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INVESTIGATIVE REPORT

Serotonergic Markers in Atopic Dermatitis

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Stress and anxiety may worsen atopic dermatitis (AD) through the serotonin system. Serotonergic expression was measured in 28 patients with AD in relation to extent of the disease (SCORing of Atopic Dermatitis; SCORAD), pruritus intensity (visual analogue scale; VAS), anxiety traits (Swedish Universities Scales of Personality; SSP) and depression (Montgomery-Åsberg Depression Rating Scale-Self assessment; MADRS-S). Biopsies were taken from lesional and non-lesional AD skin, and investigated for expression of serotonin, its receptors 5-HT1A and 5-HT2AR, and serotonin transporter protein (SERT), using immunohistochemistry. 5-HT1AR-immunoreactivity (ir) was higher in lesional skin in apical epidermis and in mast cell-like cells in dermis, and the 5-HT2AR-ir was higher in apical epidermis and on blood vessels. In contrast, a basement membrane 5-HT2AR-ir signal was higher in non-lesional skin. The distribution of SERT-ir in the basal epidermal layer was higher in lesional skin. Positive and negative correlations were found between serotonergic markers and SCORAD, inflammation, pruritus intensity, anxiety traits, and depression score, indicating that serotonergic mechanisms are involved in AD. ***Key words: atopic dermatitis; inflammation; pruritus; serotonergic system.***

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Atopic dermatitis (AD) is a chronic, inflammatory, and often highly pruritic, disease with a dry skin. Global prevalence rates range from approximately 1% to 20% (1). AD is often clinically worsened by stress and anxiety (2–4) and a particular personality of these patients, being more prone to anxiety, has been postulated (5).

There is bilateral contact between the neuroendocrine system and the immune system, including the skin (6). While acute stress involves activation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, and neuropeptides, chronic stress has a more complex effect. Different mediators are responsible for this contact between the neuroendocrine system and the skin, an important mediator being serotonin (5-hydroxy-tryptamine; 5-HT).

5-HT has profound effects both at the central and peripheral levels of the neuroendocrine system and acts via different receptors. In humans it is mainly present in peripheral tissues, and platelets, while in other animals it is also found in mast cells (7). The major source of 5-HT is in the gut (enterochromaffin cells). The serotonin transporter protein (SERT) determines the magnitude and duration of the serotonergic response.

5-HT exerts its effects via at least 21 receptors (8), of which the best characterized are the 5-HT1A and 5-HT2A receptors (R) (9). These receptors, besides their involvement in anxiety and stress (10, 11) also have a role in inflammation. Thus, agonists to 5-HT1AR, buspirone (12) and spiperone (13) diminished contact allergy in rodents, while an antagonist to 5-HT2AR, ketanserin, has been reported to decrease contact allergy (14, 15). SERT is also involved in inflammation via different neuronal and non-neuronal pathways (16).

Patients with AD have been reported to have a higher serum level of 5-HT compared with patients with psoriasis and normal healthy controls (17). In addition, tandospirone, a 5-HT1AR agonist, improved the clinical and psychiatric symptoms of AD (18, 19).

With the aim of initiating the study of serotonergic mechanisms in AD, we investigated the expression of the serotonergic markers, 5-HT, SERT and the receptors 5-HT1A and 5-HT2A, in skin biopsies from patients with AD, using immunohistochemistry. These patients were characterized regarding disease extent, degree of inflammation, pruritus intensity, personality traits with somatic trait anxiety and psychic trait anxiety, stress susceptibility and depression score, and we correlated these parameters with the expression of these key serotonergic markers.

MATERIALS AND METHODS

Patients

Twenty-eight patients with AD, 18 females and 10 males, mean age 29.5 years (range 19–48 years) were recruited. The patients did not receive systemic therapy.

SCORAD and pruritus intensity

The extent of the disease was determined using SCORing of Atopic Dermatitis (SCORAD) (21). Pruritus intensity was determined using a visual analogue scale (VAS), linear 0–10.

Psychodemographic data

Somatic trait anxiety, psychic trait anxiety and stress susceptibility were evaluated using the Swedish Universities Scales of Personality (SSP) (22). Absolute values were calculated. For depression score Montgomery-Åsberg Depression Rating Scale-Self assessment (MADRS-S) (23) was used.

Processing of biopsy specimens and immunohistochemistry

Biopsies (3 mm thick) were taken from lesional (L) skin of the elbow, and non-lesional (NL) skin (lower back region). Lana's fixative (4% formaldehyde containing 0.2% picric acid) was applied for 2 h at 4ºC. After fixation, biopsies were rinsed in 0.1 M Sörensen's phosphate buffered saline (PBS) supplemented with 10% sucrose for at least 24 h and then rapidly frozen. They were later cut into 14 µm thick sections.

Sections were then incubated with antibodies against the serotonergic markers (Appendix S1[1]). Thereafter, incubation with biotin-labelled anti-rabbit (BA-1000) or anti-mouse (BA-2000) IgG (both diluted 1:200; Vector), followed by treatment with the fluorochrome Cy2-labelled streptavidin (PA42001, 1:2000; Amersham Pharmacia Biotech, Uppsala, Sweden), was performed.

Microscopy

Coded sections were evaluated by 2 observers, who recorded similar scores.

Hyperkeratosis, acanthosis and degree of cellular infiltration in the dermis were graded semiquantitatively, 0–3 (0 = normal appearance, 1 = mild, 2 = moderate and 3 = severe). The degree of 5-HT immunoreactivity was determined semiquantitatively, 0–3 (0 = no signal, 1 = slight, 2 = moderate and 3 = strong) in the epidermis and inflammatory infiltrates, while the absolute number of 5-HT-positive platelets was determined. For 5-HT1AR the fraction of positive staining of the total thickness of epidermis was evaluated, 0 = 0%, 1 ≤ 25%, 2 ≤ 50% and 3 ≤ 75%. The absolute number of positive 5-HT1AR inflammatory mononuclear cells in the papillary dermis was determined. For 5-HT2AR the epidermal fraction expressing this receptor of the total thickness of epidermis was, similar to the 5-HT1A epidermal fraction, graded 0–3. The basement membrane staining intensity was graded 0 for no staining, and 1–3 for increased staining intensity, 1 = slight, 2 = moderate and 3 = strong staining. The number of vessels expressing 5-HT2AR in papillary dermis was graded 0–3 (0 < 40, 1 = 40–59, 2 = 60–79 and 3 ≥ 80 vessels per section). The absolute number of SERT-positive mononuclear cells was counted in the epidermis and papillary dermis, respectively. In addition, the SERT signal intensity of the basal epidermal layer was assessed 0–3, as 0 = minimal, 1 = slight, 2 = moderate and 3 = strong staining.

Statistical analysis

The χ^2 test and/or Fisher's exact test were used in non-dependent samples, and the Student's *t*-test or non-parametric test was used for dependent samples. Correlations were determined using Pearson's or Spearman's test. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

Clinical and psychodemographic data

The objective SCORAD was 42.3 ± 11.5 (mean ± SD) (range 21.2–65.5) and subjective SCORAD 51.6 ± 13.4 (range 26.2–73.5) (Table I). The pruritus intensity, using the VAS scale, was 5.2 ± 2.4 (range 0–10).

Somatic trait anxiety was 15.1 ± 4.3 (range 8–22), psychic trait anxiety 15.2 ± 3.8 (range 9–25), and stress susceptibility 16.3 ± 4.1 (range 7–24). The score for MADRS-S was 8.0 ± 6.5 (range 0–24).

General histopathological findings

The degree of hyperkeratosis was higher ($p < 0.001$) in L, 1.9 ± 0.7, compared with NL, 1.2 ± 0.4, skin. The degree of acanthosis was 2.1 ± 0.8 in L and 0.6 ± 0.8 in NL skin, with a significant difference ($p < 0.001$). The degree of inflammation was higher ($p < 0.001$) in L, 2.4 ± 0.7, compared with 1.1 ± 0.8 in NL skin.

5-HT

The epidermal immunoreactivity for 5-HT was similar, 2.1 ± 0.4 in L and 2.0 ± 0.3 in NL skin (Fig. 1, showing L skin). 5-HT staining of the inflammatory infiltrate was 2.0 ± 0.6 in L and 1.8 ± 0.5 in NL skin. A higher ($p < 0.001$) number of 5-HT-positive platelets, 5.0 ± 2.3, was recorded in L skin, being 2.0 ± 0.8 in NL skin.

5-HT1AR

A 5-HT1AR-positive epidermal fraction was observed in the apical part of the epidermis, more evident ($p < 0.001$) in the L, 1.1 ± 0.7, compared with NL, 0.3 ± 0.5, skin (Fig. 2, Fig. S1a[1]), and also with a higher signal intensity. There were also dermal inflammatory, mast cell-like, cells that expressed the 5-HT1AR, their number being higher ($p < 0.001$) in L, 31.9 ± 10.6, compared with NL skin, 17.5 ± 6.0 (Fig. S1b[1]).

Table I. *Clinical and psychodemographic data for the patients with atopic dermatitis (AD)*

Characteristics	
Age, years, mean (range)	29.5 (19–48)
Sex, F:M, *n*	18:10
Objective SCORAD, mean ± SD (range)	42.3 ± 11.5 (21.2–65.0)
Pruritus (0–10 cm), mean ± SD (range)	5.2 ± 2.4 (0–10)
Somatic trait anxiety, mean ± SD (range)	15.1 ± 4.3 (8–22)
Psychic trait anxiety, mean ± SD (range)	15.2 ± 3.8 (9–25)
Stress susceptibility, mean ± SD (range)	16.3 ± 4.1(7–24)
MADRS-S, mean ± SD (range)	8.0 ± 6.5 (0–24)

SCORAD: SCORing of Atopic Dermatitis; MADRS-S: Montgomery–Åsberg Depression Rating Scale-Self assessment.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2354

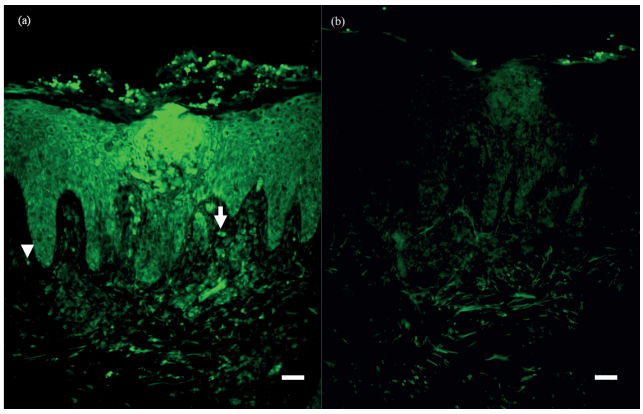

Fig. 1. (a) Epidermal, inflammatory infiltrate, and platelets expressing 5-hydroxy-tryptamine (5-HT), in lesional atopic dermatitis (AD) skin. *Arrow*: positive inflammatory cell; *arrowhead*: positive platelet. Conglomerate of positive cells is seen (*strong staining*). (b) Control in the absence of the primary antibody. *Scale bars*: 20 μm.

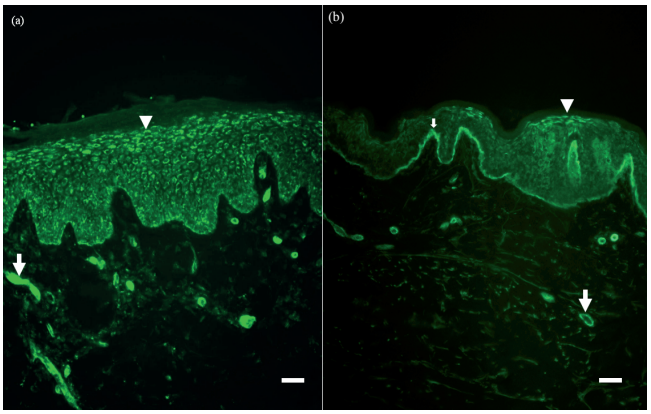

Fig. 3. Epidermal, basement membrane and vessel 5-HT2AR expression, in (a) lesional and (b) non-lesional atopic dermatitis (AD) skin. *Arrowheads*: positive apical epidermal fraction (higher in a than in b). *Small arrow*: staining intensity of basement membrane (strong in b, absent in a); *(ordinary) arrows*: positive vessels. *Scale bars*: 20 μm.

5-HT2AR

There was a difference ($p < 0.05$) in the epidermal fraction expressing 5-HT2AR in L compared with NL skin, reaching mean 1.8 ± 0.7 in L and 1.3 ± 1.1 in NL skin (Fig. 3, Fig. S1c[1]). There was a more evident ($p < 0.001$) basement membrane signal in NL, 2.3 ± 0.7, compared with L skin, 1.6 ± 0.6. The number of 5-HT2AR immunoreactive vessels in papillary dermis was increased ($p < 0.001$) from NL, 0.8 ± 0.7, to L, 2.3 ± 0.8, skin (Fig. S1d[1]).

SERT

There was a higher number ($p < 0.05$) of epidermal SERT-positive cells, in L, 20.4 ± 12.0, compared with NL, 13.8 ± 5.7, skin (Fig. 4). The dermal SERT-positive cells were 39.9 ± 9.2 and 20.3 ± 4.5 in L and NL skin, respectively, with a significant difference ($p < 0.001$). There was a significantly higher ($p < 0.001$) degree of SERT immunoreactivity in the basal layer of L skin, 1.6 ± 0.6, compared with NL skin, 0.5 ± 0.5 (Fig. S1e[1]).

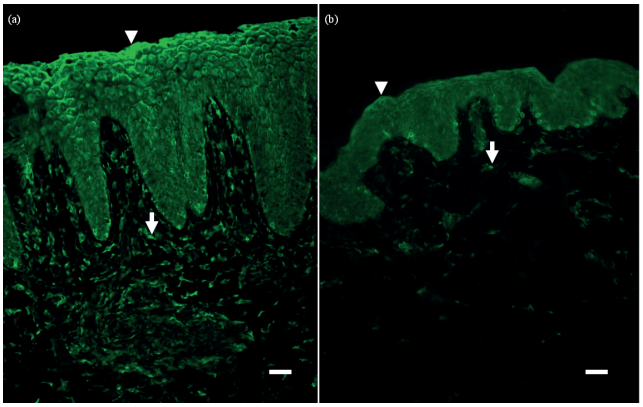

Fig. 2. Epidermal and dermal inflammatory cellular 5-HT1AR expression, in (a) lesional and (b) non-lesional atopic dermatitis (AD) skin. *Arrowheads*: positive fraction of the epidermis (higher in a than in b); *arrows*: positive inflammatory dermal cell. *Scale bars*: 20 μm.

Correlations

No correlation was found for extent of the disease and the psychodemographic data. The intensity of pruritus correlated positively with somatic trait anxiety ($r = 0.50$; $p = 0.01$) and stress susceptibility ($r = 0.44$; $p < 0.05$), respectively. No correlation was found between the serotonergic markers and the intensity of pruritus.

In L skin there was a positive correlation ($r = 0.38$; $p < 0.05$) between the number of 5-HT1AR-positive inflammatory dermal mast cell-like cells and objective SCORAD. There was also a positive correlation between the degree of acanthosis, and 5-HT positive inflammatory infiltrate, the number of 5-HT1AR positive mast cell-like cells, 5-HT2AR-positive vessels and the degree of basal epidermal SERT immunoreactivity. Moreover, there was a positive correlation ($r = 0.39$; $p = 0.05$) between the epidermal 5-HT1AR fraction

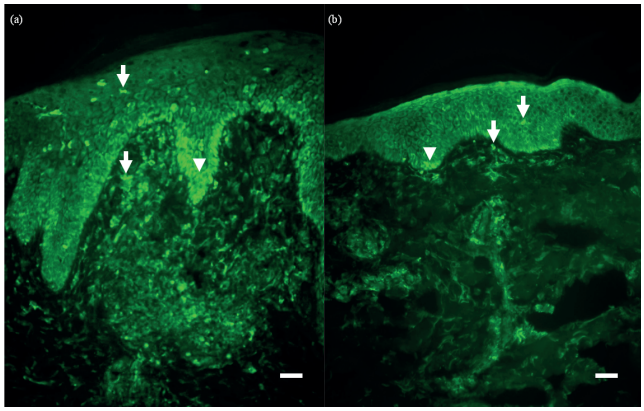

Fig. 4. Serotonin transporter protein (SERT) expression of epidermal and dermal inflammatory cells and in the basal epidermal layer, in (a) lesional and (b) non-lesional atopic dermatitis (AD) skin. *Arrows*: positive inflammatory cells in the epidermis and dermis; *arrowheads*: basal epidermal expression intensity, being higher (moderate) in a than in b (slight). *Scale bars*: 20 μm.

with the MADRS-S score and an inverse correlation ($r = -0.48$; $p < 0.05$) between the 5-HT2AR-positive vessels and the same MADRS-S score. There was an inverse correlation ($r = -0.42$; $p < 0.05$) for the degree of basal epidermal SERT immunoreactivity with stress susceptibility and a tendency ($r = -0.36$; $p = 0.07$) to an inverse correlation with psychic trait anxiety.

In NL skin the degree of acanthosis correlated positively with objective SCORAD ($r = 0.56$; $p < 0.01$). In addition, a positive correlation between the 5-HT2AR-positive vessels, the objective ($r = 0.38$; $p = 0.05$) and subjective ($r = 0.39$; $p < 0.05$) SCORAD, as well as degree of acanthosis ($r = 0.37$; $p = 0.05$), was determined.

DISCUSSION

This study found correlation between the expression of serotonergic markers and the extent of AD, as well as correlation between these markers and the inflammatory histopathological measures of AD. In addition, these markers also correlated with the depression score and the stress susceptibility.

A 5-HT1AR-positive expression was detected in the apical part of the epidermis, which was more evident in L than NL skin, indicating that this receptor has a role in keratinocyte differentiation. There were also 5-HT1AR-positive mast cell-like cells, their number being higher in L than NL skin, and these might have an impact on the inflammatory process. There was a positive correlation between the number of these 5-HT1AR-positive cells and objective SCORAD. Our earlier studies on contact eczema (25) and psoriasis (26) found a lower number of 5-HT1AR-positive dermal cells in L than NL skin.

There was a higher epidermal fraction expressing the 5-HT2AR in L than NL skin. Moreover, the number of 5-HT2AR-positive vessels in papillary dermis was increased from NL to L skin. There was a correlation between 5-HT2AR-positive vessels in L skin and the degree of acanthosis. In addition, there was a positive correlation between the number of 5-HT2AR-positive vessels in NL skin and the objective and subjective SCORAD, respectively. The finding of such positive vessels might be due to a general importance of vessels for the inflammatory process, but a more specific role of the 5-HT2AR expressed on the vessels cannot be excluded.

In L skin there was an inverse correlation for the 5-HT2AR immunoreactive vessels with the depression score. This might indicate a protective role for this receptor regarding low mood, which is a somewhat unexpected finding. In this context it should be mentioned that an anti-inflammatory effect of 5-HT2AR has been reported earlier in rheumatoid arthritis (27). At the same time there was a positive correlation between 5-HT1AR epidermal expression in L skin and the depression score. Both these receptor expression changes might be due to compensatory mechanisms.

There was a higher degree of SERT immunoreactivity in the basal layer of L compared with NL skin, which indicates that keratinocyte proliferation might be affected by modulating this protein. In L skin there was an inverse correlation of this degree of SERT immunoreactivity with stress susceptibility and a tendency to an inverse correlation with psychic trait anxiety. At the same time a correlation was evident for the degree of SERT immunoreactivity and the degree of acanthosis and a tendency to a correlation with inflammation. This highlights the importance of SERT in the inflammatory process and suggests this protein as a therapeutic target for AD. In addition, SERT may have a protective role in stress susceptibility and psychic trait anxiety in AD.

We recorded a positive correlation for pruritus intensity, pruritus being a primary and critical symptom in AD, with stress susceptibility and somatic trait anxiety. However, we did not observe a correlation between eczema severity (SCORAD) and any of the investigated psychodemographic data. Oh et al. (28) reported that pruritus in patients with AD correlated with state anxiety and trait anxiety, while the SCORAD did not show correlation with psychological parameters. Their patients included both males and females, as was the case in our study. This may have an impact on the results. There are sex differences regarding anxiety and stress susceptibility (29). Furthermore, extended studies, which incorporate sex aspects, are warranted.

Furthermore, no correlation was found between pruritus intensity and serotonergic markers in our patients. 5-HT has a pruritogenic role in both AD patient and control skin (e.g. 30). In our previous investigation (31) there were no correlations between clinical findings (i.e. eczema severity, clinical pruritus) and recorded experimental itch, or flare or wheal responses for 5-HT, in the patients with AD. Thus, 5-HT does not seem to be a major pruritogen in AD.

In conclusion, a role for the serotonergic system seems to exist in AD. This is based on the fact that there is a differential expression of 5-HT and its receptors, 5-HT1A and 5-HT2A, and its transporter protein in L compared with NL skin, and in addition, a correlation with the serotonergic markers and extent of the disease as well as with routine inflammatory histopathological parameters. Moreover, there is a positive/inverse correlation of 5-HT1A and 5-HT2A receptor expression and depression score, and an inverse correlation of degree of SERT immunoreactivity and stress susceptibility. After further studies these serotonergic molecules may become targets in the treatment of AD.

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The authors declare no conflicts of interest.

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