

STRESS AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY IN FIRST EPISODE PSYCHOSIS

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Background: Hypothalamic-pituitary-adrenal (HPA) axis is the main biological system involved in the stress response. The aim of our study was to evaluate objective and subjective stress together with HPA axis activity in first-episode psychosis patients and healthy controls. **Methods:** We recruited 40 first-episode psychosis patients (mean \pm SEM age: 29.4 \pm 1.2 yrs; gender: 35% females) and 30 controls (mean age: 27.4 \pm 1.0 yrs; gender: 23.3% females) as part of the large Genetic And Psychosis (GAP) study, carried out in South London. Information about childhood trauma, recent stressful events and perceived stress were collected using validated schedules. Salivary cortisol was obtained at awakening, at 15, 30, and 60 minutes after awakening, and at 12 pm, and 8 pm. We calculated the Areas Under the Curve to investigate the cortisol levels during the day and the cortisol response to awakening. An independent t-test and was used to analyze differences in the stress variables and cortisol secretion. Correlation analyses were run to investigate the association between stress variables and cortisol secretion. **Results:** First-episode psychosis patients reported more childhood trauma, recent stressful events, and higher perceived stress compared with controls ($P < .001$). Patients showed no significant difference in cortisol levels during the day compared with controls ($P = .2$). However, patients showed a significantly lower cortisol awakening response than controls ($P = .034$). A positive correlation was found between number of recent stressors or perceived stress and cortisol during the day in controls ($r = .377$, $P = .04$ and $r = .321$, $P = .08$). In contrast, a negative correlation between number of recent stressors or perceived stress and cortisol during the day was found in patients ($r = -.413$, $P = .01$ and $r = -.356$, $P = .04$). **Conclusions:** Our data show that first episode psychosis patients have higher number of stressful events but similar cortisol levels during the day when compared with healthy controls. First episode psychosis patients have an impaired HPA axis response to stress as shown by the blunted cortisol response to awakening and by the negative correlation between measures of recent stress and cortisol secretion during the day. **Acknowledgement:** This research is funded by NARSAD Mental Health Research Association, British Academy, and NIHR Biomedical Research Centre Institute of Psychiatry (Kings' College London).
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INFLAMMATION MARKERS IN DRUG-NAÏVE FIRST EPISODE OF NON AFFECTIVE PSYCHOSIS PATIENTS.

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A subclinical inflammatory status has been described in schizophrenia, although this relationship might be confounded by antipsychotic treatment, which is associated with weight gain and an increased risk of diabetes. Studies of antipsychotic-naïve patients found an abnormal pulse pressure and an increased risk of diabetes, which are associated with inflammation. We hypothesized that an increase in pro-inflammatory molecules would be pres-

ent in schizophrenia and related disorders prior to antipsychotic treatment. We measured fasting blood concentrations of interleukin 6 (IL6) and C-reactive protein (CRP) in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. Patients were categorized into deficit ($N = 23$) and nondeficit ($N = 41$) groups. In a logistic regression model controlling for age, gender, body mass index, smoking, and socioeconomic status, deficit patients had significantly higher IL6 concentrations than did nondeficit patients. In a linear regression model controlling for the same potential confounders, there was no difference in CRP between deficit and nondeficit groups. These findings provide further evidence that patients with nonaffective psychosis have metabolic abnormalities prior to antipsychotic treatment, which may interact with antipsychotics to increase the risk of diabetes and cardiovascular disease. Our findings also provide further evidence that deficit and nondeficit schizophrenia have differing etiopathophysiology.
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IMPAIRED CORTICAL KYNURENINE PATHWAY METABOLISM IN SCHIZOPHRENIA: FOCUS ON KYNURENINE 3-MONOOXYGENASE

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The levels of kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation, are elevated in the prefrontal cortex of individuals with schizophrenia (SZ) (Biol. Psych., 50: 521, 2001), and this increase is unrelated to antipsychotic medication. Endogenous, ie, nanomolar, concentrations of KYNA, a preferential antagonist of $\alpha 7$ nicotinic acetylcholine and NMDA receptors, reduce the extracellular levels of glutamate and dopamine in the frontal cortex of experimental animals. Therefore, it is conceivable that increased brain levels of KYNA may play a role in the pathophysiology of SZ. We now determined the activity of the enzyme kynurenine 3-monooxygenase (KMO), which appears to control the tissue levels of KYNA, in the prefrontal cortex of patients and well-matched controls ($n = 15$ each), obtained from the Maryland Brain Collection. Compared to controls, KMO activity was reduced (-36% and -38% in Brodmann areas 9 and 10, respectively; $P < .05$ each) in SZ samples. In separate post-mortem samples, we screened microarray expression profiles of several kynurenine pathway genes in 32 frontal cortical tissues (16 from SZ patients) from Brodmann area 6, a cortical area related to eye movement deficits in patients and their relatives, and examined mRNA expression of KMO by RT-qPCR. KMO expression was significantly reduced in SZ ($P < .01$). Taken together, our data demonstrate a distinct, and possibly endophenotype-specific, impairment in cortical KP metabolism in SZ. Our results raise the possibility that the normalization of cortical KP metabolism may constitute a useful new treatment strategy in SZ.
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INFLAMMATORY MARKERS IN A PSYCHOTIC CHILDREN CLINICAL IMPLICATIONS FOR PROGNOSIS

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Human and animal studies have suggested an underlying inflammatory mechanism for a variety of neurological disorders, including schizophrenia. To date, all available reports have focused on adult patients with chronic schizophrenia. Knowledge of how inflammation affects the development of schizophrenia remains limited but several studies have identified