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Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women

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ABSTRACT

Background: Hyperprolactinemia is a known side effect of antipsychotics. In recent reports it has also been shown in antipsychotic-naïve at-risk mental state (ARMS) and first-episode psychosis (FEP) patients. Prolactin is not only involved in reproduction and lactation, but is also synthesized in response to stress. As stress is thought to play an important role in the onset and relapse of schizophrenia, the aim of this study was to further elucidate the influence of prolactin in emerging psychosis.
Methods: The data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen (***FePsy***) study. Blood sample collection took place under standardized conditions between 8 and 10 am after an overnight fast and 30 minutes of rest. All patients were antipsychotic-naïve and did not take any prolactin influencing medication.
Results: Our sample consisted of 116 antipsychotic-naïve ARMS and 49 FEP patients. Hyperprolactinemia was shown in 32% of ARMS and 35% of FEP patients. After correction for the normal biological variation between the sexes, we still found higher average prolactin levels in female than in male patients ($\beta = 0.42$; $t = 2.47$; $p = 0.01$) but no difference in prolactin levels between ARMS and FEP patients ($\beta = -0.05$; $t = -0.30$; $p = 0.76$). The survival analysis revealed no significant predictive value for prolactin levels to predict transition to psychosis.
Conclusion: Our findings support a possible role of prolactin in emerging psychosis and it could be speculated that stress, which can induce hyperprolactinemia, has a stronger effect on women than on men in emerging psychosis.

1. Introduction

Prolactin is a polypeptide hormone that is predominantly synthesized and secreted by lactotroph cells of the anterior pituitary gland. While its main function is to elicit lactation in mammals (Fitzgerald and Dinan, 2008), it is also involved in a broad spectrum of functions beyond reproduction and lactation. Most importantly, it is also released in response to psychosocial stress (Fitzgerald and Dinan, 2008; Lennartsson and Jonsdottir, 2011). There is compelling epidemiological evidence that psychosocial stress is implicated in the development of psychotic symptoms (Aiello et al., 2012; van Winkel et al., 2008). Previous research has shown an association between cortisol levels and severity of positive and nonspecific symptoms (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013), as well as correlations between the stress hormone prolactin and psychopathological symptoms (Rajkumar, 2014).

The main regulatory mechanism acting on prolactin is the inhibition of prolactin synthesis by dopamine. Dopamine itself is synthesized in neurons of the hypothalamus and then secreted through portal blood into the anterior pituitary where it exerts its inhibitory actions on prolactin-producing cells through D2 receptors. Dopamine is thus the main prolactin inhibiting factor (PIF) (Fitzgerald and Dinan, 2008). On the other hand, dopaminergic neurotransmission plays an important role in the pathophysiology of schizophrenic psychoses (Howes et al., 2009) which was inferred from the link between the antipsychotic efficacy of neuroleptic drugs and their affinity for the dopaminergic D2 receptor (Bennett, 1998). Hence, hyperprolactinemia is often described as a side effect of antipsychotics in patients with schizophrenic psychoses (Peuskens et al., 2014). However, there have also been recent reports on hyperprolactinemia in antipsychotic-naïve FEP and ARMS patients. Hyperprolactinemia in these patients could probably be explained by psychosocial stress (Riecher-Rössler et al., 2013), as it is implicated in the development of psychotic symptoms (van Winkel et al., 2008) and

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known to stimulate prolactin synthesis and release (Lennartsson and Jonsdottir, 2011). Riecher-Rössler et al. (2013) suggested that stress induces hyperprolactinemia and the resulting increase of dopamine in psychosis might be, at least in part, a regulatory mechanism to down regulate prolactin. The European First Episode Schizophrenia Trial (EUFEST) (Riecher-Rössler et al., 2013) found elevated prolactin levels in 40.5% of antipsychotic-naïve FEP patients. In a further study by Aston et al. (2010) hyperprolactinemia was found in 33.3% of antipsychotic-naïve FEP patients and even in 23.8% of ARMS patients. A recent meta-analysis (Gonzalez-Blanco et al., 2016) reported higher prolactin levels in antipsychotic-naïve male and female patients with schizophrenia compared to control groups of the same gender, although the effect was much more pronounced in men than in women. A recent study also found higher prolactin serum levels in drug naïve newly diagnosed patients with schizophrenia and other psychotic disorders compared to HC (Petrikis et al., 2016). Furthermore, Labad et al. (2015) showed that ARMS patients who later made a transition to psychosis (ARMS-T) had higher prolactin levels than those who did not (ARMS-NT). Moreover, one study conducted in patients with pituitary microadenoma (Cheng et al., 2013) showed significantly higher prolactin serum levels in antipsychotic-naïve patients with a pituitary microadenoma *with* psychosis than in patients with a pituitary microadenoma *without* psychosis. All these findings provide further evidence for an association of elevated prolactin levels and psychosis.

To further elucidate the role of prolactin in emerging psychosis we formulated the following hypotheses based on previous findings. We expected I) increased frequencies of hyperprolactinemia in ARMS and FEP patients (Aston et al., 2010), II) higher prolactin levels in FEP as compared to ARMS patients, and III) more elevated prolactin levels in men than in women (Gonzalez-Blanco et al., 2016). Moreover, as prolactin is also a stress hormone and stress is thought to have an influence on psychopathology (Aiello et al., 2012; Holtzman et al., 2013; Walker et al., 2013) we hypothesized to find IV) a positive association of prolactin with psychopathological symptoms and V) higher baseline prolactin levels being predictive of transition to psychosis in ARMS patients.

2. Methods

2.1. Setting and recruitment

The data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen **(*FePsy*)** study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). Participants were recruited for the study via the ***FePsy*** Clinic at the Psychiatric University Outpatient Department of the Psychiatric University Hospital Basel, which was set up specifically to identify and treat individuals in the early stages of emerging psychosis.

The study was approved by the ethics committee of the University of Basel and all participants provided written informed consent.

2.2. Screening procedure

Screening was performed with the Basel Screening Instrument for Psychosis (Riecher-Rössler et al., 2008). This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung et al., 2007; Yung et al., 1998) and has been shown to have a good interrater reliability ($\kappa = 0.67$) for the assessment of the main outcome category "at risk for psychosis" and a high predictive validity (Riecher-Rössler et al., 2008). Individuals were classified as being in an ARMS for psychosis, having a FEP, or being not at risk for psychosis (usually other psychiatric disorders).

For this study we included all ARMS and FEP patients that were recruited for the ***FePsy*** study from March 1, 2000 to February 29, 2016 who had undergone prolactin measurement. We excluded all patients who had ever taken antipsychotics or any prolactin-influencing medication at the time of assessment (i.e. hormonal contraception). Likewise, we excluded all patients with a medical condition potentially influencing prolactin status, such as hypothyroidism or pituitary abnormalities or in whom blood sampling and psychopathological assessment were >60 days apart.

All ARMS patients were followed-up at regular intervals for up to 5 years (in the first year monthly, second and third year 3-monthly and the last two years every year) (Riecher-Rössler et al., 2009) in order to distinguish those who later transitioned to frank psychosis (ARMS-T) from those who did not (ARMS-NT) using the transition criteria of Yung et al. (1998).

2.3. Prolactin measurement

The patients were asked to avoid stress, sports, physical activity, stimulation of breast and smoking during the last 12 h before blood sampling. Blood sample collection took place between 8 and 10 am after overnight fast and 30 min of rest (7.5 ml whole blood without any additions).

The **E**lectro**C**hemi**L**uminescence **I**mmuno**A**ssay "ECLIA" (Ref. Number 03203093 190, Roche Diagnostics GmbH D-68305 Mannheim) was used to measure prolactin levels. The method has been standardized against the 3rd IRP WHO Reference Standard 84/500 and hyperprolactinemia in this reference is defined as a value above the 97.5th percentile, that is >324 mU/l in men and >496 mU/l in women.

2.4. Psychopathological assessment

The Brief Psychiatric Rating Scale Expanded Version (BPRS-E) (Lukoff et al., 1986; Ventura et al., 1993) was used to assess positive psychotic symptoms, symptoms of depression/anxiety, negative symptoms as well as symptoms of activation as defined by Velligan et al. (2005).

2.5. Statistical analyses

All data were analysed using the R environment for statistical computing (R Core Team, 2015). Differences in sociodemographic and clinical characteristics between ARMS and FEP patients were tested with *t* and χ^2 tests. Prolactin was analysed both on a continuous and binary scale (above reference range of corresponding sex vs. within normal range) using linear and logistic regression models, respectively. In both models, prolactin served as dependent variable and group (ARMS vs. FEP) and sex (men, women) as independent variables. The models also included an interaction term between group and sex. When analysed on a continuous scale, prolactin values were first log-transformed (to accommodate positive skew) and then normalized for men and women separately based on the log transformed reference ranges for healthy men and women. The means and SDs of the log transformed normative samples for men and women were calculated by taking the means of log transformed upper and lower bounds of the reference ranges and by dividing the differences between log transformed upper and lower bounds of the reference ranges by 3.92, respectively. Thus, the normal sex difference in prolactin seen in healthy individuals was partialled out from our continuous prolactin measure before inclusion to the models.

To analyse the relationship between prolactin, group (ARMS, FEP) and psychopathology, linear regression models were performed with the four BPRS composite scores (see psychopathological assessment) serving as dependent variables. All continuous variables were centered and all analyses were performed with and without covariates (age and current use of antidepressants). Furthermore, *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

Finally, to test whether prolactin is predictive of later transition to psychosis (event) in the ARMS group and whether its association with

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