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Review

Immunomodulatory effects of clozapine and their clinical implications: What have we learned so far?

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ABSTRACT

Clozapine remains the drug of choice for treatment resistant schizophrenia, but is associated with potentially life threatening side effects, including agranulocytosis and myocarditis. Immunological mechanisms may be involved in the development of these side effects or in the unique antipsychotic efficacy in subgroups of schizophrenia patients. This systematic review presents the immunomodulatory effects of clozapine from human in vitro and in vivo studies and relates these findings to the developments of adverse and therapeutic effects of clozapine. Several studies confirm the immunomodulatory actions of clozapine, but only few studies investigated their relationship to the unique adverse and therapeutic effects of clozapine. During the first month of clozapine treatment, up to 50% of patients develop fever and flu like symptoms, which is seemingly driven by increased cytokines. Within the same time period, the risk of side-effects with a suspected immunological mechanism peaks. Patients developing fever during the first weeks of treatment should have a thorough physical examination, and measurements of white blood cell count, absolute neutrophil count, ECG, C-reactive protein, creatinine kinase, and troponin to exclude infection, agranulocytosis, myocarditis and neuroleptic malignant syndrome. To what degree the unique antipsychotic efficacy of clozapine in subgroups of schizophrenia patients is related to its immunomodulatory effects has not been studied. Research relating the immunomodulatory actions of clozapine and its early markers to clinically relevant adverse and therapeutic outcomes is hoped to provide new leads for the understanding of the pathophysiology of schizophrenia and aid the development of novel treatment targets.

1. Introduction

Schizophrenia is a debilitating disease affecting 7‰ of the population (Saha et al., 2005; Munk-Jørgensen et al., 2009). The incidence peaks between 18 and 25 years of age, with a five year delay in females. The aetiology remains unclear, but psychological, genetic and environmental causes, such as obstetric complications and early infections have been suggested (Byrne et al., 2007). An immunological hypothesis has also been proposed (Eaton et al., 2006; Potvin et al., 2008; Patterson, 2009). Supporting this notion, several abnormalities in leukocyte subsets, autoantibodies and cytokine levels have been observed in schizophrenia patients compared to healthy controls (Rothermundt et al., 2001).

A recent systematic review and meta-analysis (Miller et al., 2011) suggested that in schizophrenia, interleukin (IL)-1β, IL-6, and transforming growth factor-β (TGF-β) may be state markers, as they were elevated in acutely exacerbated and first episode patients, and normalized with antipsychotic treatment. Conversely, IL-12, interferon gamma (IFNG), tumour necrosis factor (TNF), and soluble IL-2 receptor (sIL-2R) seemed to be trait markers because levels were elevated during acute exacerbation and remained elevated after antipsychotic treatment. Moreover, sIL-2R was suggested as a potential marker for treatment resistance. However, the authors cautioned that the results were based on studies with very different methodologies and that major potential confounds, such as elevated body mass index (BMI), antipsychotic-related weight gain and smoking, were rarely accounted for. Based on these findings, three potentially competing hypotheses for an immunological basis of schizophrenia have been proposed. These include the macrophage-lymphocyte generated pro-inflammatory state (Smith and Maes, 1995), the antibody related T helper cell-related pro-inflammatory response (Schwarz et al., 2001), and the microglial originating pro-inflammatory state (Monji et al., 2009). Moreover, one study showed that TNF levels decreased after dopamine administration in mice (Matalka et al., 2011), confirming that dopamine receptors are involved in cytokine production.

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Among patients with schizophrenia, approximately 20% (Elkis, 2007) are considered treatment resistant, although this entity is difficult to define (Suzuki et al., 2012). Clozapine, a dibenzodiazepine developed in 1961, remains the most effective antipsychotic drug (Kane et al., 1988; Essali et al., 2009; Leucht et al., 2009), but is not considered as a first line drug due to several, potentially life threatening side-effects (Buchanan et al., 2010), including agranulocytosis (Nielsen et al., 2011), aspiration pneumonia (Nielsen et al., 2009), ileus (Nielsen and Meyer, 2012), type II diabetes (Nielsen et al., 2010a, 2010b), myocarditis and cardiomyopathy (Michelsen and Meyer, 2007). However, clozapine remains the drug of choice for treatment resistant schizophrenia with response rates of up to 60%, despite non-response to prior antipsychotic medications. Interestingly, clozapine only shows this superiority in treatment resistant patients (Lieberman et al., 2003; Woerner et al., 2003), suggesting a unique and different mechanism of action compared to other antipsychotics and that treatment resistant patients may have converging biological abnormalities.

Notably, immunological mediated mechanisms have been suggested for some of the side effects of clozapine, including agranulocytosis (Whiskey and Taylor, 2007), myocarditis (Merrill et al., 2005), pericarditis (Merrill et al., 2005), and serositis (Mouaffak et al., 2009). In addition, more than 50% of patients experience another possibly immunologically mediated condition, benign hyperthermia (Lowe et al., 2007). This self-limiting side-effect occurs after approximately 1–2 weeks of treatment and is accompanied by flu-like symptoms and lasts for 2–4 days (Tham and Dickson, 2002). Often, clozapine is discontinued for a few days or the dose is reduced, but the necessity for these interventions remains unknown. Furthermore, a recent study suggested that treatment with clozapine was associated with an increased risk of acute myeloid leukaemia (Nielsen and Boysen, 2010), which could be due to effects on myeloid differentiation (Deliliers et al., 1998).

Based on the possible immunological pathomechanism of schizophrenia (Rothermundt et al., 2001; Eaton et al., 2006; Blanco et al., 2008; Potvin et al., 2008; Patterson, 2009) and the knowledge that clozapine is both the most effective antipsychotic and at the same time associated with unique adverse effects that seem immunologically mediated, we performed a systematic review of the immunological effects of clozapine, focusing on side-effects and a possible association to clinical response.

2. Methods

The databases PubMed and Google Scholar were searched from database inception until 30. April 2012 for the following terms: “Clozapine” combined with “immun*”, “cytokines”, “in vitro”, “fever”, “neutropenia”, “eosinophilia”, “agranulocytosis”, “myocarditis”, “serositis” or “pancreatitis”. Articles were reviewed manually for relevance and bibliographies of relevant articles were checked for additional references.

Quality of the methodology of in vitro studies was assessed according to a rating system developed by the authors since we were unable to identify a pre-existing rating system of such studies. One point (as opposed to zero) was assigned for each of the following characteristics of in vitro study: sample size >/=20; therapeutic (rather than supratherapeutic) clozapine concentrations; publication after 2001 (to account for improvements in analysis techniques; cytokine expression studies examining a single cell type instead of whole blood (since a mixture of cells could dilute results from a single cell type resulting in a type II error); and direct (as opposed to indirect) quantification of apoptosis in studies assessing toxic effects of clozapine. This rating system resulted in a total score between 0 and 4 and quality was classified as “poor” (0–1 points), “fair” (2–3 points) and “good” (4 points).

Likewise, in vivo studies were awarded 1 point for the following characteristics: sample size >/=20; published after 2001; prospective (as opposed to cross-sectional) design. This rating system resulted in a total score between 0 and 3 and quality was classified as “poor” (0–1 points), “fair” (2 points) and “good” (3 points).

3. Effect of clozapine on the immunoregulatory system

3.1. Cytokines

The recent decades' advances in molecular immunology have uncovered a vast continuum of signalling molecules, called cytokines, working in concert to regulate the immune system and its response to exogenous and endogenous threats (infection, cancer etc.). Most cytokines are also detectable in minute concentrations in the general circulation, making them interesting as biomarkers of inflammation and immune activation, but also possible markers of treatment effects. Numerous studies have also shown their involvement in autoimmune diseases (O'Shea et al., 2002; Blanco et al., 2008). Below, we focus on the effects of clozapine on cytokines in in vitro and in vivo studies. Functions of cytokines mentioned in this review are summarized in Fig. 1.

3.1.1. In vitro studies

To date, only seven studies examined clozapine effects on cytokine production in cell cultures. In all, cultured cells were stimulated to produce cytokines and co-cultured with clozapine. Unfortunately, studies were very heterogeneous regarding donors (controls or schizophrenia patients), cell type, stimulant, stimulation time, clozapine levels (therapeutic or supratherapeutic) and examined cytokines. According to our quality assessment system, five of these studies were labelled “fair” in quality, while two were “poor”. Main problems were low sample number, culture type and earlier publication year. Complete results and specific methodological problems are presented in Table 1.

In the group of cytokines responsible for adaptive immune response modulation, several conflicting observations were made. IFNG production increased by clozapine addition to stimulated cultures in three studies (Song et al., 2000; Rudolf et al., 2002; Szuster-Ciesielska et al., 2004) whereas another study found inhibitory effects (Leykin et al., 1997). One study found no significant changes to IL4 levels (Szuster-Ciesielska et al., 2004), while another found that IL4 increased in samples treated with clozapine or a metabolite (Himmerich et al., 2011). This was contradicted by a third study that found dose-dependent inhibitory effect (Leykin et al., 1997). Clozapine inhibited the production of IL12 (Szuster-Ciesielska et al., 2004) and GM-CSF in a dose-dependent fashion at supratherapeutic concentrations (Sperner-Unterweger et al., 1993).

Clozapine also influenced pro-inflammatory cytokines. One study found inhibitory effects of a clozapine metabolite (N-desmethylclozapine) on TNF, but stimulatory effects of clozapine on IL17 (Himmerich et al., 2011). However, clozapine did not affect IL6 (Song et al., 2000; Himmerich et al., 2011). Three studies showed that clozapine at therapeutic concentrations inhibited IL2 release (Leykin et al., 1997; Szuster-Ciesielska et al., 2004; Himmerich et al., 2011), but this was contradicted by a fourth study (Rudolf et al., 2002).

In summary, no clear effect of clozapine on in vitro cytokine expression can be deduced. The diverging results are most likely partly due to different stimulants used in these studies, as the immune system expectedly responds differently to bacteria derivates as opposed to stimulants, which function as superantigens. In vivo conditions are only in part retained when using whole blood cultures and the method has some setbacks as diverging results from different types of blood cells may have confounded the results.

3.1.2. In vivo studies

Several studies examined clozapine effects on plasma cytokine levels in humans. Most are prospective, examining cytokines before and after various durations of treatment (Table 2). Two of these studies were labelled of “fair” quality, while five were “poor”. Main problems included the low number of participants, study design and lack of information, see Table 2.