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Allostatic load is associated with psychotic symptoms and decreases with antipsychotic treatment in patients with schizophrenia and first-episode psychosis

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ABSTRACT

Current pathophysiological models of schizophrenia suggest that stress contributes to the etiology and trajectory of the disorder. We investigated if allostatic load (AL), an integrative index of neuroendocrine, immune and metabolic dysregulation in response to chronic stress, is elevated in patients with schizophrenia (SCZ) and first-episode psychosis (FEP) and related to psychotic symptoms and social and occupational functioning. Additionally, we assessed the temporal dynamics of AL in response to treatment with second-generation antipsychotics. AL, psychotic symptoms and psychosocial functioning were assessed in a longitudinal design in patients with SCZ (n = 28), FEP (n = 28), and healthy controls (n = 53) at baseline and 6 and 12 weeks after commencement of antipsychotic therapy. AL at baseline was higher in patients with SCZ and FEP relative to controls, but not different between patients with SCZ and FEP. Adjusting for age and smoking, we found that positive symptoms were positively correlated with AL and psychosocial functioning was negatively correlated with AL at trend level. Linear mixed model analysis demonstrated that AL decreased after treatment was commenced in patients with SCZ and FEP between the baseline assessment and the 6 and 12-week follow-up. AL was not predictive of treatment response or symptomatic remission. Our data provide evidence for cumulative physiological dysregulation in patients with SCZ and FEP that is linked to the experience of current positive psychotic symptoms. AL could be a useful tool to monitor biological signatures related to chronic stress and unhealthy behaviors in schizophrenia.

1. Introduction

A large body of studies supports the notion that chronic experiences of chronic stress and malfunctioning of the biological stress response are associated with the onset and progression of psychotic disorders (Howes and Murray, 2014; Moghaddam, 2002). This is evidenced by findings of dysregulations of the stress hormone cortisol in patients with psychotic disorders (Berger et al., 2016; Girshkin et al., 2014). Observations that stressful life events can trigger and/or worsen psychotic symptoms lend support to a causative role of stress processes (Reininghaus et al., 2016). The stressful experience of psychosis itself in turn can activate the body's stress systems, thus contributing further to physiological dysregulation. Recently, these observations have reshaped pathophysiological theories of the disorder and have contributed to contemporary reconceptualizations of psychosis (Davis et al., 2016; Owen et al., 2016).

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The allostatic load (AL) model is a framework aimed at understanding stress pathophysiology by encompassing a range of physiological systems (McEwen and Stellar, 1993). AL is measured by indexing neuroendocrine, immune, metabolic and cardiovascular dysregulation. AL algorithms characterize subtle pathogenic deviations of peripheral biomarkers involved in chronic adaptation to situational demands (McEwen, 1998; McEwen and Gianaros, 2010). Unlike homeostasis, which describes precise regulation of physiological parameters within a narrow range, allostasis refers to dynamic adaptation in response to external stimuli such as stressful life events. Central to these processes is the brain that mediates biobehavioral adaptations (McEwen, 1998). Within the AL framework, environmental stressors induce the release of primary mediators such as cortisol that over time lead to primary effects including elevations of pro-inflammatory cytokines, oxidative stress or mitochondrial dysfunction (Juster et al., 2010; Picard et al., 2014). These then contribute to damaging effects to the CNS and other organs, including altered gene expression, telomere shortening and ultimately affect blood pressure, lipid metabolism, cognition and neurodegeneration (Juster et al., 2010; Picard et al., 2014). Thus, chronic or repeated exposure to stress is believed to cause elevated AL in the long term and elevated AL in turn has been shown to predict adverse health indicators. For example, longitudinal studies demonstrate that high AL is associated with all-cause mortality and cognitive decline (Seeman et al., 2001) and reductions in AL are conversely associated with reductions in mortality (Karlamangla et al., 2006).

Elevated levels of AL primary mediators and primary effects are frequently observed in patients with psychotic disorders (Berger et al., 2016; Bizik et al., 2013; Fillman et al., 2014; Goldsmith et al., 2016; Misiak et al., 2014; Schwarz et al., 2012b). This suggests that AL may be elevated in patients with SCZ. In accordance, a recent study found increased AL in a small sample of patients with chronic SCZ that was related to positive symptoms and impaired functional capacity (Nugent et al., 2015). AL may contribute to the excess mortality observed in patients with SCZ (Saha et al., 2007) and possibly to the pathophysiology of the disorder, given that AL entails heightened levels of pro-inflammatory cytokines, glucocorticoids and oxidative and metabolic stress (Juster et al., 2010; McEwen, 1998).

Collectively, pathogenic AL processes are known to have damaging effects on the brain, including regions that are important to the etiopathogenesis of psychotic disorders, such as the hippocampus and the prefrontal cortex (Booth et al., 2014; McEwen, 1998, 2000; Zierhut et al., 2013a; Zierhut et al., 2013b). Psychotic disorders on the other hand may contribute to heightened allostatic load through stress-mediated release of glucocorticoids and sympathetic activation, but also through unhealthy lifestyle factors associated with psychotic disorders such as smoking and through the metabolic side effects of antipsychotic medication. While it is unknown if AL is a risk for or the consequence of psychosis, AL and psychopathology may mutually sustain each other in a bi-directional fashion through the above mechanisms.

Given its associations with adverse health outcomes, the AL model may be helpful in detecting multisystem dysfunction of and risk for physiological comorbidities in severe mental illness that commonly accompany psychotic disorders. Beyond associations of AL with adverse physical health outcomes, the multisystem dysregulation encompassed by the AL framework might also contribute to the progression of severe mental illnesses (Berk et al., 2011; Kapczinski et al., 2016). This is relevant, as biomarkers are urgently needed for current attempts at staging in psychiatry (Kupfer et al., 2015). This concept proposes that it is possible to differentiate illness stages based on clinical characteristics and biological phenotypes. Although no study to date has directly addressed the question of whether AL is related to the staging and neuroprogression frameworks, one study in a small sample of patients with bipolar disorder used a 'systemic toxicity index' that was conceptually similar to AL and observed higher systemic toxicity in patients with acute mania or dysthymia but not in euthymic patients (Kapczinski et al., 2010).

The aims of the present study were twofold. First, we aimed to test whether AL is elevated in unmedicated patients with SCZ relative to healthy controls and predictive of clinically relevant outcomes. Second, we aimed to study dynamic changes in AL in patients with SCZ. We hypothesized that AL would be associated with disease severity in patients with psychosis. Specifically, AL would be higher in patients with SCZ relative to patients with first-episode psychosis (FEP) and healthy controls and elevations in AL would be related to the duration of psychosis. We also hypothesized that AL would be associated with clinical symptoms and psychosocial functioning, predictive of treatment response to second-generation antipsychotic medication and associated with symptomatic remission.

2. Methods

2.1. Study design

Data for this study came from a blood bank of patients with schizophrenia, first-episode psychosis and healthy controls at the Department of Psychiatry, University of Magdeburg, Germany (Steiner et al., 2013). The biospecimens used in this study were collected in a naturalistic study of acutely ill in-patients who were un-medicated for at least 6 weeks prior to inclusion into the study. AL and relevant psychometric variables were assessed at baseline and 6 and 12 weeks later. All patients received second-generation antipsychotic medication after the baseline assessment.

Exclusion criteria were substance abuse disorder and/or psychosis induced by another medical condition. Patients with a history of immune diseases, immunomodulatory treatment, cancer, chronic terminal disease, cardiovascular disorders including hypertension, dyslipidemia, diabetes mellitus, substance abuse, severe trauma or clinical/paraclinical findings indicative of these disorders were excluded. Controls were screened for personal or family history of neuropsychiatric disorders. The study was approved by the institutional review board and written informed consent was obtained from all participants. Details concerning the study design have been published previously (Steiner et al., 2013).

2.2. Sample

Participants included 28 patients with schizophrenia, 28 patients with first-episode psychosis (26 with a final diagnosis of schizophrenia and 2 with a final diagnosis of schizoaffective disorder; mean duration of untreated psychosis = 7.3 months, standard deviation = 8.9 months) and 53 healthy controls were recruited into the present study (Table 1). All patients were acutely ill in-patients who were un-medicated for at least 6 weeks prior to inclusion into the study, and received one of the second-generation antipsychotics risperidone, olanzapine and quetiapine after inclusion into the study. Patients were recruited from all eligible consecutive admissions to the psychiatric inpatient unit between February 2008 and March 2010 who fulfilled all inclusion criteria and none of the exclusion criteria. Healthy controls were recruited from the community and consisted mainly of blood donors, tertiary students and hospital staff/their family members. Controls were screened for personal or family history of neuropsychiatric disorders using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

2.3. Psychometric assessments

Diagnoses were ascertained according to DSM-IV criteria with the Structured Clinical Interview (SCID-I). The Positive and Negative Symptoms Scale (PANSS) was used to assess psychotic symptoms (Kay et al., 1987). The Global Assessment of Functioning (GAF) scale was used to measure social, occupational and psychological functioning