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 PGE_2. 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*

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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 (Weschenfelder 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 serotonergic 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 PGE_2, 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 PGE_2.

A role for an inflammatory process has also been postulated in schizophrenia. A prenatal immune challenge during the second trimenon 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 electroconvulsive therapy and later neuroleptic treatment.

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

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

EPA: eicosapentaenoic acid

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).

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

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

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). 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).

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 sore > 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 3. Clinical studies of selective COX-2 inhibitors in affective states

Authors	Diagnosis	Duration of trial	N	Study design	Concomitant drug	COX-2 inhibitor	Outcome
Collantes-Esteves et al. 2003	depressive syndrome, comorbid to osteoarthritis	mean 33 days	343	open	not specified	Rofecoxib 12.5 or 25 mg/day	significant reduction of self-reported depression
Müller et al. 2006	major depression	6 weeks		randomized double-blind, placebo-controlled add-on	Reboxetine (flexible dose)	Celecoxib 400 mg/day	significant superiority of the COX-2 inhibitor
Akhondzadeh et al. 2008	major depression	6 weeks	50	randomized, double-blind, placebo-controlled add-on	Fluoxetine (flexible dose)	Celebrex 400 mg/day	significant superiority of celecoxib
Abbasi et al. 2012	Major depression	6 weeks	40	randomized, double-blind, placebo-controlled	Sertraline 200 mg/day	Celecoxib 400 mg/day	Significant superiority and more responders in celecoxib group IL-6 levels predict response and remission
Nery et al. 2008	bipolar disorder, depressive or mixed episode	6 weeks	28	randomized, double-blind, placebo-controlled	mood stabilizer or atypical antipsychotics	Celecoxib 400 mg/day	Significant superiority after 1 weeks, no difference at end-point
Begemann et al. 2008	bipolar depression, rapid cycling	>5 months	1	open	not specified	Celecoxib 400 mg/day	Significant improvement of depressed and manic symptoms
Müller et al. in preparation	Major depression	6 weeks	66 (30)	randomized, double blind, placebo-controlled	Sertraline 100-150 mg/day	Cimicoxib 50 mg/day	No difference in total group, significant superiority in several depressed (HamD ≥25)

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).

References

1. *Abbasi SH, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S: Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: Randomized double-blind placebo-controlled study. J Affect Disord 2012; 141:308-314.*

2. *Ahuja N, Carroll BT: Possible anti-catatonic effects of minocycline in patients with schizophrenia. Prog. Neuropsychopharmacol Biol Psychiatry 2007; 31:968-969.*

3. *Akhondzadeh S, Jafari S, Raisi F, Ghoreishi A: A clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Booklet - WPA Section on Immunology and Psychiatry - Workshop PsychoNeuroImmunology 2008.*

4. *Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, Mohebbi-Rasa S, Raznahan M, Kamalipour A: Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety 2009; 26:607-611.*

5. *Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi Abhari SA, Abbasi SH, Behnam B: Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res 2007; 90:179-185.*

6. *Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, MacKinnon A, McGorry PD, Berger GE: Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010; 67:146-154.*

7. *Begemann M, Sargin D, Rossner MJ, Bartels C, Theis F, Wichert SP, Stender N, Fischer B, Sperling S, Stawicki S, Wiedl A, Falkai P, Nave KA, Ehrenreich H: Episode-specific differential gene expression of peripheral blood mononuclear cells in rapid cycling supports novel treatment approaches. Mol Med 2008; 14:546-552.*

8. *Benicky J, Sanchez-Lemus E, Honda M, Pang T, Orecna M, Wang J, Leng Y, Chuang DM, Saavedra JM: Angiotensin II AT(1) receptor blockade ameliorates brain inflammation. Neuropsychopharmacology 2011; 36:857-870.*

9. *Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB: Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry 2011; 168:1303-1310.*

10. *Bentsen H: The Norwegian study on the treatment of schizophrenia and schizoaffective disorder with ethyl-EPA and antioxidants. Presented at second conference on Brain Phospholipids, Aviemore, Scotland, March, 2006.*

11. *Berger GE: Ethyl-eicosapentaenoic acid (E-EPA) supplementation in early psychosis: A double-blind randomised placebo-controlled add on study in 80 drug-naive first episode psychosis patients. Int. J. Neuropsychopharmacol 2004; 8:S422.*

12. *Brunello N, Alboni S, Capone G, Benatti C, Blom JM, Tascedda F, Kriwin P, Mendlewicz J: Acetylsalicylic acid accelerates the antidepressant effect of fluoxetine in the chronic escape deficit model of depression. Int Clin Psychopharmacol 2006; 21:219-225.*

13. *Casolini P, Catalani A, Zuena AR, Angelucci L: Inhibition of COX-2 reduces the age-dependent increase of hippocampal inflammatory markers, corticosterone secretion, and behavioral impairments in the rat. J Neurosci Res 2002; 68:337-343.*

14. *Chaves C, Marque CR, Chaudhry IB, Hussain FM, Oliveira JP, Wichert-Ana L: Short-term improvement by minocycline added to olanzapine antipsychotic treatment in paranoid schizophrenia (abstract). Schizophr Bull 2009; 35:354.*

15. *Collantes-Esteves E, Fernandez-Perrez Ch: Improved self-control of ostheoarthritis pain and self-reported health status in non-responders to celecoxib switched to rofecoxib: results of PAVIA, an open-label post-marketing survey in spain. Curr Med Res Opin 2003; 19:402-410.*

16. *Cumiskey D, Curran BP, Herron CE, O'Connor JJ: A role for inflammatory mediators in the IL-18 mediated attenuation of LTP in the rat dentate gyrus. Neuropharmacology 2007; 52:1616-1623.*

17. *Dantzer R, Bluthe RM, Castanon N, Kelly KW, Konsman JP, Laye S, Lestage J, Parnet P: Cytokines, sickness behaviior, and depression. In: Ader, R. (Ed.), Psychoneuroimmunology Elsevier, New York, 2007; pp. 281-318.*

18. *Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, Yolken RH: Reduction of symptoms by valacyclovir in cytomegalovirus-seropositive individuals with schizophrenia. Am J Psychiatry 2003; 160:2234-2236.*

19. *Dickerson FB, Stallings CR, Boronow JJ, Origoni AE, Sullens A, Yolken RH: Double blind trial of adjunctive valacyclovir in individuals with schizophrenia who are seropositive for cytomegalovirus. Schizophr Res 2009a; 107:147-149.*

20. *Dickerson FB, Stallings CR, Boronow JJ, Origoni AE, Yolken RH: A double-blind trial of adjunctive azithromycin in individuals with schizophrenia who are seropositive for Toxoplasma gondii. Schizophr Res 2009b; 112:198-199.*

21. *Ehrenreich H, Hinze-Selch D, Stawicki S, Aust C, Knolle-Veentjer S, Wilms S, Heinz G, Erdag S, Jahn H, Degner D, Ritzen M, Mohr A, Wagner M, Schneider U, Bohn M,*

Huber M, Czernik A, Pollmacher T, Maier W, Siren AL, Klosterkotter J, Falkai P, Ruther E, Aldenhoff JB, Krampe H: Improvement of cognitive functions in chronic schizophrenic patients by recombinant human erythropoietin. Mol Psychiatry 2007; 12:206-220.

22. *Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ: Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. Am J Psychiatry 2002; 159:1596-1598.*

23. *Emsley R, Niehaus DJ, Koen L, Oosthuizen PP, Turner HJ, Carey P, van Rensburg SJ, Maritz JS, Murck H: The effects of eicosapentaenoic acid in tardive dyskinesia: a randomized, placebo-controlled trial. Schizophr Res 2006; 84:112-120.*

24. *Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M: A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. Am J Psychiatry 2001; 158:2071-2074.*

25. *Krause D, Matz J, Weidinger E, Wagner J, Wildenauer A, Obermeier M, Riedel M, Muller N: The association of infectious agents and schizophrenia. World J Biol Psychiatry 2010; 11:739-743.*

26. *Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, Fennig S, Treves I, Kron S: A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010; 71:138-149.*

27. *Litherland SA, Xie XT, Hutson AD, Wasserfall C, Whittaker DS, She JX, Hofig A, Dennis MA, Fuller K, Cook R, Schatz D, Moldawer LL, Clare-Salzler MJ: Aberrant prostaglandin synthase 2 expression defines an antigen-presenting cell defect for insulin-dependent diabetes mellitus. J Clin Invest 1999; 104:515-523.*

28. *Melnikova T, Savonenko A, Wang Q, Liang X, Hand T, Wu L, Kaufmann WE, Vehmas A, Andreasson KI: Cycloxygenase-2 activity promotes cognitive deficits but not increased amyloid burden in a model of Alzheimer's disease in a sex-dimorphic pattern. Neuroscience 2006; 141:1149-1162.*

29. *Meyer U, Schwarz MJ, Müller N: Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. Pharmacol Ther 2011; 132:96-110.*

30. *Mizoguchi H, Takuma K, Fukakusa A, Ito Y, Nakatani A, Ibi D, Kim HC, Yamada K: Improvement by minocycline of methamphetamine-induced impairment of recognition memory in mice. Psychopharmacology (Berl) 2008; 196:233-241.*

31. *Müller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, Möller HJ, Klauss V, Schwarz MJ, Riedel M: Celecoxib treatment in an early stage of schizophrenia: Results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. Schizophr Res 2010a; 121:119-124.*

32. *Müller N, Myint AM, Schwarz MJ: The impact of neuro-immune dysregulation on neuroprotection and neuro-toxicity in psychiatric disorders--relation to drug treatment. Dialogues Clin Neurosci 2009; 11:319-332.*

33. *Müller N, Myint AM, Schwarz MJ: Inflammation in schizophrenia. Am J Psychiatry 2012a; (in press).*

34. *Müller N, Riedel M, Dehning S, Spellmann I, Müller-Arends A, Cerovecki A, et al: Is the therapeutic effect of celecoxib in schizophrenia depending from duration of disease? Neuropsychopharmacology 2004a; 29:176.*

35. *Müller N, Riedel M, Scheppach C, Brandstätter B, Sokullu S, Krampe K, Ulmschneider M, Engel RR, Möller HJ, Schwarz MJ: Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 2002; 159:1029-1034.*

36. *Müller N, Riedel M, Schwarz MJ, Engel RR: Clinical effects of COX-2 inhibitors on cognition in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2005a; 255:149-151.*

37. *Müller N, Schwarz MJ: Immune System and Schizophrenia. Curr Immunol Rev 2010b; 6:213-220.*

38. *Müller N, Schwarz MJ: Immunological Treatment Options for Schizophrenia. Curr Pharm Biotechnol 2012b; 13:1606-1613.*

39. *Müller N, Schwarz MJ, Dehning S, Douhet A, Cerovecki A, Goldstein-Müller B, Spellmann I, Hetzel G, Maino K, Kleindienst N, Möller HJ, Arolt V, Riedel M: The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Molecular Psychiatry 2006; 11:680-684.*

40. *Müller N, Schwarz MJ, Riedel M: COX-2 inhibition in schizophrenia: focus on clinical effects of celecoxib therapy and the role of TNF-alpha. In Eaton WW (ed): Medical and psychiatric comorbidity over the course of life, 265-276. American Psychiatric Publishing, 2005b.*

41. *Müller N, Ulmschneider M, Scheppach C, Schwarz MJ, Ackenheil M, Möller HJ, Gruber R, Riedel M: COX-2 inhibition as a treatment approach in schizophrenia: immunological considerations and clinical effects of celecoxib add-on therapy. Eur Arch Psychiatry Clin Neurosci 2004b; 254:14-22.*

42. *Müller N, Wagner JK, Krause D, Weidinger E, Wildenauer A, Obermeier M, Dehning S, Gruber R, Schwarz MJ: Impaired monocyte activation in schizophrenia. Psychiatry Res 2012c; 198:341-346.*

43. *Myint AM, Steinbusch HW, Goeghegan L, Luchtman D, Kim YK, Leonard BE: Effect of the COX-2 inhibitor celecoxib on behavioural and immune changes in an olfactory bulbectomised rat model of depression. Neuroimmunomodulation 2007; 14:65-71.*

44. *Nery FG, Monkul ES, Hatch JP, Fonseca M, Zunta-Soares GB, Frey BN, Bowden CL, Soares JC: Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum Psycho-pharmacol 2008; 23:87-94.*

45. *Nitta M, Kishimoto T, Müller N, Weiser M, Davidson M, Kane JM, Correll CU: Adjunctive Use of Nonsteroidal Anti-inflammatory Drugs for Schizophrenia: A Meta-analytic Investigation of Randomized Controlled Trials. Schizophr Bull 2013; May 29 [Epub ahead of print].*

46. *Peet M: Omega-3 polyunsaturated fatty acids in the treatment of schizophrenia. Isr J Psychiatry Relat Sci 2008; 45:19-25.*

47. *Peet M, Brind J, Ramchand CN, Shah S, Vankar GK: Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res 2001; 49:243-251.*

48. *Peet M, Horrobin DF: A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. J. Psychiatr Res 2002; 36:7-18.*

49. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH: A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression: The Role of Baseline Inflammatory Biomarkers. Arch Gen Psychiatry 2012; 1-11.

50. Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D: Celecoxib augmentation of continuously ill patients with schizophrenia. Biol Psychiatry 2005; 57:1594-1596.

51. Rappart F, Müller N: Celecoxib Add-on Therapy does not have beneficial antipsychotic Effects over Risperidone alone in Schizophrenia. Neuropsychopharmacology 2004; 29(Suppl 1):222.

52. Ross BM, Seguin J, Sieswerda LE: Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis 2007; 6:21.

53. Saavedra JM, Sanchez-Lemus E, Benicky J: Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: Therapeutic implications. Psychoneuroendocrinology 2011; 36:1-18.

54. Sandrini M, Vitale G, Pini LA: Effect of rofecoxib on nociception and the serotonin system in the rat brain. Inflamm Res 2002; 51:154-159.

55. Schwieler L, Erhardt S, Erhardt C, Engberg G: Prosta-glandin-mediated control of rat brain kynurenic acid synthesis--opposite actions by COX-1 and COX-2 isoforms. J Neural Transm 2005; 112:863-872.

56. Sommer IE, de WL, Begemann M, Kahn RS: Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J Clin Psychiatry 2012; 73:414-419.

57. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R: Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 2006; 367:29-35.

58. van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, Luurtsema G, Windhorst AD, Cahn W, Lammertsma AA, Kahn RS: Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry 2008; 64:820-822.

59. Wagner von Jauregg J: Fieberbehandlung bei Psychosen. Wien Med Wochenschr 1926; 76:79-82.

60. Weschenfelder J, Sander C, Kluge M, Kirkby KC, Himmerich H: The influence of cytokines on wakefulness regulation: clinical relevance, mechanisms and metho-dological problems. Psychiatr Danub 2012; 24:112-126.

61. Wüstenberg T, Begemann M, Bartels C, Gefeller O, Stawicki S, Hinze-Selch D, Mohr A, Falkai P, Aldenhoff JB, Knauth M, Nave KA, Ehrenreich H: Recombinant human erythropoietin delays loss of gray matter in chronic schizophrenia. Mol Psychiatry 2011; 16:26-36.

62. Zhang Y, Chun Chen D, Long Tan Y, Zhou DF: A double-blind, placebo-controlled trial of celecoxib added to risperidone in first-episode and drug-naive patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 2006; 256(Suppl 2):50.

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