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The role of CGRP and *CALCA* T-692C single-nucleotide polymorphism in psoriasis vulgaris

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Calcitonin gene related protein (CGRP) is increased in both lesional and non-lesional psoriasis. The role of CGRP in the pathogenesis of psoriasis vulgaris is still not clear. We designed to determine the *CGRP-I* (or *CALCA*), *II* (or *CALCB*) gene expression and morbidity and *CALCA* T-692C single-nucleotide polymorphism (SNP). Peripheral blood mononuclear cells (PBMCs) and plasma samples were collected, and CGRP level and *CGRP-I, II* mRNA expression were measured in psoriasis patients and healthy controls. The *CALCA* T-692C genetic polymorphism in psoriasis and control subjects was also compared. A higher expression of *CGRP-I, II* mRNA in PBMCs in psoriasis patients. The plasma CGRP level in psoriasis patients was also higher than that in healthy subjects. SNP analysis showed carriers of the T-692C allele were over-represented in non-drinking Patients. The plasma CGRP level was higher in alcohol-drinking patients with TT genotype than that with TC genotype. The plasma CGRP level is increased in psoriasis patients and *CALCA* T-692C polymorphism TT genotype is a factor for the affectability in alcohol-drinking Psoriasis vulgaris patients.

1. Introduction

Psoriasis is a chronic disorder of the skin characterized by reddish, scaly patches of inflammation. The pathogenesis is complex and multiple factors are involved (Haligur et al. 2012; Thorleifsdottir et al. 2012). Intravascular molecules, such as reactive oxygen species (ROS), intercellular adhesion molecule (ICAM) and TNF-α, have been reported to play important roles in the pathogenesis of psoriasis vulgaris (Asadullah et al. 1999). Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide, and is widely expressed in both the central and peripheral nervous systems (Suzuki et al. 2001). CGRP released from the unmyelinated C and myelinated A delta nerve fibres is important in mediating pain (Dawson et al. 2011). T lymphocytes and endothelial cells can also synthesize and release CGRP (Kay et al. 2007; Luo et al. 2008). CGRP acts as a growth factor for cells such as Schwann cells and endothelial cells (Murinson et al. 2005; Zhou et al. 2010). Pro-inflammatory properties of CGRP are also observed in multiple diseases (Byers et al. 1987; Gamse et al. 1987; Yaraee et al. 2003). Previous immunohistochemical studies revealed a marked proliferation of cutaneous nerves in psoriasis (Scholzen et al. 1998; Misery 2000). In addition, CGRP was detected in the plaques of psoriasis (Jiang et al. 1998), and has been shown to contribute to the psoriatic progress (Scholzen et al. 1998; Misery 2000).

Two isoforms of human CGRP, namely CGRP-1 (*CALCA*) and CGRP-2 (*CALCB*), have been identified (Hoovers et al. 1993). The human *CALCA* gene is located on chromosome 11p15.2-p15.1 and encodes both calcitonin and CGRP-1 through alternative RNA splicing. Several single nucleotide polymorphisms (SNPs) have been identified at the *CALCA* locus, and we have observed that the T-692C polymorphism in the promoter of *CALCA* is associated with the risk for essential hypertension in a Chinese population (Luo et al. 2008). Both candidate gene based association studies and genome wide association studies (GWAS) have identified a number of susceptibility genes for psoriasis (Sun et al. 2010). Because of the important role of CGRP in immune regulation and inflammation, we propose that *CALCA* is a candidate gene for psoriasis.

In this study, we compared the levels of CGRP mRNA expression and plasma CGRP in psoriasis and healthy subjects, and assessed the association between *CALCA* T-692C polymorphism and risk for psoriasis in a Chinese population.

2. Investigations and results

2.1. Differences in PBMC CGRP mRNA expression and plasma CGRP levels between psoriasis patients and controls

The expression of both *CGRP-I* and *CGRP-II* mRNA in PBMCs from psoriasis vulgaris patients was significantly higher than that in the healthy controls ($p < 0.01$, for both *CGRP-I* and *CGRP-II*; Fig. 1). Psoriasis patients also had significantly higher plasma levels of CGRP than that in the controls ($P < 0.05$, Fig. 2).

2.2. Correlation between CALCA T-692C polymorphism and psoriasis

The characteristics of the 293 psoriasis vulgaris cases and 313 controls are summarized in Table 1. The genotype distribu-

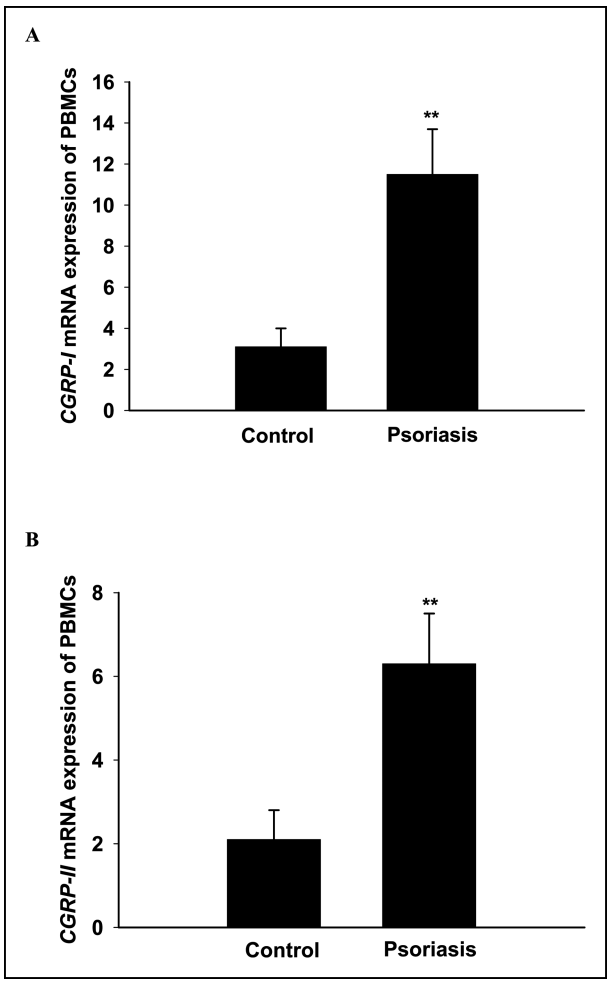

Fig. 1: *CGRP-I* (a) and *CGRP-II* (b) mRNA expression in PBMCs in psoriasis patients and controls (Mean ± S.E.M). n = 15, $^{**}P < 0.01$, *vs* controls.

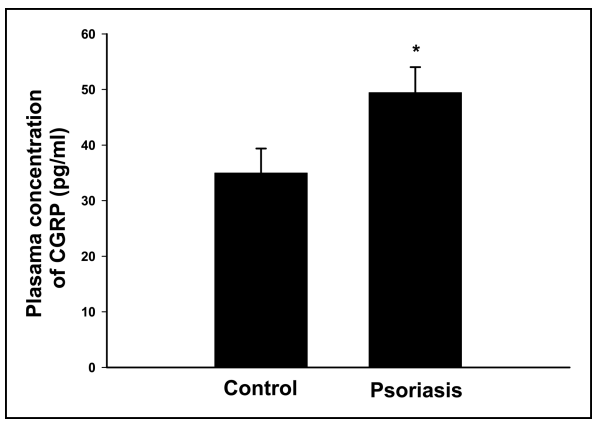

Fig. 2: Plasma CGRP concentration in psoriasis patients (n = 41) and controls (n = 45) (Mean ± S.E.M). $^{*}P < 0.05$, *vs* controls.

tions of *CALCA* T-692C are shown in Table 2. The frequencies for the *CALCA* -692TT, -692TC and -692CC genotypes were 74.1%, 23.6% and 2.3%, respectively, in the controls, and 76.1%, 20.8%, and 3.1%, respectively, in the patients. The observed genotypes distribution in both the control subjects and the patients were in Hardy-Weinberg equilibrium. No significant difference in the genotype distribution of the polymorphism was observed between the psoriasis cases and controls ($\chi^2 = 2.06$, $P = 0.82$, Table 2). Logistic regression analyses revealed that the polymorphism was not associated with the risk for psoriasis (Table 2).

2.3. Association of CALCA T-692C polymorphism with decreased risk for psoriasis in alcohol drinkers

Alcohol consumption has been reported to be a risk factor for psoriasis (Qureshi et al. 2010). When stratified by drinking history, carriers of the minor -692C allele (CC + TC genotypes) were significantly lower in patients than controls in alcohol drinkers (14.7% VS 30.9%, $P = 0.01$, Table 2). No difference in the polymorphism distribution was observed in non-drinking cases and controls. Carriers of the -692C allele were overrepresented in non-drinking patients as compared with drinking cases (32.6% *vs* 14.7%, crude odds ratio (Crude OR) = 0.38, $P = 0.01$, Table 2). However, we have not observed difference in the polymorphism as stratified by age, gender, and smoking history (Table 3).

2.4. Association of CALCA T-692C polymorphism with plasma CGRP concentration

The association of *CALCA* T-692C polymorphism with plasma concentration of CGRP was analyzed in the randomly selected 50 psoriasis patients. The -692 TC heterozygotes showed no significance compared to carriers of the -692 TT genotype. ($P = 0.22$, Table 4). However, among the alcohol-drinking patients, carriers of the -692TT homozygous genotype showed significantly higher plasma CGRP concentrations (76.3 ± 5.2 pg/mol) as compared with the -692TC genotype (57.6 ± 8.5 pg/mol, $P = 0.04$). No differences of plasma CGRP concentrations were observed between non-drinking cases carrying the -692 TT genotype compared with TC heterozygotes.

3. Discussion

In the skin, CGRP is present mainly at the dermoepidermal junction but can be observed intraepidermally (Almarestani et al. 2008). It is a potent vasodilator in human skin, and several studies have identified it as a key component of skin homeostasis (Croom et al. 1997). Intradermal injection of CGRP increases blood flow and causes persistent local erythema by inducing microvascular dilatation (Bileviciute et al. 1998). Vasodilatation of capillary beds is characteristic of plaques in multiple skin dis-

Table 1: General characteristics of the study participants

Variable	Control	Psoriasis	*P* value
n	313	293	
Gender			
Male (%)	216 (69.0%)	202 (68.9%)	0.936
Female (%)	97 (31.0%)	91 (31.1%)	
Age or age at diagnosis (years)	36 ± 11	29 ± 13	
Smoking history (%)	97 (31.0%)	146 (49.8%)	1.5×10^{-6}
Drinking history (%)	70 (22.4%)	112 (38.2%)	2×10^{-5}

Table 2: Genotype distribution of the *CALCA* T-692C polymorphism in controls and psoriasis patients in overall subjects and subgroups stratified by drinking habit

	Controls	Cases	Crude	Adjusted
Overall subjects	313	293	OR (95% CI)	OR (95% CI)
TT	232 (74.1%)	223 (76.1%)	1.00	1.00
TC	74 (23.6%)	61 (20.8%)	0.90	0.98 (0.80−1.19)
CC	7	9		
Stratified by drinking history				
Non-drinkers				
TT	181 (73.9%)	124 (67.4%)	1.00	1.00
TC	58 (23.6%)	52 (28.3%)	1.29	1.10 (0.87−1.40)
CC	6	8		
Drinkers				
TT	47 (69.1%)	93 (85.3%)	1.00	1.00
TC	20 (29.4%)	15 (13.8%)	0.38 [a]	0.60 (0.40−0.91)[b]
CC	1	1		

[a] $P = 0.01$, [b] $P = 0.01$

Table 3: Genotype distribution of the *CALCA* T-692C polymorphism in controls and psoriasis patients as stratified by age, gender, and smoking history

	Controls	Cases	Crude OR	Adjusted OR
Age stratification				
< 40 year				
TT	154 (75.9%)	176 (75.9%)	1	0.91 (0.70−1.19)
TC + CC	49 (24.1%)	56 (24.1%)		
≥ 40 year				
TT	78 (70.9%)	47 (77.0%)	0.73	0.76 (0.49−1.17)
TC + CC	32 (29.1%)	14 (23.0%)		
Gender stratification				
Males				
TT	158 (73.1%)	149 (74.3%)	0.94	0.94 (0.73−1.20)
TC + CC	58 (26.9%)	52 (25.7%)		
Females				
TT	74 (76.3%)	73 (79.3%)	0.84	0.98 (0.65−1.46)
TC + CC	23 (23.7%)	19 (20.7%)		
Smoking stratification				
Non-smoking				
TT	157 (72.7%)	109 (74.1%)	0.91	0.92 (0.69−1.21)
TC + CC	59 (27.3%)	38 (25.9%)		
Smoking				
TT	75 (77.3%)	115 (78.8%)	0.92	1.02 (0.71−1.45)
TC + CC	22 (22.7%)	31 (21.2%)		

Table 4: The effect of *CALCA* T-692C polymorphism and drinking habit on plasma concentration of CGRP in psoriasis patients

	n	Plasma concentration of CGRP (pg/ml)	*P* value
Genotype			
TT	35	71.5 ± 4.8	0.22
TC	15	58 .4 ± 5.7	
Drinking habit			
Non-drinker	33	55.3 ± 3.1	0.37
Drinker	17	68 .0 ± 7.9	
Drinking habit + Genotype			
Non-drinker + TT	21	66.1 ± 8.2	0.52
Non-drinker + TC	8	59.4 ± 7.7	
Drinker + TT	14	76.3 ± 5.2	0.04
Drinker + TC	7	57.6 ± 8.5	

ease, suggesting a role of CGRP in the pathogenesis of cutaneous inflammation. Furthermore, CGRP-containing sensory nerves appear closely associated with different cutaneous structures including endothelial cells, and there is intimately association between Langerhans' cells and CGRP-positive nerve fibres in the epidermis (Torii et al. 1998).

In the course of inflammatory skin diseases, the neuro-immunocutaneous system is often destabilized (Rossi et al. 1998). Previous data strongly suggested that sensory nerve transmitters serve important mediators in different stages of the psoriatic inflammation (Misery 2000). It is generally believed that the neuropeptide CGRP plays an integral role in the pathophysiology of psoriasis.

It has been shown that plasma CGRP was increased in psoriasis in a number of studies (Reich et al. 2007). Also, CGRP-containing nerve fibers were denser in the psoriatic epidermis (Jiang et al. 1998). CGRP is chemotactic to neutrophils and mitogenic to keratinocytes and endothelial cells. And a psoriasis-like pro-proliferation role of CGRP in HaCaT keratinocyte was observed by Yu et al. (2009). Local therapeutic effect of immunosuppression by chronic, repeated subinflammatory UV exposure, reduced the continuous release of CGRP into psoriatic lesions (Legat et al. 2002). The present study showed that CGRP mRNA and plasma levels in the PBMCs of psoriasis patients were higher than controls. These results further established CGRP release as an important factor for the pathogenesis of psoriasis.

Although there is strong evidence for the genetic basis of psoriasis, only a few genes have been identified thus far as independent susceptibility genes for psoriasis (Zhang 2012). A previous study showed that CGRP played a key role in the development phase of psoriasis (Rossi et al. 1998). *CALCA* genetic polymorphism has been putatively associated with a variety of diseases (such as Parkinson's disease, ovarian cancer and bone mineral density) (Buervenich et al. 2001; Goodman et al. 2005; Magana et al. 2006), suggesting a pathogenic role of *CALCA* gene polymorphism in these conditions. However, there has been no report regarding the relationship between the *CALCA* gene variants and psoriasis. We propose, based on the findings of the current study, which *CALCA* gene polymorphisms may contribute to psoriasis susceptibility in the general population. To identify genetic risk factors in psoriasis, we conducted a case-control study. (*CALCA* T-692C) polymorphism has no influence on the risk of psoriasis in a Han population in Hunan province of central China.

Smoking and alcohol may trigger psoriasis onset and quitting these habits are essential in managing severe psoriasis patients (Hayes et al. 2010). The present study suggests that both smoking and drinking are independent risk factors for psoriasis. More interestingly, in all subjects, alcohol drinkers with TT genotype were more susceptible to psoriasis vulgaris. Within the drinking psoriasis patients, the plasma CGRP concentration with *CALCA* -692 TT genotype was higher than those with TC genotype. It was reported that ethanol could activate primary sensory neurons, resulting in neuropeptide release in the skin (Trevisani et al. 2002), indicating that *CALCA* -692 TT polymorphism is a genetic predisposing factor for alcohol-related psoriasis. A possible mechanism is that alcohol activates the capsaicin receptor and triggers CGRP release from sensory nerves.

In conclusion, the morbidity of psoriasis likely involves the elevated CGRP expression and its release. *CALCA* T-692C TT genotype is a risk factor for psoriasis vulgaris in people with alcohol drinking habit

4. Experimental

4.1. Subjects

All psoriasis patients and healthy controls were from Hunan Province, China and were recruited from October 2008 to September 2010 in the Department of Dermatology, Xiangya Hospital. The psoriasis group consisted of 293 psoriasis cases. Diagnosis of psoriasis vulgaris was made based on both clinical features and skin biopsy (Fredriksson et al. 1978). The control group consisted of 313 subjects which were recruited from individuals undergoing routine health screening in the same hospital. The controls were apparently healthy, and all had a negative history of cardiovascular diseases (such as hypertension, ischemic heart disease, and chronic heart failure) and skin diseases (such as atopic dermatitis and eczema). All subjects were interviewed by experienced research assistants and completed structured questionnaires. The questionnaire consisted of several categories: (a) sociodemographic characteristics, including age, and marital, occupational and educational status; (b) habitual behaviors, including physical activity, cigarette smoking, alcohol consumption; and (c) medical history, including history of diabetes mellitus, hypertension, hyperlipidemia, cancer. Subjects with current or previous smoking habit were classified as smokers. Alcohol consumers were defined as individuals who consume more than 40 grams of alcohol per day. Venous blood samples were collected from all participants. All participants are Han Chinese from Changsha or the surrounding counties. All subjects signed the informed consent to the study, which was approved by the Ethics Committee of the School of Pharmaceutical Sciences, Central South University.

4.2. Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMCs) were isolated by gradient centrifugation, using the density separation medium Lymphoprep (Sigma, Saint Louis, Missouri, USA) as reported previously (Guo et al. 2008).

4.3. Real-time polymerase chain reaction analysis

Total RNA was extracted from PBMCs using a Trizol reagent. One μg RNA from each sample was reverse-transcribed. Quantitative analysis of *CGRP* mRNA expression was performed using the SYBR Green method on an ABI 7300 real-time polymerase chain reaction system (ABI, Carlsbad, California, USA) (Guo et al. 2008). Sequences of primers were as follows: *CGRP-I*: 5-CCCAGAAGAGAGCCTGTGACA-3 and 5-CTTCACCACACCCCCTGATC-3; *CGRP- II*: 5-TCTTTCGGAGCCATCCTGTT-3

and 5'-GATTTCACGTCCCCCTAAGGTT-3' *GAPDH*: 5-CTGCACCACCAACTGCT TAG-3 and 5-AGGTCCACCACTGACACGTT-3 (Luo

et al. 2008) (Sangon, Shanghai China). Results were expressed as the ratio of *CGRP- I*, *II* mRNA to *GAPDH* mRNA.

4.4. Measurement of CGRP content in plasma

For the measurement of plasma CGRP concentration, blood samples (2 ml) were collected in tubes containing 10% Na_2EDTA (30 µl) and aprotinin 400 U/ml. Plasma was obtained by centrifugation (1000 g, 15 min, 4 °C), and then frozen at − 20 °C until the assays were performed. To determine the immunoreactivity of CGRP in the plasma, a commercially available rabbit anti-human CGRP radioimmunoassay kit (Dong-Ya, Beijing, China) was used. This antibody has 100% reactivity with human CGRP-I and 79% with CGRP-II. There is no cross-reactivity with human amylin, calcitonin, somatostatin, or substance P (Deng et al. 2004).

4.5. Genotyping for *CALCA* T-692C polymorphism

Genomic DNA was extracted from the peripheral blood leukocytes by a standard method with proteinase K digestion and followed by phenol-chloroform extraction and ethanol precipitation. The *CALCA* T-692C polymorphism was genotyped by the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. The primers for genotyping were as follows: 5′-CGCATCTGTACCTTGCAACT-3′ (forward) and 5′-TCAAATT CCCGCTCACTTTA-3′ (reverse). The 20 µl PCR reaction system consisted of 100 ng of genomic DNA, 40 pmol of each primer, 40 pmol dNTP, 2 µl 10 × PCR buffer, and 2 U Taq DNA polymerase (Sangon, Shanghai, China). The PCR profile consisted of an initial melting step of 94 °C for 5 min, 38 cycles of 94 °C for 50 s, 57 °C for 50 s and 72 °C for 1 min, and a final extension step of 72 °C for 10 min. The 636 bp PCR product was then digested overnight by 1 U of *PshA* I (TaKaRa, Dalian, Liaoning, China) (Luo et al. 2008). The 692 TT genotype produced a single band at 636 bp, and the CC genotype produced two bands of 235 bp and 401 bp. The 692CT heterozygotes showed all three fragments of 636 bp, 235 bp and 401 bp. The investigator performing the genotyping experiments had no information on the status of the subjects. Twelve DNA samples of psoriasis cases were randomly selected for confirmation by direct sequencing. The genotyping results were 100% concordant with the PCR-RFLP results.

4.6. Statistical analysis

The differences of *CGRP* mRNA expression and plasma CGRP level between the patients and controls were analyzed by Student's *t* test. Frequencies of the genotypes and alleles of *CALCA* polymorphism were evaluated using the chi-square test. The Hardy-Weinberg equilibrium was tested by a chi-square test to compare the observed genotype frequencies with the expected frequency in the controls and cases. Association of *CALCA* polymorphism with psoriasis risk was evaluated by logistic regression analysis with adjustment for gender, age, smoking and drinking history. All the statistical analyses were performed with the Statistical Package for the Social Science (SPSS) 16.0. All the *P* values were two sided and with the significant levels of $P < 0.05$.

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