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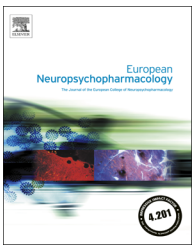

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IGF-I in major depression and antidepressant treatment response

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Abstract
We analyzed insulin-like growth factor I (IGF-I) in serum of 78 inpatients with depression and 92 healthy controls. Patients were selected according to remission status after 6 weeks of antidepressant treatment with remission defined by Hamilton depression rating scale (HAM-D) 21-item score <10 (39 remitters and 39 non-remitters).
IGF-I was analyzed in patients at admission and after 6 weeks of psychopharmacological treatment. IGF-I levels were compared between patients and controls and between remitters and non-remitters with general linear model using age, gender, and body mass index as covariates.
In patients, IGF-I levels were significantly higher at admission ($p=3.29E-04$) and in week 6 ($p=0.002$) compared to controls. Furthermore, non-remitters showed significantly higher IGF-I levels at admission ($p=0.046$) and a trend for higher IGF-I levels in week 6 ($p=0.11$) compared to remitters. In remitters change in IGF-I levels during treatment was significantly correlated with change in cortisol levels ($p=0.019$).
A genetic association analysis of polymorphisms in 10 genes contributing to the IGF-I system (IGF1, IGF1R, IGFBP1 to IGFBP7, and IGFBPL1) in the currently largest genetic databases for major depression (Psychiatric Genomics Consortium) revealed nominal associations with susceptibility for depression and treatment response, although results did not remain significant after multiple testing correction.

Abbreviations: ACTH, adrenocorticotropic hormone; AD, antidepressant; BMI, body mass index; FOXO3, forkhead-box-protein O3; GENDEP project, Genome-Based Therapeutic Drugs for Depression project; GH, growth hormone; HAM-D, Hamilton depression rating scale; 11ß-HSD, 11ß-hydroxysteroid dehydrogenase; HPA-axis, hypothalamus-pituitary-adrenal-axis; IGF-I, insulin-like growth factor I; IGF1R, IGF-I receptor; IGFBP, IGF-I binding protein; IGFBPL1, IGF binding protein-like 1; kb, kilobase; MARS, Munich Antidepressant Response Signature; PGC, Psychiatric Genomics Consortium; RPA, replication protein A; SNP, single nucleotide polymorphism; SNRI, serotonin-norepinephrine reuptake inhibitor; SPOCK2, sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 2; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TCA, tricyclic antidepressant.

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In our study, elevated IGF-I levels were significantly associated with depression and impaired treatment response. Based on these findings IGF-I signaling could play a role in the pathophysiology of depression and could possibly influence the response to antidepressant treatment.

1. Introduction

In patients with depression, several neuroendocrine disturbances have been described. It is well known that the dysfunction of the hypothalamus-pituitary-adrenal-axis (HPA-axis) plays a functional role in depression (Bonfiglio et al., 2011; Holsboer, 2000). Mostly, hypercortisolism can be observed in depressive patients (Wolkowitz et al., 2009). Since the corticotropic axis is connected to the somatotropic axis (Unterman et al., 1993), disturbances in the regulation of somatotropic hormones could play a role in depressive disorders.

IGF-I as a mediator of the somatotropic axis is able to cross the blood-brain-barrier (Reinhardt and Bondy, 1994). Additionally, IGF-I is known to be produced in the brain itself (Torres-Aleman, 2010), and is supposed to influence mood regulation (Sievers et al., 2008). Only a few small studies on IGF-I in depressed patients have been published so far: Lesch et al. (1988) reported elevated IGF-I levels in 34 patients with major depression. Deuschle et al. (1997) studied 24 severly depressed patients and 33 healthy controls observing that IGF-I levels were higher in depressed patients and decreased during response to antidepressant treatment. According to Weber-Hamann et al. (2009), total IGF-I was shown to correlate with HPA axis function but free IGF-I was not altered in treatment responders. In contrast, Schilling et al. (2011) demonstrated that IGF-I levels increased in the cerebrospinal fluid during treatment with antidepressants in 11 from a total of 12 patients.

In order to elucidate the role of IGF-I in depression and antidepressant treatment response, we examined IGF-I levels in patients with depression participating in the Munich Antidepressant Response Signature (MARS) project and compared IGF-I levels in patients and healthy controls. To elucidate IGF-I with regard to treatment response, IGF-I levels were compared in remitters and non-remitters at admission and after 6 weeks of treatment.

Additionally, 10 genes constituting the IGF-I system were analyzed in the to date largest genome-wide association datasets (Psychiatric Genomics Consortium (PGC); https://pgc.unc.edu/) for major depression and antidepressant treatment response to elucidate possible genetic mechanisms of IGF-I related genes in depression and antidepressant treatment response.

2. Experimental procedures

2.1. Participants

Inpatients suffering from a depressive episode were selected from the Munich Antidepressant Response Signature (MARS) project (www.mars-depression.de), an ongoing observational study designed to identify predictive factors for antidepressant response. All included individuals were Europeans of Caucasian descent. Study details have been described previously (Hennings et al., 2009).

88 depressed patients and 96 psychiatric healthy controls (details previously described by Kohli et al. (2011)) were selected for IGF-I level analyses. Controls and patients were matched for age and gender. Patients were selected according to their remission status after 6 weeks of antidepressant treatment with remission defined as a Hamilton depression rating scale (HAM-D) 21-item score <10 following previous reports from the MARS study (Zobel et al., 2001; Binder et al., 2004; Horstmann et al., 2010) and other studies (Mehtonen et al., 2000; Wiethoff et al., 2010). HAM-D ratings were assessed by trained raters at admission and weekly intervals.

As IGF-I concentrations and IGF-I assays are affected by multiple variables (Clemmons, 2011), we excluded subjects with body mass index (BMI) <16 kg/m^2 or >40 kg/m^2, diabetes mellitus or treatment with oral estrogens. Additionally, patients with HAM-D 21-item scores <13 at admission were excluded from the analysis. Patients suffering from any serious physical illness have not been included in the study. After applying these criteria, 78 depressed patients ($n=39$ remitters and $n=39$ non-remitters) and 92 controls remained for further analyses.

At study entry 16.7% of patients received no actual antidepressant medication, 52.6% received one antidepressant (AD monotherapy), and 21.8% patients were treated with antipsychotic co-medication. 15.4% of patients showed treatment resistance (not responding to two or more sufficient AD treatment attempts) during the current depressive episode (see Table 1).

During the study period, 67.9% of patients were treated with one antidepressant (AD monotherapy) for 5 or more weeks and 25.6% received an augmentation with antipsychotics (see Table 1).

Remitters and non-remitters showed no significant difference in disease duration, previous episodes, treatment resistance, and medication at study entry or medication during the study, except for benzodiazepines, which were more often additionally administered in the non-remitter group for 5 or more weeks (see Table 1). IGF-I levels at baseline were not associated with psychopharmacological treatment at admission (ADs, antipsychotics). Further and detailed subject characteristics are shown in Table 1.

All subjects gave informed written consent. The study was approved by the local ethics committee of the Ludwig Maximilians University in Munich and was carried out according to the Declaration of Helsinki.

2.2. IGF-I and cortisol measurements

In patients, IGF-I levels and cortisol levels were measured in the morning under fasting conditions. Blood was drawn by a venous puncture at 8.00 a.m. IGF-I levels and cortisol levels