment with neuroleptics and stimulatory effects of clozapine on serum leukemia inhibitory factor receptor. *Schizophrenia Research*, **54**, 281-291. doi:10.1016/S0920-9964(00)00094-3

[45] Maes, M., Chiavetto, L.B., Bignotti, S., Battisa Tura, G.J., Pioli, R., Boin, F., Kenis, G., Bosmans, E., De Jongh, R., Lin, A., Racagni, G. and Altamura, C.A. (2000) Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. *European Neuropsychopharmacology*, **10**, 119-124. doi:10.1016/S0924-977X(99)00062-0

[46] Maes, M., Bosmans, E., Kenis, G., De Jong, R., Smith, R.S. and Meltzer, H.Y. (1997) *In vivo* immunomodulatory effects of clozapine in schizophrenia, *Schizophrenia Research*, **26**, 221-225. doi:10.1016/S0920-9964(97)00057-1

[47] Maes, M., Bosmans, E., Calabrese, J., Smithe, R. and Meltzer, H.Y. (1995) Interleukin-2 and Interleukin-6 in schizophrenia and mania: Effects of neuroleptics and mood stabilizers. *Journal of Psychiatric Research*, **26**, 141-152. doi:10.1016/0022-3956(94)00049-W

[48] Meyer, J.M., McEvoy, J.P., Davis, V.G., Goff, D.C., Nasrallah, H.A., Davis, S.M., Hsiao, J.K., Swartz, M.S., Stroup, T.S. and Lieberman, J.A. (2009) Inflammatory markers in schizophrenia: Comparing antipsychotic effects in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness Study. *Biological Psychiatry*, **66**, 1013-1022. doi:10.1016/j.biopsych.2009.06.005

[49] Monteleone, P., Fabrazzo, M., Tortorella, A. and Maj, M. (1997) Plasma levels of interleukin-6 and tumor necrosis factor alpha in chronic schizophrenia: Effects of clozapine treatment, *Psychiatry Research*, **71**, 11-17. doi:10.1016/S0165-1781(97)00036-X

[50] Müller, N., Ulmschneider, M., Scheppach, C., Schwarz, M.J., Ackenheil, M., Möller, H.J., Gruber, R. and Riedel M. (2004) COX-2 inhibition as a treatment approach in schizophrenia: Immunological considerations and clinical effects of celecoxib add-on therapy. *European Archives of Psychiatry and Clinical Neuroscience*, **254**, 14-22. doi:10.1007/s00406-004-0478-1

[51] Müller, N., Empl, M., Riedel, M., Schwarz, M. and Ackenheil, M. (1997) Neuroleptic treatment increases soluble IL-2 receptors and decreases soluble IL-6 receptors in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, **247**, 308-313. doi:10.1007/BF02922260

[52] Pollmächer, T., Hinze-Selch, D., Mullington, J. and Holsboer, F. (1995) Clozapine-induced increase in plama levels of soluble interleukin-2 receptors. *Archives of General Psychiatry*, **52**, 877-878. doi:10.1001/archpsyc.1995.03950220087016

[53] Sarandol, A., Kirli, S., Akkaya, C., Ocak, N., Eroz, E. and Sarandol, E. (2007) Coronary artery disease risk factors in patients with schizophrenia: Effects of short term antipsychotic treatment. *Journal of Psychopharmacology*, **21**, 857-863. doi:10.1177/0269881107077609

[54] Sirota, P., Meiman, M., Herschko, R. and Bessler, H. (2005) Effect of neuroleptic administration on serum levels of soluble IL-2 receptor-alpha and IL-1 receptor antagonist in schizophrenic patients. *Psychiatry Research*, **134**, 151-159. doi:10.1016/j.psychres.2004.04.012

[55] Song, X.Q., Lv, L.-X., Li, W.-Q., Hao, Y.-H. and Zhao, J.-P. (2009) The interaction of nuclear factor-kappa B and cytokines is associated with schizophrenia. *Biological Psychiatry*, **65**, 481-488. doi:10.1016/j.biopsych.2008.10.018

[56] Zhang, X., Zhou, D.F., Qi, L.Y., Chen, S., Cao, L.Y., Chen, D.C., Xiu, M.H., Wang, F., Wu, G.Y., Lu, L., Kosten, T.A. and Kosten, T.R. (2009) Superoxide dismutase and cytokines in chronic patients with schizophrenia: association with psychopathology and response to antipsychotics. *Psychopharmacology*, **204**, 177-184. doi:10.1007/s00213-008-1447-6

[57] Rapaport, M.H. and Lohr, J.B. (1994) Serum-soluble interleukin-2 receptors in neuroleptic-naive schizophrenic subjects and in medicated schizophrenic subjects with and without tardive dyskinesia. *Acta Psychiatrica Scandinavica*, **90**, 311-315. doi:10.1111/j.1600-0447.1994.tb01599.x

[58] Zalcman, S.S., Patel, A., Mohla, R., Zhu, Y. and Siegel, A. (2012) Soluble cytokine receptors (sIL-2Ra, sIL-2Rb) induce subunit-specific behavioral responses and accumulate in the cerebral cortex and basal forebrain. *PLoS One*, **7**, e36316. doi:10.1371/journal.pone.0036316

[59] Bradley, J.R. (2008) TNF-mediated inflammatory disease. *Journal of Pathology*, **214**, 149-160. doi:10.1002/path.2287

[60] Borst, S.E. (2004) The role of TNF-alpha in insulin resistance. *Endocrine*, **23**, 177-182. doi:10.1385/ENDO:23:2-3:177

[61] Chen, X., Xun, K., Chen, L. and Wang, Y. (2009) TNF-alpha, a potent lipid metabolism regulator. *Cell Biochemistry & Function*, **27**, 407-416. doi:10.1002/cbf.1596

[62] Iosif, R.E., Ekdahl, C.T., Ahlenius, H., Pronk, C.J., Bonde, S., Kokala, Z., Jacobsen, S.E. and Lindvall, O. (2006) Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *Journal of Neuroscience*, **26**, 9703-9712. doi:10.1523/JNEUROSCI.2723-06.2006

[63] Bast, T. (2011) The hippocampal learning-behavior translation and the functional significance of hippocampal dysfunction in schizophrenia. *Current Opinion in Neurobiology*, **21**, 492-501. doi:10.1016/j.conb.2011.01.003

[64] Hebel, K., Rudolph, M., Kosak, B., Chang, H.D., Butzmann, J. and Brunner-Weinzierl, M.C. (2011) IL-1beta and TGF-beta act antagonistically in induction and differentially in propagation of human proinflammatory precursor CD4+ T cells. *Journal of Immunology*, **187**, 5627-5635. doi:10.4049/jimmunol.1003998

[65] Regateiro, F.S., Howe, D., Nolan, K.F., Agorogiannis, E.I., Greaves, D.R., Cobbold, S.P. and Waldmann, H. (2011) Generation of anti-inflammatory adenosine by leucocytes is regulated by TGF-beta. *European Journal of Immunology*, **41**, 2955-2965. doi:10.1002/eji.201141512

[66] Tsianakas, A., Varga, G., Barczyk, K., Bode, G., Nippe, N., Kran, N., Roth, J., Luger, T.A., Ehrchen, J. and Sunderkoetter, C. (2012) Induction of an anti-inflammatory human monocyte subtype is a unique property of glucocorticoids, but can be modified by IL-6 and IL-10. *Immunobiology*, **217**, 329-335. doi:10.1016/j.imbio.2011.10.002

[67] Sanjabi, S., Zenewicz, L.A., Kamanaka, M. and Flavell, R.A. (2009) Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. *Current Opinion in Pharmacology*, **9**, 447-453. doi:10.1016/j.coph.2009.04.008

[68] Rummel-Kluge, C., Komossa, K., Schwarz, S., Hunger, H., Schmid, F., Lobos, C.A., Kissling, W., Davis, J.M. and Leucht, S. (2010) Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*, **23**, 225-233. doi:10.1016/j.schres.2010.07.012

[69] Devaraj, S., Singh, U. and Jialal, I. (2009) Human C-reactive protein and the metabolic syndrome. *Current Opinion in Lipidology*, **20**, 182-189. doi:10.1097/MOL.0b013e32832ac03e

[70] Juge-Aubry, C.E., Somm, E., Giusti, V., Pernin, A., Chicheportiche, R. and Verdumo, C. (2003) Adipose tissue is a major source of interleukin-1 receptor antagonist: upregulation in obesity and inflammation. *Diabetes*, **52**, 1104-1110. doi:10.2337/diabetes.52.5.1104

[71] Sommer, I.E., de Witte, L., Begemann, M. and Kahn, R.S. (2012) Nonsteroidal anti-inflammatory drugs in schizophrenia: Ready for practice or a good start? A meta-analysis. *Journal of Clinical Psychiatry*, **73**, 414-419. doi:10.4088/JCP.10r06823

[72] Reale, M., Patruno, A., De Litis, M.A., Pesce, M., Felaco, M., Di Giannantonio, M., Di Nicola, M. and Grilli, A. (2011) Dysregulation of chemo-cytokine production in schizophrenic patients versus healthy controls. *BMC Neuroscience*, **12**, 13. doi:10.1186/1471-2202-12-13

[73] Reyes-García, M.G. and García-Tamayo, F. (2009) A neurotransmitter system that regulates macrophage pro-inflammatory functions. *Journal of Neuroimmunology*, **216**, 20-31. doi:10.1016/j.jneuroim.2009.06.024

[74] Pacheco, R., Riquelme, E. and Kalergis, A.M. (2010) Emerging evidence for the role of neurotransmitters in the modulation of T cell responses to cognate ligands. *Central Nervous System Agents in Medicinal Chemistry*, **10**, 65-83.

[75] Levine, S.J. (2008) Molecular mechanisms of soluble cytokine receptor generation. *Journal of Biological Chemistry*, **283**, 14177-14181. doi:10.1074/jbc.R700052200

[76] Steptoe, A., Hamer, M. and Chida, Y. (2007) The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, **21**, 901-912. doi:10.1016/j.bbi.2007.03.011

[77] Wolf, J.M., Rohleder, N., Bierhaus, A., Nawroth, P.P. and Kirschbaum, C. (2009) Determinants of the NF-kappaB response to acute psychosocial stress in humans. *Brain, Behavior, and Immunity*, **23**, 742-749. doi:10.1016/j.bbi.2008.09.009

[78] Zhang, X.Y., Zhou, D.F., Cao, L.Y., Wu, G.Y. and Shen, Y.C. (2005) Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: Association with psychopathology and response to antipsychotics. *Neuropsychopharmacology*, **30**, 1532-1538. doi:10.1038/sj.npp.1300756

[79] Gadek-Michalska, A., Tadeusz, J., Rachwalska, P., Spyrka, J. and Bugajski, J. (2011) Effect of prior stress on interleukin-1beta and HPA axis responses to acute stress. *Pharmacological Reports*, **63**, 1393-1403.

[80] Black, P.H. (2003) The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain, Behavior, and Immunity*, **17**, 350-364. doi:10.1016/S0889-1591(03)00048-5

[81] Gnacinska, M., Malgorzewicz, S., Lysiak-Szydlowska, W. and Sworczak, K. (2010) The serum profile of adipokines in overweight patients with metabolic syndrome. *Endokrynologia Polska*, **61**, 36-41.

[82] Edwards, C. (2012) Sixty years after Hench—Corticosteroids and chronic inflammatory disease. *Journal of Clinical Endocrinology & Metabolism*, **97**, 1443-1451. doi:/10.1210/jc.2011-2879

[83] Toda, N. and Nakanishi-Toda, M. (2011) How mental stress affects endothelial function. *Pflugers Archives*, **462**, 779-794. doi:10.1007/s00424-011-1022-6

[84] Dunn, A.J. (2006) The effects of cytokines and infections on brain neurochemistry. *Clinical Neuroscience Research*, **6**, 52-68. doi:10.1016/j.cnr.2006.04.002

[85] Connor, T.J., Song, Leonard, B.E., Merali, Z. and Anisman, H. (1998) An assessment of the effects of central interleukin-1beta, -2, -6, and tumor necrosis factor-alpha administration on some behavioural, neurochemical, endocrine and immune parameters in the rat. *Neuroscience*, **84**, 923-933. doi:10.1016/S0306-4522(97)00533-2

