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EDITORIAL

Inflammation: its role in schizophrenia and the potential anti-inflammatory effects of antipsychotics

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Over the last few years, inflammation has made a major comeback as a pathogenic theory of schizophrenia. Its effects on monoamine metabolism, neuroendocrine function, and synaptic plasticity have all been proposed as potential pathways mediating the link between inflammation and schizophrenia (Haroon et al. 2012). Further support for a link between activation of the immune system and schizophrenia is seen in this month's issue of *Psychopharmacology*, where Song et al. report high levels of interleukin (IL)1β, IL6 and tumour necrosis factor (TNF)α in drug naïve-first episode schizophrenia patients when compared with healthy controls matched for age, gender, smoking status, and body mass index (Song et al. 2013). These findings extend a growing body of literature on inflammation in schizophrenia by giving a better insight on longitudinal changes in cytokine levels in the context of treatment with antipsychotics. Recent reviews and meta-analysis of the literature show that increased blood levels of IL1β, IL6 and TNFα are consistently reported in patients at the onset of this disorder (Di Nicola et al. 2013; Miller et al. 2011; Mondelli et al. 2011).

However, how much of these peripheral abnormalities reflect central inflammation and contribute to the development of schizophrenia remains still debated. Indeed, while the evidence of increased peripheral immune activation in schizophrenia has become more consistent over the years, the presence of a neuroinflammatory state in these patients has been the object of more controversy. Post-mortem studies in subjects with schizophrenia have reported mixed findings, possibly in relation also to some methodological issues; most post-mortem studies have been conducted on relatively small samples, included mainly elderly subjects in whom incidental lesions are common, and have used different methods for counting astrocytes and microglia (Schnieder and Dwork 2011). Nevertheless, more recent studies quantifying microglia activation in vivo, by using positron emission tomography, have reported increased microglia activation (Doorduin et al. 2009; van Berckel et al. 2008) supporting the role of neuroinflammation in the pathophysiology of schizophrenia.

Interestingly, cytokine abnormalities differ between acute and stable phases of schizophrenia, suggesting either that some cytokines could be influenced by antipsychotic treatment or that these differences may reflect different stages of illness (Miller et al. 2011). Studies on the effect of antipsychotic treatment on inflammation, and more specifically on cytokine levels, have so far given mixed findings, showing an increase, a decrease, or unchanged levels of cytokines after antipsychotic treatment (reviewed by Zajkowska and Mondelli 2013). One potential explanation for the mixed findings is that antipsychotic agents might exert different effects on the immune system, having both a direct anti-inflammatory activity and an indirect pro-inflammatory activity, mediated by their effect on weight-gain and increased adiposity. Interestingly, this dual anti- and pro-inflammatory action of antipsychotics is supported by the longitudinal study from Song et al., who observed a decrease in IL1β and IL6 levels in the first weeks of treatment with risperidone, followed by an increase back to baseline levels by the end of 6 months treatment, which happened alongside a steady weight gain (Song et al. 2013). The findings suggest that when

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assessing the effect of antipsychotic treatment on inflammatory markers, the timing of the assessment (i.e. how many days/weeks after starting antipsychotic) and the degree of antipsychotic induced weight gain and metabolic dysregulation might play a role in the differences observed so far. They also add to the literature on the impact of weight gain and metabolic dysfunction related to antipsychotic treatment (Howes et al. 2004; Mondelli et al. 2013; Ou et al. 2013), and highlight the potential importance of treating it early (Poyurovsky et al. 2013)

The evidence of an inflammatory status at onset of psychosis and of a possible anti-inflammatory action of antipsychotic treatment supports inflammation as a potential new therapeutic target for schizophrenia. In line with this, there have been a number of recent trials of nonsteroidal anti-inflammatory drugs (NSAIDs) as adjuncts to antipsychotic drugs. However, a recent meta-analysis of the trials conducted with NSAIDs as adjuncts to antipsychotics to date, suggests that whilst NSAIDs have a benefit for positive symptoms, the effect is small (Nitta et al. 2013). These modest benefits may reflect the inclusion of patients without an inflammatory diathesis. Support for this idea in another condition comes from findings from a recent randomised-controlled trial with a TNFα antagonist (Infliximab) in patients with treatment-resistant depression. This found that TNF antagonism does not have generalised efficacy in treatment-resistant depression, but may improve depressive symptoms in patients with high levels of inflammatory markers at baseline (Raison et al. 2013). Further research would need to clarify which individuals might most benefit from treatments targeting inflammation and to give a better understanding of current antipsychotic effects on immune system.

References

Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, Murray RM, Dazzan P, Pariante CM, Mondelli V (2013) Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun 31:90–95

Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC (2009) Neuroinflammation in schizophrenia-related psychosis: a PET study. J Nucl Med 50:1801–1807

Haroon E, Raison CL, Miller AH (2012) Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 37:137–162

Howes OD, Bhatnagar A, Gaughran FP, Amiel SA, Murray RM, Pilowsky LS (2004) A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. Am J Psychiatr 161:361–363

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011) Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 70:663–671

Mondelli V, Cattaneo A, Belvederi Murri M, Di Forti M, Handley R, Hepgul N, Miorelli A, Navari S, Papadopoulos AS, Aitchison KJ, Morgan C, Murray RM, Dazzan P, Pariante CM (2011) Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. J Clin Psychiatry 72:1677–1684

Mondelli V, Anacker C, Vernon AC, Cattaneo A, Natesan S, Modo M, Dazzan P, Kapur S, Pariante CM (2013) Haloperidol and olanzapine mediate metabolic abnormalities through different molecular pathways. Transl Psychiatry 3:e208

Nitta M, Kishimoto T, Muller N, Weiser M, Davidson M, Kane JM, Correll CU (2013) Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. Schizophr Bull 39:1230–1241

Ou JJ, Xu Y, Chen HH, Fan X, Gao K, Wang J, Guo XF, Wu RR, Zhao JP (2013) Comparison of metabolic effects of ziprasidone versus olanzapine treatment in patients with first-episode schizophrenia. Psychopharmacology 225:627–635

Poyurovsky M, Fuchs C, Pashinian A, Levi A, Weizman R, Weizman A (2013) Reducing antipsychotic-induced weight gain in schizophrenia: a double-blind placebo-controlled study of reboxetine-betahistine combination. Psychopharmacology 226:615–622

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH (2013) A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70:31–41

Schnieder TP, Dwork AJ (2011) Searching for neuropathology: gliosis in schizophrenia. Biol Psychiatry 69:134–139

Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, Harrington A, Ziedonis D, Lv L (2013). Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first episode schizophrenia. Psychopharmacology. doi:10.1007/s00213-013-3382-4

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

Zajkowska Z, Mondelli V (2013) First episode psychosis: an inflammatory state? NeuroImmunoModulation. doi:10.1159/000356536