Rheumatol Int (2009) 29:1109–1111
DOI 10.1007/s00296-008-0803-5

SHORT COMUNICATION

Decrease in adhesion molecules on polymorphonuclear leukocytes of patients with fibromyalgia

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Received: 10 March 2008 / Accepted: 3 September 2008 / Published online: 4 December 2008

Abstract Fibromyalgia (FM) is a chronic widespread pain condition in highly stressed humans. Because stress is known to modulate adhesion molecule expression, we determined L-selectin (CD62L) and β_2-integrin (CD11b/CD18) expression on the surface of polymorphonuclear leukocytes in 22 patients with FM. As compared to age and sex-matched healthy controls, FM patients showed a significantly decreased expression of CD62L ($p < 0.01$) and CD11b/CD18 ($p < 0.05$) on polymorphonuclear leukocytes. These changes might lower the rate of polymorphonuclear leukocyte migration to sites of inflammation and thereby compromise defense against infections and pain control.

Keywords Fibromyalgia · Polymorphonuclear leukocyte · Adhesion molecule · L-selectin (CD62L) · β_2-integrin (CD11b/CD18)

Introduction

Fibromyalgia (FM) is one of the most important chronic pain syndromes with a high prevalence [1]. Self-reported chronic widespread pain and 11 or more anatomically defined tender points upon palpation [2] leading to physical inactivity [3], and extremely stressful experiences [4] are characteristic for FM patients. Because stress has been shown to modulate adhesion molecules [5], we determined the expression of the adhesion molecules L-selectin (CD62L) and β_2-integrins (CD11b/CD18) on polymorphonuclear leukocytes of FM patients.

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Materials and methods

The study was approved by the local ethics committee, and informed consent for blood withdrawal was obtained from all subjects. The trial was conducted in accordance with the guidelines of the declaration of Helsinki and its amendment in Tokyo (1975) and Hongkong (1989).

Subjects

Seventeen female and five male FM outpatients ($n = 22$; 53.1 ± 2.1 years) were enrolled in this prospective study (ethical protocol number #324/02) if they met the criteria for FM as proposed by the *American College of Rheumatology* [2]. Twenty-two healthy subjects of comparable age (51.0 ± 2.6 years) and sex (17 females, 5 males) served as controls. Study exclusion criteria were psychiatric disorders, infections, hypertension, immunosuppression, and pregnancy. All patients were investigated while on their current medication that included amitriptyline, tramadol and acetaminophen. They had, however, abstained from their medication for at least 26 h (26:35–31:25 h) before blood sampling. All FM patients had high summary scores on the fibromyalgia impact questionnaire (FIQ; 46.0 ± 10.1), visual analog scale (VAS; 6.4 ± 1.4) and the post-traumatic-stress–symptom-10 score (PTSS-10; 46.7 ± 3.5).

Methods

Following measurements of total white blood cell count and leukocyte subpopulations, CD62L and CD11b/CD18 on polymorphonuclear leukocytes were determined. In brief, heparinized blood samples were washed two times with ice-cold, isotonic Hanks buffered salt solution. Washed blood samples were reconstituted to the initial hematocrit and incubated for 20 min on ice with fluorescein isothiocyanate (FITC)-labeled monoclonal antibodies Dreg-200 bind specifically to L-selectin or IB4 bind specifically to β_2-integrins. After lysis of erythrocytes, samples were measured by flow cytometry as previously described [6].

Statistics

Based on an alpha error of 0.05 and ≥80% power to detect a difference of one standard deviation between the two study groups, 22 patients (cases) per group were recruited to the study. Geometric means were compared by Student's *t* test and considered to be significantly different at $p < 0.05$. Results are expressed as mean ± standard error (SEM).

Results

As compared with healthy controls, expression of L-selectins [36.7 ± 3.1 vs. 24.3 ± 1.3 MFI (mean fluorescence intensity); $p < 0.01$] and β_2-integrins (28.6 ± 4.7 vs. 17.3 ± 1.8 MFI; $p < 0.05$) were significantly lower on polymorphonuclear leukocytes obtained from FM patients (Fig. 1).

Discussion

The exact cause for a lowered adhesion molecule cell surface expression on polymorphonuclear leukocytes in diseases associated with chronic pain and stress is unknown. However, there is some evidence from in vitro experiments that mediators released by the sympathetic nervous system or by the hypothalamic-pituitary-adrenal axis are involved in the suppression of adhesion molecules. For instance, catecholamines especially those with β-adrenergic activities, like epinephrine or norepinephrine, can inhibit CD11b/CD18 expression [7]. In addition, glucocorticoids were shown to suppress CD62L and CD11b/CD18 on bovine polymorphonuclear leukocytes [8]. In this context, it is interesting to note that not only patients with FM but also other chronic pain patients, e.g., those suffering from the complex regional pain syndrome, are characterized by lower levels of CD62L and CD11b/CD18 expression on their polymorphonuclear leukocytes [7]. In contrast, determining the percentages of polymorphonuclear leukocytes positive for cell surface adhesion molecule expression, Macedo et al. (2007) [9] found an increase for CD62L and no change for CD11b, respectively. Together with our results, it could be concluded that the decrease in the absolute number of adhesion molecule expression per cell is stronger for CD62L than for CD11b/CD18.

With regard to the potential functional consequences of a decreased adhesion molecules expression, it is important to know that CD62L and CD11b/CD18 play a key role in recruitment and transmigration of polymorphonuclear leukocytes. Moreover, CD11b/CD18 represents the complement receptor type III (CR3) required for recognition, ingestion and removal of opsonized particles, debris or microorganisms. Thus, a lowered number of both adhesion

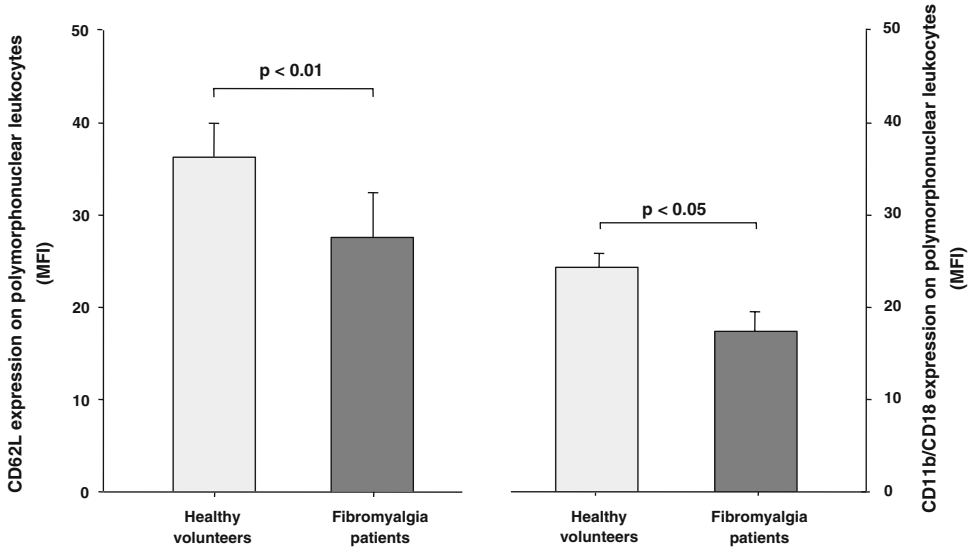

Fig. 1 Expression of L-selectin (CD62L) and of the β_2-integrin (CD11b/CD18, complement receptor type III) on the surface of polymorphonuclear leukocytes of healthy volunteers and patients with fibromyalgia. Values are means ± SEM of 22 individuals per group. *MFI* mean fluorescence intensity

molecules may impair recruitment of polymorphonuclear leukocytes at inflamed sites. This may hamper cellular debris removal and thereby sustain pathological conditions. Furthermore, the decline of CD62L and CD11b/CD18 was also suggested to be directly involved in stress-induced opioid-mediated antinociception. In animal experiments, blocking of both CD62L and CD11b/CD18 completely abolished peripheral intrinsic nociception, and this effect was due to decreased migration of opioid-producing leukocytes to injured tissue [10]. Although our study does not allow conclusions as to the contribution of this effect to overall pain in FM, the decline in CD62L and CD11b/CD18 could be clinically relevant, because it is well documented in patients that immune cells-derived opioids can effectively reduce pain [11].

One important study limitation is that an influence of the pain medication—paused for > 26 h—on adhesion molecule expression cannot be excluded. However, with regard to the pharmacodynamic and pharmacokinetic properties it is very unlikely that medication affected the study results.

In summary, this study shows that FM is associated with a decreased expression of adhesion molecules on polymorphonuclear leukocytes, giving rise to functional changes that might contribute to chronic inflammation and local pain. Further studies are needed to evaluate the relationship between changes in phenotypic properties of polymorphonuclear leukocytes and the development of chronic pain syndromes.

Acknowledgments The authors gratefully acknowledge the skillful technical assistance of Marion Hoerl and Gabriele Gröger from the Department of Anesthesiology, Location Klinikum Großhadern, Medical Faculty of Ludwig-Maximilians University of Munich, Germany.

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