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Activation of the cholinergic anti-inflammatory system in peripheral blood mononuclear cells from patients with Borderline Personality Disorder

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ABSTRACT

A case–control study including patients ($n = 20$) with Borderline Personality Disorder (BPD) and healthy controls ($n = 33$) was carried out. To avoid interferences of other clinical conditions on biological findings, patients were free of current major depressive episodes or substance dependence disorders, and had no life history of schizophrenia, bipolar or neuropsychiatric disorders. Patients were free of medication for at least two weeks at the time of the study. Studies carried out in peripheral mononuclear blood cells and plasma evidence a systemic inflammatory condition in unstable-impulsive BPD patients. Specifically, a significant increase in some intracellular components of two main pro-inflammatory pathways such as iNOS and COX-2, as well as an increase in the plasma levels of the inflammatory cytokine IL1β. Interestingly, patients have an increase in the protein expression of the anti-inflammatory subtype of nicotinic receptor α7nAChR. This finding may reflect a possible mechanism trying to maintain intracellular inflammation pathways under control. All together, these results describe an imbalanced, pro-inflammatory and oxidant phenotype in BPD patients independent of plasma cotinine levels. Although more scientific evidence is needed, the determination of multiple components of pro- and anti-inflammatory cellular pathways have interesting potential as biological markers for BPD and other generalized impulsive syndromes, specially data obtained with α7nAChR and its lack of correlation with plasma levels of nicotine metabolites. Their pharmacological modulation with receptor modulators can be a promising therapeutic target to take into account in mental health conditions associated with inflammatory or oxido/nitrosative consequences. Also, identifying at-risk individuals would be of importance for early detection and intervention in adolescent subjects before they present severe behavioural problems.

1. Introduction

Borderline Personality Disorder (BPD) is considered as a persistent impulsive behavioural condition that affects 2–3% of people (Grant et al., 2008; Korzekwa et al., 2008). According to American Psychiatric Association DSM-IV (2000), the essential feature of BPD is a pervasive pattern of instability of interpersonal relationships, self-image and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts, as indicated by five (or more) of the following: 1) Frantic efforts to avoid real or imagined abandonment. 2) A pattern of unstable and intense interpersonal relationships. 3) Identity disturbance. 4) Impulsivity in areas potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). 5) Recurrent suicidal or self-mutilating behaviour. 6) Affective instability due to a marked reactivity of mood. 7) Chronic feelings of emptiness. 8) Difficulty controlling anger. 9) Transient, stress-related paranoid ideation or severe dissociative symptoms. A considerable number of subjects with persistent abnormally impulsive behaviour do not meet the full set of criteria for BPD (they are often diagnosed as histrionic or non-specified personality disorders) but still can be included in the general concept of "impulsive personality disorders" (IPD)

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(Lawrence et al., 2010; Jacob et al., 2010; Tragesser and Robinson, 2009; Chapman et al., 2008; Zanarini et al., 2007).

The mainstay of treatment for BPD, in the long run, continues to be psychotherapy. As to date there is little agreement regarding the appropriate use of medication (Tyrer and Silk, 2011) in this disorder and probably less than 50% of patients with BPD respond to initial treatments with drugs currently available. According to recent metaanalyses, pharmacological response could be especially positive for some aspects of the disorder like depression and anger symptoms (Mercer et al., 2009).

The data about pathophysiology are scarce and there is no data available about possible biomarkers. Alterations in some neurotransmitter have been proposed (Gurvits et al.,2000) as well as genetic abnormalities (Vogel et al., 2012). Among the neurochemical research studies on BPD patients, dysfunctional serotonergic regulation (Coccaro et al., 2003, 2010) and hypothalamic–pituitary–adrenal (HPA) axis overreactivity (Zimmerman and Choi-Kain, 2009) are the most consistently reported findings. Due to the association of BPD symptoms and comorbid posttraumatic stress features (Grossman et al.,2003), stress-related biological changes have been proposed, and some non-specific changes were found such as enhanced cortisol suppression on the dexamethasone suppression test (Grossman et al., 2003; Carrasco et al.,2003).

Efforts to identify possible biomarkers are cornerstone for personalized therapeutical approaches aimed to tailoring diagnostic and drug therapy. Such findings could lead to development of diagnostic tests to help clinical psychiatrists identify and classify vulnerable patients early in the disease process, allowing for earlier and more effective therapeutic intervention (Schwarz et al., 2011, 2012).

As stated before, impulsive personality disorders are closely linked with stress dysregulation and often presents abnormalities in glucocorticoids (Grossman et al., 2003; Carrasco et al., 2003), which in turn participate in the modulation of inflammatory processes (rev. in Sorrells and Sapolsky, 2007). Stress exposure in both experimental models and humans (psychological stress) has been demonstrated to initiate mechanisms leading immuno-inflammatory and oxidative and nitrosative responses and elicit increases in brain and periphery (Bierhaus et al., 2003; García-Bueno et al.,2008).

Changes in the regulation of the inflammatory response in psychopathology are being studied in different mental disorders such as depression (Maes, 2008, 2011; Maes et al., 2011a,b), schizophrenia (Yao and Keshavan, 2011; Meyer, 2011; Meyer et al., 2011; Müller and Schwarz, 2008; Fan et al., 2007), and bipolar disorder (Berk et al.,2011; Hope et al., 2011) and other related/comorbid, stress-related immuno-inflammatory conditions (e.g. posttraumatic stress syndrome and chronic fatigue syndrome – rev. in Maes, 2011–). A few studies had been developed in impulsive disorders. Specifically, Kahl et al. (2006) suggested that depressed patients with comorbid BPD display endocrine and immune alterations: elevated concentrations of serum cortisol, cortisol/DHEA ratios, and pro-inflammatory cytokines were shown in those patients. Other studies suggested that individuals with high scores on neuroticism or low on conscientiousness show elevated levels of the inflammatory cytokine interleukin 6, IL-6 (Sutin et al., 2010). The regulation of the whole inflammatory-immunological process emerges as a key focus of interest in the search of new pathophysiological data in mental diseases. There are many intra- and intercellular components regulating this process in order to switch it on when necessary (i.e. to face external injuries) and switch it off (i.e. when occurring against own components). Its precise regulation involves intracellular machinery pathways controlling the synthesis, expression and function of inflammatory mediators. On the other hand, anti-inflammatory signalling pathways (both intra and intercellular) are also involved in its regulation: prostaglandins, membrane receptors (nicotine Ach-ergic), nuclear factors, cytokine-induced glucocorticoids, anti-inflammatory cytokines or cytokine receptors, elements in tryptophan metabolism, exhaustion of immune cells by cytokines, haptoglobin and others. All of these mechanisms have been described as part of the CARS mechanisms that exert inflammatory surveillance (CARS = compensatory anti-inflammatory reflex system) (rev. in Maes, 2011).

Based on data obtained in experimental (stress models) and clinical (schizophrenia) studies (García Bueno et al., 2010; Martínez Gras et al., 2011), we hypothesized that the physiological equilibrium on pro-inflammatory/anti-inflammatory pathways may be disrupted in BPD. Thus, we designed a case-control study in IPD with strictly recruited patients between the years 2010–2011 in our Personality Disorders day-care Unit.

In particular we decided to explore both intracellular and soluble components of inflammatory and oxidative response in biological samples of these patients: **a)** inducible isoforms of two main inflammatory enzymes: nitric oxide synthase (iNOS) and cyclooxygenase (COX-2), as well as soluble markers of its activity: NO_x^- (nitrites, the stable forms of nitric oxide, $NO^{\bullet}$) and prostaglandin E2 (PGE_2) respectively; **b)** soluble markers of oxido-nitrosative stress: TBARS (Thiobarbituric Acid Reactive Substances) as an index of lipid peroxidation (by-products after the attack of reactive oxygen species to lipidic components of the cellular membranes); **c)** two of the main pro-inflammatory cytokines, interleukin 1β (IL1β) and tumour necrosis factor α (TNFα); **d)** possible intracellular mechanisms controlling iNOS and COX-2 expression: nuclear transcription factor κB (NFκB) (rev.in García-Bueno et al., 2010). On the other hand, components of the anti-inflammatory pathway: **e)** the main cyclooxygenase derived anti-inflammatory product is 15 deoxy prostaglandin J2 (15d-PGJ_2), a non enzymatic metabolite of the prostaglandin D2 (PGD2), and its nuclear target: **f)** a transcription factor inhibiting gene expression and synthesis of inflammatory mediators: peroxisome proliferator-activated receptor gamma (PPARγ); finally, **g)** an alternative anti-inflammatory mechanism, in fact a component of the CARS, the α7 subunit of the nicotinic receptor (α7nAChR), which has been implicated in controlling NFκB mediated inflammatory mechanisms (Meyer, 2011).

2. Methods and materials

2.1. Participants

Patients with current diagnosis of Borderline Personality Disorder (BPD) were included in the present study. Subjects were selected consecutively at the Personality Disorders Unit of the Hospital Clínico San Carlos and evaluated by a senior psychiatrist with structured interviews for mental disorders (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders) (First et al., 2002a) and for personality disorders (Structured Clinical Interview for DSM-IV Axis II Personality Disorders) (First et al., 2002b). Healthy controls were age and sex matched.

The final sample was composed of 20 patients with a current diagnosis of BPD and 33 healthy controls. To avoid interferences of other clinical conditions on biological findings, BPD patients included were free of current major depressive episodes or substance dependence disorders, had no life history of schizophrenia, bipolar or neuropsychiatric disorders and were free of fever, infection, trauma or other general conditions. Patients were free of medication (including vaccination) for at least two weeks (6 months in the case of vaccines) at the time of the study.