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The effect of the antipsychotic drug quetiapine and its metabolite norquetiapine on acute inflammation, memory and anhedonia

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ABSTRACT

The atypical antipsychotic drug, quetiapine, has recently been suggested to not only show efficacy in schizophrenia, bipolar, major depressive and general anxiety disorders, but to also have a possible anti-inflammatory effect, which could be important in the treatment of the inflammatory aspects of psychiatric diseases. Male C57BL/6 mice were given either quetiapine (i.p. 10 mg/kg), its main active metabolite norquetiapine (i.p. 10 mg/kg), or saline as a vehicle control, once a day for 14 days. On the 14th day, this dose was followed by a single dose of either LPS (i.p. 1 mg/kg) or saline. 24 h post LPS short-term recognition memory and anhedonia behaviour were measured using the Y-maze and saccharin preference test respectively. Immediately following behavioural testing, mice were culled before serum, prefrontal cortex and hippocampal analysis of cytokine levels was conducted. It was found that LPS challenge led to increased serum and brain cytokine levels as well as anhedonia, with no significant effect on recognition memory. Quetiapine and norquetiapine both increased levels of the anti-inflammatory cytokine IL-10 and decreased levels of the pro-inflammatory cytokine IFN-γ in serum 4 h post LPS. Within the brain, a similar pattern was seen in gene expression in the hippocampus at 4 h for *Il-10* and *Ifn-γ*, however norquetiapine led to an increase in *Il-1β* expression in the PFC at 4 h, while both drugs attenuated the increased *Il-10* in different regions of the brain at 24 h. These effects in the serum and brain, however, had no effect on the observed LPS induced changes in behaviour. Both quetiapine and its metabolite norquetiapine appear to have a partial anti-inflammatory effect on IL-10 and IFN-γ following acute LPS challenge in serum and brain, however these effects did not translate into behavioural changes.

1. Introduction

Quetiapine is an atypical anti-psychotic drug, which is primarily used in schizophrenia, but has also been used in bipolar disorder, major depressive disorder and general anxiety disorder (Baune, 2008; Dannlowski et al., 2008). Quetiapine, and its main active metabolite norquetiapine, interact with the dopaminergic, serotonergic and noradrenergic systems to achieve their anti-psychotic action (Lopez-Munoz and Alamo, 2013). It has recently been suggested that quetiapine may also have an anti-inflammatory effect (Baune and Eyre, 2010; Bian et al., 2008; Kim et al., 2012) which could be important for comorbid inflammatory conditions such as arthritis, or for the inflammatory aspects of various psychiatric diseases.

Quetiapine and norquetiapine have mostly similar, but also varying effects in the CNS. Both are antagonists at the dopamine D_1 and D_2 receptors, as well as the serotonin $5HT_{2A}$ receptor, which leads to a decrease in dopamine signalling. They are also both partial agonists at the presynaptic $5HT_{1A}$ receptor, while norquetiapine is a potent noradrenaline uptake inhibitor and increases noradrenaline function further by blocking presynaptic α_2 receptors (Lopez-Munoz and Alamo, 2013). Research has shown a role for both neurotransmitters such as 5-HT and dopamine, as well as the immune system in depression (Muller, 2014a) and possibly schizophrenia (Muller, 2014b). There is a clear link between neurotransmitter pathways and immune pathways. For example, cytokine administration in the periphery can lead to alterations in monoamine activity in various regions of the brain (Song et al., 1999; Zalcman et al., 1994). Damaging dopaminergic neurons have been shown to lead to loss of astrocytes and activation of microglia, while depletion of dopamine can also lead to decreased infiltration of peripheral macrophages (Espinosa-Oliva et al., 2014), showing a clear role for dopamine in inflammation. The action of quetiapine to block dopamine signalling (Lopez-Munoz and Alamo, 2013) may therefore be predicted to have an anti-inflammatory effect through these mechanisms. Noradrenaline and agonists of its receptors have also been shown to increase plasma concentration of anti-inflammatory cytokines, and decrease concentration of pro-inflammatory cytokines (Padro and Sanders, 2014). The action of norqetiapine to block noradrenaline uptake would lead to increased levels of noradrenaline in

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the brain (Lopez-Munoz and Alamo, 2013) and could in turn contribute to any anti-inflammatory effects of norquetiapine.

There are various pieces of evidence for an anti-inflammatory effect of quetiapine. Recently our research group discovered this effect in a case study. A patient presenting with major depressive disorder, and already being treated with disease-modifying antirheumatic drugs and SSRIs was started on additional quetiapine treatment. After 12 months of observations, the patient showed significantly decreased levels of depression as well as decreased levels of physical pain and symptoms of arthritis. Importantly, they also showed decreased levels of systemic inflammation as measured by levels of C-reactive protein in the blood (Baune and Eyre, 2010).

In vitro studies have demonstrated that several anti-psychotic drugs, including quetiapine, have an anti-inflammatory effect in cell culture (Al-Amin et al., 2013; Bian et al., 2008; Krause et al., 2013). Quetiapine, perospirone and ziprasidone were all shown to inhibit the pro-inflammatory release of nitric oxide generation from activated microglia and both quetiapine and perospirone also inhibited release of the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) from activated microglia (Bian et al., 2008). Peripheral blood mononuclear cells (PBMCs) from schizophrenia patients have been shown to have a reduced IFN-γ response to lipopolysaccharide (LPS) compared to control cells which was reversed by addition of quetiapine or risperidone (Krause et al., 2013). Another study using PBMCs from first episode schizophrenia patients showed that quetiapine and haloperidol increased the levels of the anti-inflammatory cytokine IL-4 and decreased the pro-inflammatory cytokine IFN-γ in LPS stimulated cells (Al-Amin et al., 2013).

More recently, the effect of quetiapine on inflammation has been investigated in a mouse model of arthritis. In this study, quetiapine was given for a period of 2 weeks following induction of arthritis by collagen. It was shown that quetiapine decreased symptoms of arthritis in mice, measured by an arthritic score and measuring hind paw thickness. Quetiapine also reversed the increased serum levels of pro-inflammatory cytokines interleukin (IL)-6 and IL-17 which were seen in untreated arthritic mice (Kim et al., 2012). Mouse studies have also shown anti-inflammatory effects of other related anti-psychotic drugs. Risperidone has been shown to reduce microglia activation and behavioural deficits in adult mice challenged with LPS as pups (Zhu et al., 2014), while paliperidone prevented LPS-induced behavioural deficits when both drugs were given prenatally (Kumar and Mohanty, 2014).

A pathophysiological relationship between inflammation and cognitive decline as well as the development of depressive symptoms has been described extensively. Human studies have shown an association between inflammation and mild cognitive impairment in the ageing brain (Baune et al., 2008a, 2012a; Trollor et al., 2010), as well as links between inflammation and depression (Maes et al., 2011; Raedler, 2011) and symptoms of depression (Baune et al., 2012b; Dantzer et al., 2008). Further mechanistic studies in animals have also extensively shown the relationships between inflammation and cognitive impairment or depression-like behaviour in mice, in particular after administration of LPS. LPS induces a potent and robust model of acute sickness behaviour, triggering activation of toll-like receptors resulting in up-regulation of chemokines and cytokines like TNF-α, IL-1β and CXCL1 (Golan et al., 2005; Ortega et al., 2011), and leads to decreased food intake, lethargy, fever and changes in mood in mice similar to those seen in psychiatric disorders (Dantzer et al., 2008). For example, LPS administration can impair cognition in behavioural tests such as the Morris Water maze (Lee et al., 2008; Richwine et al., 2009), contextual fear response (Terrando et al., 2010), passive avoidance (Jain et al., 2002) and the Y-maze (Noble et al., 2007). LPS administration also leads to increased immobility time in forced swim and tail suspension tests (despair), as well as decreased sucrose preference (anhedonia), indicating increased depression-like behaviour (Kang et al., 2011; Painsipp et al., 2011; Pitychoutis et al., 2009).

Anti-inflammatory treatments have been investigated in the treatment of depression, anxiety and cognitive impairment. Various studies have shown beneficial effects of anti-inflammatory drugs, and other compounds with anti-inflammatory properties, to improve cognition or depression-like behaviour (Guo et al., 2009; Kang et al., 2011; Loftis et al., 2010; Wang et al., 2011). A recent study in our laboratory has also shown that treatment of LPS-induced sickness behaviour with the anti-TNF drug etanercept can reverse anxiety behaviour seen in LPS challenged mice (Camara et al., 2015). In addition, recent publications indicate a possible clinical usefulness of non-steroidal anti-inflammatories (NSAIDs) as adjunctive treatments in depression (Eyre et al., 2015; Kohler et al., 2014). The potential anti-inflammatory properties of these and similar drugs that have clinical use in psychiatric conditions warrant further exploration. The current study was designed to investigate the anti-inflammatory effects of quetiapine on systemic and CNS inflammation, including measures of serum cytokines and brain cytokine gene expression, as well as cognition- and depression-like behaviours, using an LPS model of systemic inflammation. We hypothesise that quetiapine and norquetiapine exert anti-inflammatory effects, thereby decreasing the effects of LPS on cytokine levels and ameliorate detrimental effects of LPS on behaviour in mice.

2. Methods

2.1. Mice and drugs

154 mice in total, aged 2 months at the start of drug dosing, were used for the experiments. All experimental mice were housed in groups of 2–5 in individually ventilated cages during the experimental period, with food and water available ad libitum. Ambient temperature of the housing and testing rooms was 22 ± 1 °C. Mice were housed under a 12-h light–dark cycle, lights on at 07:00 h, and all behavioural testing was conducted between 08:00 and 16:00 h. All experimentation was approved by the University of Adelaide Animal Ethics Committee and followed the Australian code of practice for the care and use of animals for scientific purposes.

Quetiapine and norquetiapine were supplied by AstraZeneca and were dissolved in pyrogen free saline (Teknova, Hollister, CA, USA) to a concentration of 1 mg/ml. LPS (*Escherichia coli*, 0111:B4) was purchased from Sigma (St Louis, MO, USA). Drugs and saline vehicle control were given at a dose volume of 10 ml/kg.

2.2. Experimental plan

Male C57BL/6NHsd mice were given either quetiapine (10 mg/kg), its main active metabolite norquetiapine (10 mg/kg) or saline as a vehicle control once a day for 14 days (anti-psychotic treatment) based on previous protocols which showed that this dose was able to reverse behavioural deficits induced by several different interventions (Tanibuchi et al., 2009; Xu et al., 2010; Yan et al., 2007a, 2007b). On the 14th day, this dose was followed by a single dose of either LPS (1 mg/kg) or saline as the vehicle control (endotoxin challenge) based on previous protocols showing that this or similar doses are able to provoke a behavioural sickness response in mice (Singal et al., 2004; Terrando et al., 2010; Yirmiya et al., 2001). There were a total of 6 groups of mice, tested in three cohorts. 24 h following LPS or saline, 8–10 mice/group (total 58) were tested in the Y-maze (Noble et al., 2007) and immediately following behavioural testing, mice were culled (by a lethal dose of sodium pentobarbitone (60 mg/kg) via i.p. injection). A further 7–8 mice/group (total 47) were used for the saccharin preference test, starting immediately after LPS or saline injection, lasting for 24 h. 4–6 mice/group from the Y-maze cohort, and all mice from the saccharin preference cohort had blood collected via cardiac puncture for serum analysis. All mice from the saccharin preference cohort had prefrontal cortex (PFC) and hippocampus brain tissue collected for gene expression analyses. A final cohort of 8 mice/group (total 48) were culled