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Plasma insulin-like growth factor I levels are higher in depressive and anxiety disorders, but lower in antidepressant medication users

Mariska Bot[a,*], Yuri Milaneschi[a], Brenda W.J.H. Penninx[a], Madeleine L. Drent[b]

[a] VU University Medical Center and GGZ inGeest, Department of Psychiatry, EMGO Institute for Health and Care Research, Amsterdam, The Netherlands
[b] VU University Medical Center, Department of Internal Medicine, Endocrine Section, Department of Clinical Neuropsychology, Faculty of Psychology and Education, VU University, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

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ABSTRACT

It has been postulated that many peripheral and (neuro)biological systems are involved in psychiatric disorders such as depression. Some studies found associations of depression and antidepressant treatment with insulin-like growth factor 1 (IGF-I) – a pleiotropic hormone affecting neuronal growth, survival and plasticity – but evidence is mixed. We therefore studied whether depressive and anxiety disorders were associated with plasma IGF-I, and explored the role of antidepressant medication in this association in a large observational study.

The sample consisted of 2714 participants enrolled in The Netherlands Study of Depression and Anxiety, classified as healthy controls (n = 602), antidepressant users (76 remitted and 571 with current depressive and/or anxiety disorder(s), n = 647), persons having remitted depressive and/or anxiety disorder(s) without antidepressant use (n = 502), and persons having current depressive and/or anxiety disorder(s) without antidepressant use (n = 963). Associations with IGF-I concentrations were studied and adjusted for socio-demographic, health, and lifestyle variables.

Relative to healthy controls, antidepressant-free individuals with current disorders had significantly higher IGF-I levels (Cohen's d = 0.08, p = 0.006), whereas antidepressant-free individuals with remitted disorders had a trend towards higher IGF-I levels (d = 0.06, p = 0.09). Associations were evident for depressive and for anxiety disorders. In contrast, antidepressant users had significantly lower IGF-I levels compared to healthy controls (d = −0.08, p = 0.028).

Our findings suggests that antidepressant medication use modifies the association between depressive/anxiety disorders and plasma IGF-I. These results corroborate with findings of some previous small-scale case-control and intervention studies. The higher IGF-I levels related to depression and anxiety might point to a compensatory mechanism to counterbalance the impaired neurogenesis, although future studies are needed to support this hypothesis.

1. Introduction

Insulin-like growth factor 1 (IGF-I), a hormone that is mainly produced by the liver upon stimulation by growth hormone, has pivotal roles in somatic growth and metabolism. IGF-I is produced throughout life, with the highest circulating levels during adolescence and a subsequent progressive decline over time. Apart from its anabolic peripheral roles, IGF-I has profound central actions and is an acknowledged neurotrophic factor and stimulates neuronal growth, survival and plasticity throughout the lifespan (Aberg et al., 2000; Torres-Aleman, 2000). IGF-I and its receptors are widely expressed in the brain (Fernandez and Torres-Aleman, 2012) and studies indicate that peripheral IGF-I can be transported across the blood-brain barrier (Armstrong et al., 2000; Pan and Kastin, 2000).

Accumulating evidence suggests that neuroplasticity and neurogenesis is disrupted in major depressive disorder (MDD) (Pittenger and Duman, 2008). MDD is a prevalent (lifetime prevalence: 17%), burdensome psychiatric disorder with a complex pathophysiology with central as well as peripheral dysregulations (Kessler and Wang, 2008). It has been postulated that reduced adult hippocampal neurogenesis may be an underlying mechanism in the etiology of MDD, and that efficacy of antidepressants depends on the upregulation of hippocampal neurogenesis (Eisch and Petrik, 2012). Several neurotrophic factors and growth factors involved in neuronal growth, differentiation, maturation and survival have been linked to MDD (Duman, 2004). Of these, brain-derived neurotrophic factor (BDNF) is the most extensively investigated marker

* Corresponding author at: VU University Medical Center, Department of Psychiatry, AJ Ernststraat 1187, 1081 HL Amsterdam, The Netherlands.
E-mail address: m.bot@ggzingeest.nl (M. Bot).

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in relation to MDD, but IGF-I has also attracted research attention. In adult mice that overexpress IGF-I, rates of hippocampal neurogenesis were increased (O'Kusky et al., 2000). Also, peripheral injections of IGF-I induced neurogenesis on hippocampal progenitors in adult rats (Aberg et al., 2000). Furthermore, the formation of new neurons in the adult hippocampus is thought to be involved in learning and memory, and there is meta-analytic evidence that better cognitive function (e.g. mental process speed, spatial memory, and information processing speed) is related to higher IGF-I levels in healthy elderly (Arwert et al., 2005). Impairments of cognitive functions are frequently reported in persons with MDD (Trivedi and Greer, 2014). Furthermore, studies report associations of IGF-I with pro-inflammatory cytokines (O'Connor et al., 2008) and increased hypothalamic-pituitary-adrenal (HPA)-axis activity (Weber-Hamann et al., 2009), which both have been implicated in the pathogenesis of MDD (Miller et al., 2009; Stetler and Miller, 2011). Taken together, IGF-I could potentially be considered as a marker contributing to the pathophysiology of MDD (Szczesny et al., 2013).

Several studies provide evidence for an association of IGF-I with depression. Experimental studies in rats and mice generally show that increasing IGF-I, either centrally (Hoshaw et al., 2005; Malberg et al., 2007) and peripherally (Duman et al., 2009), results in increased mobility in forced swim tests (Duman et al., 2009, Hoshaw et al., 2005) and tail suspension tests (Malberg et al., 2007). Increased mobility might be indicative of reduced depressive behavior, however, these animal models have been criticized as they measure behavior in acute stress situations rather than depression (Molendijk and de Kloet, 2015). Studies on the association between IGF-I and depression in humans showed very mixed results. Both growth hormone deficiency and acromegaly – two conditions characterized by disturbed growth hormone and IGF-I levels – are associated with poorer mental health (Rosen et al., 1994; Sievers et al., 2009). In line with the hypothesized role of IGF-I in neuronal growth, survival and plasticity, a previous study found that low IGF-I levels were related to depression onset in women (Sievers et al., 2014). For the male participants, however, high IGF-I levels were associated with the onset of depression (Sievers et al., 2014). Another study found distinct associations with IGF-I and depressive symptoms for older males versus females (van Varsseveld et al., 2015). Other studies found higher serum IGF-I levels in depressed patients compared to controls (Deuschle et al., 1997; Franz et al., 1999; Kopczak et al., 2015), whereas some found no cross-sectional association between IGF-I and depression (Lin et al., 2014; Sievers et al., 2014), or in women only (Emeny et al., 2014). These higher IGF-I levels in depression could potentially point to a compensatory mechanism to counterbalance the impaired neurogenesis (Kopczak et al., 2015). In addition, most studies in humans did not investigate the influence of antidepressant medication, or had conflicting findings, with studies showing either decreased levels of serum IGF-I (Deuschle et al., 1997; Kopczak et al., 2015; Weber-Hamann et al., 2009) or increased levels of cerebrospinal fluid IGF-I (Schilling et al., 2011) after antidepressant medication use. Moreover, previous studies are either limited by the small sample sizes [<100 participants, (Deuschle et al., 1997; Franz et al., 1999; Lin et al., 2014); <100 patients (Kopczak et al., 2015)], or use of self-reported instruments rather than clinical interviews to assess the presence of psychiatric disorders (Emeny et al., 2014; Sievers et al., 2014; van Varsseveld et al., 2015). Finally, the association between IGF-I and anxiety disorders in humans has not been investigated, but given the high comorbidity between depressive and anxiety disorders and partial overlap in symptoms (Lamers et al., 2011), it is important to study this as well. Because of the limitations and conflicting findings of previous studies in humans, the objective of this study is to investigate the relationship between depressive and anxiety disorders with plasma IGF-I levels in a large well-characterized psychiatric cohort study (n = 2714, with 1534 persons having a current depressive and/or anxiety disorder). Our second objective was to investigate the role of antidepressant medication in this relationship.

2. Materials and methods

Netherlands Study of Depression and Anxiety (NESDA) is an ongoing longitudinal cohort study on predictors, course and consequences of depressive and anxiety disorders (Penninx et al., 2008). The NESDA sample consists of 2981 participants aged 18–65 years, comprising persons with no depressive or anxiety disorder, persons who have had a disorder in the past, and persons with a current depressive and/or anxiety disorder. To represent the various stages of the depression and anxiety psychopathology, individuals were recruited from the general population (n = 564), primary care (n = 1610), and specialized mental health care (n = 807). Exclusion criteria were (1) a primary clinical diagnosis of a psychiatric disorder not under study in NESDA (psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder), and (2) not being fluent in Dutch. Between September 2004 and February 2007, all participants completed the 4-h baseline assessment at one of the research centers, which included face-to-face interviews, written questionnaires, and biological measurements. The research protocol was approved by the Ethical Committee of the participating centers, and all participants provided written informed consent. The present cross-sectional study was based on the baseline assessment.

2.1. Depression and anxiety

During the baseline interview, the presence of depressive disorder (major depressive disorder, dysthymia) and anxiety disorder (generalized anxiety disorder, social phobia, panic disorder, agoraphobia) was ascertained using the Composite Interview Diagnostic Instrument (CIDI) version 2.1 according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. The CIDI was administered by specially trained research staff and is a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994). We distinguished healthy controls (no lifetime psychiatric diagnosis, no antidepressant use), individuals with remitted (lifetime but not in the past 6 months) disorders, and individuals with current (in the past 6 months) disorders. In addition, as a secondary psychopathological measure, the severity of depression and anxiety was measured in all participants using the 30-item self-reported Inventory of depressive symptomatology (Rush et al., 1996) and the 21-item self-reported Beck Anxiety Inventory (Beck et al., 1988), respectively.

Furthermore, participants were asked to bring their medication containers to the visit. Antidepressant (AD) medication taken on a regular basis (at least 50% of the time in the past month) was classified using the World Health Organization Anatomical Therapeutic Chemical classification system codes as tricyclic antidepressants (TCA; N06AA), selective serotonin reuptake inhibitors (SSRI; N06AB), and other antidepressants (N06AX, N06AF, N06AG) (World Health Organization Collaboration Centre for Drug Statistics Methodology, 2007). To be able to study a potential dose-response relationship, derived daily doses were calculated by dividing the participant's mean daily dose by the defined daily dose (DDD) of the World Health Organization. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Derived daily doses exceeding 10 times the DDD, or less than 0.1 times the DDD were set on missing as these were considered very unlikely.