36 Molecular Pathogenesis for Schizophrenia and Major Depression

Norbert Müller and Markus J. Schwarz

Keywords Schizophrenia; Major depression; Th1/Th2 balance; Pro-inflammatory cytokines; NMDA hypothesis; Glutamate; Serotonin; Tryptophan; Kynurenine; Kynurenic acid; HPA axis

36.1. Introduction

In schizophrenia, dopaminergic hyperfunction in the limbic system and dopaminergic hypofunction in the frontal cortex are discussed to be the main neurotransmitter disturbances. Recent research provides further insight that glutamatergic hypofunction might be the cause for this dopaminergic dysfunction. In major depression, in contrast, glutamatergic hyperfunction seems to be closely related to the lack of serotonergic and noradrenergic neurotransmission and to the core symptoms of major depression. Therefore, glutamatergic dysfunction seems to be a common pathway in the neurobiology of schizophrenia and depression. The function of the glutamatergic system is closely related to the immune system and to the tryptophan-kynurenine metabolism, which both seem to play a key role in the pathophysiology of schizophrenia and major depression (Müller and Schwarz, 2006, 2007).

36.2. Glutamatergic Neurotransmission and NMDA-Receptor Function in Schizophrenia and Major Depression

36.2.1. Schizophrenia

A disturbance in the dopaminergic neurotransmission plays a key-role in the pathogenesis of schizophrenia (Carlsson, 1988). Most drugs ameliorating psychotic symptoms act as dopamine receptor blockers, in particular D2 receptor blockers. In light of only a portion of patients responding to antipsychotic drugs and unsatisfactory long term outcomes, attempts to explain the disease solely in terms of dopaminergic dysfunction leave many aspects of schizophrenia unsolved.

The glutamate hypothesis of schizophrenia postulates an equilibrium between inhibiting dopaminergic and inhibiting glutamatergic neurons; the model of a cortico-striato-thalamo-cortical control loop integrates the glutamate hypothesis with neuroanatomical aspects on the pathophysiology of schizophrenia (Carlsson et al., 2001). Hypofunction of the glutamatergic cortico-striatal pathway is associated with opening of the thalamic filter, which leads to an uncontrolled flow of sensory information to the cortex and to psychotic symptoms. Hypofunction of the glutamatergic neurotransmitter system as a causal mechanism in schizophrenia was first proposed due to the observation of low concentrations of glutamate in the CSF of schizophrenic patients (Kim et al., 1980).

Treatment with NMDA receptor antagonists leads to a marked, dose-dependent increase of amphetamine-induced dopamine release (Miller and Abercrombie, 1996). In schizophrenics, this amphetamine-induced dopamine release is much higher compared to healthy controls (Laruelle et al., 1996). This observation is in accordance with the view that activation of the nigrostriatal dopamine system can take place by opposing activation of inhibitory striatongiral GABAergic projection neurons (Carlsson et al., 2001).

Phencyclidine (PCP), Ketamin, and MK-801 all block the N-methyl-D-aspartate (NMDA) receptor complex and are associated with schizophrenia-like symptoms through hypofunction of the glutamatergic neurotransmission (Krystal et al., 1994; Olney and Farber, 1995). Other NMDA antagonists have psychotogenic properties, too (CPP, CPP-ene, CGS 19755). NMDA receptor hypofunction can explain schizophrenic positive and negative symptoms, cognitive deterioration and structural brain changes (Olney and Farber, 1995).
Findings of decreased plasma levels of the NMDA co-agonist glycine in schizophrenics and a correlation of glycine levels with schizophrenic negative symptoms are in line with decreased NMDA-receptor function (Sumiyoshi et al., 2004). Baseline glycine levels predicted the treatment outcome of clozapine on negative symptoms (Sumiyoshi et al., 2005). Clinical investigations targeted the glycine co-agonistic site of the NMDA receptor by administering the amino acids glycine or D-serine, or a glycine pro-drug such as milacemide (Tamminga et al., 1992). Some of these studies have yielded positive results, particularly against the schizophrenic deficit syndrome (Heresco-Levy et al., 1999).

36.2.2. Major Depression

Overwhelming evidence collected over the last 40 years suggests that disturbances in the serotonergic and noradrenergic neurotransmission are the crucial factor in the pathogenesis of major depression (Matussek, 1966; Coppen and Swade, 1988). The common therapeutic mechanism of antidepressant drugs is the increase of serotonergic and/or noradrenergic neurotransmission. Intense research, however, has not yet been able to discover the mechanisms leading to disturbances of the serotonergic/noradrenergic neurotransmission.

Although the glutamatergic system may influence directly or indirectly the serotonergic and noradrenergic neurotransmission, only few data have been published with regard to this interaction. NMDA receptor antagonists increase the serotonin levels in the brain (Yan et al., 1997; Martin et al., 1998). Several studies showed an increased activity of the glutamatergic system in the peripheral blood of depressive patients (Kim et al., 1982; Altamura et al., 1993; Mauer et al., 1998). This result could not be replicated by all authors (Maes et al., 1998). The inconsistency of the findings, however, might be due to methodological problems (Kugaya and Sanacora, 2005).

Support for increased glutamatergic activity in depression comes from magnetic resonance spectroscopy: Elevated glutamate levels were found in the occipital cortex of unmedicated subjects with major depression (Sanacora et al., 2004a). An increased level of a certain neurotransmitter is often associated with a down-regulation of the respective receptor. Accordingly, a reduced glycine binding site of the NMDA receptor was found in the brains of suicide victims and patients with depression (Nowak et al., 1995; Nudmamud-Thanoi and Reynolds, 2004). Moreover, a decrease in the NMDA agonistic MK-801 binding in bipolar patients was observed (Scarr et al., 2003).

Consistent with the view that an increased activity of the glutamatergic system and NMDA receptor agonism is associated with depressed mood, a reduction of the glutamatergic activity through NMDA receptor antagonism might exert antidepressant effects. NMDA antagonists such as MK-801 (Maj et al., 1992; Trullas and Skolnick, 1990), ketamine (Yilmaz et al., 2002), memantine (Ossowska et al., 1997), and others (Kugaya and Sanacora, 2005) exhibited antidepressant effects in different animal models. In humans, D-cycloserine, a partial NMDA receptor agonist, which acts as a NMDA receptor antagonist in high doses, demonstrated antidepressant effects in high doses (Crane, 1959). Slight antidepressive effects have also been observed with amantadine (Huber et al., 1999; Stryjer et al., 2003). Moreover, preliminary data show antidepressant effects of the NMDA receptor antagonist ketamine (Kudoh et al., 2002; Ostroff et al., 2005) and riluzole, an antiglutamatergic agent believed to increase the glutamatergic uptake into the astrocytes, is under intensive investigation for its antidepressant efficacy (Fritzo et al., 2004). A recent series of open-labelled studies and case reports demonstrated the efficacy of riluzole (Coric et al., 2003; Sanacora et al., 2004b; Zarate et al., 2004, 2005).

36.3. Inflammation in Schizophrenia and Depression

36.3.1. Schizophrenia

Infection during pregnancy, in particular in the second trimester, in mothers of off-springs later developing schizophrenia has been repeatedly described (Brown et al., 2004; Buka et al., 2001; Westergaard et al., 1999). As opposed to any single pathogen, the immune response, itself, of the mother may be related to the increased risk for schizophrenia in the offspring (Zuckerman and Weiner, 2005). Indeed, increased IL-8 levels of mothers during the second trimester were associated with an increased risk for schizophrenia in the offspring (Brown et al., 2004). A fivefold increased risk for developing psychoses later on, however, was also observed after infection of the CNS in early childhood (Gattaz et al., 2004; Koponen et al., 2004).

Signs of inflammation were found in schizophrenic brains (Körschenhausen et al., 1996), and the term 'mild localized chronic encephalitis' to describe a slight but chronic inflammatory process in schizophrenia was proposed (Bechter et al., 2003).

36.3.2. Major Depression

An inflammatory model of major depression (MD) is ‘sickness behaviour’, the reaction of the organism to infection and inflammation. Sickness behaviour is characterised by weakness, malaise, listlessness, inability to concentrate, lethargy, decreased interest in the surroundings, and reduced food intake—all of which are depression-like symptoms. The sickness-related psychopathological symptomatology during infection and inflammation is mediated by proinflammatory cytokines such as IL-1, IL-6, tumor-necrosis-factor-α (TNF-α), and IFN-γ. The active pathway of these cytokines from the peripheral immune system to the brain is via afferent neurons and through direct targeting of the amygdala and other brain regions after diffusion at the circumventricular organs and choroid plexus (Dantzer, 2001).