Melatonin receptor 1b polymorphisms in women with systemic lupus erythematosus

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ABSTRACT

Aim: The pineal hormone melatonin could exert an important influence on the immune system and autoimmunity. Its effect on the immunocompetent cells might be mediated at least partially through specific melatonin receptors. However, the role of melatonin - melatonin receptor 1B (MTNR1B) interrelations in human autoimmune diseases is still unknown. Therefore, the present study aimed to investigate the possible influence of the MTNR1B gene polymorphisms for the development and clinical expression of systemic lupus erythematosus (SLE).
Methods: 109 female SLE patients and 101 healthy women were genotyped for the MTNR1B rs1562444, rs10830962 and rs10830963 polymorphisms.
Results: No genotype distribution differences were found between patients and controls. The presence of MTNR1B rs10830963 C/C genotype was related to increased prevalence of leucopenia compared to genotypes C/G and G/G after Bonferroni correction for multiple comparisons [36.5% vs. 14.5%, p=0.014]. Moreover, the rs10830963 G/G carriers had lower number of lupus criteria in comparison to patients with C/C genotype.
Conclusions: The present data suggested that MTNR1B polymorphisms could influence the clinical features in lupus patients, and especially the susceptibility to leucopenia.

Keywords: Genetic association; Melatonin receptor 1B; Polymorphisms; Systemic lupus erythematosus; Leucopenia, Myelosupression.

INTRODUCTION

The pineal hormone melatonin is widely known for its immunostimulatory and antiapoptotic role[1]. A bidirectional association between the pineal gland and the immune system has been suggested based on the immunomodulating features of melatonin and the pineal regulation by different lymphokines[2]. Moreover, different immune cells and tissues are able to synthesize melatonin[3]. The hormone might act directly on immunocompetent cells and it could influence the development of autoimmune diseases as well as their clinical expression[1]. Circadian rhythm disturbances of the melatonin secretion were already described in patients with rheumatoid arthritis[4].

The effects of melatonin on immunocompetent cells and hematopoiesis are accomplished at least in part through its action on the specific melatonin receptors (reviewed in Pandi-Perumal *et al.* 2008)[5]. Experimental studies indicated that melatonin receptor type 1B (MTNR1B) could be involved in melatonin-induced enhancement of cell-mediated and humoral immune response[6]. However, it is not clarified, if the single nucleotide polymorphisms of the MTNR1B gene might influence the interactions between the melatonin and melatonin receptor as well as their complex effects on the immune system and autoimmunity. A significant association was found between the MTNR1B rs1562444 polymorphism and the development of rheumatoid factor positive rheumatoid arthritis in Korean patients[7], while the role of MNTR1B polymorphisms in systemic lupus erythematosus (SLE) was not clarified.

Therefore, our study aimed to investigate the possible role of MTNR1B gene polymorphisms rs1562444, rs10830962 and rs10830963 for the clinical expression of SLE.

MATERIALS AND METHODS

SUBJECTS

Two hundred and ten Caucasian women were included in the study. One hundred and nine patients (mean

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age 41.72±11.71 years [20-67]) were recruited from the Department of Rheumatology. They fulfilled the modified 1997 American College Rheumatology (ACR) classification criteria for systemic lupus erythematosus[8]. The Systemic Lupus International Collaborating Clinics/ACR (SLICC) index[9] were determined by one rheumatologist (D.T.). All women underwent a complete general assessment and the presence of the lupus features such as malar rash, discoid rash, photosensitivity, oral ulcer, non-erosive arthritis, serositis, renal disorder, neurological disorder, hematological disorder (including presence of anemia, leucopenia, lymphopenia or thrombocytopenia), immunological disorder (including positive anti-DNA antibodies, positive anti-Smith antibodies or positive finding of antiphospholipid antibodies) as well as the presence of antinuclear antibodies were registered. The previous and current medication with corticosteroids and immunosuppressors such as cyclophosphamide, azathioprine, and methotrexate was registered.

One hundred and one age matched controls (mean age 39.36±11.97 years [22-68]) were collected from the medical staff and students. They were all clinically healthy women without connective tissue diseases. The experimental protocol was explained to all participants and written informed consent was obtained. The study was approved by the institutional ethic commission.

MELATONIN RECEPTOR 1B POLYMORPHISMS

All participating women provided peripheral blood samples for DNA. Genotyping was performed by PCR-RFLP analysis. The three different regions rs1562444, rs10830962 and rs10830963 were amplified by PCR in three reactions. Each PCR was performed in a total volume of 15 µl containing 2.0 mmol/L MgCl2, 0.5U Prime Taq DNA polymerase with the appropriate buffer (GenetBio, Korea) and 0.2 pmol/µl of each of the primers:

rs10830962: F 5'–TACTAGATATTAGCTGTGTGCTAGTGACT–3'/ R 5' TCTGGGCAACTCAGTGAAACC–3';

rs10830963: F 5'–ATGCTAAGAATTCACACCAGCT-3'/ R 5'–CACAGTGCAGACTGTTTTCTAATC–3';

rs1562444: F 5'–GAAAACACTCTTGGTGGTGTCTT–3'/ R 5'-GATGTGGTGGCTATGTGTGTGTGTA-3'.

Thermal cycling was performed with initial denaturation 95°C for 7 min, followed by 33 cycles of 95°C for 30 sec/ 60°C for 30 sec/ 72°C for 60 sec (for rs10830962); 95°C for 30 sec/ 54°C for 30 sec/ 72°C for 30 sec (for rs10830963); 95°C for 30 sec/ 60°C for 60 sec/ 72°C for 30 sec (for rs1562444). The final elongation step was 7 minutes at 72°C. PCR products for rs10830962, rs10830963 and rs1562444 were digested with restriction endonucleases - HinfI, PvuII and NlaIII (New England BioLabs Inc, USA), respectively. The digested products were analyzed on 2.5% agarose gel stained with ethidium bromide. Since the G to C (rs10830962), C to G (rs10830963) and A to G (rs1562444) transitions create an endonuclease recognition site, the PCR fragment following enzyme digestion reveals two types of alleles. The absence of restriction site for rs10830962 G/C referred to allele G (210 bp) and the presence of restriction site - referred to allele C (with 184 bp and 26 bp fragments). For rs10830963 C/G polymorphism the sizes of detected alleles were 105 bp and 20 bp (allele G) and 125 bp (allele C). The amplification region of 400 bp for rs1562444 A/G was digested with NlaIII restriction endonuclease and two fragments were revealed – 319 bp and 81 bp. The A to G transition creates additional NlaIII restriction site. The 2.5% agarose gel electrophoresis reveals three different patterns of genotypes: G/G (with 319 bp and 81 bp bands), G/A (with 319 bp, 163 bp, 156 bp and 81 bp) and A/A (163 bp, 156 bp and 81 bp). Several randomly selected samples were sequenced and their sequence identities were confirmed. The distribution of all investigated genotypes in healthy females was in agreement with the Hardy-Weinberg equilibrium. The genetic team was not aware of any clinical data concerning SLE patients.

STATISTICAL ANALYSIS

The results were presented as mean ±SD (median) for continuous variables or as a frequency (%) for dichotomous variables. Categorical data were analyzed through $\chi 2$ test or Fisher's exact test. After a Kolmogorov–Smirnov test for normality of the distribution differences between two groups were established with an independent t-test or Mann-Whitney test. Comparisons between three groups were calculated through one-way ANOVA with post hoc Bonferroni test (equal variances assumed) and Tamhane's T2 test (unequal variances assumed) or non-parametric Kruskal-Wallis test according to normality of the distribution. All results were considered significant at the 0.05 level. Logistic regression analysis was used where appropriate. The Bonferroni adjustment for multiple testing was applied and the significance of the p value was set at 0.017 (0.05/3 considering the three investigated polymorphisms). Statistical analysis was conducted through SPSS v. 11 for Windows (SPSS, Chicago, IL, USA).

RESULTS

A total of 100 healthy women and 106 female patients were genotyped for the single nucleotide polymorphism **rs1562444** in the melatonin receptor type 1B gene. No significant differences in the genotype frequencies of patients and controls were observed (Figure 1). Considering clinical characteristics of the SLE patients, the rs1562444 polymorphism was found to be related to the development of leucopenia, while no other relations with ACR criteria were established (Table I). Patients with G/G genotype had increased risk for leucopenia development in comparison to A/A carriers (OR 3.771; 95CI [1.135 – 12.533], p=0.030), but the results were not significant after the Bonferroni correction for multiple testing.

A group of 95 healthy women and 101 female patients was genotyped for the single nucleotide polymorphism **rs10830962** in the melatonin receptor type 1B gene. No significant differences in the genotype distribution of patients and controls were observed (Figure 2). Patients with rs10830962 C/C genotype had increased risk for immunological disturbances (OR 3.134; 95CI [1.035 – 9.486], p=0.043) in comparison to those with G/G genotype (Table II). The presence of C/C genotype was related to increased prevalence of leucopenia compared to both genotypes containing G allele (G/G and G/C) [38.2% vs. 17.9%, p=0.031]. C/C genotype increased the risk for leucopenia development (OR 2.837; 95CI [1.117 – 7.205], p=0.028). C/C

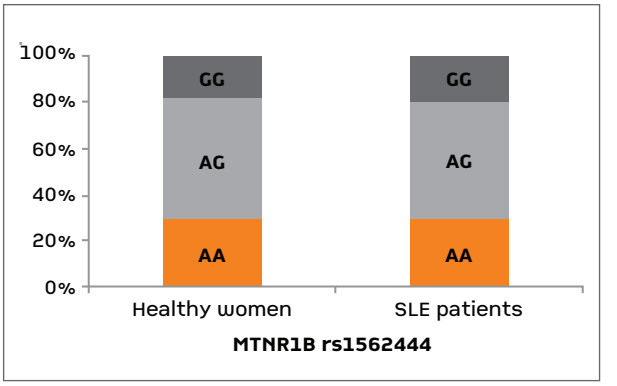

FIGURE 1. MTNR1B rs1562444 genotypes in patients with SLE and healthy controls (p>0.05)

TABLE I. MTNR1B RS1562444 GENOTYPE DISTRIBUTION IN SLE PATIENTS WITH DIFFERENT CLINICAL CHARACTERISTICS

Clinical characteristics of lupus patients (n=106)	N (% of all)	MTNR1B rs1562444 genotypes AA n=31 (29.2)	AG n=54 (50.9)	GG n=21(19.9)	P
Age		44.19±10.15	41.22±12.17	38.67±12.17	0.235
Age at diagnosis		38.52±9.46	32.67±13.17	32.43±11.00	0.068
Malar rash	40 (37.7)	11 (27.5)	23 (57.5)	6 (15.0)	0.520
Discoid rash	15 (14.2)	6 (40.0)	5 (33.3)	4 (26.7)	0.263
Photosensitivity	76 (71.7)	26 (34.2)	35 (46.1)	15 (19.7)	0.181
Oral ulcers	24 (22.6)	9 (37.5)	9 (37.5)	6 (25.0)	0.339
Non-erosive arthritis	104 (98.1)	30 (28.8)	53 (51.0)	21 (20.2)	1.000
Serositis	18 (17.0)	5 (27.8)	10 (55.6)	3 (16.7)	1.000
Renal disorder	27 (25.5)	7 (25.9)	15 (55.6)	5 (18.5)	0.915
Neurological disorder	35 (33.0)	10 (28.6)	17 (48.6)	8 (22.9)	0.825
Haematological disorder	67 (63.2)	19 (28.4)	32 (47.8)	16 (23.9)	0.382
Immunological disorder	78 (73.6)	21 (26.9)	40 (51.3)	17 (21.8)	0.616
Antinuclear antibody	81 (76.4)	25 (30.9)	41 (50.6)	15 (18.5)	0.753
Anaemia	24 (22.6)	9 (37.5)	12 (50.0)	3 (12.5)	0.481
Leucopenia	**26 (24.5)**	**7 (26.9)**	**8 (30.8)**	**11 (42.3)**	**0.005**
Thrombocytopenia	16 (15.1)	7 (43.8)	6 (37.5)	3 (18.8)	0.373
ACR criteria (number)		5.52±1.41 (5)	5.18±1.06 (5)	5.57±1.63 (5)	0.662
SLICC		0.90±1.24 (0)	0.65±0.89 (0)	0.71±1.06 (0)	0.830

Data are presented as number (percent) or as a mean±SD (median)

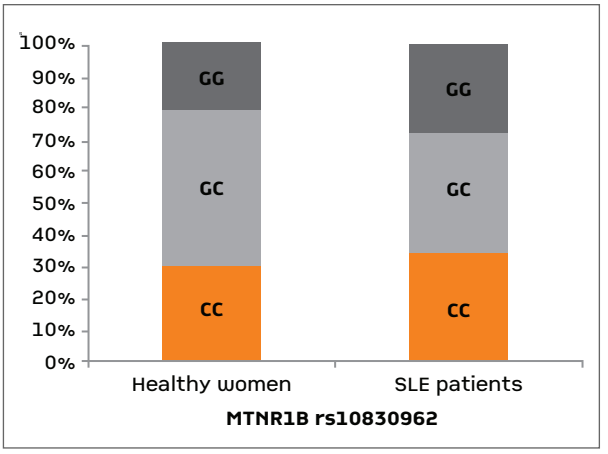

FIGURE 2. MTNR1B rs10830962 genotypes in patients with SLE and healthy controls (p>0.05)

carriers had increased number of ACR criteria compared to G allele carriers [5.79±1.47 (5.5) vs. 5.07±1.09 (5), p=0.017]. However, after the Bonferroni correction for multiple testing the present results were not statistically significant.

A total of 100 healthy women and 107 SLE patients were genotyped for MTNR1B **rs10830963**. No significant differences in the genotype frequencies of patients and controls were established (Figure 3). The number of ACR criteria was significantly lower in G/G patients (Table III). The presence of C/C genotype was related to increased prevalence of leucopenia compared to genotypes C/G and G/G [36.5% vs. 14.5%, p=0.014]. C/C genotype increased significantly the risk for leucopenia development (OR 3.383; 95CI [1.324 – –8.645], p=0.011). Similar results were obtained after adjustment for age and immunosuppressive treatment with cyclophosphamide, methotrexate and azathioprine (OR 3.947; 95CI [1.437 – 10.845], p=0.008). The prevalence of hematological disturbances was increased in C/C genotype lupus patients (75.0% vs. 52.7%, p=0.026) compared to G allele carriers, but the results were not significant after Bonferroni correction for multiple testing.

DISCUSSION

The present study showed that the MTNR1B poly-

TABLE II. MTNR1B RS10830962 GENOTYPE DISTRIBUTION IN SLE PATIENTS WITH DIFFERENT CLINICAL CHARACTERISTICS

Clinical characteristics of lupus patients (n=101)	N (% of all)	MTNR1B rs10830962 genotypes CC n=34 (33.7)	GC n=38 (37.6)	GG n=29 (28.7)	p
Age		38.44±12.21	42.26±10.39	44.45±12.38	0.117
Age at diagnosis		31.53±12.63	34.92±10.93	37.21±13.20	0.180
Malar rash	37 (36.6)	10 (27.0)	14 (37.8)	13 (35.1)	0.448
Discoid rash	15 (14.9)	6 (40.0)	4 (26.7)	5 (33.3)	0.642
Photosensitivity	72 (71.3)	22 (30.6)	27 (37.5)	23 (31.9)	0.489
Oral ulcers	22 (21.8)	11 (50.0)	6 (27.3)	5 (22.7)	0.239
Non-erosive arthritis	99 (98.0)	33 (33.3)	37 (37.4)	29 (29.3)	1.000
Serositis	15 (14.9)	7 (46.7)	6 (40.0)	2 (13.3)	0.337
Renal disorder	26 (25.7)	12 (46.2)	7 (26.9)	7 (26.9)	0.266
Neurological disorder	32 (31.7)	13 (40.6)	12 (37.5)	7 (21.9)	0.507
Haematological disorder	65 (64.4)	26 (40.0)	21 (32.3)	18 (27.7)	0.162
Immunological disorder	**74 (73.3)**	**27 (36.5)**	**31 (41.9)**	**16 (21.6)**	**0.041**
Antinuclear antibody	77 (76.2)	29 (37.7)	26 (33.8)	22 (28.6)	0.238
Anaemia	23 (22.8)	9 (39.1)	6 (26.1)	8 (34.8)	0.437
Leucopenia	25 (24.8)	13 (52.0)	6 (24.0)	6 (24.0)	0.082
Thrombocytopenia	16 (15.8)	4 (25.0)	9 (56.3)	3 (18.7)	0.298
ACR criteria (number)		5.79±1.47 (5.5)	5.05±1.11 (5)	5.10±1.08 (5)	0.060
SLICC		0.44±0.66 (0)	0.74±0.82 (1)	1.07±1.46 (1)	0.181

Data are presented as number (percent) or as a mean±SD (median)

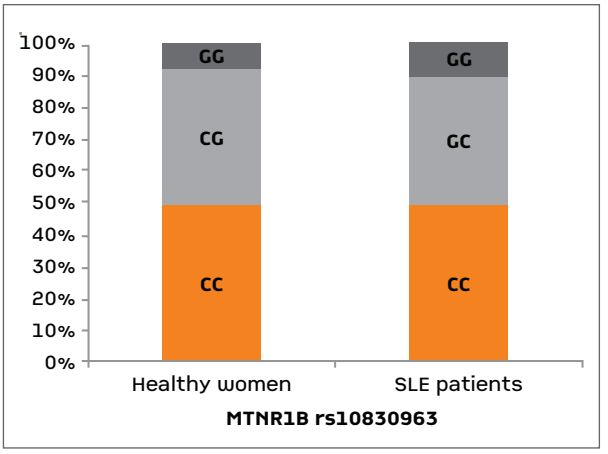

FIGURE 3. MTNR1B rs10830963 genotypes in patients with SLE and healthy controls (p>0.05)

morphisms rs1562444, rs10830962 and rs10830963 were not related to the development of SLE in women. However, an interesting finding was the significant association between MTNR1B polymorphisms and the susceptibility for leucopenia development. Patients with rs1562444 GG, rs10830962 CC and rs10830963 CC genotypes were at increased risk for leucocytes number decrease during the lupus flare but after Bonferroni correction for multiple comparisons only rs10830963 CC genotype remained as significant risk factor. The leucopenia in lupus could be caused by the presence of autoantibodies, complement cascade dysfunction, bone marrow suppression and splenic pooling[10]. The results suggested that melatonin receptor 1B and its polymorphisms might have an important role for the human myelopoesis or leukocyte survival *in vivo*. Melatonin administration in animal models protected bone marrow from the damaging effects of cytotoxic drugs and stimulated bone marrow cells mitosis[11,12]. Moreover, recent studies demonstrated that the pineal hormone could reduce apoptosis in human leucocytes[13,14]. Espino *et al.* studied the underlying mechanisms and found that, besides its antioxidant actions, melatonin probably required membrane receptor MTNR1A/MTNR1B interaction in order to counteract the TNF-alpha-stimulated human leukocyte apoptosis[15]. According to Lissenko *et al.* MTNR1B rs10830963 G allele carriers showed higher expression of MTNR1B in pancreas islet cells in comparison to carriers of the

TABLE III. MTNR1B RS10830963 GENOTYPE DISTRIBUTION IN SLE PATIENTS WITH DIFFERENT CLINICAL CHARACTERISTICS

Clinical characteristics of lupus patients (n=107)	N (% of all)	MTNR1B rs10830963 genotypes CC n=52 (48.6)	CG n=45 (42.1)	GG n=10 (9.3)	p
Age		39.67±11.98	43.56±10.62	44.10±14.07	0.212
Age at diagnosis		32.33±11.96	35.69±11.76	39.40±14.88	0.162
Malar rash	42 (39.3)	23 (54.8)	16 (38.1)	3 (7.1)	0.589
Discoid rash	15 (14.0)	7 (46.7)	5 (33.3)	3 (20.0)	0.268
Photosensitivity	76 (71.0)	34 (44.7)	36 (47.4)	6 (7.9)	0.170
Oral ulcers	24 (22.4)	15 (62.5)	8 (33.3)	1 (4.2)	0.335
Non-erosive arthritis	105 (98.1)	51 (48.6)	44 (41.9)	10 (9.5)	1.000
Serositis	18 (16.8)	12 (66.7)	6 (33.3)	0 (0.0)	0.180
Renal disorder	29 (27.1)	17 (58.6)	9 (31.0)	3 (10.4)	0.362
Neurological disorder	35 (32.7)	18 (51.4)	17 (48.6)	0 (0.0)	0.053
Hematological disorder	68 (63.6)	39 (57.4)	24 (35.3)	5 (7.4)	0.052
Immunological disorder	79 (73.8)	42 (53.2)	31 (39.2)	6 (7.6)	0.237
Antinuclear antibody	82 (76.6)	42 (51.2)	32 (39.0)	8 (9.8)	0.526
Anaemia	24 (22.4)	12 (50.0)	9 (37.5)	3 (12.5)	0.789
Leucopenia	**27 (25.2)**	**19 (70.4)**	**6 (22.2)**	**2 (7.4)**	**0.022**
Thrombocytopenia	16 (15.0)	6 (37.5)	9 (56.2)	1 (6.3)	0.522
ACR criteria (number)		**5.79±1.40 (6)**	**5.09±1.16 (5)**	**4.60±0.70 (4.5)**	**0.005**
SLICC		0.56±0.96 (0)	0.87±1.14 (0)	0.90±0.88 (1)	0.162

Data are presented as number (percent) or as a mean±SD (median)

C allele[16]. A potential increase of MNTR1B expression in leukocytes amplifying the melatonin signal could protect lupus rs10830963 G carriers from leucopenia.

Leukocytes number decrease might be associated not only with the lupus disease, but also with the SLE treatment[10]. The main limitation of our study was the fact, that almost all patients had conducted long-term treatment with immunosuppressive drugs and corticosteroids that could had influenced the bone marrow function. However, the association between leucopenia and MTNR1B polymorphism was still present after adjustment for immunosuppressive treatment.

The MTNR1B rs10830962 and rs10830963 polymorphisms have been predominantly investigated in the context of metabolic disorders[16-18]. *MTNR1B* rs10830962 and rs10830963 G alleles were associated with reduced insulin secretion, increased fasting plasma glucose concentrations and increased risk for type 2 diabetes in different populations[16-18]. To the best of our knowledge this is the first study investigating the relationships between systemic lupus erythematosus and MTNR1B polymorphisms. In conclusion, our results showed that melatonin receptor 1B polymorphisms could affect the clinical expression of SLE in women, and especially the development of leucopenia. Further studies are needed to reveal the significance of MTNR1B receptor polymorphisms for bone marrow function in lupus patients from other ethnic groups and for women with myelosuppression due to different causes.

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