Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effects of antipsychotics on cortisol, interleukin-6 and hippocampal perfusion in healthy volunteers

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ARTICLE INFO

Article history:
Received 8 December 2015
Received in revised form 29 March 2016
Accepted 31 March 2016
Available online xxxx

Keywords:
Cortisol
Inflammation
Antipsychotic
Cerebral blood flow
Hippocampus
Dopamine

ABSTRACT

This randomized within-subject, double blind study aimed to compare the effects of a single dose of two different antipsychotics (haloperidol and aripiprazole) on cortisol, interleukin (IL)-6 and hippocampal regional Cerebral Blood Flow (rCBF) in the same 17 healthy male individuals. Subjects received a single dose of haloperidol (3 mg), aripiprazole (10 mg) and placebo, in a randomized order on three study appointments. We measured salivary cortisol levels at multiple time points, IL-6 levels from plasma samples, and resting cerebral blood flow (rCBF), using a pulsed continuous arterial spin labeling (pCASL) sequence (1.5T). We found significantly lower cortisol levels in the haloperidol condition ($F(2,32) = 5.78$, $p = 0.007$), than in either placebo ($p = 0.013$; CI = 0.45, 0.406) or aripiprazole ($p = 0.037$; CI = −0.520, −0.014). Interleukin-6 levels were also lower following haloperidol ($F(2,22) = 4.19$, $p = 0.048$) in comparison with placebo ($p = 0.02$; CI = 0.14, 1.8), but not with aripiprazole. Finally, we found a greater rCBF in the right (peak voxel: $T = 6.47$, $p < 0.0001$) and left (peak voxel $T = 5.17$, $p < 0.01$) hippocampus following haloperidol compared with placebo, and at trend level also in the left hippocampus following aripiprazole compared with placebo ($T = 4.07$, $p = 0.057$). These differences in hippocampal rCBF after both antipsychotics were no longer evident (haloperidol) or present at trend level (aripiprazole), after controlling for cortisol and IL-6 levels. Our findings suggest that haloperidol can directly regulate the hypothalamic-pituitary-adrenal (HPA) axis and immune system through a pharmacological action via D2 receptor antagonism. Finally, our data suggest that the increased hippocampal rCBF is a manifestation of the reduction in IL-6 and cortisol which follows the administration of haloperidol.

1. Introduction

Over the past few decades, an increasing number of studies have reported a hyper-activation of the hypothalamic-pituitary-adrenal (HPA) axis and of the immune system in patients with psychosis. These two biological systems are responsible for the main brain and behavioural changes occurring in response to stress, as well as for our defence against external pathogens. Of note, both the HPA axis and the immune system have been shown to contribute to some of the abnormalities in brain structure and function found at psychosis onset (Borges et al., 2013; Mondelli et al., 2011; Zajkowska and Mondelli, 2014), and have been proposed as optimal targets for developing new treatments for psychosis. However, it remains unclear if and how HPA axis and the immune system are affected by antipsychotic medications, and indeed if the effect of antipsychotics on the brain is partly mediated by the modulation of these biological systems.

Elevated levels of cortisol, the final hormone produced by the activation of the HPA axis, and of inflammatory markers, such interleukin (IL)-6, have been consistently shown in subjects with psychosis (even prior to treatment) and in non-psychotic at-risk individuals, indicating that the activation of these biological systems partly predate the onset of psychosis (Aiello et al., 2012; Borges et al., 2013). A dysregulation of these systems may result from prolonged exposure to psychosocial stress, and represent the biological mediator underpinning the relationship between stressful events (for example in childhood) and the development of psychotic symptoms (Walker and Diforio, 1997).

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http://dx.doi.org/10.1016/j.schres.2016.03.039

Although the mechanisms through which increased HPA axis activity and inflammation lead to the onset of psychotic symptoms remain unknown, multiple pathways modulating monoaminergic systems and synaptic plasticity have been proposed. Interestingly, both cortisol and IL-6 directly interact with the hippocampus, a brain region consistently reported as altered in structure, function and activity in psychosis (Tamminga et al., 2010), suggesting that stress hormones and pro-inflammatory markers play a key role in mediating some of the key physiological brain changes observed in this condition. Indeed, elevated levels of both cortisol and IL-6 have been related with smaller hippocampal volumes in healthy subjects, as well as in subjects with first episode psychosis (Marsland et al., 2008; Mondelli et al., 2011).

We have previously reported that some of the structural and functional brain changes observed in psychosis are related to antipsychotic treatment (Dazzan et al., 2005; Goozee et al., 2015; Navari and Dazzan, 2009), and that the mechanisms underpinning these changes might partly depend on alterations in resting cerebral blood flow (rCBF) (Goozee et al., 2014; Handley et al., 2013). In particular, in a previous study in healthy volunteers, we showed that a single dose of either haloperidol or aripiprazole affects rCBF in the same brain regions which have been reported as structurally and functionally altered in psychosis (Handley et al., 2013). However, the mechanisms through which antipsychotic treatment affects rCBF remain unclear. Only very few human studies have linked cerebral perfusion and cortisol levels, with most data coming from animal studies. Interestingly, increased CBF in hippocampus (and to a lesser degree in the prefrontal cortex) has been described in adrenalectomized rats (Endo et al., 1994), while reduced hippocampal rCBF has been reported after 12 weeks of corticosterone administration (Endo et al., 1997) or a similar period of stress exposure in rats (Endo et al., 1999). Similarly, studies in humans mostly report an inverse correlation between cortisol levels and cerebral perfusion in the medial temporal lobe and anterior cingulate cortex (Bonne et al., 2003; Hodkinson et al., 2014). Furthermore, the inflammatory cytokine IL-6 has been reported as a potent vasoconstrictor (Tarkowski et al., 1995) and antibodies against IL-6 attenuate post-hemorrhagic vasospasm (Bowman et al., 2004), possibly leading to a decrease in cerebral perfusion.

Evidence from our and other groups suggests that the levels of both cortisol and IL-6 are affected by antipsychotic medications, which possibly re-establish 'normal' levels of these biomarkers and their regulatory processes (Miller et al., 2011; Mondelli et al., 2010a). However, it remains unclear whether this reflects a direct effect of these drugs on the stress response system, or rather an indirect effect of the amelioration of psychotic symptoms induced by these drugs. Furthermore, it is yet to be established whether antipsychotics with different pharmacological profiles affect these stress response markers, and any potentially associated brain change, differently.

Both first (FGA) and second (SGA) generation antipsychotics have been associated with cortisol changes in patients with psychosis, but increasing evidence suggests that SGAs reduce cortisol to a greater extent than FGAs (Jakovljevic et al., 2007; Popovic et al., 2007; Tanaka et al., 2008; Zhang et al., 2005). Most direct comparisons of the effects of FGAs and SGAs on stress markers have been conducted in patient populations, with only one study conducted in a small sample of healthy volunteers (Cohrs et al., 2006). This study demonstrated no effect of the dopaminergic antagonist haloperidol on cortisol levels, and a reduction on cortisol levels induced by SGA antipsychotics like quetiapine and risperidone. The effect of SGAs on cortisol has been suggested to reflect differences in affinity and occupancy at the D2 and 5-HT receptor subtypes (Meltzer, 1989).

Data on the effects of antipsychotics on IL-6 appear less consistent (Baumeister et al., 2016). For example, in patients, FGAs and SGAs have been found to increase, reduce or have no effect on IL-6 levels (Maes et al., 1995; Tourjman et al., 2013; Zhang et al., 2005). Two recent meta-analyses also reported conflicting results, indicating no significant effect of antipsychotic treatment on IL-6 (Tourjman et al., 2013) in one study, and a reduction of IL-6 after antipsychotic treatment in another (Miller et al., 2011). In one in vitro investigation in healthy females, IL-6 levels remained unchanged after both first and second generation antipsychotics (Himmerich et al., 2011). However, to the best of our knowledge, the effects of FGA or SGAs on IL-6 in healthy volunteers (in vivo) have never been investigated. Furthermore, no evidence exists, from either patients or healthy individuals, on the effects of a "third" generation antipsychotic such as aripiprazole on cortisol or IL-6.

Given that antipsychotics directly affect cortisol and IL-6, and that there is an association between these markers and cerebral blood flow, it is possible that the effect of antipsychotics on brain structure and blood flow is partly mediated by these biomarkers. Understanding the differential effects of FGAs and SGAs will help clarify whether the level of antagonism at D2, or other neurotransmitter receptors, such as the serotonin, are important in regulating cortisol and IL-6 levels, and whether these biomarkers mediate the drug-induced changes evident in hippocampal rCBF.

This study compared the effects of two antipsychotics with very different mechanisms of action: haloperidol, a strong D2 receptor antagonist with comparatively lower affinity for other receptors, such as serotonin 5-HT2 (Meltzer, 1989), and aripiprazole, a partial D2 and 5HT1A receptor agonist with a lower affinity for the serotonin 5-HT2A than for the dopamine D2 receptor subtype (Mamo et al., 2007). We compared the effects of a single dose of these two drugs on cortisol, IL-6 and hippocampal rCBF in the same healthy individuals in comparison with placebo. This is the first investigation of aripiprazole and haloperidol (in vivo) effects on cortisol and IL-6. Moreover, it is the only exploration of the effects of different antipsychotics on cortisol, IL-6 and hippocampal perfusion in the same individuals. Amongst the various pro-inflammatory cytokines which have been reported increased in psychosis, we focussed in particular on IL-6 as this remains the main pro-inflammatory cytokine which has been reported as elevated in patients with psychosis, and as being linked to activation of the HPA axis. We hypothesised that i) aripiprazole but not haloperidol would reduce cortisol; ii) both antipsychotics would reduce IL-6 levels and iii) reductions in these biomarkers would account for some of the rCBF change evident in the hippocampus following administration of these antipsychotics.

2. Methods

Seventeen healthy right-handed English speaking Caucasian males, aged 18 to 32 (mean 22 years, SD 4.1) provided salivary cortisol samples across the day and underwent a brain scan for the investigation of resting blood flow (rCBF). Twelve of them also provided blood samples for the measurement of IL-6 levels. Mean body mass index was within the normal range (mean 23.5, SD 3.7). Participants were non-smoking, university students with no recent or current drug or medication use and had no exposure to psychotropic medication, or history of personal or familial psychiatric diagnosis. The study was approved by the Human Research Ethics Committee of the Institute of Psychiatry, London, and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the experimental procedures was explained to them.

Subjects received a single dose of haloperidol (3 mg), aripiprazole (10 mg) and placebo, in a randomized order on three study appointments. A fully counterbalanced, randomized within-subject, double blinded cross-over design was used, ensuring neither participant or researcher were aware of the intervention administered on each appointment. Compounds were administered in identical capsules. Fourteen days minimum separated each study appointment to allow for drug washout. No alcohol or medications were used for 24 h, or caffeine for 6 h, prior to scanning.

Clinical side effects, measured using the Barnes Akathisia scale (Barnes, 1989), the Simpson Angus scale (Simpson and Angus, 1970), and the Abnormal Involuntary Movement Scale (AIMS: National Institute of Mental Health), were evaluated 3 hours post intervention.

Please cite this article as: Handley, R., et al., Effects of antipsychotics on cortisol, interleukin-6 and hippocampal perfusion in healthy volunteers, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.03.039