Inflammatory Cytokine Alterations in Schizophrenia: A Systematic Quantitative Review

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Background: Cytokines play an important role in infection and inflammation and are crucial mediators of the cross-talk between the brain and the immune system. Schizophrenia would be associated with an imbalance in inflammatory cytokines, leading to a decrease in Th1 and an increase in Th2 cytokine secretion. However, data published so far have been inconsistent. The primary objective of the present meta-analysis was to verify whether the cytokine imbalance hypothesis of schizophrenia is substantiated by evidence.

Methods: Cross-sectional studies were included if they assessed in vivo plasma or serum cytokine concentrations and/or in vitro secretion of cytokines by peripheral blood leukocytes from schizophrenia patients and healthy volunteers.

Results: Data from 62 studies involving a total sample size of 2298 schizophrenia patients and 1858 healthy volunteers remained for analysis. Ten cytokines were assessed, including the prototypic Th1 and Th2 cytokines gamma interferon (IFN-γ) and interleukin 4 (IL-4) as well as IL-2, soluble IL-2 receptor (sIL-2R), IL-1β, IL-1 receptor antagonist (IL-1RA), tumor necrosis factor-alpha (TNF-α), IL-6, soluble IL-6 receptor (sIL-6R), and IL-10. The results show that an increase occurs in in vivo IL-1RA, sIL-2R, and IL-6 and a decrease occurs in in vitro IL-2 in schizophrenia. No significant effect sizes were obtained for the other cytokines.

Conclusions: These findings provide the first evidence of establishment of an inflammatory syndrome in schizophrenia, which refutes the current hypothesis of a Th2 slant. Caveats are presented to data interpretation, including the role of stress and the effect of weight gain that develops in schizophrenia.

Key Words: Autoimmunity, inflammatory cytokines, meta-analysis, schizophrenia

Among etiological explanations of schizophrenia, several hypotheses concerning immune-related disorders such as infections and autoimmune inflammatory diseases have been proposed (1,2). One of the approaches to investigate this literature is to examine evidence based on studies measuring cytokines. Considered as the hormones of the immune system, cytokines include a large and expanding number of proteins, which are involved in regulation of immunologic and inflammatory responses in physiologic and pathologic conditions (3). Cytokines are also important mediators of the cross-talk between the central nervous system (CNS) and the immune system, which might have implications for clinical psychiatry (4,5). Examples of cytokines include interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF), and chemokines. These molecules are synthesized and secreted by a variety of cell types, including not only immune cells such as T lymphocytes, natural killer (NK) cells, dendritic cells, polymorphonuclear leukocytes, monocytes/macrophages, and microglia but also non-immune cells, such as fibroblasts, endothelial cells, adipocytes, and neurons. Cytokines are key players in the coordinate responses of cells of the innate immune system (e.g., polymorphonuclear leukocytes, monocyte/macrophages, and NK cells) and those of the adaptive immune system (e.g., T and B lymphocytes). Most cytokines exert pleiotropic and overlapping effects through interaction with specific receptors expressed on different target cells. Cytokine receptors also exist in soluble forms, such as the soluble IL-2 receptor (sIL-2R) which is shed from the membrane surface of activated immune cells and can inhibit the biological activity of IL-2, an important T-cell growth factor, by preventing its binding to membrane-anchored receptors. Therefore, sIL-2R is viewed as a marker of immune activation. In contrast, binding of soluble IL-6 receptor (sIL-6R) to IL-6 forms a complex that enhances the biological activity of IL-6. Cytokine actions can be inhibited also by naturally occurring cytokine receptor antagonists such as the IL-1 receptor antagonist (IL-RA), which competes with the physiologic ligand for binding to membrane IL-1 receptors. The IL-1RA is produced in response to several inflammatory stimuli, including IL-1β and IL-6, and is elevated in a variety of infections and inflammatory diseases (6). The IL-1β, IL-6, TNF-α, and IFN-γ are considered pro-inflammatory, in the sense that they augment the immune response to infection and inflammation by promoting leukocyte recruitment to inflammatory sites and/or by activating inflammatory cells. The IL-1RA, IL-4, and IL-10 are anti-inflammatory cytokines that contribute to dampen the immune and inflammatory response.

The cytokine production profile of CD4+ T helper (Th) lymphocytes allowed the identification of at least two distinct subsets: Th1 and Th2 (7). The Th1 cells produce IFN-γ, a potent activator of cell-mediated immunity, and Th2 cells produce IL-4, IL-5, and IL-13, potent inducers of B-cell immunoglobulin (Ig) isotype switching to IgE and activators of eosinophil recruitment (7,8). The cytokine environment produced by dendritic cells and other cell sources during inflammatory responses is essential in driving the differentiation of naive CD4+ T cells into Th1 or Th2 lineages. The IL-12 produced by antigen-presenting cells (e.g., dendritic cells and macrophages) acts via the transcription factors

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Received March 30, 2007; revised July 30, 2007; accepted September 29, 2007.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2007.09.024

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Stat4 and T-bet to promote the development of Th1 cells, whereas IL-4 produced by activated T cells and cells of the innate immune system acts via Stat6 and GATA3 to drive the differentiation of Th2 cells. The IFN-γ–producing Th1 cells are responsible for eradication of intracellular pathogens (e.g., intracellular bacteria, viruses, and some protozoa), whereas IL-4-producing Th2 cells enhance elimination of extracellular organisms (e.g., helminths) and are involved in allergy responses and asthma. Autoimmune inflammatory diseases (e.g., rheumatoid arthritis, type 1 diabetes, and multiple sclerosis) do not fit very well into the Th1/Th2 paradigm, and recent work indicates that two other T cell subsets might play a role in these cases, namely IL-17–producing T cells (Th17) that induce autoimmunity and Foxp3+ regulatory T cells (Treg) that inhibit autoimmune tissue injury. The development of Th17 cells is induced by TGF-β1 in the presence of IL-6, and their expansion depends on IL-23. The TGF-β1 also promotes the development of Treg cells, by inducing the transcription factor Foxp3, an outcome that is inhibited in the presence of IL-6 (8–11).

Schizophrenia might be associated with an imbalance in Th1/Th2 cytokines, with a shift toward the Th2 system (12–15). Empirical evidence in support of the Th1/Th2 imbalance has been inconsistent. To date, the most frequently studied cytokines in schizophrenia have been IL-2 and IL-6. Although there is evidence of decreased IL-2 levels in schizophrenia (16,17), some studies do not confirm this trend (18), whereas other studies actually show the reverse relationship (19). As for the predicted increase in IL-6 levels in schizophrenia, results reported so far have been more consistent, but not all groups have replicated this observation (20–22). As for other cytokines, the lack of consistency of results has been noticed by many authors (4,13,23). Another drawback in the field has been the discovery of the impact of antipsychotic drugs on immune parameters (24,25), which has fed skepticism about the conceptualization of schizophrenia as an autoimmune disorder. Hinze-Selch and Pollmächer (26) performed an extensive review of the data on in vitro cytokine secretion in patients with schizophrenia but found out the available literature as published by March 2001 was plagued with considerable heterogeneity, not amenable to meta-analytic treatment. Since then, numerous cross-sectional in vivo and in vitro studies have been published on the topic, making the feasibility of meta-analysis more likely. The current meta-analysis was conducted to verify whether the cytokine imbalance hypothesis of schizophrenia is substantiated by evidence.

Methods and Materials

Data Sources

A search of computerized literature databases (PubMed and EMBASE) was conducted, with the following key words: "schizophrenia," "cytokine," "interleukin," "interferon," and "tumor necrosis factor." Studies were also identified by cross-referencing of included studies. A consensus has been reached among authors on the studies retained or discarded, on the basis of the following inclusion and exclusion criteria.

Study Selection

Inclusion criteria were: 1) patients with a schizophrenia spectrum disorder: schizophrenia, schizoaffective disorder, and schizophreniform disorder; 2) cross-sectional studies comprising a control group of healthy volunteers; 3) studies assessing circulating cytokine levels with plasma or serum samples (in vivo studies) or in vitro cytokine secretion by peripheral blood leukocytes stimulated or not by mitogens (in vitro studies); 4) studies assessing one or more of the prototypic Th1 and/or Th2 cytokines, soluble cytokine receptors, endogenous cytokine antagonists, and other inflammatory cytokines; 5) studies in English language published before 52nd week of 2005. Exclusion criteria were: 1) studies assessing cytokine genes; 2) studies assessing immune markers other than cytokines (e.g., immunoglobulins); and 3) prospective studies (mostly pharmacologic studies) with no control group.

Data Extraction and Quantitative Data Synthesis

Two reviewers independently extracted data (n, mean & SD) to avoid potential mistakes. Discrepancies in data entry were double-checked by the two reviewers with the original published data, and a consensus was reached. With Comprehensive Meta-Analysis (27), effect size estimates of the differences in cytokine levels between schizophrenia patients and healthy volunteers were calculated. Effect size estimates were calculated from means and SD or t test (for two studies, effect sizes were derived from Dunn t tests). In the case of studies with analyses of variance, the effect size estimate was calculated with D-STAT (28). Within a random effect model, effect size estimates were derived with Hedges's g (29), which provides unbiased effect sizes adjusted for sample size. Taking into account variability in effect size estimates, random effect models allow population-level inferences and are more stringent than fixed effect models (30). The direction of the effect size was positive if schizophrenia patients showed: 1) lower Th1 cytokine levels than healthy volunteers, 2) higher Th2 cytokine levels, and 3) higher levels of all other inflammatory cytokines or immune activation markers. The level of significance for the effect size estimates was set at $p < .05$.

Obviously, the studies retained in the meta-analysis did not assess all of the aforementioned cytokines. For each study, an effect size estimate was calculated for each cytokine assessed. A composite effect size estimate was then calculated by pooling effect size estimates across studies, cytokine by cytokine. Publications pertaining to the same research group and studying the same cytokine were checked for potential data overlap. In this latter case, corresponding authors were contacted, and the publication with the most complete data set was retained for the meta-analysis (Supplement 1).

For some studies, the cytokine levels were only provided for specific subgroups of patients (e.g., acute versus remission/medicated versus non-medicated). To calculate the effect size for these studies, the subgroup cytokine levels were collapsed (weighted average) with D-STAT. The subgroup cytokine levels were used, however, for secondary analyses (see Results section).

For studies assessing cytokines in vitro, cytokine secretion was unstimulated and/or stimulated with diverse mitogens, therefore providing diverse cytokine levels. Furthermore, some in vitro studies were done on whole blood and others on isolated blood lymphocytes or mononuclear cells. To calculate the effect size estimates for these studies, the cytokine levels were collapsed (weighted average), again with D-STAT.

Homogeneity of Effect Size Estimates

It is more legitimate to aggregate effect size estimates when they are homogeneous. Thus, we have calculated the Q statistic for the effect size estimates of the studies included in the meta-analysis. Level of significance of heterogeneity was set at $p < .1$, as recommended by Song *et al.* (31).

Table 1. Composite Effect Size Estimates/Cytokine in In Vivo and In Vitro Studies

Cytokine	Studies (*n*)	Subjects (*n*)	Effect Size	*p*	95% CI	Q-Test	*p*
In Vivo							
IL-1β	8	409	−.110	.780	(−.879–.660)	84.88	.0001[a]
IL-1RA	7	371	.523	.0001[a]	(.253–.792)	8.72	.190
IL-6	19	1219	.465	.0001[a]	(.279–.652)	38.84	.003[a]
sIL-6R	7	326	−.010	.972	(−.589–.568)	37.11	.0001[a]
TNF-α	8	499	.209	.427	(−.307–.724)	48.31	.0001[a]
IL-2	10	590	.245	.458	(−.402–.891)	112.80	.0001[a]
sIL-2R	17	1126	.599	.0001[a]	(.344–.853)	63.42	.0001[a]
In Vitro							
IL-2	20	1149	−.420	.023[a]	(−.058–−.781)	149.89	.0001[a]
IFN-γ	10	708	.204	.351	(−.224–.631)	67.98	.0001[a]
IL-4	4	352	.095	.744	(−.475–.664)	25.02	.0001[a]
IL-10	6	315	.038	.914	(−.644–.719)	48.29	.0001[a]

CI, confidence interval; IL, interleukin; IFN, interferon; RA, receptor antagonist; TNF, tumor necrosis factor.
[a]Effect size was significant at $p < .05$, and heterogeneity (Q-test) was significant at $p < .1$.

Results

Study Characteristics

A total of 544 studies were identified; 457 studies were rejected for the following reasons: 1) type of article (e.g., review, letter, case report; 223 studies); 2) methodology (e.g., no control group, immunoglobulin assessment; 92 studies); 3) study population (e.g., depression, bipolar mania, twin subjects; 57 studies); 4) type of study (e.g., immunotherapy, genetic study; 75 studies); 5) cytokines were measured in the cerebrospinal fluid; 4 studies); and 6) foreign language (6 studies).

Eighty-seven articles responded to our search criteria. Of 87 studies identified, 25 articles could not be entered in the meta-analysis, for the following reasons: 1) data were not available, even after contacting the authors (6 studies); 2) data were incomplete (6 studies); 3) schizophrenia patients suffered from malignant tumors (1 study); 4) cytokine levels were not detectable (2 studies); and 5) articles—from foreign countries—were not retrievable, even after contacting authors (10 studies).

Thus, 62 articles were available for meta-analysis (16–22, 25,32–85) for a total sample size of 2298 schizophrenia patients and 1858 healthy volunteers. For these 62 studies, very few data were missing or unfit for meta-analytic treatment (e.g., range instead of mean). As per our own estimate, more than 95% of the relevant data were retrievable. Even so, authors were contacted to gather missing data. As described in Supplement 1, studies included were heterogeneous in terms of cytokines assessed, medication (antipsychotic, non-medicated, or mixed), psychiatric state (acute/inpatient, non-acute/outpatient, or mixed), experimental condition (in vivo or in vitro), and location of study (Europe, Asia, and so forth). Cytokines assessed in three studies or fewer (e.g., IL-5, IL-8, IL-12, IL-13, IL-18, and TGF-β1) were not retained in the meta-analysis. The most frequently assessed cytokines were IL-2, sIL-2R, and IL-6, and the most frequently used assay was enzyme-linked immunosorbent assay (ELISA; 83% of the studies), whereas radio-immunoassay (RIA) and bioassays were used in only 9% and 8% of the studies, respectively (Supplement 1).

Quantitative Data Synthesis: Composite Effect Size Estimates

On the basis of the 62 studies included in the composite analysis, an effect size estimate was produced for 10 cytokines including the prototypic Th1 and Th2 cytokines, IFN-γ and IL-4, respectively, as well as the following inflammatory cytokines, their soluble receptors, or natural antagonists: IL-1β, IL-1RA, IL-2, sIL-2R, TNF-α, IL-6, sIL-6R, and IL-10, with the relevant studies. The respective numbers of in vivo / in vitro studies responding to our inclusion criteria were as follows: IFN-γ (3/10), IL-4 (2/4), IL-1β (8/2), IL-1RA (7/0), IL-2 (10/20), sIL-2R (17/2), TNF-α (8/2), IL-6 (19/1), sIL-6R (7/0), and IL-10 (2/6). Therefore, the available studies were predominantly in vivo (IL-1β, IL-1RA, sIL-2R, TNF-α, IL-6, and sIL-6R) or in vitro (IFN-γ, IL-2, IL-4, and IL-10), depending on the cytokines. In vivo and in vitro data were kept separate, assuming that they do not represent the same biological mechanisms (Table 1). Some articles contributed for both in vivo and in vitro studies on the same cytokine. In this case, the data for each experimental condition were considered separately, but each article was counted only once in the total number of 62 studies.

For studies assessing in vivo peripheral levels of cytokines, a moderate and highly significant effect size emerged for IL-1RA (7 studies), IL-6 (19 studies), and sIL-2R (17 studies), suggesting an increase in these cytokines in schizophrenia (Table 1; Figures 1 and 2). Nonsignificant effect size estimates were obtained for IL-1β (8 studies), sIL-6R (7 studies), TNF-α (8 studies), and IL-2 (10 studies) (Table 1). For studies assessing in vitro cytokine secretion, a significant moderate effect size was obtained for IL-2 (20 studies), suggesting a decrease in IL-2 secretion in schizo-

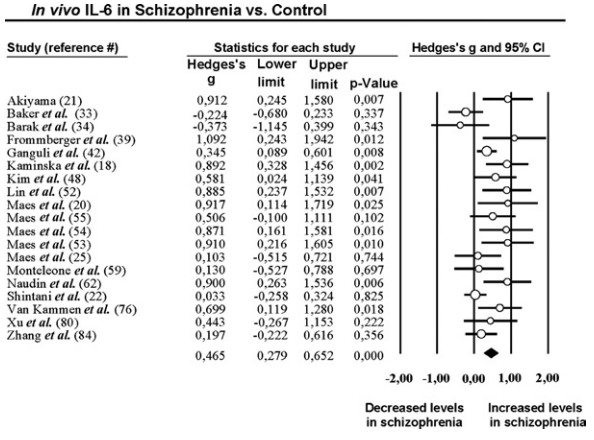

Figure 1. Forest plot of the effect size estimates of in vivo interleukin (IL)-6 in schizophrenia relative to control subjects. CI, confidence interval.

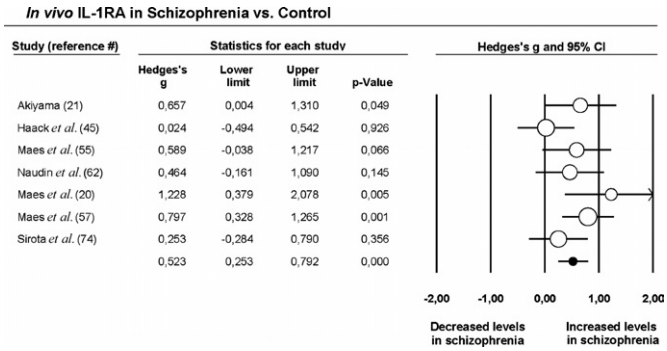

Figure 2. Forest plot of the effect size estimates of in vivo interleukin (IL)-1 receptor antagonist (RA) in schizophrenia relative to control subjects. The arrow corresponding to the study of Maes *et al.* (20) shows that the confidence interval expands beyond the limit for the effect size range (−2.00 to 2.00). CI, confidence interval.

phrenia patients. Nonsignificant effect size estimates were obtained for IFN-γ (10 studies), IL-4 (5 studies), and IL-10 (6 studies) (Table 1).

Subanalyses

Sets of studies used for the composite analysis were heterogeneous for all cytokines, except for IL-1RA, as reflected by the *p* values of the Q-test (Table 1). For this reason, secondary analyses were performed in subsets of studies on the basis of antipsychotic medication (medicated or not), psychiatric setting (acute or not), and location of study (Supplement 1). For location of study, we treated studies of patients recruited in Middle-East and Asian countries (mostly non-Caucasian) and studies of patients recruited in European and North American countries (mostly Caucasian) separately.

When an analysis was performed in the subset of studies assessing in vivo sIL-2R in European and North American patients receiving antipsychotic treatment ($n = 7$), heterogeneity was eliminated (Table 2). With this subset of studies, a moderate and very significant effect size was obtained. This latter result highlights an increase in in vivo sIL-2R in schizophrenia patients, relative to healthy volunteers, insofar as patients are European or North American and treated with an antipsychotic medication.

As for in vivo IL-6, heterogeneity was substantially reduced when secondary analyses were conducted with studies including: 1) European or North American patients (15 studies); and 2) non-medicated patients (13 studies). These subanalyses produced very significant moderate effect size estimates, suggesting an increase in IL-6 levels in European or North American and/or non-medicated patients, relative to healthy volunteers (Table 2).

In the case of in vitro IL-2 secretion, heterogeneity was not corrected by any of the secondary analyses performed (Table 2). Furthermore, the level of significance of the effect size remained moderate with subsets of studies specific to European or North American patients (16 studies), whereas it was higher in patients receiving antipsychotic treatment (12 studies).

Discussion

The current meta-analysis was conducted to verify whether the cytokine imbalance and Th2 predominance hypotheses of schizophrenia are substantiated by evidence. The results suggest an increase in in vivo peripheral levels of IL-1RA, sIL-2R, and IL-6 and a decrease in in vitro IL-2 secretion in schizophrenia patients. No significant effect sizes were obtained for IFN-γ, IL-4, IL-1β, TNF-α, sIL-6R, and IL-10. The absence of significant changes of IFN-γ and IL-4 does not support the Th2 shift hypothesis of schizophrenia, at least in the peripheral blood. Until recently, IL-2 and IL-6 were classified as Th1 and Th2 type cytokines, respectively (7,86,87). This probably contributed to the formulation of the hypothesis of a shift from Th1 to Th2 cytokines on the basis of studies showing decreased in vitro IL-2 secretion and increased in vivo circulating sIL-2R and IL-6 levels in schizophrenia patents (14). However, classification of cytokines is being re-examined, because new CD4+ T cell subsets, such as Th17 and Treg (8,11) are emerging. Unfortunately and because of the novelty of the findings, the data on Th17 and Treg defining cytokines in schizophrenia are still lacking or insufficient at this time point. As a consequence, speculations on a specific deviation of CD4+ T cell differentiation in schizophrenia, if any, await further research.

The significant increases in in vivo peripheral levels of IL-1RA, sIL-2R, and IL-6 in schizophrenia patients as shown in this meta-analysis provide evidence of immune activation and inflammatory syndrome in schizophrenia, as pointed out by several previous studies (18,45,52,63,74,76). Most studies assessing combinations of IL-1RA, sIL-2R, and IL-6 in the same schizophrenia patients have found concordant upregulation of these cytokines (18,21,45,55,82), indicating some correlation in their dysregulation. Interestingly, these cytokines, notably IL-1RA and IL-6, are predominantly produced by cells of the innate immunity, suggesting primary alterations of this arm of the immune system in schizophrenia patients. The elevated circulating levels of IL-1RA in schizophrenia is particularly intriguing in view of its known protective effects against rheumatoid arthritis (6) and the

Table 2. Subanalyses of In Vivo sIL-2R, In Vivo IL-6, and In Vitro IL-2 in Schizophrenia

Cytokine	Studies (*n*)	Subjects (*n*)	Subgroup	Effect Size	*p*	95% CI	Q-Test	*p*
In Vivo								
sIL-2R	9	612	Antipsychotic	.837	.0001[a]	(.437–1.237)	40.12	.0001[a]
sIL-2R	7	458	Antipsychotic & E or NA	.550	.0001[a]	(.320–.780)	9.34	.155
IL-6	15	867	E or NA	.499	.0001[a]	(.278–.719)	30.02	.008[a]
IL-6	13	747	Non-medicated	.480	.0001[a]	(.264–.697)	20.43	.059[a]
In Vitro								
IL-2	16	985	E or NA	−.429	.013[a]	(−.089–−.769)	98.69	.0001[a]
IL-2	12	701	Antipsychotic	−.594	.0001[a]	(−.281–−.908)	42.34	.0001[a]

E or NA, European or North American; Antipsychotic, receiving antipsychotic medication; Non-medicated, non-medicated at the moment of blood collection (>1 week), other abbreviations as in Table 1.

[a]Effect size was significant at $p < .05$, and heterogeneity (Q-test) was significant at $p < .1$.

reportedly lower than expected prevalence of this autoimmune disease in schizophrenia patients as shown in a number of settings (88–90). This raises the possibility that elevated IL-1RA is involved in the negative relationship between schizophrenia and rheumatoid arthritis.

The findings of the current meta-analysis must be interpreted cautiously. Alterations in the cytokine network could be related to the physiopathology of schizophrenia or even its etiology. Alternatively, these alterations might also be the byproduct of the stress associated with the disorder. Schizophrenia patients are sensitive to stress, which is known to trigger psychotic relapses (91). It is likely that the elevated peripheral levels of inflammatory cytokines are induced by stress as observed in other major psychiatric disorders such as depression, by mechanisms involving defective glucocorticoid-mediated feedback inhibition and/or exaggerated sympathetic nervous system-mediated activation of immune responses (92,93). Similarly, cytokine alterations in schizophrenia might be secondary to weight gain. Patients with schizophrenia are at greatest risk for metabolic disorders and obesity (94). Obesity in schizophrenia is accentuated by poor dietary conditions, sedentary lifestyles, and antipsychotic drugs, especially second-generation antipsychotics (95). Of interest, some cytokines, namely TNF-α and IL-1RA, seem to contribute—either as a cause or consequence—to weight gain in psychiatric as well as non-psychiatric conditions (96,97), and adipocytes are a major source of inflammatory cytokines production, including IL-6 (98).

Alterations in the cytokine network in schizophrenia could be secondary also to antipsychotic treatment, which has been regularly shown to significantly impact on the immune system (24,25,99). Subanalyses conducted in the current meta-analysis did substantiate the importance of antipsychotic treatment. For instance, the decrease in in vitro IL-2 secretion was only true for patients treated with antipsychotic medication, not for non-medicated patients at the moment of sample collection, although at least some studies found in vitro IL-2 abnormalities in drug-naïve patients as well (17,36,40,43,47,65,78,83). Similarly, the increase in in vivo sIL-2R levels was only true for patients treated with antipsychotic drugs. This strongly suggests that IL-2 and sIL-2R alterations in schizophrenia are directly related to medication and not to the disease per se. However, for IL-6, the reverse pattern was observed. Indeed, the increase in IL-6 levels in schizophrenia was only applicable to untreated patients, not to patients receiving antipsychotic medication at the moment of blood collection. Thus, it seems more than likely that IL-6 alterations in schizophrenia are related to the disease in itself, not to the effects of medication. However, it must be considered that only 3 of 13 "non-medicated patient" studies actually involved drug-naïve patients (21,36,42). Most of these studies included patients unmedicated at the time of blood collection (time span: 1 week to 6 months). Like the results for IL-6, the results obtained for IL-1RA did not seem to be related to antipsychotic medication. To verify this, a subanalysis was conducted with IL-1RA studies of treated and untreated patients. In both cases, subanalyses with homogeneous sets of studies produced very significant moderate effect size estimates.

Apart from medication, psychiatric state of patients (acutely ill or not) did not appear to impact on the strength and significance of effect size estimates, for any cytokines. This suggests that cytokine alterations in schizophrenia are not state-dependent. Conversely, there was a relationship between location of study and abnormal cytokine concentrations in schizophrenia patients. For instance, control for location of study substantially reduced heterogeneity of studies assessing in vivo IL-6 or in vivo sIL-2R.

Despite the extent of controls performed in the current meta-analysis, heterogeneity remained a concern. Yet uncontrolled factors include smoking, dietary habits, type of antipsychotic drug (first- or second-generation), duration of treatment, concomitant use of other medications, substance abuse, gender, weight gain, and age, which are all factors potentially influencing the immune system (26,100). It must be mentioned that a regression analysis was performed for each cytokine, to control for age. For each study, the mean age of the patient group was used as the explanatory variable. No relationship was found between age and any cytokine (data not reported here). As for body mass index, it was only reported by a minority of studies, insufficient for meta-analytic treatment.

The meta-analysis comprised limitations. First, some data were not available, whereas some articles—mostly from Eastern Europe journals—could not be retrieved, even after contacting authors and journal editors. One might think that authors of negative findings were less likely to respond to queries than authors of studies with statistically significant findings. However, the fail-safe number of additional negative studies (i.e., studies reporting no cytokine differences between patients and control subjects) required to nullify the significance of our composite analyses was high: 34 studies for IL-1RA, 244 for IL-2, 195 for sIL-2R, and 229 studies for IL-6. Another limitation was related to heterogeneity. Heterogeneity was, after controlling for medication and location of study, substantially reduced or eliminated for studies assessing sIL-2R and IL-6. However, these factors did not explain the heterogeneity in studies assessing IFN-γ, IL-4, IL-1β, IL-2, TNF-α, sIL-6R, and IL-10. In addition, study heterogeneity will need to be further tracked down by searching for potential confounding factors, such as weight gain. Another potential limitation is that the grouping of some studies does not take into account methodological differences in sample handling, storage conditions, and methods of cytokine assessment, which can influence cytokine levels and the overall results. However, Hinze-Selch and Pollmächer have previously shown that variability in methodology does not explain inconsistency of results, at least for in vitro cytokine secretion studies in individuals with schizophrenia (26).

To our knowledge, this is the first meta-analysis to be conducted on cytokines in schizophrenia, at the level of the proteins, although a number of studies have been performed on cytokine genes (101,102). The meta-analysis was conducted with a large set of studies ($n = 62$), involving a very large sample size (2298 schizophrenia patients and 1858 healthy volunteers). Furthermore, effect size estimates were produced for seven cytokines (IL-1β, IL-2, IFN-γ, TNF-α, IL-4, IL-6, and IL-10), one cytokine receptor antagonist (IL-1RA), and two soluble cytokine receptors (sIL-2R and s-IL6R). In sets of homogeneous studies, a very significant increase in IL-1RA, sIL-2R, and IL-6 levels was observed in schizophrenia, supporting the existence of an ongoing inflammatory process. In the case of IL-6 and most probably IL-1RA, the alterations were not related to antipsychotic medication. Thus, the current findings lead us to propose that IL-6 and IL-1RA alterations in schizophrenia are linked to the physiopathology of schizophrenia or to phenotypic traits of the disorder yet to be characterized. Although the classical actions of these molecules have been described in the immune system, it is possible that they might have as yet unknown actions in the nervous system unrelated to immunity and inflammation. In the same line, it must be pointed out that, even in studies showing cytokine alterations, most of the subjects with schizophrenia showed no clinical evidence of immunologic dysfunction. This

suggests that, if immunologic processes do play a role in schizophrenia, this is likely to be the case in only a relatively small subgroup of the individuals who clinically meet the criteria for the diagnosis. In another valuable finding, the current meta-analysis helps to identify two factors explaining part of study heterogeneity, namely location of study and antipsychotic medication, and it emphasizes the need for the design of a more focused and refined research study to elucidate the role of cytokine imbalance in schizophrenia.

This work was supported in part by an operating Grant, MOP-67183 from the Canadian Institutes of Health Research (CIHR), to Edouard Kouassi. Emmanuel Stip is holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal. Stéphane Potvin is holder of a scholarship from the CIHR. Drs. Potvin, Stip, Gendron, and Kouassi, Mr. Sepebry, and Mrs. Bah reported no biomedical financial interest or potential conflict of interest.

We would like to thank Dr. Y.K. Kim and Dr. J. Kowalski for generously providing their data. We would also like to thank Dr. Ron Sullivan for his comments and Karine Damiens for her contribution to data compilation.

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