*Neurotoxicity Research,* 2006, VOL. 10(2). pp. 131-148

F.P. Graham Publishing Co.

# Schizophrenia as an Inflammation-Mediated Dysbalance of Glutamatergic Neurotransmission

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*(Submitted 19 October 2005; Revised 5 July 2006; In final form 5 July 2006)*

**This overview tries to bridge the gap between psychoneuroimmunological findings and recent results from pharmacological, neurochemical and genetic studies in schizophrenia. Schizophrenia is a disorder of dopaminergic neurotransmission, but modulation of the dopaminergic system by glutamatergic neurotransmission seems to play a key role. This view is supported by genetic findings of the neuregulin- and dysbindin genes, which have functional impact on the glutamatergic system. Glutamatergic hypofunction, however, is mediated by the *N*-methyl-D-aspartate (NMDA)-receptor antagonism. The only endogenous NMDA receptor antagonist identified up to now is kynurenic acid (KYNA). Despite the NMDA receptor antagonism, KYNA also blocks, in lower doses, the nicotinergic acetycholine receptor, *i.e.*, increased KYNA levels can explain psychotic symptoms and cognitive deterioration. KYNA levels are described to be higher in the cerebrospinal fluid (CSF) and in critical central nervous system (CNS) regions of schizophrenics as compared to controls.**

**Another line of evidence suggests that a (prenatal) infection is involved in the pathogenesis of schizophrenia. Due to an early sensitization process of the immune system or to a (chronic) infection, which is not cleared through the immune response, an immune imbalance between the type-1 and the type-2 immune responses takes place in schizophrenia. The type-1 response is partially inhibited, while the type-2 response is over-activated. This immune constellation is associated with inhibition of the enzyme indoleamine dioxygenase (IDO), because IDO - located in astrocytes and microglial cells - is inhibited by type-2 cytokines. IDO catalyzes the first step in tryptophan metabolism, the degradation from tryptophan to kynurenine, as does tryptophan 2,3-dioxygenase (TDO). Due to the inhibition of IDO, tryptophan-kynurenine is predominantly metabolized by TDO, which is located in astrocytes, not in microglial or other CNS cells. In schizophrenia, astrocytes in particular are activated, as increased levels of S100B appear. Additionally, they do not have the enzymatic equipment for the normal metabolism-route of tryptophan. Due to the lack of kynurenine hydroxylase (KYN-OHase) in astrocytes, KYNA accumulates in the CNS, while the metabolic pathway in microglial cells is blocked. Accordingly, an increase of TDO activity has been observed in critical CNS regions of schizophrenics. These mechanisms result in an accumulation of KYNA in critical CNS regions. Thus, the immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia. Therapeutic consequences, *e.g.*, the use of anti-inflammatory cyclo-oxygenase-2 inhibitors, which can also decrease KYNA directly, are discussed.**

*Keywords: Schizophrenia; Inflammation; Astrocytes; Microglia; Cyclo-oxygenase-2 inhibitors; Type 1 immune response; Type 2 immune response; Kynurenic acid; Indoleamine dioxygenase; Tryptophan dioxygenase; Glutamate; Dopamine; NMDA;*

## INTRODUCTION

An involvement of glutamatergic neurotransmission in the pathogenesis of schizophrenia has been discussed for many years (Kim *et al.*, 1980; Carlsson, 1998; Jentsch and Roth, 1999; Kornhuber *et al.*, 2004). This view results from findings of the glutamatergic system in schizophrenia and from the mechanisms of interaction between the glutamatergic system and the dopaminergic system. Additional evidence supporting this hypothesis comes from recent findings in molecular genetics of schizophrenia showing that schizophrenia risk genes are involved in the genetic determination

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ISSN 1029 8428 print/ ISSN 1476-3524 online. 

of the function of the glutamatergic system (Collier and Li, 2003). Furthermore, recent research on psychoneuroimmunology and inflammation shows that the immunological constellation in schizophrenia - an underactivation of the type-1 immune response and an overactivation of the type-2 immune response - is associated with the increased production of inflammatory degradation proteins of the kynurenine metabolism, which act as the *N*-methyl-D-aspartate (NMDA) receptor antagonists. It is hypothesized that the immune - kynurenine interaction bridges the gap between psychoneuroimmunological findings and recent results from pharmacological, neurochemical and genetic studies in schizophrenia.

## INFLAMMATION AND SCHIZOPHRENIA

The role of infection in the aetiology of schizophrenia is presently under discussion (Müller, 2004). Infection during pregnancy in mothers of offspring later developing schizophrenia has been repeatedly described (Mednick *et al.*, 1988; Cannon *et al.*, 1996; Takai *et al.*, 1996; Suvisaari *et al.*, 1999; Westergaard *et al.*, 1999; Brown *et al.*, 2004; Buka *et al.*, 2001) and is discussed as an explanation for the increase of schizophrenic births between December and May ("seasonality of birth") (Torrey *et al.*, 1997). Interesting epidemiological studies have also focussed on the relationship between infection and increased risk of schizophrenia. Results of the Northern Finland 1966 birth cohort have shown that infection of the central nervous system (CNS) in childhood increases the risk of becoming psychotic later on five-fold (Rantakallio *et al.*, 1997; Koponen *et al.*, 2004). In a follow-up study of children who had suffered from a (bacterial) meningitis at age 0 to 5 years during an epidemic in Brazil, a five-fold increased risk for developing psychoses later on was observed (Gattaz *et al.*, 2004). Since the development of the brain is not finalized at birth but is still ongoing for the first years of life, an infection during early childhood is still in accordance with the assumption that an infection-triggered disturbance in brain development plays a key role in schizophrenia.

A persistent (chronic) infection, possibly sustained by the disability of the immune system in clearing an infectious process, as a patho-aetiological factor in schizophrenia has been discussed for many years. Signs of inflammation have been observed in schizophrenic brains but not in control brains (Körschenhausen *et al.*, 1996). The term 'mild localized chronic encephaltis' was proposed for the description of the inflammatory process in schizophrenia (Bechter *et al.*, 2003). Due to the characteristics of infectious agents, there are difficulties in proving a localized infection. A virus possibly infects cells by 'hitting and running away' and several viruses or other intracellular infectious agents may be silently hidden in cells of the lymphoid or the nervous system and exacerbate under certain conditions, such as stress. The estimation of serum-antibody-titers against diverse infectious agents is a rough method with limited sensitivity for a localized mild infectious process. Nevertheless, antibody titers against viruses were examined in the sera of schizophrenic patients for many years (Yolken and Torrey, 1995). The results, however, were inconsistent, possibly also due to the fact that interfering factors such as medication were not been controlled.

An interesting study measured antibodiy-titers against infectious agents not only in the serum, but also in the cerebrospinal fluid (CSF) of individuals with recent onset of schizophrenia. Titers against cytomegalovirus (CMV) and *toxoplasma gondii* were significantly increased in non-medicated patients, while this relationship could not be confirmed in medicated patients (Leweke *et al.*, 2004). The finding that the antibody levels are associated with the medication state might partly explain earlier controversial results, although studies with antibody-titers must be interpreted cautiously. The conclusion that certain infectious agents - not restricted to viruses - and not one single pathogen is related to the onset in some cases of schizophrenia infers the involvement of a possible immune mechanism. From an immunological point of view, a defect in the clearing of the pathogen by the cellular type-1 immune response might lead to (chronic) type-2 activation. This effect might also take place in the developing brain, where an infection may prime an early type-1/type-2 imbalance of the CNS immune system mediated by cytokines.

There is major evidence supporting pre- or perinatal exposure to infection as a risk factor for developing schizophrenia, with main focal points on the influenza, rubella, measles, and herpes simplex viruses (Pearce, 2001). Moreover, viral infections during childhood (Koponen *et al.*, 2004) and even preceding the onset of the illness have been associated with schizophrenia (Rapaport and Müller, 2001; Leweke *et al.*, 2004).

However, results from animal experiments and a study in pregnant mothers point out that not a certain infectious agent but the maternal immune response increases the risk for schizophrenia in the offspring: Interleukin- (IL-)8, a product of inflammation, was determined in pregnant mothers. IL-8 levels were increased in the serum during the second trimenon of mothers, whose offspring developed schizophrenia later, *i.e.*, increased IL-8 levels were associated with an

increased risk for schizophrenia in the offspring (Brown *et al.*, 2004). The induction of a maternal immune response with the immune stimulator poly I:C - mimicking a viral infection - in the 2. trimenon was shown to lead to post-pubertal schizophrenia-typical behavior in an animal model. This behavior was increased by the NMDA antagonist MK-801 and reversed by clozapine (Zuckerman and Weiner, 2005). In a similar study it was observed that the induction of a maternal immune response with poly I:C in the 2. trimenon led to decreased cognition, deficits in prepulse inhibition, more anxious behavior, increased amphetamine induced behavior, and increased dopamine turnover in adult - not in juvenile - offspring, i. e., parallel to schizophrenia the deficits were observed only in adulthood, not in childhood or adolescence. The cognitive deficits were improved by clozapine (but not by haloperidol) (Nilsson *et al.*, 2005; Ozawa *et al.*, 2005).

In parallel to the mimicked viral infection, also the induction of a maternal immune response with lipopolysacharides (LPS) - mimicking a bacterial infection - led to an increased startle response and increased amphetamine-induced behavior in the adult offspring in an animal study (Fortier *et al.*, 2004). Another study observed that the induction of a maternal immune response with LPS, associated with an increase of IL-1, IL-6, and tumor-necrosis-factor-α (TNF-α) in the mother, led to an increase of IL-1 in the fetal serum (Ashdown *et al.*, 2006). Although the exact mechanism of the relationship between early immune stimulation and characteristic deficits in adulthood needs to be elucidated, the mechanism of immune sensitization seems to play a role. An early priming of the immune imbalance seems to be the basis for subsequent immune alterations in schizophrenia. In this respect, several mechanisms for cytokines to invade the brain are known: 1. Active transport mechanisms through the blood-brain-barrier for certain cytokines, *e.g.*, IL-1 are described (Banks *et al.*, 1993; see Müller and Ackenheil, 1998), 2. Cytokines can move passively into the CNS via the circumventricular organs (Hashimoto, 1991), 3. In particular in schizophrenia, around one third of patients show a disturbed blood-brain barrier (Müller and Ackenheil, 1995).

A (persisting) infection due to an insufficient immune response, not allowing for the infectious agent to be cleared, would be associated with an increased cytokine production in the CNS.

## IMMUNE SENSITIZATION DURING THE PRE- AND POSTNATAL PERIOD

The neurodevelopmental hypothesis of schizophrenia implies that an early damage of the CNS, *e.g.*, by obstetric complications, infections, or other noxious events leads to an increased susceptibility to become schizophrenic later on. The mechanism of 'sensitization' to pro-inflammatory stimuli plays a role. A sensitization during the peri- and postnatal period was observed regarding the cytokine-neurotransmitter interactions. In humans as in rodents, both the brain and the catecholaminergic system are not yet fully developed at birth. The concept of sensitization implies a long lasting modification of susceptibility to stimuli under certain conditions. Recently it was shown that the postnatal administration of IL-1, a pleiotropic cytokine which normally is released from immune cells during the early phase of inflammation, changes the neurotransmitter response to IL-1 in later life. The application of a low dose of IL-1 during the first days of life resulted in decreased dopamine content in the hypothalamus in adulthood (Kabiersch *et al.*, 1998). These results indicate that an increased production of IL-1 during infectious or inflammatory processes in the perinatal period may induce long-lasting, probably permanent, alterations in the central (and peripheral) neurotransmitter systems. Moreover, it was shown that the glucocorticoid function, *i.e.*, the response of corticosterone to IL-1, could also be programmed in early life (Furukawa *et al.*, 1998). These results show that the response to pre-/perinatal infection or inflammation can result in neurotransmitter changes in adulthood. This was shown for dopamine. Whether direct changes in the glutamate concentration can be observed has not yet been elucidated.

### Polarized Type-1 and Type-2 Immune Responses

The cellular arm of the adaptive immune system mainly operates through cytokines, which are defined in the mouse model as the T-helper-1 (TH-1) cells and produce the activating 'immunotransmitters' IL-2 and Interferon-γ (IFN-γ). However, since not only T-helper cells ($CD4^+$-cells) but also monocytes/macrophages and other cell-types produce these cytokines, this immune response is named *type-1 immune response*. In contrast, the humoral arm of the adaptive immune system is mainly activated via the *type-2 immune response*. T-helper-2 cells (TH-2) or monocytes/ macrophages (M2) produce mainly IL-4, IL-10, and IL-13 (Mills *et al.*, 2000). Other pro-inflammatory cytokines such as TNF-α and IL-6 are primarily secreted from monocytes and macrophages. TNF-α is a ubiquitious cytokine mainly activating the type-1 response, IL-6 activates the type-2 response including antibody production (Table I).

In humans, the type-1 and type-2 immune responses are defined by the respective cytokines. Although

Table I Cellular source of the polarized immune response (* concept not yet established)

| | Type-I | Type-II |
|---|---|---|
| Blood and lymphatic organs | Monocytes/ Macrophages Type 1 (M1) | Monocytes/ Macrophages Type 2 (M2) |
| T-Helper-cells | $CD4^+$(TH-1) | $CD4^+$ (TH-2) |
| CNS | Microglia * | Astrocytes * |

Table II Findings of the type-1/type-2 immune response in schizophrenia (adapted from Schwarz *et al.*, 2001); ↑ increase, ↓ decrease, ↔ no change, ↑↑ ↓↓ replicated)

| Site of cytokine expression | Type-1 | Type-2 |
|---|---|---|
| In-vitro production | IFN-γ ↓↓<br>IL-2 ↓↓ | IL-10 ↑<br>IL-3 ↑ |
| Peripheral levels | IFN-γ ↔<br>IL-2 ↔<br>sIL-2R ↑↑<br>sICAM-1 ↓<br>Neopterin ↓ | IgE ↑↑<br>antibodies against several antigens ↑↑<br>IL-6 ↑↑<br>After remission: IL-6 ↓↓ |
| CSF levels | IL-2 ↓↑<br>IFN-γ ↓<br>sICAM-1 ↓ | IgG ↑<br>IL-4 ↑<br>TGF-β1 ↔<br>TGF-β2 ↔ |

the immunological concept of the type-1 and type-2 immune response in humans is highly sophisticated and cannot be fully explained in this article, it is a valuable concept for a better understanding of the complex interrelationship within the immune system (Mills *et al.*, 2000). Moreover, although the attempts to dichotomize a complex disease such as schizophrenia in terms of just type-1 or type-2 may be an oversimplification, the concept not only clearly allows a better understanding of the immune mechanisms involved in schizophrenia, but also provides possible new strategies for treatment. Simplified, the type-1 system mainly promotes the cell-mediated immune responses against intracellular pathogens, whereas the type-2 response helps B-cell maturation and promotes mainly the humoral immune responses against extracellular pathogens. Type-1 and type-2 cytokines antagonize each other in promoting their own type of response, while suppressing the immune response of the other. Which system will dominate over the other one depends on the relative timing and ratio between IL-4 and IFN-γ together with IL-12 (Seder and Paul, 1994; Romagnani, 1995; Paludan, 1998). In humans, however, the immune response is seldom highly polarized; often a mixed phenotype of the immune response takes place showing a priority to type-1 or type-2.

**Astrocytes, Microglia, and Type-1/Type-2 Response**

Recent research points out that the polarized immune response is represented in the CNS by the polarization of astrocytes and microglia cells. The polarization has impact on the recruitment of macrophages from the periphery into the CNS and for the function of microglial cells. Microglial cells, deriving from peripheral macrophages, secrete preferably type-1 cytokines such as IL-12. Astrocytes inhibit the production of IL-12 and intercellular adhesion molecule 1 (ICAM-1), both part of the type-1 system, while they secrete the type-2 cytokine IL-10 (Aloisi *et al.*, 1997; 2000; Xiao and Link, 1999; Marshall *et al.*, 2001).

The view of an over-activation of astrocytes in schizophrenia is supported by the findings of increased levels of S100B in schizophrenia. S100B is a marker of astrocyte activation (Zimmer *et al.*, 1995). S100B is increased in the serum and in the CSF of schizophrenic patients (Rothermundt *et al.*, 2004a, b), independent of the medication state (Rothermundt *et al.*, 2004c). Microglia activation, however, was only found in a small percentage of schizophrenics and is discussed to be a medication effect (Bayer *et al.*, 1999). A type-1 immune activation as an effect of neuroleptic treatment has been observed repeatedly (see below).

**Reduced Type-1 Immune Response in Schizophrenia**

A well established finding in schizophrenia is the decreased *in vitro* production of IL-2 (Villemain *et al.*, 1989; Bessler *et al.*, 1995; Ganguli *et al.*, 1995; Hornberg *et al.*, 1995; Cazzullo *et al.*, 1998). The observation of decreased production of IL-2 fits well with another finding: the decreased production of IFN-γ (Rothermundt *et al.*, 1996; Wilke *et al.*, 1996). Both findings point to a blunted production of type-1 related cytokines in schizophrenia. A lack of activation of the type-1 arm of the cellular immune system has also been postulated by other researchers, due to the decreased levels of neopterin, a product of activated monocytes/ macrophages in unmedicated schizophrenics (Sperner-Unterweger *et al.*, 1999). Moreover, a decreased response of lymphocytes after stimulation with various specific antigens was found (*e.g.*, tuberculin), reflecting a reduced capacity for a type-1 immune response in schizophrenia, as well (Müller *et al.*, 1991).

ICAM-1 is a molecule that mediates the adhesion of lymphocytes to other cells, including endothelial cells. It also mediates the activation of the cellular immune system as part of the type-1 immune response (Kuhlmann *et al.*, 1991). In schizophrenics, decreased levels of the soluble (s)ICAM-1 have been described (Schwarz *et al.*, 2000). Decreased levels of the sICAM-

1 also represent an under-activation of the type-1 immune system.

One of the 'classical' epidemiological findings in schizophrenia research is the negative association between schizophrenia and rheumatoid arthritis (Vinogradov *et al.*, 1991; Neidhart *et al.*, 1995). This finding can be interpreted as two sides of the type-1/type-2-balance coin - represented by increased sICAM-1 levels in rheumatoid arthritis and decreased sICAM-1 levels in schizophrenia. Although the vice versa sICAM-1 levels don't explain the negative association, this finding might contribute to better insight into the pathomechanisms of the disorders (Krönig *et al.*, 2005).

A blunted response of the skin to different antigens in schizophrenia was observed before the era of antipsychotics (Molholm, 1942; Özek *et al.*, 1971). A study using a skin-test of the cellular immune response (Multitest Merieux) in unmedicated schizophrenic patients also showed a decreased reaction (Riedel *et al.*, 2006).

**IL-6 and Schizophrenia**

Several reports described increased serum IL-6 levels in schizophrenia (Ganguli *et al.*, 1994; Maes *et al.*, 1995; Frommberger *et al.*, 1997; Lin *et al.*, 1998). The findings suggest that IL-6 serum levels might be especially high in patients with an unfavourable course of the disease. Investigations of the soluble IL-6 receptor (sIL-6R) - a marker of the activity of the IL-6 system - in the CSF showed that high levels of sIL-6R are observed especially in schizophrenic patients with a more marked paranoid-hallucinatory syndrome (Müller *et al.*, 1997b).

**Type-2 Immune Response Activation in Schizophrenia**

IL-6 is a product of activated monocytes and of the activation of the type-2 immune response. Increased numbers of monocytes have been described in schizophrenia (Wilke *et al.*, 1996). Additionally, several other signs of activation of the type-2 immune response in schizophrenia have been described in schizophrenia, including the increased production of IgE (Ramchand *et al.*, 1994; Müller *et al.*, 2000; Schwarz *et al.*, 2001). Additionally, an increase of IL-10 - a characteristic cytokine of the type-2 immune response - has been observed in schizophrenics (Cazzullo *et al.*, 1998; Haack *et al.*, 1999). Another study points out, that IL-10 levels in the CSF are related to the severity of the psychosis, especially to negative symptoms (van Kammen *et al.*, 1997).

A lot of studies described an increased antibody production - reflecting type-2 activation - in schizophrenic patients, those observations leading to the discussion of an autoimmune origin of schizophrenia (Ganguli *et al.*, 1987). Although findings have repeatedly shown that about 20%-35% of schizophrenic patients show features of an autoimmune process (Müller and Ackenheil, 1998), the role of actual or former therapy with neuroleptics may not have been sufficiently taken into consideration. An increase of IgG - antibodies are mainly IgG-antibodies - in the CSF has been described especially in patients whith predominant negative symptoms (Müller and Ackenheil, 1995). Increased antibodies against heat shock protein 60 are one of the recent interesting findings in schizophrenia, because it may reflect a mechanism of loss of neuronal protection (Kilidirias *et al.*, 1992; Schwarz *et al.*, 1999).

The key-cytokine for the type-2 immune response is IL-4. Increased levels of IL-4 in the CSF of juvenile schizophrenic patients have recently been reported (Mittleman *et al.*, 1997). The CSF findings point out that the increased type-2 response in schizophrenia is not only a phenomenon of the peripheral immune system, it is also observed in the CNS immune system.

**The effects of anti-psychotic therapy in schizophrenia rebalance the type-1 / type-2 imbalance.**

*In vitro* studies show that the blunted IFN-γ production becomes normalized after therapy with neuroleptics (Wilke *et al.*, 1996). An increase of $CD4^+CD45RO^+$ cells ('memory cells') during antipsychotic therapy with neuroleptics was observed by different groups (Müller *et al.*, 1997c; Cazzullo *et al.*, 1998). $CD4^+CD45RO^+$ cells are one of the main sources of IFN-γ production. The increase of this subpopulation during therapy may contribute to an increase of the IFN-γ production. Additionally, an increase of soluble IL-2 receptors (sIL-2R) during antipsychotic treatment was described by several groups (Maes *et al.*, 1995; Pollmächer *et al.*, 1996; Müller *et al.*, 1997a). SIL-2R is shed by activated T-cells. The increase reflects an increase of activated, IL-2 bearing T-cells. The reduced sICAM-1 levels in the serum show a significant increase during short term anti-psychotic therapy (Schwarz *et al.*, 2000) and the leucocyte function antigen-1 (LFA-1) molecule on $CD4^+$ cells, the ligand of ICAM-1, shows a significantly increased expression during anti-psychotic therapy (Müller *et al.*, 1999). Moreover, the blunted reaction to vaccination with salmonella was not observed in patients medicated with antipsychotics (Özek *et al.*, 1971). These studies show that the type-1 immune response is activated during anti-psychotic therapy. Recently, an elevation of IL-18 serum levels was described in medicated schizophrenics (Tanaka *et al.*, 2000). Since IL-18 plays a pivotal role in the type-1 immune response, this finding is consistent with other descriptions of type-1 activation

during antipsychotic treatment.

Regarding the type-2 response, there are several observations that anti-psychotic therapy with neuroleptics is accompanied by a functional decrease of the IL-6 system. A significant decrease of IL-6 during therapy with antipsychotics was described (Maes *et al.*, 1995). Two studies found a significant decrease of sIL-6R levels during antipsychotic therapy (Maes *et al.*, 1995; Müller *et al.*, 1997a). There are indications suggesting a time-dependent effect of antipsychotic treatment on IL-6: one study reported that short term treatment with clozapine (12 days) induced an increase in IL-6 levels (Maes *et al.*, 1997), and another group found an increase of IL-6 after two weeks of clozapine treatment, but a decrease after an additional four weeks of treatment (Pollmächer *et al.*, 1996).

**$PGE_2$, Inflammation, and Immune Dysbalance**

In schizophrenia, however, the data on Prostaglandin $E_2$ ($PGE_2$) are not conclusive: while in several elder studies increased blood levels of $PGE_2$ were described (Kaiya *et al.*, 1989), a more recent study found no increase of $PGE_2$ levels in the CSF of schizophrenics (Nishino *et al.*, 1998). There are indications that the $PGE_2$ level might be related to the actual psychopathology (Kaiya *et al.*, 1989). However, more data are needed, in particular since there are several methodological pitfalls in the estimation of $PGE_2$ from blood or CSF. Additionally, $PGE_2$ has local paracrine effects, therefore a lack of increase of $PGE_2$ in a body fluid does not exclude local effects of locally increased $PGE_2$, *e.g.*, in the CNS.

With regard to the type-1 / type-2 balance, $PGE_2$ has been shown to enhance the production of type-2 cytokines such as IL-4, IL-5, IL-6, and IL-10; $PGE_2$ also drastically inhibits the production of the type-1 cytokines IFN-γ, IL-2, and IL-12 (Hilken *et al.*, 1996; Hinsen *et al.*, 1996; Stolina *et al.*, 2000). In sum, $PGE_2$ has a type-2 inducing and type-1 inhibiting activity (Stolina *et al.*, 2000; Harris *et al.*, 2002). Therefore, inhibition of $PGE_2$ synthesis is hypothesized to be beneficial in the treatment of disorders with dysregulated immune responses (Harris *et al.*, 2002), which will later be discussed with respect to the effects of COX-2 inhibition.

**NMDA-Receptor Hypofunction and Schizophrenia**

A functional impairment of the glutamatergic neurotransmission, in particular of the NMDA receptor complex as an important factor in the pathogenesis of schizophrenia has been discussed for more than 25 years. Hypofunction of the glutamatergic neurotransmitter system as a causal mechanism in schizophrenia was first proposed by Kim *et al.* (1980), due to their observation of low concentrations of glutamate in the CSF of schizophrenic patients.

Phencyclidine, known as PCP or angels dust, blocks the NMDA receptor and is associated with hypofunction of glutamatergic neurotransmission and with schizophrenia-like symptoms (Lodge *et al.*, 1987). Ketamine and MK-801, which act at the same target within the NMDA receptor complex as 'open channel blockers', provoke the same psychotic symptoms (Krystal *et al.*, 1993; 1994) as PCP. Other substances, however, acting at the NMDA receptor complex as antagonists, but not at the PCP site of the NMDA receptor, have psychotogenic properties, too. Other NMDA receptor antagonists such as *m*-chlorophenylpiperazine (CPP), d-phosphonopropenylpiperazin-carboxylic acid (CPP-ene), and a substance called CGS 19755 block NMDA receptors by acting at the NMDA recognition site. All three substances induce a phencyclidine-like psychotic reaction (Kristensen *et al.*, 1992; Grotta, 1994; Herrling, 1994).

NMDA receptor hypofunction can explain schizophrenic positive-, negative-symptoms and disorganized symptoms. The onset in early adulthood after a first hit during neurodevelopment, cognitive deterioration and structural brain changes can be a consequence of NMDA receptor dysfunction (Olney and Farber, 1995).

Moreover, decreased plasma levels of glycine, a co-agonist of NMDA receptors, are described in schizophrenic patients and a negative correlation of glycine levels with schizophrenic negative symptoms was found (Sumiyoshi *et al.*, 2004). Additionally, baseline glycine levels predicted the treatment outcome of clozapine of schizophrenic negative symptoms (Sumiyoshi *et al.*, 2005).

Clinical investigations targeted the glycine co-agonist site of the NMDA receptor by administering the amino acids glycine or D-serine, or a glycine pro-drug such as milacemide. Some of these studies have yielded positive results, particularly against the deficit syndrome and when high doses of the co-agonist were used (Leiderman *et al.*, 1996; Tsai *et al.*, 1998; Heresco-Levy *et al.*, 1999).

**Dopaminergic - Glutamatergic Dysbalance in Schizophrenia**

There is no doubt that a disturbance in the dopaminergic neurotransmission plays a key-role in the pathogenesis of schizophrenia (Carlsson, 1978; 1988). This view is based on the evidence that most drugs that ameliorate psychotic symptoms act as dopamine receptor blockers, in particular $D_2$ receptor blockers. However, despite the fact that only a part of the patients respond to antipsychotic drugs and the long-term outcome of

antipsychotic treatment is unsatisfactory in many cases (Möller, 2003), attempts to explain the disease solely in terms of dopaminergic dysfunction leave many aspects of schizophrenia unsolved. Clozapine, still today the gold-standard for antipsychotic drugs, seems to contribute this unique status to the effects on multiple neurotransmitter systems including NMDA receptor agonism (Hersco-Levy, 2003) and possibly also affects the immune system (Pollmächer *et al.*, 1996).

The glutamate hypothesis postulates the equilibrium between inhibiting dopaminergic and inhibiting glutamatergic neurons (Carlsson, 1988). The model of a cortico-striato-thalamo-cortical control loop integrates the glutamate hypothesis with neuroanatomical aspects of the pathophysiology of schizophrenia (Calsson, 1998). A hypofunction of the glutamatergic cortico-striatal pathway is associated with an opening of the thalamic filter, which leads to an uncontrolled flow of sensory information to the cortex and to psychotic symptoms.

In animal experiments it was demonstrated that treatment with NMDA receptor antagonists (MK-801) leads to a marked, dose-dependent increase of amphetamine-induced dopamine release (Miller DW and Abercrombie, 1996). Accordingly, amphetamine induced a much higher dopamine release in schizophrenics compared to healthy controls (Laruelle *et al.*, 1996). This observation fits with the view that activation of the nigrostriatal dopamine system can take place by opposing activation of inhibitory striatonigral GABAergic projection neurons (Calsson, 1998).

**The Cholinergic - Dopaminergic - Glutamatergic Interaction in Schizophrenia**

Although the hypotheses regarding an altered dopaminergic and glutamatergic neurotransmission in schizophrenia retain considerable theoretical strength, these two neurotransmitter systems alone can not fully explain all features of this disorder. Beginning with the notion that the atypical antipsychotic clozapine has remarkable anti-cholinergic activity, acetylcholine (ACh) was recognized as additional neurotransmitter system probably being involved in schizophrenia pathology. There are several lines of evidence underlining the pivotal role of the cholinergic system in schizophrenia. First, both types of ACh receptors - muscarinic and nicotinic receptors - are modulating CNS functions including cognition, motor activity, sleep, anxiety, or sensory processing, all of them being involved in the core-symptoms of schizophrenia (Picciotto *et al.*, 2000; Hyde and Crook, 2001). Second, postmortem studies repeatedly described a decreased expression of muscarinic (Sarter *et al.*, 2005) and nicotinic (Hyde and Crook, 2001) receptors in several brain regions of schizophrenia patients. Since ante-mortem nicotine exposures paradoxically induces an up-regulation of nicotinic receptors, the well known enhanced tobacco consumption of schizophrenic patients cannot be attributed to these findings (Hyde and Crook, 2001). This leads to the third point of evidence - the high rate of cigarette smoking of about 80-90% of schizophrenic patients (Lohr and Flynn, 1992). Smoking is discussed to be an attempt to alleviate symptoms of the illness and to reduce neuroleptic-induced side effects such as iatrogenic parkinsonism (Martin *et al.*, 2004). Fourth, atypical antipsychotics interact in different ways with the cholinergic system, mostly blocking muscarinic ACh receptors (Shayegan and Stahl, 2004) and anticholinergic medication counteracts the extrapyramidal side-effects of dopamine-blocking substances (Miller R and Chouinard, 1993).

Due to the strong dopaminergic-cholinergic balance in the CNS, the dopamine receptor blockade leads to cholinergic activation (Miller R and Chouinard, 1993). On the other hand, a loss of cholinergic function is associated with increased glutamatergic neurotransmission, *i.e.*, an enhanced sensitivity for the effects of PCP (Mattsson *et al.*, 2005), while the activation of presynaptic muscarinic ACh receptors leads to an inhibitory effect of NMDA agonist, at least in glial cells (Grishin *et al.*, 2005). Especially nicotinic ACh receptors are involved in the regulation of several neurotransmitter systems including dopamine and glutamate (Martin *et al.*, 2004), leading to the above mentioned effects on CNS functions. The eminent role of α-7 nicotinic receptors in sensory gating and several others of the cholinergic activities has led to the suggestion that α-7 nicotinic receptor agonists may serve as potential new candidates for the treatment of schizophrenia (Martin *et al.*, 2004). Getting back to the role of the kynurenine metabolism in schizophrenia, it is remarkable that kynurenic acid (KYNA) has been identified as a potent antagonist of both, the NMDA receptor and the α-7 nicotinic receptor (Parsons *et al.*, 1997; Hilmas *et al.*, 2001). Moreover, antipsychotic drugs like haloperidol and clozapine significantly reduce brain levels of KYNA (Ceresoli-Borroni *et al.*, 2006), leading to the suggestion that enhancing glutamatergic and cholinergic neurotransmission by reducing brain KYNA levels may play a role in the antipsychotic effects of these drugs.

Moreover, cholinergic neurotransmission is influenced by the immune system: Stimulation of the cholinergic system downregulates the inflammatory immune response, what is called the 'cholinergic anti-inflammatory pathway' (van Westerloo *et al.*, 2005). Activation of the vagus nerve significantly inhibits the release of TNF-α and attenuates the systemic inflam-

matory response (Tracey, 2002). The downregulation of TNF-α, but also of $CD19^+$-B cells is mediated by the α-7 nicotinic ACh receptor (Skok *et al.*, 2005; Wang *et al.*, 2003). Therefore it would be expected that the α-7 nicotinic receptor antagonism of KYNA might contribute to the inhibition of this cholinergic anti-inflammatory pathway. Indeed, increased numbers of $CD19^+$B-cells have repeatedly been described in acute schizophrenic patients (DeLisi *et al.*, 1982; Mach *et al.*, 1983; McAllister *et al.*, 1989), which are downregulated during neuroleptic therapy (Müller *et al.*, 2004b; Maino *et al.*, 2006), but studies of the relationship between the immune response and cholinergic neurotransmission in schizophrenics are still missing.

**Genetics of the Immune System and of NMDA Receptor Dysfunction**

Recent data reveal that the contribution of genetic heritability to the occurance of schizophrenia is 50% - 80% (Cardno *et al.*, 1999). It is a genetically complex disorder, the most probable genetic basis of schizophrenia involves a mode of transmission with several to multiple susceptibility genes (Jablensky, 2000; Sullivan *et al.*, 2003). Given the hereditary component of schizophrenia and the role of an inflammatory/ immunological process in schizophrenia, immunologically relevant genes may shape up as susceptibility genes for schizophrenia, altering the immune defense.

It was shown repeatedly that genetic factors influence acquiring infectious diseases (*e.g.*, tuberculosis in dizygote twins concordance rate 25%, in monozygote twins 87%) (Kallmann and Reisner, 1943), both with respect to susceptibility (Blackwell, 2001; Cook and Hill, 2001) and to resistance to infection (Hill, 1999). Mechanisms for genetically mediated responses to infection occur through genetic variations in immune mediators such as cytokines and human leucocyte antigene (HLA) genes. The HLA region on chromosome 6 is located within or very near a region which has a high susceptibility risk for schizophrenia, as was repeatedly demonstrated in family studies (Schwab *et al.*, 1995; 2000). So far, associations of certain HLA-loci with schizophrenia (Laumbacher *et al.*, 2003) or certain subtypes (Grosskopf *et al.*, 1998; Müller *et al.*, 1998) were described, but replication in larger, independent samples is still lacking. Studies of genetic polymorphisms in the promoter region of the pro-inflammatory cytokine TNF-α, which is also located in the HLA region of chromosome 6, show divergent results (Boin *et al.*, 2001; Riedel *et al.*, 2002; Meira-Lima *et al.*, 2003), the difference in the outcome possibly being related to ethnic differences between the samples. Regarding the functional dysbalance of the type-1/type-2 immune response, an analysis of polymorphisms of the type-1 cytokine IL-2 and the type -2 cytokine IL-4 revealed a possible genetic base for this imbalance (Schwarz *et al.*, 2005). Several other cytokine genes and components of the immune system have been studied without conclusive results. Among others, methodological problems in diagnosis, sample -distribution and -size, ethnic differences may contribute to the inconclusive results. On the other hand, the small genetic load of every individual gene within the multiple genetic interactions and - in particular regarding the immune system - the pleiotropic function of the immune components and their marked functional compensatory abilities may explain weak genetic associations.

There is consensus that genetic variations of neuregulin-1, located at chromosome 8p (Stefansson *et al.*, 2002; 2003; Williams *et al.*, 2003) and dysbindin, located also on chromosome 6p22 (Straub *et al.*, 2002; Schwab *et al.*, 2003; Numakawa *et al.*, 2004) are associated with an increased risk for schizophrenia. Both genes have been identified in large-scale studies over the last years. Although the functions of the genes have not yet been fully elucidated and at least the neuregulin-1 has multiple functions in a variety of tissues including acting as glial growth factor and migration of cortical neurons (Buonanno and Fischbach, 2001), interestingly, both genes code for proteins which are involved in glutamatergic neurotransmission (Collier and Li, 2003). Neuregulin-1 regulates the NMDA receptor expression/presence in glutamatergic synaptic vesicles, dysbindin is located presynaptically in glutamatergic neurons and is reduced at these locations in schizophrenia, especially in the hippocampus and the dentate gyrus (Talbot *et al.*, 2004). These recent genetic findings support the view that the glutamatergic neurotransmission plays a key role in schizophrenia.

**Neurodevelopmental Aspects of Inflammation and NMDA Receptor Dysfunction**

The discovery of environmental risk factors for schizophrenia, acting before, during and shortly after birth has been central for the neurodevelopmental hypothesis of schizophrenia (Murray and Lewis, 1987). Genetic and environmental risk factors interact during the crucial phase of development of the CNS, causing subtle abnormalities, which leave the individual vulnerable to psychosis in later life (Dean and Murray, 2005). Established risk factors are obstetric complications (McNeil *et al.*, 2000; Cannon *et al.*, 2002) or prenatal and postnatal infections. Cytokines, mediators of the immune response, are growth factors of the nervous system and of glial cells, therefore crucial for the development of the CNS. Obstetric complications such as hypoxia and

injury of the CNS are associated with a change in cytokine release in the CNS (Tohmi *et al.*, 2004).

On the other hand, it has been argued that the effect of obstetric complications might be mediated by glutamatergic excitotoxic damage in the fetal/neonatal brain (Fearon *et al.*, 2000). This view is supported by an animal model which shows that glutamatergic damage is not associated with functional impairment in early life, but regularly manifests itself during early adulthood (Farber *et al.*, 1995). The sensitization of the CNS to glutamatergic toxicity seems to be a process of maturation, becoming symptomatic during adulthood. Accordingly, the occurrence of psychotic symptoms following the use of the NMDA receptor antagonist ketamine in humans is age dependent, with psychotic symptoms occurring rarely, if ever, in prepubertal children, but manifesting in nearly 50% of young to middle-aged adults (Marshall and Longnecker, 1990).

**Type I - type II immune response dysbalance in schizophrenia promotes the production of endogenous KYNA.**

More than 95% of L-tryptophan in mammals is degraded through the kynurenine pathway generating a number of biologically active compounds (Gholson *et al.*, 1960). The close interaction between cytokine effects and the tryptophan/kynurenine metabolism is the basis for the possible role of the kynurenine metabolism in schizophrenia. The dysbalance of the type-1 / type-2 immune response in schizophrenia is outlined above. This dysbalance of the immune response is associated with a dysbalance in kynurenine metabolism.

The two enzymes capable of catalyzing the first step in the pathway, tryptophan 2,3-dioxygenase (TDO) and indoleamine dioxygenase (IDO), play a key role in the regulation of kynurenine metabolism. IDO catalyzes the degradation from tryptophan to kynurenine (Grohmann *et al.*, 2003). The activity of IDO, however, is related to the type-1/type-2 immune response balance (Grohmann *et al.*, 2003). Th-1 or type-1 cytokines, such as IFN-γ and IL-2 stimulate the activity of IDO, the tryptophan catabolism to kynurenine (Carlin *et al.*, 1989; Grohmann *et al.*, 2003).

Although the physiologic significance of the TDO/IDO dichotomy in tryptophan metabolism has not yet been fully elucidated, it is known that it plays a role in schizophrenia. There is a mutual inhibitory effect of TDO and IDO: a decrease in TDO activity occurs concomitantly with IDO induction, resulting in a coordinate shift in the site (and cell types) of tryptophan degradation (Takikawa *et al.*, 1986). In CNS cells, the consequence seems to be that tryptophan degradation shifts from one cell type to another. While it has been known for a long time that IDO is expressed in different types of CNS cells, TDO was thought to be restricted to liver tissue for many years (Kotake and Masayama, 1937). It is known today, however, that TDO is also expressed in CNS cells (Gal, 1974; Haber *et al.*, 1993).

There are several arguments supporting the view that the type-1 / type-2 immune response in the CNS is represented by different cell types, astrocytes and microglial cells (Aloisi *et al.*, 2000). While the type-1 immune response in the CNS mainly takes place in the CNS-macrophages, the microglial cells, the type-2 immune response mainly takes place in astrocytes (Aloisi *et al.*, 2000). While the type-1 cytokine IL-12 is produced in microglial cells, the secretion is inhibited by astroglial cells (Aloisi *et al.*, 1997; Stalder *et al.*, 1997). Astrocytes and microglial cells are involved in the balance between type-1 and type-2 regulating signals in the CNS (Xiao and Link, 1999).

The type-2 or Th-2 shift in schizophrenia (Müller *et al.*, 2000; Schwarz *et al.*, 2001) may result in two functional consequences: the expression of IDO, normally activated during an immune response by type-1 cytokines, in particular IFN-γ, is not activated or even inhibited, while TDO is activated. The type-1 / type-2 imbalance seems to be reflected in the IDO/TDO imbalance. Second, due to the type-1 / type-2 imbalance, the IDO/TDO imbalance is reflected by the activation of astrocytes, which are more strongly involved in the type 1 / type 2 imbalance as compared to microglial cells (Aloisi *et al.*, 2000).

Indeed, a study referring to the expression of IDO and TDO in schizophrenia showed exactly these results. An increased expression of TDO compared to IDO was observed in schizophrenic patients and the increased TDO expression was found, as expected, in astrocytes, not in microglial cells (Miller CL *et al.*, 2004). In this study, only tissue from the frontal cortex was analyzed. Frontal cortex, however, is typically affected in schizophrenia, although other regions, such as the hippocampus and the thalamus, are known to be altered in schizophrenia, too (Harrison and Weinberger, 2005).

KYNA is the only known naturally occurring NMDA receptor antagonist in the human CNS (Stone, 1993). The finding of decreased levels of KYNA after application of dopamine and dopamine-agonistic substances support the view of a regulatory feed-back mechanism between kynurenine metabolism, dopaminergic and possibly also glutamatergic neurotransmission (Wu *et al.*, 2002). The exact mechanism still remains to be elucidated. Kynurenine metabolism is involved in the inhibition of the inhibitory glutamatergic pathway, *i.e.*, blockade of the negative feed-back loop between the dopaminergic and glutamatergic neurotransmis-

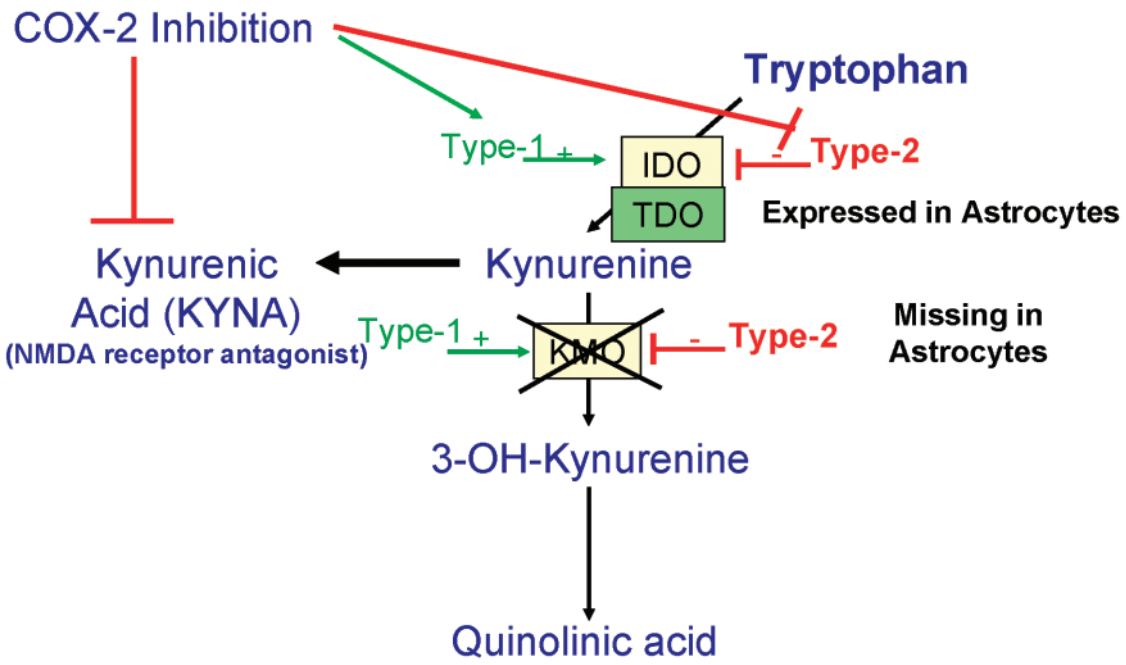


**Figure 1:Metabolization pathways form tryptophane/kynurenine to KYNA and quinolinic acid. IDO and KMO are activated by type-1 cytokines and inhibited by type-2 cytokines. KMO is missing in astroctes, only expressed in microglia. TDO in brain is only expressed in astrocytes. In astrocytes, only the pathway to KYNA can take place. Dependent from the IDO inhibition, the whole pathway is inhibited in microglia. COX-2 inhibits KYNA effects and rebalances the type-1 / type-2 response.**

sion (Carlsson *et al.*, 2001). Whether inversely the kynurenine metabolism can be down-regulated via this mechanism remains to be studied.

Monocytic cells infiltrating the CNS are a second key-player in metabolizing 3-hydroxy-kynurenine. They help astrocytes in the further metabolism to quinolinic acid (Guillemain *et al.*, 2003). However, the low levels of sICAM-1 (ICAM-1 is the molecule that mainly mediates the penetration of peripheral monocytes and lymphocytes into the CNS) in the serum and in the CSF of nonmedicated schizophrenic patients (Müller *et al.*, 2000) and the increase of adhesion molecules during antipsychotic therapy (Müller *et al.*, 1999) indicate that the penetration of monocytes and lymphocytes may be reduced in nonmedicated schizophrenic patients.

**Cellular Source of KYNA in the CNS**

Given that kynurenine metabolism in schizophrenia is influenced by the type 1/type 2 imbalance and the related changes including differing activation of astrocytes and microglial cells, consequences would be expected in schizophrenia. Several findings suggest that astrocytes play a key role in the production of KYNA in the CNS, because astrocytes are the main source of KYNA. The cellular localization of kynureneine metabolism is primarily in macrophages and microglial cells (Heyes *et al.*, 1996; Espey *et al.*, 1997), but also in astrocytes (Heyes *et al.*, 1997a,b; Speciale and Schwarcz, 1993).

Interestingly, it has been shown that KYN-OHse, a critical enzyme in kynurenine metabolism, is absent in human astrocytes (Guillemain *et al.*, 2003). Accordingly, it has been described that astrocytes cannot produce 3HK but are able to produce large amounts of the early kynurenine metabolites, such as kynurenine and KYNA (Guillemain *et al.*, 2003). This supports the observation in animal experiments that inhibition of KYN-OHse leads to an increase of the KYNA production in the CNS (Chiarugi *et al.*, 1996). This takes place in animals and in human cells; astrocytes are the main source of KYNA (Kiss *et al.*, 2003). The complete metabolism of kynurenine to quinolinic acid, however, is observed only in microglial cells, not in astrocytes. Due to the lack of KYN-OHse, KYNA accumulates in astrocytes. These findings support the view that a dysbalance in the activation of microglia and astrocytes might be associated with the accumulation of KYNA in the CNS.

**The Possible Role of KYNA in Schizophrenia**

Due to the type-1 / type-2 imbalance and activation of astrocytes, the levels of the NMDA receptor antagonist KYNA increase in the CNS. The accumulation of KYNA

may lead to schizophrenic symptoms as the pharmacological application of other NMDA receptor antagonists, such as PCP or MK 801 (Erhardt *et al.*, 2003).

Accordingly, increased levels of KYNA have been observed in the CSF of schizophrenic patients as compared to healthy controls (Erhardt *et al.*, 2001a). Since most of the patients in this study were drug-naive first-episode patients, this increase could not be caused by antipsychotic drug treatment. At any rate, chronic drug treatment with antipsychotics does not result in an increase of KYNA, but rather in a decrease (Adler *et al.*, 1998; Ceresoli-Borroni *et al.*, 1999; Schwarcz *et al.*, 2001).

An investigation of CNS tissue specimens of 31 schizophrenics in different cortical regions revealed increased KYNA levels compared to a carefully selected control sample, particularly in the prefrontal cortex (Brodman area 9) (Schwarcz *et al.*, 2001). The prefrontal cortex is an area, traditionally thought to be involved in the pathophysiology of schizophrenia (Andreasen *et al.*, 1992).

In recent years, pharmacological substances acting as elevators of endogenous KYNA in the CNS have been identified. One of these substances is PNU 156561A, an inhibitor of KYN-OHse. This substance enables studies of the effects of increased endogenous KYNA levels in animals (Speciale *et al.*, 1996). The effects, which could be observed in the experiments, were similar to the effects observed after systemic administration of the psychotomimetic drugs MK-801 or PCP (Erhardt *et al.*, 2001b; 2002). In particular, dopaminergic neurons in the midbrain showed an increase in activity (Erhardt *et al.*, 2001b). These studies show that KYNA levels influence the dopaminergic activity in critical brain regions, as would be expected for a substance involved in the pathogenesis of schizophrenia. The atypical antipsychotic clozapine, however, has modulating, in higher doses inhibitory effects on the activity of dopaminergic neurons in the midbrain (Schwieler *et al.*, 2004). This inhibitory effect of clozapine, which is mediated by the glycine-site of the NMDA receptor, may account for its beneficial effects in ameliorating symptoms of schizophrenia.

Besides the effects on the NMDA-receptor, KYNA is also a potent antagonist of the α-7 nicotinic ACh receptors (Hilmas *et al.*, 2001). Antagonism of ACh receptors is associated with cognitive impairment, a key syndrome in schizophrenia. Kraepelin (1899) and Bleuler (1911) already described cognitive decline as a key symptom of schizophrenia. Cognitive deficits often precede all other schizophrenic symptoms (Weickert and Goldberg, 2000) and sometimes occur already during childhood (Cornblatt *et al.*, 1999). Compared to other schizophrenic symptoms, cognitive decline is a basic disturbance in schizophrenia (Huber, 1983; Green and Nuechterlein, 1999).

It was shown *in-vitro* and *in-vivo* that the antagonism of KYNA on ACh receptors takes place already at lower concentrations of KYNA compared to the antagonism to the NMDA receptor. Studies show that the affinity of KYNA to the α-7 nicotinic ACh receptors is about double in comparison to the glycine-site of the NMDA receptor (Hilmas *et al.*, 2001). This finding must be interpreted to mean that the impairment of cognitive functions takes place at lower concentrations of KYNA, while psychotic symptoms appear only at higher concentrations of KYNA. This view fits with the earlier onset of cognitive disturbance in schizophrenia compared to the acute psychotic symptoms, the latter triggered by the NMDA antagonism of the substance. Moreover, it has to be postulated that psychotic symptoms are always associated with cognitive impairment but cognitive impairment can be observed without psychotic symptoms. This constellation is observed typically in schizophrenia (Kraepelin, 1899; Bleuler, 1911).

**Cyclo-oxygenase 2 inhibitors rebalance the type-1 / type-2 immune response and inhibit the production of KYNA.**

One class of modern drugs is well known to induce a shift from the type-1 like to a type-2 dominated immune response: the selective cyclo-oxygenase-2 (COX-2) inhibitors. Several studies demonstrated the type-2 inducing effect of $PGE_2$ - the major product of COX-2, while inhibition of COX-2 is accompanied by inhibition of type-2 cytokines and induction of type-1 cytokines (Pyeon *et al.*, 2000; Stolina *et al.*, 2000). $PGE_2$ levels in schizophrenia have not been well studied; increased levels of $PGE_2$, however, have been described (Kaiya *et al.*, 1989). $PGE_2$, however, induces the production of IL-6, a cytokine which is consistently described to be increased in schizophrenia (see above). Moreover, increased COX expression was also found in schizophrenia (Das and Khan, 1998). Therefore COX-2 inhibition seems to be a promising approach in the therapy of schizophrenia. COX-2 inhibition seems to balance the type-1/type-2 immune response by inhibition of IL-6, $PGE_2$ and by stimulating the type-1 immune response (Litherland *et al.*, 1999).

Therefore a prospective, randomized, double-blind study of therapy with the COX-2 inhibitor celecoxib add-on to risperidone in acute schizophrenia was performed. A therapeutic effect of celecoxib was observed (Müller *et al.*, 2002). Immunologically, an increase of the type-1 immune response was found in

the celecoxib treatment group (Müller *et al.*, 2004a). The clinical effect of COX-2 inhibition was especially pronounced regarding cognition of the schizophrenic patients (Müller *et al.*, 2005). The finding of a clinical advantage of COX-2 inhibition, however, could not be replicated in a second study in 40 schizophrenic patients. A further analysis of the data revealed that the outcome of the COX-2 inhibition therapy depends on the duration of the disease (Müller *et al.*, unpublished data). The efficacy of anti-inflammatory therapy seems most pronounced in the first years of the schizophrenic disease process. This observation is in accordance with results from animal studies which show that the effects of COX-2 inhibition on cytokines, hormones, and particularly on behavioural symptoms are dependent on the duration of the changes and the time of application (Casolini *et al.*, 2002). It seems that there is a point of no return for therapeutic effects regarding the pathological changes during an inflammatory process and its sequelae.

Additionally to the immunological mechanism, selective COX-2 inhibitors reduce the KYNA levels by a prostaglandin-mediated mechanism (Schwieler *et al.*, 2005). COX-inhibition provokes differential effects on kynurenine metabolism: while COX-1 inhibitors increase the levels of KYNA, COX-2 inhibitors decrease them. Therefore, psychotic symptoms and cognitive dysfunctions, observed during therapy with COX-1 inhibitors, were assigned to the COX-1 mediated increase of KYNA (Tharumaratnam *et al.*, 2000; Clunie *et al.*, 2003; Schwieler *et al.*, 2005).

Regarding the role of the inflammatory process in schizophrenia and possibly other psychiatric disorders, anti-inflammatory therapy should be taken into the focus of further research (Müller *et al.*, 2004b); COX-2 inhibition is one option among others. Therapeutic research, however, has to consider different levels and different mechanisms for therapeutic targets in the neuroimmune system, tryptophan-kynurenine metabolism and the dopmaninergic-glutamatergic neurotransmission circuits.

## OUTLOOK

Given that an increased genetic risk for schizophrenia is related to glutamatergic neurotransmission, prevention of additional risks for a hypofunction of the glutamatergic system is one of the goals for schizophrenic patients. The increased production of KYNA due to infection and an immune dysbalance is an additional risk. For both the glutamatergic system and the inflammatory approach, a sensitization is described which can explain the 'two hit model' of schizophrenia, in which schizophrenia-specific genetic factors combine in an additive fashion with environmental insults to produce the illness. However this may be oversimplified. The data are consistent with a more complex model in which nonspecific genetic factors that increase susceptibility to developmental abnormalities interact with insults and specific genetic factors.

### *Acknowledgements*

This article is dedicated to Manfred Ackenheil (1939-2006), the pioneer in Psychoneuroimmunology.

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