THE ROLE OF ANTI-INFLAMMATORY TREATMENT IN PSYCHIATRIC DISORDERS

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SUMMARY

Anti-inflammatory treatment could be expected to show positive effects in the subgroup of psychiatric patients who show signs of inflammation, i.e. an increase in proinflammatory cytokines and PGE2. Cyclooxygenase-2 (COX-2) not only reduces the levels of proinflammatory cytokines, but also affects glutamatergic neurotransmission and tryptophan/kynurenine metabolism. In the meantime, several studies have been performed with the COX-2 inhibitor celecoxib in schizophrenia; the studies found a therapeutic effect, mainly in the early stages of the disorder. We were able to demonstrate a statistically significant therapeutic effect of celecoxib on depressive symptoms in a study in patients with major depression (MD). Another study in fifty patients with MD also showed a statistically significant better outcome with celecoxib.

This paper will discuss immune-based therapeutic approaches in both schizophrenia and depression.

Key words: inflammation – schizophrenia - major depression – treatment - COX-2 inhibition

INTRODUCTION

Proinflammatory cytokines, such as interleukin (IL-)6, IL-1 and tumor necrosis factor alpha (TNF-α) contribute to different psychic states such as ‘sickness behavior’ (Dantzer et al. 2007) and the regulation of sleep (Weschchenfelder et al. 2012) and they are elevated in the peripheral blood of depressed patients suffering from major depression (MD). Proinflammatory cytokines drive the activity of indoleamine 2,3-dioxygenase (IDO), a key enzyme in tryptophan/kynurenine metabolism. This metabolism produces the neurotoxic metabolite quinolinic acid, which is described to be enhanced in certain brain regions and the cerebrospinal fluid of depressed patients. One mechanism of action of proinflammatory cytokines in MD is the increased production of quinolinic acid, another is the contribution of IDO to the serotoninergic deficiency (Müller et al. 2009). Moreover, effects on other neurotransmitters, for example on glutamatergic neurotransmission, are well known. Although IL-6 does not directly act on IDO, its elevated levels in serum may contribute to IDO activation within the central nervous system (CNS) through the stimulatory effect on PGE2, which acts as a cofactor in the activation of IDO. This fits with a report on the correlation of increased in vitro IL-6 production with decreased tryptophan levels in depressed patients. Anti-inflammatory treatment would be expected to show positive effects in the subgroup of psychiatric patients showing an increase in proinflammatory cytokines and PGE2.

A role for an inflammatory process has also been postulated in schizophrenia. A prenatal immune challenge during the second trimester of pregnancy might be crucial for the development of schizophrenia (Meyer et al. 2011). A persistent (chronic) infection has been discussed for many years as an aetiological factor in schizophrenia. Research indicates that presumably not one single pathogen but the immune response of the mother to such a persistent infection is related to the increased risk for schizophrenia in the offspring (Krause et al. 2010). Several markers of the type 1 immune response are decreased in the majority of schizophrenia patients and signs of activation of the type 2 immune response have been described. A monocytic dysfunction, however, is also involved in schizophrenia (Müller et al. 2012c). Several reports have described increased serum IL-6 levels in schizophrenia. Mechanisms involved in the inflammatory process in schizophrenia include microglia cells, the macrophages of the brain.

Cyclooxygenase-2 (COX-2) inhibition affects glutamatergic neurotransmission and tryptophan/kynurenine metabolism: all three components - COX-2, tryptophan/kynurenine metabolism, and glutamatergic neurotransmission - are involved in the pathophysiology of schizophrenia. Interestingly, infections and autoimmune disorders increase the risk for a later diagnosis of schizophrenia in a ‘dose-dependent’ way (Benros et al. 2011).

IMMUNE-MODULATION–BASED TREATMENT OPTIONS FOR SCHIZOPHRENIA

An immune-based therapeutic approach for schizophrenia was proposed decades ago: the Nobel laureate Julius Ritter Wagner von Jauregg developed a vaccination therapy for psychoses (the term schizophrenia was not yet in use at that time) (Wagner von Jauregg 1926). He treated patients successfully with vaccines for tuberculosis, malaria or Salmonella typhi, which stimulated a type 1 immune response (Müller et al. 2005b). Immune-based ‘vaccination’ therapy – although promising – was developed during the first decades of the 20th century but not followed up outside German-speaking countries, especially not after the introduction of electro-convulsive therapy and later neuroleptic treatment.
Besides anti-inflammatory drugs – in particular the COX-2 inhibitors discussed below – only very preliminary data exist for other therapeutics related to immune function. Several studies have been performed with omega-3 fatty acids in schizophrenia: so far results have been inconsistent and the overall effect size is small in comparison with placebo in first-episode and chronic schizophrenia (Ross et al. 2007). More intriguing is the result of a 12-month study by Amminger and colleagues (Amminger et al. 2010) in a group of persons at high risk for schizophrenia and already showing prodromal symptoms. The study found a significantly lower transition rate to psychosis in persons who received omega-3 fatty acid capsules than in placebo-treated controls. The results of the studies in schizophrenia are shown in Table 1.

Erythropoetin shows immune-modulating effects, among others. A 12-week placebo-controlled study with rh-erythropoetin in chronic schizophrenia patients was associated with significantly improved cognitive performance compared to placebo. No better outcome compared to placebo was found in the PANSS overall psychopathology or PANSS positive and negative symptom subscales, or regarding social functioning (Ehrenreich et al. 2007). Interestingly, rh-erythropoietin seems to delay the loss of CNS volume in schizophrenia patients (Wüstenberg et al. 2011).

Furthermore, there is recent evidence indicating that a tetracycline antibiotic is effective as an add-on treatment in schizophrenia (Chaves et al. 2009). Although minocycline has a wide range of actions in the brain, its anti-inflammatory effect via modulation of the nitric oxide system is the most predominant one. Moreover, minocycline inhibits microglia activation. Microglia, the monocyte-/macrophage-derived CNS cells, have been shown to be more activated in schizophrenia than in healthy controls (van Berckel et al. 2008). Case reports and a prospective double-blind study confirm clinical effects of minocycline in schizophrenia (Ahuja et al. 2007, Levkovitz et al. 2010). In animal experiments, an effect of minocycline on cognitive functions has been observed (Mizoguchi et al. 2008).

No positive effects on the clinical symptoms of schizophrenia were found in a small group of schizophrenia patients who tested seropositive for cytomegalovirus (CMV) in a double-blind, randomized, prospective add-on study with the virustatic valacyclovir (Dickerson et al. 2003, Dickerson et al. 2009a). Azithromycin was also not found to be superior to placebo in schizophrenia patients who tested seropositive for toxoplasmosis (Dickerson et al. 2009b).

### COX-2 INHIBITION AS A THERAPEUTIC APPROACH IN SCHIZOPHRENIA

Inhibition of the two COX isoforms has differential effects on kynurenine metabolism: while COX-1 inhibition increases the levels of KYNA, COX-2 inhibition decreases them (Schwieler et al. 2005). Therefore, psychotic symptoms and cognitive dysfunctions observed during treatment with COX-1 inhibitors were attributed to the COX-1–mediated increase of KYNA. The reduction of KYNA levels – by a prostaglandin-mediated mechanism – might be an additional mechanism through which selective COX-2 inhibitors have therapeutic effects in schizophrenia (Schwieler et al. 2005).

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**Table 1. Double-blind, placebo-controlled studies of omega-3 fatty acids in schizophrenia (adapted from Peet 2008)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Primary analysis</th>
<th>Secondary analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amminger et al. 2010</td>
<td>Mono; EPA-rich oil vs placebo</td>
<td>EPA &gt; placebo</td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peet et al. 2001</td>
<td>Mono; 2g: EPA vs placebo</td>
<td>EPA &gt; placebo for antipsychotic drug requirement</td>
<td></td>
</tr>
<tr>
<td>Berger 2004</td>
<td>Add-on; 2g: EPA vs placebo</td>
<td>EPA = placebo</td>
<td>EPA &gt; placebo for antipsychotic dose</td>
</tr>
<tr>
<td>Chronic schizophrenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peet et al. 2001</td>
<td>Add-on; 2g: EPA vs DHA vs placebo</td>
<td>EPA &gt; placebo</td>
<td>EPA &gt; DHA</td>
</tr>
<tr>
<td>Fenton et al. 2001</td>
<td>Add-on; 3g. EPA vs placebo</td>
<td>EPA = placebo</td>
<td>EPA (2g) &gt; placebo in clozapine subgroup</td>
</tr>
<tr>
<td>Peet &amp; Horrobin 2002</td>
<td>Add-on; 1, 2 &amp; 5g: EPA vs placebo</td>
<td>EPA = placebo</td>
<td></td>
</tr>
<tr>
<td>Emsley et al. 2002</td>
<td>Add-on; 3g: EPA vs placebo</td>
<td>EPA &gt; placebo</td>
<td>EPA + antioxidants = placebo</td>
</tr>
<tr>
<td>Bentsen 2006</td>
<td>Add-on; 2g: EPA vs antioxidants vs combination vs placebo</td>
<td>EPA &lt; placebo</td>
<td>EPA = placebo</td>
</tr>
<tr>
<td>Emsley et al. 2006</td>
<td>Add-on, 2g: EPA vs placebo</td>
<td>N/A (primary analysis for effect on tardive dyskinesia)</td>
<td>EPA = placebo</td>
</tr>
</tbody>
</table>

EPA: eicosapentaenoic acid
A therapeutic effect of celecoxib was indeed observed in a prospective, randomized, double-blind study of the COX-2 inhibitor celecoxib as an add-on to risperidone in acute exacerbation of schizophrenia (Müller et al. 2002): an increase of the type 1 immune response was found in the celecoxib treatment group (Müller et al. 2004a). This is in accordance with the findings of a type-1 and type-2 rebalancing effect of COX-2 inhibition (Litherland et al. 1999). The finding of a clinical advantage of COX-2 inhibition, however, could not be replicated in a second study. Further analysis of the data revealed that the outcome depends on the duration of the disease (Müller et al. 2004b). This observation is in accordance with results from animal studies showing that the effects of COX-2 inhibition on cytokines, hormones and particularly behavioural symptoms are dependent on the duration of the preceding changes and the time of administration of the COX-2 inhibitor (Casolini et al. 2002). Similar positive results of COX inhibition were obtained in subsequent clinical studies with a similar randomized, double-blind, placebo-controlled, add-on design of 400 milligram celecoxib to risperidone (in one study risperidone or olanzapine) in partly different patient populations – a Chinese population of first manifestation schizophrenia patients (Zhang et al. 2006) and in an Iranian sample of chronic schizophrenia patients (Akhondzadeh et al. 2007). However, no advantage of celecoxib was found in continuously ill schizophrenia patients (Rapaport et al. 2005). A recent six-week, randomized, double-blind study with celecoxib add-on to amisulpride in first-manifestation schizophrenia underlines the effect of short-term treatment with a COX-2 inhibitor in the early stages of schizophrenia: the celecoxib group showed a significantly better outcome not only on the PANSS total score, but also on the PANSS negative and global scores (Müller et al. 2010a). The PANSS global score in part reflects the cognitive function of schizophrenia patients.

Effects of COX-2 inhibitors on cognition (Müller et al. 2005a) and on general psychopathology (Akhondzadeh et al. 2007) have been described before. An effect on cognition could also have been expected from the animal data of COX-2 inhibitors: COX-2 inhibition directly attenuates inflammation-induced inhibition of long-term potentiation (LTP), an animal model of cognition (Cumiskey et al. 2007, Müller et al. 2005a) and on general psychopathology (Akhondzadeh et al. 2007) have been described before. Animals with a genetic over-expression of COX-2 showed more prominent deficits in cognition, which were attenuated by a selective COX-2 inhibitor (Melnikova et al. 2006).

Table 2 presents an overview of clinical studies with COX-2 inhibitors in schizophrenia.

In schizophrenia, COX-2 inhibition showed beneficial effects mostly in the early stages of the disease. The data regarding chronic schizophrenia are controversial, perhaps in part for methodological reasons. The data are still preliminary and further research is required, e.g. with other COX-2 inhibitors. In the meantime, two meta-analyses have been published on this topic showing that the use of COX-2 inhibitors in schizophrenia shows beneficial effects (Sommer et al. 2012), especially in early stages of the disease or in first manifestations (Nitta et al. 2013).

**Table 2. Overview of clinical studies with COX-2 inhibitors in schizophrenia**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Diagnosis</th>
<th>Course and duration</th>
<th>Duration of trial</th>
<th>N</th>
<th>Study design</th>
<th>Concomitant drug</th>
<th>COX-2 inhibitor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. 2006</td>
<td>Schizophrenia</td>
<td>First manifestation</td>
<td>12 weeks</td>
<td>40</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Risperidone (flexible dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant advantage of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Müller et al. 2010a</td>
<td>Schizophrenia</td>
<td>First manifestation</td>
<td>6 weeks</td>
<td>49</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Amisulpride (flexible dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant advantage of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Müller et al. 2002</td>
<td>Schizophrenia</td>
<td>Not specified mean 5.9 y</td>
<td>5 weeks</td>
<td>50</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Risperidone (flexible dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant advantage of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Rappard &amp; Müller 2004</td>
<td>Schizophrenia</td>
<td>≤10 years</td>
<td>11 weeks</td>
<td>270</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Risperidone (flexible dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>No advantage of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Rapaport et al. 2005</td>
<td>Schizophrenia</td>
<td>Continuously ill mean 20 y</td>
<td>8 weeks</td>
<td>38</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Risperidone or olanzapine (constant dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>No advantage of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Akhondzadeh et al. 2007</td>
<td>Schizophrenia</td>
<td>Chronic type (active phase)</td>
<td>8 weeks</td>
<td>60</td>
<td>Double-blind, randomized, placebo-controlled, add-on</td>
<td>Risperidone (fixed dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant advantage of the COX-2 inhibitor</td>
</tr>
</tbody>
</table>

**COX-2 INHIBITION AS A THERAPEUTIC APPROACH IN MAJOR DEPRESSION**

COX-2 inhibitors also influence the CNS serotonergic system, either directly or via CNS immune mechanisms. In a rat model, treatment with rofecoxib was followed by an increase of serotonin in the frontal and the temporoparietal cortex (Sandrini et al. 2002). In the depression model of the bulbectomized rat, a decrease in hypothalamic cytokine levels and a change...
in behaviour were observed after chronic celecoxib treatment (Myint et al. 2007). Therefore COX-2 inhibitors could be expected to have also a clinical antidepressant effect. In another animal model of depression, however, the mixed COX-1/COX-2 inhibitor acetylsalicylic acid showed an additional antidepressant effect by accelerating the antidepressant effect of fluoxetine (Brunello et al. 2006). A significant therapeutic effect of the COX-2 inhibitor celecoxib in MD was also found in a randomized, double-blind pilot add-on study of reboxetine and celecoxib versus reboxetine and placebo (Müller et al. 2006). Interestingly, the ratio of kynurenine to tryptophan, which represents the activity of the pro-inflammatory cytokine-driven enzyme IDO, predicted the antidepressant response to the celecoxib therapy. Patients with high IDO activity, i.e. a high degree of pro-inflammatory activity, responded better to celecoxib (Müller et al. submitted). Another randomized, double-blind study in 50 depressed patients with MD also found a significantly better outcome with fluoxetine plus celecoxib than with fluoxetine alone (Akhondzadeh et al. 2008, 2009). This finding was recently replicated with a combination sertraline and celecoxib in forty depressed patients (Abbasi et al. 2012). Interestingly, the blood levels of IL-6 predicted the antidepressant response in both the sertraline (plus placebo) and celecoxib (plus sertraline) groups. A double-blind, placebo-controlled study with a different COX-2 inhibitor – cimicoxib – added on to sertraline did not find a significantly better outcome with the COX-2 inhibitor than with placebo. However, the group of severely depressed patients (Hamilton scale score > 25) showed a significantly better antidepressant response with cimicoxib than with placebo (unpublished results).

It is well known that controlled antidepressant studies show a high placebo response rate of 30%–35% for the placebo monotherapy arm. To exhibit a statistically significant placebo-verum difference with an add-on design under the basic medication of an effective antidepressant is a big challenge for a study and demands a large therapeutic effect of the add-on verum. The literature shows clearly that the more severely depressed the patients are, the smaller the placebo effect is. These methodological considerations underline that the COX-2 inhibitor has a distinct antidepressant effect.

Table 3 presents an overview of clinical studies with COX-2 inhibitors in major depression.

### OTHER IMMUNE-BASED THERAPY APPROACHES IN MAJOR DEPRESSION

The anti-TNF-α antibody infliximab, which blocks the interaction of TNF-α with cell-surface receptors, i.e. the TNF-α effect, and was developed for the therapy of inflammatory joint disorders and psoriasis, showed a highly significant antidepressant effect in an open-label study in psoriasis patients (Tyring et al. 2006). An overall antidepressant effect could not be shown, however, in a placebo-controlled add-on study in treatment-resistant depressed patients. Three infusions of infliximab or placebo were given in a 12-week trial (n=60) in partly medication free (n=23) non-responders to antidepressant therapy. No overall better outcome could be shown with infliximab than with placebo.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diagnosis</th>
<th>Duration of trial</th>
<th>N</th>
<th>Study design</th>
<th>Concomitant drug</th>
<th>COX-2 inhibitor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collantes-Esteves et al. 2003</td>
<td>depressive syndrome, comorbid to osteoarthritis</td>
<td>mean 33 days</td>
<td>343</td>
<td>open</td>
<td>not specified</td>
<td>Rofecoxib 12.5 or 25 mg/day</td>
<td>significant reduction of self-reported depression</td>
</tr>
<tr>
<td>Müller et al. 2006</td>
<td>major depression</td>
<td>6 weeks</td>
<td>100</td>
<td>randomized double-blind, placebo-controlled add-on</td>
<td>Reboxetine (flexible dose)</td>
<td>Celecoxib 400 mg/day</td>
<td>significant superiority of the COX-2 inhibitor</td>
</tr>
<tr>
<td>Akhondzadeh et al. 2008</td>
<td>major depression</td>
<td>6 weeks</td>
<td>50</td>
<td>randomized, double-blind, placebo-controlled add-on</td>
<td>Fluoxetine (flexible dose)</td>
<td>Celebrex 400 mg/day</td>
<td>significant superiority of celecoxib</td>
</tr>
<tr>
<td>Abbasi et al. 2012</td>
<td>Major depression</td>
<td>6 weeks</td>
<td>40</td>
<td>randomized, double-blind, placebo-controlled</td>
<td>Sertraline 200 mg/day</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant superiority and more responders in celecoxib group</td>
</tr>
<tr>
<td>Nery et al. 2008</td>
<td>bipolar disorder, depressive or mixed episode</td>
<td>6 weeks</td>
<td>28</td>
<td>randomized, double-blind, placebo-controlled</td>
<td>mood stabilizer or atypical antipsychotics</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant superiority after 1 week, no difference at end-point</td>
</tr>
<tr>
<td>Begemann et al. 2008</td>
<td>bipolar depression, rapid cycling</td>
<td>&gt;5 months</td>
<td>1</td>
<td>open</td>
<td>not specified</td>
<td>Celecoxib 400 mg/day</td>
<td>Significant improvement of depressed and manic symptoms</td>
</tr>
<tr>
<td>Müller et al. in preparation</td>
<td>Major depression</td>
<td>6 weeks (30)</td>
<td>66</td>
<td>randomized, double-blind, placebo-controlled</td>
<td>Sertraline 100-150 mg/day</td>
<td>Cimicoxib 50 mg/day</td>
<td>No difference in total group, significant superiority in several depressed (HamD ≥25)</td>
</tr>
</tbody>
</table>
There was a significant interaction between treatment, time and baseline C-reactive protein (CRP) (≤5mg/L): patients with higher baseline CRP (≤5mg/L) had a greater response rate to infliximab (62%) than to placebo (33%). Moreover, the baseline concentrations of TNF-α, TNFR1 and TNFR2 were significantly higher in infliximab responders (p≤0.01). Additionally, infliximab responders exhibited significantly greater decreases in CRP (p≤0.01) than non-responders (Raison et al. 2012).

Interestingly, preliminary findings show that angiotensin II AT1 receptor blockade has anti-inflammatory effects in the CNS and ameliorates stress, anxiety and CNS inflammation (Benicky et al. 2011, Saavedra et al. 2011).

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