Journal of Neuroimmunology 334 (2019) 576993

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Increased plasma levels of high mobility group box 1 protein in patients with bipolar disorder: A pilot study

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ARTICLE INFO

Keywords:
HMGB1
Bipolar disorder
Plasma
Inflammation

ABSTRACT

High mobility group box 1 (HMGB1) is a pro-inflammatory cytokine that emerges as a promising peripheral marker of inflammation. HMGB1 and C-reactive protein levels were assessed in plasma of control subjects and remitted patients with bipolar disorder (BD). HMGB1 levels were significantly higher in patients with BD as compared to control subjects whereas C-reactive protein levels did not differ between the two groups. No significant effect of potential covariates was identified. The results of this pilot study suggest that HMGB1 might be a specific peripheral marker of inflammation in BD.

1. Introduction

Bipolar disorders (BD) are major affective disorders characterized by recurrent manic and depressive episodes and associated with considerable burden and costs (Gore et al., 2011). Numerous biological markers related to the immune and inflammatory systems have been reported as abnormal in BD, mainly in the direction of an elevation of central and peripheral markers of inflammation (Dargél et al., 2015; Modabbernia et al., 2013), therefore suggesting an association between BD and a chronic low grade inflammation (Leboyer et al., 2016). A recent meta-analysis conclude that levels of several pro-inflammatory cytokines are consistently found increased during acute episodes (Rowland et al., 2018). However, among all the tested markers no single inflammatory biomarker could differentiate patients with bipolar disorder from control subjects (Rowland et al., 2018). Nevertheless, this literature suggests that these markers are part of the BD susceptibility and the search of novel relevant candidates might help unraveling the underlying physiological processes. (Ligthart et al., 2018; Yirün et al., 2017).

HMGB1 (high–mobility group box 1) is a non-histone protein involved in nuclear functions such as regulation of gene expression, recombination, DNA repair, or nucleosome structure (Chirico et al., 2014). HMGB1 can also be released extracellularly and has been involved in the regulation of neuroinflammation after brain diseases (review in Paudel et al., 2018). Interestingly, HMGB1 can also bind to Toll Like Receptor (TLR) such as TLR2 and TLR4, and HMGB1-induced depressive behaviors in mice is related to TLR4 activation (Lian et al., 2017; Wang et al., 2017; Wu et al., 2015). Furthermore, improving low-grade inflammation by targeting HMGB1 might represent a therapeutic pathway (Wang et al., 2017).

We therefore, initiate a pilot study to test whether this biomarker might be relevant to the multisystemic inflammation in BD. This study compared HMGB1 plasma levels between euthymic patients with BD and control subjects. Plasma levels of one of the most studied blood biomarker of inflammation, C-reactive protein (CRP), were also measured.

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https://doi.org/10.1016/j.jneuroim.2019.576993
Received 18 March 2019; Received in revised form 5 June 2019; Accepted 6 June 2019

2. Material and methods

2.1. Subjects

The study group consisted of 17 patients who presented with a diagnosis of BD according to DSM-IV criteria and 16 controls from the previously described GAN study (Genetic Actigraphy and Neuropsychology in BD, Clinical Trials Number NCT02627404) (Etain et al., 2014). After written informed consent, all participants were assessed by a psychiatrist with the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). Patients had to be in symptomatic remission for at least three months and with scores on the Montgomery-Åsberg depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS) lower than 5 at inclusion. Healthy controls subjects were recruited as volunteers from the general population and were screened for the absence of individual and familial (first-degree relatives) history of psychiatric disorders (mood disorders, schizophrenia and suicide attempts) using the DIGS.

2.2. HMGB1 ELISA and CRP assays

Plasma samples were prepared using standard procedures. The concentrations of HMGB1 were measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (IBL International, Germany). Plasma CRP was performed by quantitative immunoturbidimetry using the MULTIGENT CRP vario assay and C8000 Architect® analyzer (Abbott, IL, USA). Blinded sample analyses were carried. The quantification limit of the method was 0.5 ng/mL, and the precision was of 0.5 ng/mL (defined as the half-width of the 95% calibration interval).

2.3. Statistical analysis

All analyses were performed with R version 3.5.1. HMGB1 and CRP concentrations were analyzed after logarithmic transformation. Comparisons between controls and BD patients used linear mixed effects models, with clinical status (BD or control) as a random effect. Effect of covariates on HMGB1 levels was analyzed, using test of correlation or Student's *t*-test or analysis of variance. Additionally, analyses were also performed after including potential confounders (age, tobacco usage status, BMI) in linear models. Hypothesis tests were considered significant if $p < .05$, after multiplicity correction (using the Holm method). Since all plasma samples were not collected exactly at the same time in the study, we also tested for any potential variations of HMGB1 plasma levels over 24 h in healthy controls.

3. Results

The clinical and demographic characteristics of the subjects included in this study are summarized in Table 1. As shown in Fig. 1A, HMGB1 plasma level was significantly higher in patients as compared to control subjects. The median levels of HMGB1 were 3.78 ng/mL ([min; max]: [1.389; 15.33]) in the BD group and 0.45 ng/mL [0.074; 0.744] in the control group ($p < .0001$). Interestingly, there was no overlap between the HMGB1 concentrations of the two groups. As shown in Fig. 1B, no significant difference between the two groups was found for the plasma levels of CRP. The median levels of CRP were 0.7 mg/mL [0.2; 6] in the BD group and 0.9 mg/mL [0.2; 8.4] in the control group ($p = .761$).

BD and control subjects significantly differed in term of age and tobacco use (Table 1). Possible relationships between several clinical covariates and HMGB1 plasma levels were then analyzed (Table 2). We observed a trend for a significant difference in patients treated with Li alone vs with combinations of psychotropic medications. A trend for a positive correlation between age of onset and HMGB1 plasma levels in patients and a negative correlation between duration of illness and HMGB1 plasma levels were also observed. However, these differences and correlations did not resist Holm's correction. No significant correlation or difference was observed with all the other tested clinical variables. A linear mixed-effects model of log-transformed HMGB1 levels was used to test for the covariate effects of age, sex, BMI, and tobacco. No significant effects of any of these covariates was found (Supplementary Table 1).

Finally, the study of the potential circadian variations of HMGB1 expression was performed in 20 healthy male subjects (aged 20.2 to 33.2 years) and did not show any variations over 24 h (Supplementary Fig. 1).

Table 1
Clinical and demographic characteristics of control subjects and patients with bipolar disorder included in this study. Data are given as numbers or as median [minimum;maximum] (*a* Mann and Whitney test, *b* Fisher exact test). * $p < .05$. —: not applicable.

	Control Subjects	BD patients	*p*
Sex (M/F)	7/9	7/10	1 [b]
Age (years)	28 [18; 53]	40 [27; 63]	0.0009 [a]*
Body Mass Index (kg/m^2)	23.2 [17.6; 30.9]	23.3 [19.3; 34]	0.2797 [a]
Current tobacco use (%)	12.5%	56.25%	0.0367 [b]*
Never (N)	9	5	
Past (F)	5	2	
Current (U)	2	9	
Age of onset	–	21 [9; 52]	–
Duration of illness (years)	–	18 [10; 35]	–

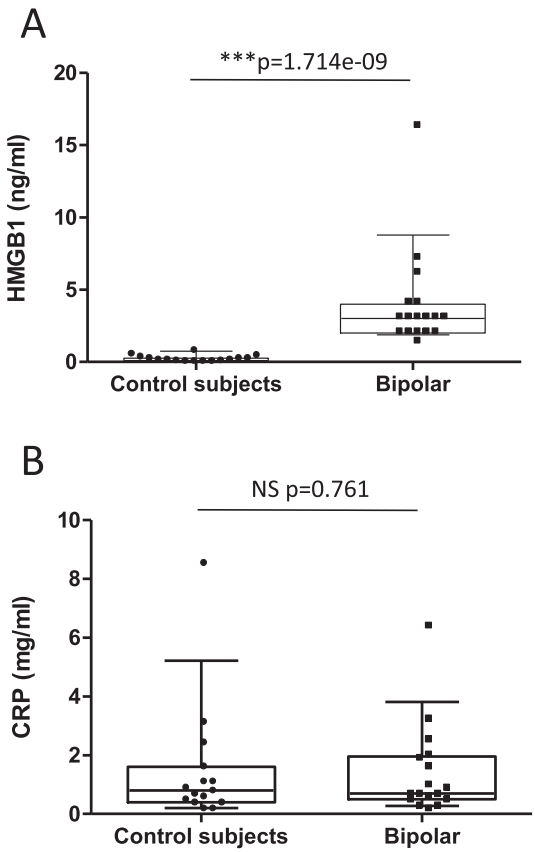

Fig. 1. Plasma HMGB1 (1A) and CRP (1B) levels of control subjects and bipolar patients. Each point is the average of the two duplicate assays for a given patient. *P*-values are from Mann and Whitney test. NS: non significant.

Table 2
Relationships between covariates and HMGB1 plasma levels in bipolar patients. Quantitative data were analyzed using Spearman's rank correlation (ρ), qualitative data using Kruskal-Wallis test. * p < .05, ** *p* < 0,01; pH: p-value after multiplicity correction by Holm's method.

	ρ	*p*	*pH*
Sex	–	0.8874	1
Tobacco use (never vs past vs current)	–	0.8052	1
Li alone	–	0.0348*	0.3132
Age	0.004	0.9914	1
BMI	−0.1152	0.6595	1
Age of onset	0.6519	0.0053**	0.0530
CRP	0.0296	0.9109	1
Duration of illness	−0.4991	0.0439*	0.3512
YMRS	−0.4425	0.0778	0.5446
MADRS	0.2073	0.4138	1

4. Discussion

We report for the first time higher HMGB1 plasma levels in remitted patients with BD as compared to control subjects, with no overlap of the HMGB1 distribution between the two groups. Interestingly, no significant difference in CRP levels between patients with BD and control subjects was observed.

In this pilot study, we paid attention in excluding some potential biases that may have confounded our results. First, blood-sampling times between patients and control subjects might differ. Circadian regulation of HMGB1 expression has been described in several organisms (Hoppe et al., 2007; O'Neill and Zheng, 1998; Yuan et al., 2016; Zheng et al., 1993), but no data were available in humans. We found no significant variations of HMGB1 plasma levels over 24 h. Second, HMGB1 plasma levels have been shown to decrease with age (Fu et al., 2016; Lehner et al., 2012). As the BD group was older than the control group, the higher HMGB1 plasma levels observed is unlikely to be due to any age differences between groups, and indeed correcting for age did not change the results. Third, despite the higher prevalence of current tobacco use in patients with BD, we found no relationship between the HMGB1 plasma levels and tobacco use in this group; furthermore, correcting for tobacco use in multivariate analysis neither changed the results.

In this study, we did not find any differences in CRP levels between the BD and control group. HMGB1 and CRP have been repeatedly found to be positively correlated in several pathologies (Amini et al., 2019; Bobek et al., 2014; Wang et al., 2018; Wu et al., 2012; Zhu et al., 2011). However, in several pathological conditions (such as stable coronary artery disease, obesity, alcohol consumption, pancreatitis, ischemia…), HMGB1 was identified as a more sensitive biomarker with better clinical significance as compared to CRP (Andrassy et al., 2012; Arrigo et al., 2013; Balan et al., 2019; Gao et al., 2018a, 2018b; Tsukagawa et al., 2017; YAO et al., 2013). Our results are in line with these latter cases. As CRP is known to be a non-specific blood biomarker of inflammation (Young et al., 1991), this result suggests that the mechanisms involved in HMGB1 mediated inflammation might be more specific of the BD pathophysiology. Since HMGB1 is elevated in a broad range of acute or chronic inflammatory conditions in humans (Andersson et al., 2018), our study adds to the current knowledge of low grade inflammatory processes in patients with BD. Indeed, BD is now considered as a multisystemic disorder with low-grade inflammation (Leboyer et al., 2016). HMGB1 partners include TLR receptors such as TLR2, TLR4 and TLR9 or RAGE (receptor for advanced glycation end-products) (review in Paudel et al., 2018) 20937362. The observed high plasma HMGB1 levels in patients with BD is consistent with the implication of several of these pathways in BD pathophysiology (Barbosa et al., 2013; do Prado et al., 2013; Wieck et al., 2013).

The present study has some limitations. The observed difference between patients and control subjects may result from uncontrolled confounding factors as among which mood symptoms. However, patients with BD were euthymic at the time of the inclusion and no correlation of HMGB1 levels was found with residual symptoms, as measured with MADRS and YMRS. We were not able to control for the effect of current psychotropic treatments because of the small sample size and the complex matrix of treatments currently prescribed to patients. To which extend some specific psychotropic drugs are likely to influence HMGB1 plasma levels however deserves further investigations. Interestingly, all patients included in this study were treated with lithium and the only reported effect of lithium on HMGB1 levels is a decrease in cancer cells (Razmi et al., 2018). This may suggest that HMGB1 levels would in fact be even higher in untreated BD patients, that would deserve to be investigated in drug naïve patients.

If confirmed these results may have several implications. In accordance with previous work indicating that abnormal immuno-inflammatory response may be associated with BD vulnerability (Drexhage et al., 2010; Kauer-Sant'Anna et al., 2009; Mesman et al., 2015; Snijders et al., 2017), HMGB1 could be proposed as a novel candidate marker for the vulnerability to BD. Several studies in rodent models of traumatic brain injury, neuronal loss after cardiac arrest or neurocognitive dysfunction have shown that targeting peripheral HMGB1, with an inhibitor or an antibody, could improve the recovery (Gao et al., 2018a, 2018b; Shi et al., 2017; Terrando et al., 2016). These preclinical data suggest that strategies targeting peripheral HMGB1 could not only decrease systemic inflammation but also more specifically neuro-inflammation. If validated in independent samples, our results suggest that neutralization of peripheral HMGB1 might be interesting to be considered in patients with BD. Further studies are needed (i) to investigate to which extend this plasma marker reflect neuroinflammation in BD, (ii) to determine whether HMGB1 is a trait or a state marker, (iii) to determine if HMGB1 may help to define different subgroups of the disorder and (iv) to investigate to which extend HMGB1 could be considered as a novel pharmacological target in BD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.576993.

Acknowledgments

We thank the clinicians and nursing staff of the Clinical Investigation Center at the Georges Pompidou hospital – Paris (France) for the recruitment of healthy volunteers. We thank the clinicians and nursing staff of the Centre Expert Troubles Bipolaires in Widal Hospital – Paris (France) for the recruitment and clinical characterization of the control subjects and bipolar patients.

Sources of funding

This work was supported by INSERM (Institut National de la Santé et de la Recherche Médicale); AP-HP (Assistance Publique des Hôpitaux de Paris); the Fondation FondaMental (RTRS Santé Mentale and Marcel Dassault Prize in 2013). The group of F. Bellivier is a member of the Bio-Psy Labex under reference ANR-11-IDEX-0004-02.

Disclosures

Pr. Bellivier has received honoraria and financial compensation as an independent symposium speaker from Sanofi-Aventis, Lundbeck, AstraZeneca, Eli Lilly, Bristol-Myers Squibb and Servier.

All other authors have no conflicts of interest.

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