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ORIGINAL ARTICLE



## Expression of calcitonin gene-related peptide in atopic dermatitis and correlation with distress

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### ABSTRACT

**Background:** Atopic dermatitis (AD) is a chronic, inflammatory, often severely itching skin disorder. It may worsen due to stress, depression, or anxiety. Calcitonin gene-related peptide (CGRP) may be involved in inflammation signaling. CGRP has also been suggested in relation to stress, depression, and anxiety. This study aimed to investigate the expression of CGRP in the skin of patients with AD.

**Methods:** Twenty-seven adult patients with AD, characterized with clinical and psychodemographic parameters, were investigated regarding CGRP expression in skin biopsies, using an immunohistochemical technique.

**Results:** The total number of CGRP-positive nerve-like fibers was found to be higher in lesional skin than in non-lesional skin. Moreover, more inflammatory cells of dendritic shape intruded into the epidermis in lesional skin compared to non-lesional skin. Keratinocytes showing expression of CGRP were also found in lesional skin. Interestingly, the number of CGRP-positive nerve-like fibers in lesional skin correlated with depressive and anxiety scores. Correlation with depressive score was also found for round CGRP-positive inflammatory cells in the epidermis.

**Conclusions:** CGRP may have a role in both the inflammatory process and distress, in AD.

### ARTICLE HISTORY

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### KEYWORDS

Anxiety; atopic dermatitis; calcitonin gene-related peptide; depression; stress

### Introduction

Atopic dermatitis (AD) is a common inflammatory often severely itching skin disorder, which may worsen due to various external and internal factors, psychological stress being one such important factor [1–3]. Patients with AD are more prone to developing depression and anxiety, compared with healthy controls [4].

The neuropeptide calcitonin gene-related peptide (CGRP) is a member of the calcitonin family of peptides. It is released in response to activation of transient receptor potential vanilloid 1 in both peripheral and central neurons and immune systems. In the periphery, it is located in unmyelinated C and myelinated A delta sensory nerve fibers [5].

CGRP is functioning as a potent vasodilator and plays a role in the transmission of nociception (for references, see Noor-Mohammadi et al. [6]). Antibodies against the CGRP ligand or receptor are used in migraine prevention [7]. In human skin, intradermal injection of CGRP evokes slowly developing erythema within hours [8], though it has failed to induce a skin itch response in healthy humans [9].

CGRP is a key regulator of immune cell function, including in dendritic cells (for a review, see Assas et al. [10].

Previously, we reported a stimulatory effect of CGRP on *Leishmania major* promastigote-induced macrophage migration [11]. There is a close contact between CGRP-positive nerve fibers and Langerhans cells in the epidermis [12]. In this context, CGRP may inhibit murine contact hypersensitivity response to type 1 helper T cell-dominant haptens [13]. CGRP is also associated with other immune cells, such as mast cells and T lymphocytes [10]. There is an increased proliferation and interferon  $\gamma$  secretion in murine splenocytes upon stimulation with promastigotes in the presence of CGRP [14].

Several investigations have reported an increased number of CGRP-positive nerves in AD lesional skin, with increased mast cell-nerve fiber contacts, compared with in non-lesional skin (for references, see Choi and Di Nardo [15]), while Pincelli et al. [16] found the same expression for CGRP in nerve fibers in AD patients and control subjects.

CGRP is also involved in a range of behaviors. Exposure of humans or rodents to stressors increases substance P and CGRP expression in sensory nerves in the skin as well as in dorsal root ganglion cell [17]. Furthermore, CGRP has been reported have a role in depression and anxiety in rodents and humans. CGRP expression in the murine hippocampus

has been reported to be associated with a depression-like behavior [18]. Sink et al. [19] reported that infusion of CGRP into the lateral ventricle of rats could trigger an anxiety behavior and Carboni et al. [20] found that CGRP expression in the frontal cortex and hippocampus of an anxiety-related behavioral rat strain showed a significant correlation with an anxiety-like behavior. Moreover, CGRP levels may be increased in the spinal fluid [21], plasma and sweat patches of depressed patients [22].

In the present study, we have investigated the expression of CGRP in the skin of patients with AD for a possible correlation with clinical and psychodemographic parameters, focusing at stress, depression and anxiety.

## Patients and methods

### Patients

Twenty-seven adult AD patients, 18 females and 9 males, mean age 29.5 years (range 18–48 years), were included. These patients, where serotonergic [23] and tachykinergic [24] mechanisms have earlier been studied, were recruited among patients referred to our clinical department. The patients should have ongoing AD in accordance with the criteria of Williams et al. [25] and should not be on systemic therapy (including phototherapy and antihistamines) during the study or within one month prior to inclusion. The patients were clinically investigated, answered questionnaires, and left biopsy samples on one occasion, at their visit to the department. Two of the patients did not complete the questionnaires.

Ethical permission was obtained from the local ethical board and patients gave written informed consent to participate in the study.

### Extent of disease

The extent of the disease was assessed using SCORing of Atopic Dermatitis (SCORAD) [26]. Both objective and subjective SCORAD were recorded.

### Pruritus

The intensity of pruritus was assessed using a visual analogue scale, where patients rated their pruritus for the last three days on a scale 0–10 (0 = no pruritus, 10 = maximum pruritus).

### Psychodemographic measurements

The Swedish Universities Scales of Personality [27], a 91-item questionnaire, was used to evaluate the patients' personality traits. The questionnaires were analyzed regarding somatic trait anxiety (STA), psychic trait anxiety (PsTA), and stress susceptibility (SS). Absolute scale values were calculated. The Montgomery-Åsberg Depression Rating Scale-Self assessment [28] was used to assess the level of depressive symptoms.

### Salivary cortisol

Salivary cortisol samples were obtained from 23 of the patients. The saliva samples were collected in plastic vials at 8 AM on three consecutive days after the visit to our department. At 10 PM on the third day, 0.25 mg of dexamethasone was administered orally, with a new cortisol test taken on the following morning. The cortisol concentrations were measured using a radioimmunoassay using a rabbit polyclonal antibody 'Cortisol 3', catalog number MBS535414 (MyBioSource, San Diego, USA). Compared to cortisol its affinity for prednisolone is 37%, 11-deoxycortisol 5%, corticosterone 3%, and cortisone <1%. The intra-assay coefficient of variation for the radioimmunoassay was 7% at 10 nmol/L. The ratio of the mean of the first three values to the last cortisol value was determined, with a low ratio being an indicator of chronic stress [29].

### Skin sample processing

Biopsies, 3 mm in diameter, were taken from lesional skin on the cubital fossa, and from non-lesional skin in the sacral region. Only emollients should have been used on these areas for at least 14 days prior to inclusion in the study. Lana's fix (phosphate buffered 4% formaldehyde containing 0.2% picric acid) was used for fixation of the biopsies for 2 h at 4°C. The samples were then rinsed in 0.1 M Sörensen's phosphate buffered saline supplemented with 10% sucrose for 24 h and frozen and stored at –70°C until being cut into 14 µm thick sections for immunohistochemical staining.

### Immunohistochemistry

The sections were incubated with a rabbit polyclonal antibody against CGRP (1:10,000) from Bachem (St Helens, UK) at 4°C overnight. Thereafter, biotin-labeled goat anti-rabbit (BA-1000, 1:200, Vector Laboratories, Burlingame, CA, USA) was used as the secondary antibody, followed by the fluorochrome Alexa Fluor [6]488 streptavidin (1:1,000, Life Technologies, Stockholm, Sweden). To estimate the background staining, the primary antibody was omitted in the negative control.

### Microscopy

Immunoreactivity for CGRP was studied using epifluorescence (Zeiss Axioskop 2 MOT microscope, Carl Zeiss, Stockholm, Sweden). Nerve-like fibers that were defined as nerves are linear structures with a slight vesiculated appearance at a high magnification and were either found in the dermis, epidermis or crossing the dermal/epidermal boarder. Dendritic cells observed in the epidermis were defined as round cell bodies with dendrites.

Acanthosis, and degree of inflammation (infiltration of inflammatory cells in the dermis) were graded semi-quantitatively, 0–3 (0 = noninflammatory, 1 = mild, 2 = moderate, and 3 = severe).

The sections were counted manually by one observer (KN). Four sections per biopsy were analyzed at a magnification of  $\times 400$ . The absolute numbers of CGRP-positive epidermal inflammatory cells and nerve-like fibers were determined, a mean value was calculated for the sections, and standardized to 2.75 fields of vision. The percentage of CGRP-positive dermal inflammatory cells out of the total number of dermal inflammatory cells was calculated. The semi-quantitative evaluation for keratinocyte CGRP expression involved two observers (LL and KN) and was graded 0 (0), 1 (1–10), 2 (11–20), 3 (21–30 positive cells per standard vision field).

### Statistical analysis

The numerical values for CGRP expression were calculated using Student's *t*-test or the Mann-Whitney test (depending on the distribution of the values). For semi-quantitative evaluations, the chi-squared test was used. Correlations between the different parameters were measured using Spearman's or Pearson's tests (depending on the distribution of the values and if they were absolute numbers). Differences were considered to be statistically significant when  $p < 0.05$ .

## Results

### Clinical, laboratory and psychodemographic characteristics

The objective SCORAD of the patients was  $42.1 \pm 11.7$  (mean  $\pm$  SD) and the subjective SCORAD was  $51.4 \pm 13.7$ . The mean pruritus intensity among the patients was  $5.2 \pm 2.5$ .

The mean cortisol concentration obtained was  $84.1 \pm 84.8$  nmol/L, and the mean cortisol ratio was  $1.7 \pm 1.4$ .

The mean score among the patients for STA was  $15.2 \pm 4.3$ , for PsTA  $15.3 \pm 3.8$ , and for SS  $16.4 \pm 4.2$ . The mean depression score was  $8.0 \pm 6.6$ .

### General histopathological findings

The degree of acanthosis was higher in lesional skin ( $2.2 \pm 0.6$ ) than in non-lesional skin ( $1.2 \pm 0.5$ ;  $p < 0.05$ ). The degree of inflammation was elevated in lesional skin ( $2.1 \pm 0.6$ ) compared with in non-lesional skin ( $1.1 \pm 0.4$ ;  $p < 0.05$ ).

### CGRP expression

The total number of CGRP-positive nerve-like fibers was greater in lesional skin ( $5.1 \pm 3.7$ ) than in non-lesional skin ( $2.6 \pm 1.8$ ,  $p < 0.05$ ). There were also intraepidermal nerve-like fibers in the lesional skin (Figure 1(a);  $2.6 \pm 2.7$ ) and signs of sprouting of nerve-like fibers (Figure 1(b)).

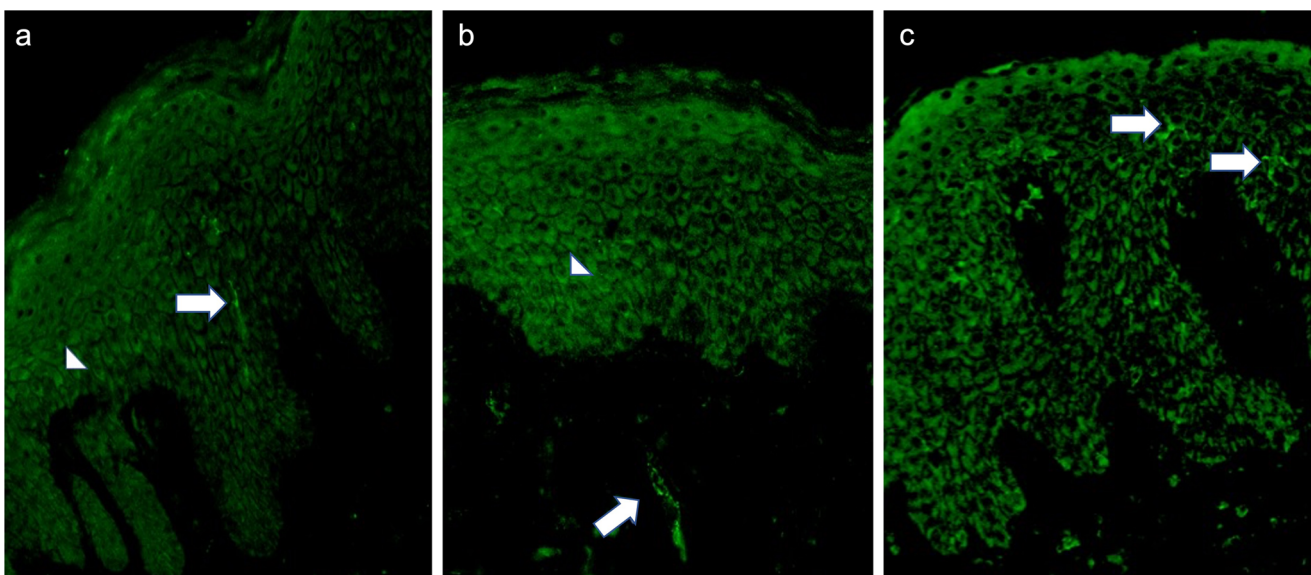
The total number of intraepidermal CGRP-positive inflammatory cells was increased in lesional skin ( $3.6 \pm 4.6$ ) compared with non-lesional skin ( $0.9 \pm 1.7$ ,  $p < 0.05$ ). The number of intraepidermal CGRP-positive round inflammatory cells did not differ significantly in lesional versus non-lesional skin ( $0.7 \pm 0.9$  vs.  $0.3 \pm 0.9$ ), but there were more intraepidermal CGRP-positive dendritic cells (Figure 1(c)) in lesional than non-lesional skin ( $2.9 \pm 4.4$  vs.  $0.6 \pm 1.6$ ;  $p < 0.05$ ).

Keratinocyte CGRP expression (Figure 1(a)) was higher in lesional than non-lesional skin ( $1.1 \pm 1.1$  vs.  $0.1 \pm 0.4$ ;  $p < 0.001$ ).

There was no difference between lesional and non-lesional skin regarding the percentage of CGRP-positive dermal inflammatory cells ( $24.4 \pm 8.6$  vs.  $22.0 \pm 7.8$ ).

### Correlation studies

In lesional skin, the total ( $r = 0.58$ ;  $p < 0.01$ ) (Figure 2), epidermal ( $r = 0.42$ ;  $p < 0.05$ ) and dermal ( $r = 0.46$ ;  $p < 0.05$ ) numbers of CGRP-positive nerve-like fibers all correlated with the depressive score. The total ( $r = 0.40$ ;  $p < 0.05$ ) (Figure 3) and dermal ( $r = 0.42$ ;  $p < 0.05$ ) numbers of CGRP-positive nerve-like fibers both correlated with degree of anxiety using Spearman's test.



**Figure 1.** Micrographs showing an intraepidermal CGRP positive nerve-like fiber (arrow) and CGRP-positive keratinocyte (arrowhead) (a), sprouting of CGRP positive nerve-like fibers and CGRP-positive keratinocyte (arrowhead) (b), CGRP-positive intraepidermal dendritic cells (c). magnitude  $\times 400$ .

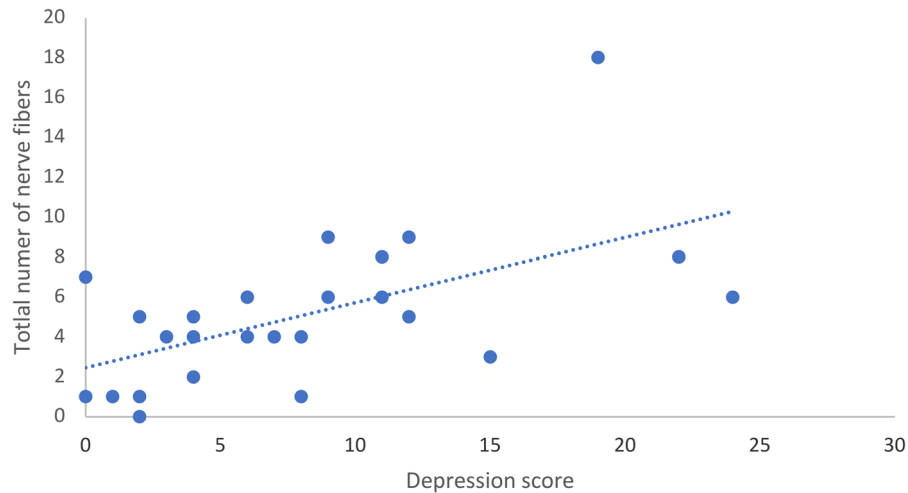


Figure 2. Regression between total number of CGRP-positive nerve-like fibers and depression scores.

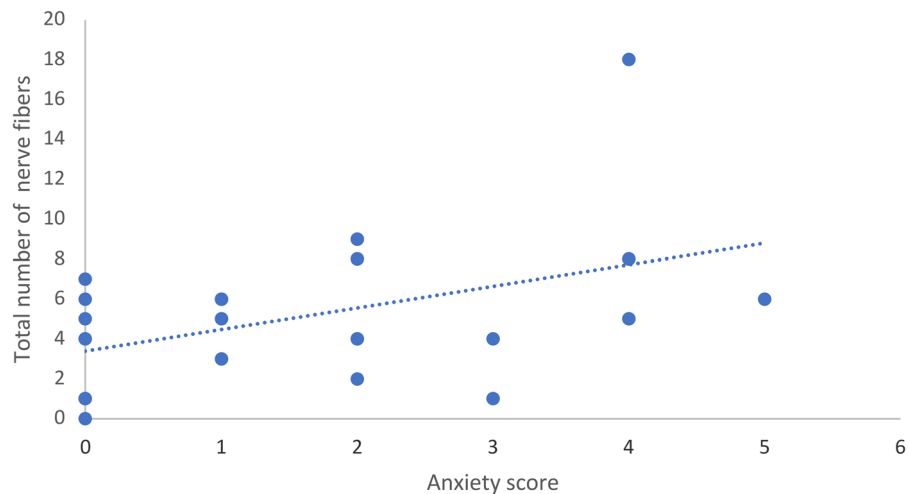


Figure 3. Regression between total number of CGRP-positive nerve-like fibers and anxiety scores.

The number of epidermal round CGRP-positive inflammatory cells correlated with the depressive score ( $r=0.40$ ;  $p<0.05$ ). In addition, the number of epidermal inflammatory round cells showed a negative correlation with the salivary cortisol value ( $r=-0.55$ ;  $p<0.01$ ).

There was a strong tendency for correlation between keratinocyte CGRP expression and PsTA score ( $r=0.39$ ;  $p=0.06$ ).

## Discussion

In the present study, we found an increased number of nerve-like fibers positive for CGRP in lesional compared with non-lesional AD skin. There was also an increase in both intraepidermal nerve-like fibers and intraepidermal inflammatory cells.

Our findings of increased numbers of CGRP nerve-like fibers in lesional compared with non-lesional AD skin are in line with other studies [15]. However, Pincelli et al. [16] found the same patterns and staining intensities for CGRP-positive nerve-like fibers in the skin of AD patients and control subjects.

In earlier studies from our group, there was no difference in the number of CGRP-positive nerve fibers between contact allergic and control human skin [30]. Moreover, there was a lower concentration of CGRP in the inflamed ears of mice with a contact allergic reaction compared with controls [31]. We previously reported a decreased concentration of CGRP in *Leishmania major* murine leishmaniasis skin compared with controls [11]. Thus, varying results have been found for CGRP content in inflamed skin.

We chose the cubital fossa for lesional skin because we wanted to find an area with substantial inflammation, whereas non-lesional skin was taken from the lower back. This anatomical difference should be considered when assessing the results. Another explanation for diverging results might be the magnitude of acanthosis and inflammation. In our study, there was no correlation between the number of CGRP-positive fibers and either degree of acanthosis or degree of inflammation. Yet another explanation might be degradation of CGRP; this neuropeptide is quickly degraded by proteases [32].

In the present study, there was a striking difference in that intraepidermal CGRP-positive nerve-like fibers were present in

AD lesional skin but significantly less in non-lesional skin. A hyperinnervation of epidermis in AD in humans and an NC/Nga atopic dermatitis mouse model has been reported in the past [33]. Regarding our finding of sprouting of CGRP-positive nerve-like fibers, such sprouting has been reported in inflamed rat molar pulp and periodontium [34]. In addition, dense CGRP-positive nerve bundles and dividing nerves have been found in the dermis of patients with the highly pruritic skin disorder prurigo nodularis [35]. These findings indicate a role for CGRP in both inflammation and pruritus. One mechanism whereby CGRP could, albeit indirectly, induce pruritus would be an interaction between CGRP and other mediators, such as the neuropoietic cytokine interleukin-6, which is also present in AD skin [36].

The CGRP immunoreactivity in epidermal dendritic cells in lesional skin presented here indicates a role for CGRP in the antigen presentation in AD, which might be of importance for disease development [37]. In this context, epidermal dendritic cells have been reported to express CGRP in psoriatic skin [38].

In our investigation, keratinocytes in AD lesional skin were positive for CGRP. Keratinocytes have previously been reported to be able to synthesize CGRP $\beta$  [39]. Furthermore, atopic keratinocytes have been shown to mediate CGRP-positive neurite outgrowth in a coculture model of human skin cells and porcine dorsal root ganglion cells [40]. In AD, CGRP might be released from keratinocytes during scratching, mediating neurite outgrowth, which might in turn increase pruritus, thus causing a vicious circle.

We did not see a correlation between CGRP expression and extent of disease or degree of pruritus. While intradermal injection of CGRP did not induce a skin itch response in healthy humans, an antagonist to CGRP has been shown to reduce itching caused by, e.g. histamine (for references, see Yang et al. [9]). A higher CGRP plasma level has been found in AD patients with more severe disease, and also in such patients with intense pruritus compared with patients without pruritus [41].

To reach a better understanding of the possible role of CGRP in AD and its psychological mechanisms, psychodemographic data were collected. In the past, it has been reported that CGRP expression in the murine hippocampus is associated with a depression-like behavior [21]. CGRP levels may be increased in the spinal fluid [21], plasma, and sweat patches [22] of depressed patients. CGRP is also involved in various behaviors suggestive of anxiety [19,20]. The data presented here supports a correlation between the number of nerve-like fibers in AD lesional skin and both depressive and anxiety scores, as well as between intraepidermal inflammatory cells and depressive scores. In addition to the signaling of CGRP itself, the potential interaction with other mediators and the proinflammatory and vasodilating action of CGRP may be possible mechanisms by which CGRP could interact with the central nervous system *via* circulation and possibly increase symptoms of distress in patients.

Interestingly, a study of another important sensory neuropeptide in the skin, substance P, which is often colocalized with CGRP, showed that the neurokinin-1 receptor-positive cells in AD are correlated with depression [24].

In the present study, intraepidermal CGRP-positive round inflammatory cells showed a negative correlation with cortisol levels, indicating a role for CGRP along the hypothalamic-pituitary-adrenal axis, and a role for CGRP in stress [18].

In summary, CGRP may have a role, in both the inflammatory process and distress, in AD.

## Author contributions

LL, KN, MH and BJ were active in the design of the study as well as contributed with scientific guidance during the process. KN, LL and SA performed the study as well as summary and analysis of results. ET performed the analysis of cortisol tests. All authors contributed to the manuscript writing and revision of the final manuscript.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

Data supporting the conclusions are presented in the manuscript. Additional information will be made available by the corresponding author upon reasonable request.

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