Celecoxib adjunctive therapy in schizophrenia rebalances immune response: role of cytokines and nitric oxide

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Abstract:

Background / purpose: *inflammation may be an important pathogenetic mechanism underlying schizophrenia. Cytokines may contribute to the effects of inflammation to the neurotransmission and to clinical symptoms of psychiatric disorders such as schizophrenia and depression. Recent immunological studies point to a dysbalance between the type-1 and type-2 immune response in schizophrenia with an over-activation of the type-2 response and a lack of type-1 response. Inhibition of cyclooxygenase-2 (COX-2) is accompanied by inhibition of type-2 cytokines and induction of type-1 cytokines. Nitric oxide (NO) is known to have effects on the storage; uptake and/or release of most other neurotransmitters in the CNS NO may have toxic effects at higher concentrations. This study aims at assessment of the efficacy of celecoxib (selective cox-2 inhibitor) as an adjunctive therapy in treatment of schizophrenic patients, and in order to evaluate the effects of the celecoxib therapy to the immune system in schizophrenia, markers of the peripheral immune system were measured in the blood of schizophrenic patients before the start of the therapy, and at the end of the study. Also, to study the role of NO in schizophrenia.*

Subjects and methods: *Fifty schizophrenic patients were included in the study (22 females, 28 males). Twenty healthy controls (11 males and 9 females) were included, they were age and sex-matched to the patients. Patients were subjected to diagnosis of schizophrenia using the semi-structured interview of the DSM-IV, rated with the Positive and Negative Syndrome Scale (PANSS), randomly allocated, 25 to risperidone 6 mg/day plus celecoxib 400 mg/day (celecoxib group) and 25 to risperidone 6 mg/day plus placebo (placebo group) for eight weeks. Blood samples were collected from patients and control, for determination of plasma interleukin-10 (IL-10), plasma transforming growth factor beta (TGF-_), plasma tumor necrosis factor–alpha (TNF-_), and serum nitric oxide (NO) at the start and end of therapy.*

Results: *celecoxib treated patients show significantly more and earlier improvement in positive, negative, psychopathology subscales and total score of PANSS compared with the placebo group. In celecoxib group before treatment, IL-10, TGF-_ and NO were high and TNF-_ was lowas compared to control, and after treatment significant decrease of IL-10, TGF–_ and NO and increase of TNF-_ occurred. In placebo group, no change of any of cytokines or before and after treatment, only NO showed significant decrease after treatment.*

Conclusion: *Selective Cox-2 inhibitor add-on therapy rebalance the immune response with shift from type-2 to type-1 immune response and reduce the elevated plasma NO causing earlier and significantly better response than resperidone alone, and the improvement of psychiatric symptoms can normalize an elevation of NO after treatment in patients with schizophrenia.*

Introduction:

Psychiatric symptoms, especially schizophrenia, have been described both during inflammation and during different types of autoimmune disorders involving the CNS. These observations led to the suggestion that inflammation may be an important pathogenetic mechanism underlying schizophrenia (Muller et al, 2004). Previous studies showed an inflammatory process in at least a subgroup of schizophrenic patients. Signs of inflammation have been found in the cerebrospinal fluid as well as in postmortem CNS tissue of schizophrenic patients (Wildenauer et al.1990; Körschenhausen et al.1996). Cytokines are known to act on the noradrenergic, serotonergic, and dopaminergic neurotransmission. For example, animal experiments show that IL-6 increases the dopaminergic neurotransmission in the hippocampus, but also IL-2 increases the hippocampal serotonergic and dopaminergic