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Associations of plasma leptin to clinical manifestations in reproductive aged female patients with panic disorder

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ABSTRACT

Preclinical studies suggest the implication of the adipocyte hormone leptin in anxiety and fear processes. We explored for potential differences regarding plasma leptin, cortisol and the ratio leptin/Body Mass Index (BMI) between 27 medication-free female patients with Panic Disorder (PD) and 42 age-matched female controls, and for potential associations between plasma leptin and psychometric evaluations including number of panic attacks during last week, Clinical Global Impression-Severity of Illness (CGI-S) and Symptoms Checklist-90-Revised (SCL-90-R). Cortisol levels showed no differences between patients and controls, or correlations to leptin or to any clinical features. Both groups demonstrated a strong positive correlation between leptin and BMI and similar leptin and leptin/BMI, despite patients' lower BMI. However, patients –but not controls- demonstrated significant negative correlations of leptin to the 'somatization', 'anxiety', and 'phobic anxiety' SCL-90-R subscales. Moreover, there was a significant negative correlation of leptin and of leptin/BMI ratio to the number of panic attacks during last week, while higher CGI-S was associated with lower leptin/BMI ratio. Our results, limited to PD female patients, suggest that lower leptin serum levels are significantly associated with greater severity of psychopathological manifestations, including number of panic attacks, symptoms of somatization, anxiety and phobic anxiety and overall clinical presentation.

1. Introduction

Leptin, a peptide hormone produced primarily by white adipose tissue, was first identified as the hormone that signals the status of fat stores to hypothalamus to control energy homeostasis through the regulation of feeding behavior and energy expenditure (Zhang et al., 1994; Elmquist et al., 1998; Chan et al., 2003). Subsequent research revealed that leptin receptors are widely expressed in limbic and other brain structures and in peripheral tissues (Mercer et al., 1996; Gautron and Elmquist, 2011). Consequently, current knowledge posits that leptin contributes to a broader array of neurobiological and psychological mechanisms including neurocognitive and emotional processes and stress regulation (Haleem, 2014).

Furthermore, leptin seems to be implicated –through the interaction with other hormones and neurotransmitters- in the etiology of certain psychiatric disorders (Farr et al., 2015; Brennan and Mantzoros, 2016). Thus, leptin is probably associated with the severity of major depression, although there is a controversy as to whether leptin levels increase (Pasco et al., 2008), decrease (Kraus et al., 2001; Jow et al., 2006), or remain unchanged (Deuschle et al., 1996). Likewise, lower leptin levels –but similar salivary cortisol levels- were reported for women with mild depressive or anxious states compared to healthy controls (Yoshida-Komiya et al., 2014). The probable contribution of leptin to the neurobiology of anxiety disorders is mainly supported by data from animal paradigms of anxiety showing that administration of leptin may exert anxiolytic-like effects (Lu et al., 2006; Liu et al., 2010; Tyree et al., 2016), possibly through the inhibition of hypothalamic-pituitary-adrenal (HPA) axis activity (Haque et al., 2013) and/or by facilitating the extinction of conditioned fear responses (Wang et al., 2015).

Despite the above-mentioned findings associating leptin to neurobiological and psychophysiological mechanisms underlying anxiety and fear, no study –to the best of our knowledge- has as yet explored the potential implication of leptin specifically in Panic Disorder (PD). Consequently, the aim of the present study is to investigate whether PD patients in the acute phase of their disorder, differ from normal controls with regard to serum leptin levels. Furthermore, we sought to explore potential associations between PD patients' severity of clinical manifestations and leptin serum levels. We report our results for a group of female PD patients, since the number of male patients assessed up to now is small for reliable results.

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2. Methods

2.1. Diagnostic procedures

Study's protocol was approved by Hospital's Ethics-Committee. All procedures followed were in accordance with the Helsinki Declaration (1975, revised 2008). Patients were consecutively referred from our Department's Outpatient Clinic. The recruitment period lasted from January 2013 up to December 2015. All subjects gave written informed-consent following a comprehensive explanation of the procedure. Patients were informed that appropriate treatment would start immediately after the end of study's procedure. Initial clinical evaluation of study's subjects, including a Structured Clinical Interview for DSM-IV (SCID) (First et al., 1998), was always performed by the first author, a psychiatrist. The definite diagnosis according to the DSM-5 criteria (American Psychiatric Association, 2013) was reached after discussion of the cases and common agreement by study's clinicians (VM, CP), both experienced clinical psychiatrists.

2.2. Study's inclusion and exclusion criteria

2.2.1. Inclusion criteria

DSM-5 Panic Disorder with or without comorbid Agoraphobia; current exacerbation of panic symptomatology; psychotropic medication-free for at least one month (three months for fluoxetine) prior to baseline evaluation.

2.2.2. Exclusion criteria

Concurrent medical/psychiatric comorbidity, except that of Agoraphobia; major medical/psychiatric (e.g. psychosis, bipolar disorders, recurrent major depression) disorders in the past, including any of the DSM-5 feeding and eating disorders; score > 10 in the Hamilton Depression Rating Scale (17-item) (Hamilton, 1960); currently undergoing any pharmacotherapy for psychiatric or other medical disorders, or psychotherapy; currently adopting any type of diet, or fasting; substance abuse disorder, except smoking; pregnancy. Patients had to be declared healthy by an internist and a cardiologist and should have normal routine blood tests (including thyroid function-tests), brain-computed tomography and electroencephalogram.

2.3. Subjects

Through the procedures described above, 27 (twenty-seven) medication-free female patients, consecutively referred from our Department's Outpatient Clinic were included in the study. All patients received a definite diagnosis of DSM-5 PD without or with (N = 22) concurrent Agoraphobia (PDA) confirmed by a SCID-Interview (First et al., 1998) and, furthermore, fulfilled all study's inclusion/exclusion criteria as specified above. All patients were normally menstruating, while none received any type of medication (study's exclusion criterion).

Control's sample included 42 (forty-two) healthy women, normally menstruating, matched for age with patients, moreover not taking any type of medication. All controls were recruited from our Hospital's Neurological Clinic where they were admitted for minor somatic complaints and were found, after diagnostic investigations, to be healthy. In line with previous reports (e.g. Schmitz et al., 1999), the Symptom Checklist–90–Revised (SCL-90-R; see below: 'Psychometric evaluations') (Derogatis, 1977; Derogatis et al., 2004) was administered as a screening instrument for mental health (healthy controls' mean total score = 54 ± 42, range = 4–189, median = 43; no extreme scores were observed in any of the SCL-90-R subscales; for the SCL-90-R global severity index [GSI], see Table 1).

In all cases, venous blood samples were collected between 08:00 and 10:00 h. Subjects were previously instructed (in a written form) to abstain from coffee and any food/beverage/drug containing caffeine (cited in a list given to them) for at least 15 h, from alcohol for at least 24 h and from smoking from at least 3 h, before the procedure.

Table 1
Data (means ± SD) for sample's medication-free female patients with Panic Disorder in the acute phase, and for the age-matched female healthy controls. Statistical evaluation by analysis of variance.

	CONTROLS	PD	$F_{1,67}$	p
N	42	27		
AGE	33.8 ± 8.7	33.0 ± 7.2	0.18	0.67
DURATION OF PD (years)		5.1 ± 5.3 (range 0.1–17)		
CGI-S		4.6 ± 1.00 (range 2–7)		
PA-7d		1.56 ± 1.60 (range 0–5)		
GSI (SCL-90)	0.60 ± 0.47	1.49 ± 0.60	**46.85**	**< 0.001**
CORTISOL (ng/ml)	127 ± 72	131 ± 77	0.04	0.84
BMI	24.4 ± 3.4	22.5 ± 4.3	**4.39**	**0.04**
LEPTIN (ng/ml)	10.5 ± 7.9	8.36 ± 5.75	1.43	0.24
LEPTIN / BMI	0.410 ± 0.260	0.355 ± 0.212	0.83	0.36

Abbreviations: BMI = Body Mass Index; **CGI-S** = Clinical Global Impressions-Severity of Illness scale; **GSI (SCL-90-R)** = Global Severity Index of the SCL-90; **PA-7d** = number of panic attacks during the last 7 days; **PD** = Panic Disorder; **SCL-90-R** = Symptom Checklist-90-Revised.

2.4. Biochemical evaluations and the leptin/BMI ratio

Leptin and cortisol were estimated in plasma using the radioimmunoassay kits of DIAsourceImmunoAssays SA, Belgium. The manufacturer gives for leptin an analytical sensitivity of 0.1 ng/ml, and intra- and inter-assay sensitivities close to 5%. We calculated an intra-assay coefficient of variation of 4.8 ± 3.8% for leptin, and 3.5 ± 2.7% for cortisol.

Taking into account the strong positive correlation of plasma leptin levels to BMI, in order to normalize leptin levels for BMI in evaluating differences between groups and searching for correlations, we used the ratio leptin/BMI (L/BMI) as a reflection of leptin synthesis and release activity of each subject.

2.5. Psychometric evaluations

(1) **Number of panic attacks according to DSM-5 criteria (APA, 2013) during the last seven days (PA-7d)** (patient-rated). A brief definition of 'panic attack' was provided typewritten, while panic attack's meaning was explained given examples of patient's own experiences.

(2) **Symptom Checklist–90–Revised (SCL-90-R)** (Derogatis, 1977; Derogatis et al., 2004). This is a self-rated, 90-item scale evaluating a broad range of current psychological symptoms and comprises the following nine subscales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Each item is rated on a five-point Likert scale ranging from 0 (not at all) to 4 (extremely), indicating the intensity of the respective symptom over the last week, including the evaluation day. For each subscale, the sum score is divided by the number of the subscale's items. Thus, each subscale's total score ranges from 0 to 4. To compute the *'global severity index' (GSI)*, we divide the sum of all items' scores by 90.
In our study, we specifically focused on the three SCL-90-R subscales more closely related to PD patients' clinical manifestations, namely the 10-item 'anxiety'-subscale (includes general manifestations of anxiety), the 7-item 'phobic anxiety'-subscale (reflects persistent and excessive fear responses to various contexts and related avoidance behaviors) and the 12-item 'somatization'-subscale (reflects distress due to the presence of various somatic manifestations) subscales.
Overall, the SCL-90-R subscales have demonstrated excellent inter-

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